12 January 2023
EMA/586384/2022
Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

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

Janus Kinase inhibitors (JAKi)

Xeljanz (tofacitinib) EMEA/H-A20/1517/C/004214/0048

Cibinqo (abrocitinib) EMEA/H-A20/1517/C/005452/0003

Olumiant (baricitinib) EMEA/H-A20/1517/C/004085/0032

Rinvoq (upadacitinib) EMEA/H-A20/1517/C/004760/0017

Jyseleca (filgotinib) EMEA/H-A20/1517/C/005113/0014

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

Janus Kinase inhibitors (JAKis) are a group of oral immunomodulatory disease-modifying anti-rheumatic drugs (DMARDs). These medicinal products inhibit different JAK isoforms. Inhibition of JAK attenuates signalling of interleukins and interferons, resulting in modulation of the immune and inflammatory response.

There are 5 JAKis authorised for the treatment of inflammatory disorders:

- **Xeljanz (tofacitinib)**in the treatment of rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), juvenile idiopathic arthritis (JIA) and ulcerative colitis (UC).
- **Rinvoq (upadacitinib)** in the treatment of RA, AS, PsA, non-radiographic axial spondyloarthritis (nr-AxSpA), ulcerative colitis (UC) and atopic dermatitis (AD).
- **Olumiant (baricitinib)** in the treatment of RA, AD, alopecia areata (AA).
- **Jyseleca (filgotinib)** in the treatment of RA and UC.
- **Cibinqo (abrocitinib)** in the treatment of AD.

ORAL Surveillance study (Study A3921133) is a Phase 3b/4 randomized, parallel arm, open-label study that evaluates the safety of tofacitinib at two doses (5 mg and 10 mg BID) versus TNF-alpha inhibitors (TNFi). This study is a post marketing commitment to assess the risk of cardiovascular events in subjects 50 years of age and older with at least one cardiovascular risk factor with moderately or severely active RA.

Interim results on thrombotic events, mortality and serious infections from the ORAL Surveillance study were assessed in **2019 in an Article 20 referral procedure (EMEA/H/A-20/1485).** Preliminary analysis on major adverse cardiovascular events (MACE) (including myocardial infarction (MI)) and malignancies excluding non-malignant skin cancer (NMSC) of the final results from the ORAL Surveillance study were assessed as part of a **signal procedure (EPITT 19382)**. Following these earlier procedures, venous thromboembolism (VTE) (pulmonary embolism (PE) and deep vein thrombosis (DVT)), MI, lymphoma and lung cancer were included as adverse drug reactions (ADRs) in Xeljanz SmPC Section 4.8. To minimise these risks, Xeljanz SmPC Sections 4.2 and 4.4 were updated with warnings that tofacitinib should only be used in patients with certain risk factors if no suitable treatment alternatives are available, i.e., in patients >65 years of age, patients who are current or past smokers, patients with other cardiovascular risk factors, and patients with other malignancy risk factors. Tofacitinib should be used with caution in patients with known risk factors for VTE.

Final results of the completed ORAL surveillance study indicate that, further to the higher incidence of MACE and malignancies reported in the preliminary analysis, a higher incidence of VTEs, all-cause mortality and serious infections is observed in patients treated with tofacitinib compared to TNFi.

No randomised controlled studies have been conducted with the other JAKis to specifically evaluate these safety concerns. However, **preliminary results** of an observational study with another JAKi (baricitinib) (**Study I4V-MC-B023 (B023)**) indicated an increased rate of MACE and VTE with baricitinib compared to TNFi in RA patients.

On 28 January 2022, the European Commission (EC) therefore 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 the safety concerns of MACE, VTE, serious infections, malignancies and deaths on the benefit-risk balance of the JAKis used in inflammatory disorders (Xeljanz (tofacitinib), Rinvoq (upadacitinib), Olumiant (baricitinib), Jyseleca (filgotinib) and Cibinqo (abrocitinib)) and to issue a

recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

The scope of this procedure was initially limited to the indications approved for the concerned products at the start of the procedure and was extended on 10 June 2022 to include the other inflammatory indications for chronic treatment which received a favourable CHMP opinion and were authorised during the referral. The COVID-19 indication for Olumiant, where short-term use of the product is foreseen, is not expected to be impacted by the safety issues and was thus excluded from the review.

The two JAKis used in the treatment of myeloproliferative disorders, Jakavi (ruxolitinib) and Inrebic (fedratinib), were excluded since patient populations are different in terms of background risks, co-morbidities, life expectancy, etc. therefore the impact of the safety findings on the benefit risk balance would require different considerations.

2. Scientific discussion

2.1. Introduction

At the PRAC February 2022, a list of questions for the MAHs was adopted by the PRAC in which the MAHs of JAKis used in the treatment of inflammatory disorders were requested to provide an overview of the marketing status and exposure stratified per indication, country and dosing regimen.

Furthermore, safety data from completed and ongoing clinical trials (including pooled clinical trial data) for their respective product(s) regarding MACE, MI, malignancy, VTE (such as DVT/PE), serious infections, and all-cause mortality were requested by indication. This analysis was also to include ongoing procedures and be accompanied by appropriate measures of frequency to include comparisons of the JAKi and active comparators, where applicable.

The MAHs were also requested to perform a thorough literature search addressing potential class effects, to provide relevant in-house data, and to provide an overall discussion whether the safety outcomes of the ORAL Surveillance study including main safety outcomes observed in patients with RA could be considered class effects of JAKis, across all indications in inflammatory diseases.

All MAHs were also asked to consider further risk minimisation measures (RMMs) including changes to the product information.

The impact of the totality of the safety data on the benefit risk balance of each JAKis in all approved indications were also to be reviewed by the MAHs. This included available efficacy data from patients previously treated with TNFi for the rheumatic disorders and UC indication, or for the atopic dermatitis indication, in patients previously treated with systemic therapy. For each indication, the MAHs were also requested to discuss whether there are patients for whom it would not be appropriate to initiate TNFi / systemic (atopic dermatitis) therapy but who would still benefit from JAKis treatment, and to consider if/how the respective indications including the AA indication should be restricted. A separate assessment was asked to be done for the atopic dermatitis indication in adolescents 12 years and older, if applicable. Furthermore, updates to the RMPs were asked to be considered. Information was also requested from all MAHs whether a randomized clinical trial with their respective JAKi is being conducted or planned with a protocol similar to the ORAL Surveillance trial.

A short summary of the different products included in this referral is provided hereafter.

Cibinqo (abrocitinib)

Cibingo was granted marketing authorisation valid throughout the European Union on **09/12/2021.**

Cibinqo is indicated for the treatment of moderate-to-severe **AD** in adults who are candidates for systemic therapy.

The recommended starting dose is **200 mg once daily**, while for patients ≥ 65 years of age a starting dose of **100** mg is recommended. Other patients may benefit from a starting dose of 100 mg as cross referred to SmPC Sections 4.4 and 4.8. The lowest effective dose for maintenance should be considered. The maximum daily dose is 200 mg.

Discontinuation of treatment should be considered in patients who show no evidence of therapeutic benefit after 24 weeks.

Jyseleca (filgotinib)

Jyseleca was granted marketing authorisation valid throughout the European Union on **24/09/2020.**

Jyseleca is indicated for the treatment of

- moderate to severe active **RA** in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). In RA, it may be used as monotherapy or in combination with methotrexate (MTX).
- adult patients with moderately to severely active **UC** who have had an inadequate response with lost response to or were intolerant to either conventional therapy or a biologic agent.

The recommended dose of filgotinib for adult RA patients is **200 mg once daily.** A starting dose of **100 mg** is recommended for patients aged 75 years and older.

The recommended dose for induction and maintenance treatment is 200 mg once daily in UC. For UC patients who do not show an adequate therapeutic benefit during the initial 10 weeks of treatment, 12 additional weeks of induction treatment with 200 mg once daily may provide additional relief of symptoms. Patients who have not shown any therapeutic benefit after 22 weeks of treatment should discontinue filgotinib. Filgotinib is not recommended in UC patients aged 75 years and older as there is no data in this population.

Olumiant (baricitinib)

Olumiant was granted marketing authorisation valid throughout the European Union on **13/02/2017.**

Olumiant is indicated for the treatment of:

- moderate to severe active **RA** in adult patients who have responded inadequately to, or who are intolerant to, one or more disease-modifying anti-rheumatic drugs; baricitinib may be used as monotherapy in cases of intolerance to MTX
- moderate to severe **AD** in adult patients who are candidates for systemic therapy
- severe **AA** in adult patients.

For these three indications, the recommended dose is **4 mg once daily**, while for some patients, a dose of **2 mg** once daily is recommended such as those aged ≥ 75 years and may be appropriate for patients with a history of chronic or recurrent infections.

Rinvoq (upadacitinib)

Rinvoq was granted marketing authorisation valid throughout the European Union on **16/12/2019.**

Rinvoq is indicated for the treatment of

- **moderate to severe active RA** in adult patients who have responded inadequately to, or who are intolerant to one or more DMARDs. Rinvoq may be used as monotherapy or in combination with methotrexate.
- **active PsA** in adult patients who have responded inadequately to, or who are intolerant to one or more DMARDs. Rinvoq may be used as monotherapy or in combination with methotrexate.
- **axial spondyloarthritis**

  Non-radiographic axial spondyloarthritis (nr-axSpA)

  active non-radiographic axial spondyloarthritis in adult patients with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI), who have responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs).

  Ankylosing spondylitis (AS, radiographic axial spondyloarthritis)

  active ankylosing spondylitis in adult patients who have responded inadequately to conventional therapy
- moderate to severe **AD** in adults and adolescents 12 years and older who are candidates for systemic therapy
- adult patients with moderately to severely **active UC** who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent

The recommended dose in RA, PsA and axial spondyloarthritis is 15 mg once daily, while in atopic dermatitis also 30 mg once daily can be used in patients with high disease burden or not responding to the lower dose. In UC, an induction dose of 45 mg once daily is recommended for 8 weeks, followed by 15 mg or 30 mg once daily as maintenance dose depending on the individual patient's response.

Xeljanz (tofacitinib)

Xeljanz was granted marketing authorisation valid throughout the European Union on **22/03/2017.**

Xeljanz is indicated for the treatment

- in combination with MTX for moderate to severe active **RA** in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying antirheumatic drugs. Tofacitinib can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate.
- of **active PsA** in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy.
- of adult patients with active **AS** who have responded inadequately to conventional therapy.
- of adult patients with moderately to severely active **UC** who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent.
- of active **polyarticular juvenile idiopathic arthritis** (rheumatoid factor positive [RF+] or negative [RF-] polyarthritis and extended oligoarthritis), and **juvenile psoriatic arthritis** (PsA) in patients 2 years of age and older, who responses inadequately to previous therapy

with DMARDs. Tofacitinib can be given in combination with MTX or as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

The recommended dose for RA, PsA and AS is **5 mg twice daily.** For UC, the recommended dose is **10 mg** given orally twice daily for induction for 8 weeks, and thereafter 5 mg twice daily.

The recommended dose in pJIA and juvenile PsA is based on body weight: 10-<20kg 3.2 mg twice daily, 20-<40kg 4mg twice daily, ≥40 kg 5 mg twice daily.

The PRAC considered available data, including non-clinical, clinical efficacy and safety data. A summary of the most relevant information is included below.

2.2. Non-clinical aspects

The non-clinical assessment aimed at evaluating similarity in terms of pharmacological effects between tofacitinib 5/10 mg studied in ORAL Surveillance study and the other JAKis, in their approved doses. All JAKis included in the referral are inhibitors of the intracellular JAK family. Within the cytokine or growth factor induced signalling pathway, JAKs phosphorylate and activate signal transducers and activators of transcription (STATs) which modulate intracellular activity including gene expression. JAKis modulate these signalling pathways by preventing the phosphorylation and activation of STATs.

Other non-clinical aspects were also considered, including non-JAK activity, general toxicity, genotoxicity and carcinogenicity. All JAKis of interest have been studied in similar, but not identical, non-clinical study packages supporting chronic administration. Most of the data is based on information in the dossiers supporting initial marketing approvals, but scientific articles that have investigated pharmacodynamic activity of several JAKis head-to-head in *in vitro* cellular assays, taking the clinical efficacious exposure into account, were also considered.

2.2.1. Cibinqo (abrocitinib)

Abrocitinib has selectivity for JAK1 over the other 3 JAK isoforms JAK2 (28-fold), JAK3 (>340-fold) and tyrosine kinase 2 (TYK2, 43-fold) in enzymatic assays. In cellular settings, it preferentially inhibits cytokine-induced STAT phosphorylation by signalling pairs involving JAK1, and spares signalling by JAK2/JAK2, or JAK2/TYK2 pairs.

In secondary screens, abrocitinib inhibited vascular endothelial growth factor 2 (VEGFR2) and monoamine oxidase A with IC_{50} values of 1.2 µM and 6 µM, respectively. Inhibition of epidermal growth factor was also observed although an IC_{50} was not determined (12.3% inhibition at 1 µM and 33.2% at 10 µM). Potential involvement of VEGFR or epidermal growth factor receptor inhibition in the skeletal and skin findings observed in the juvenile and toxicity studies was discussed during the initial marketing authorisation application and concluded to be unlikely. Moreover, a risk for serotonergic syndrome was considered unlikely (EMEA/H/C/005452/0000).

In repeat-dose toxicity studies, decreased lymphocyte counts and decreased size and/or lymphoid cellularity of organs/tissues of the immune and haematopoietic systems were observed and attributed to the pharmacological properties (JAK inhibition) of abrocitinib. In the 1-month monkey study, these immunosuppressive effects resulted in cytomegalovirus infection in all males administered 150 mg/kg/day. In juvenile, and young rats, abrocitinib administration caused macroscopic and microscopic bone findings.

Abrocitinib was not genotoxic and caused no tumours in a 6-month mouse carcinogenicity study. In a 2-year carcinogenicity study, a higher incidence of benign thymomas was noted in female rats at all tested dose levels. The benign thymomas were deemed secondary to immunosuppression.

2.2.2. Jyseleca (filgotinib)

Filgotinib preferentially inhibited the activity of JAK1 and showed > 5-fold higher potency for JAK1 over JAK2, JAK3 and TYK2 in biochemical assays. In human cellular assays, filgotinib preferentially inhibited JAK1/JAK3-mediated signaling activated by interleukin (IL)-2, IL-4 and IL-15, JAK1/2 mediated signalling activated by IL-6 and JAK1/TYK2-mediated signalling activated by type I interferons, with functional selectivity over signalling via pairs of JAK2 or JAK2/TYK2. The primary metabolite GS-829845 showed a similar JAK1 selectivity but with an approximately 10-fold lower potency as compared to filgotinib.

In *in vitro* off target screens some kinases with IC_{50} values below the C_{max} of filgotinib were identified (e.g. Liver Kinase B1 and Serine/Threonine Protein Kinase 1). Due to higher potency towards JAK1 than to these non-JAK kinases, no meaningful impact from these targets is expected. For the GS-829845 metabolite, two non-JAK kinases, Aurora B Kinase (IC_{50} 1.5 µM; involved in cell cycle regulation) and feline McDonough sarcoma (IC_{50} 3.6 µM) were inhibited. As the toxicity studies have not identified any specific GS-829845 related concerns, off-target binding by GS-829845 was considered most likely not clinically relevant.

Main organs affected in the repeat-dose toxicity studies included those related to JAK inhibition, i.e. the immune and haematopoietic systems. Effects consistent with inhibition of JAK1/3 such as decreases in circulating lymphocytes (T-cells) and natural killer (NK) cells as well as decreased cellularity and/or lymphoid depletion in lymphoid tissues, were observed both for filgotinib and GS-829845 at multiples of the clinical exposure. At the same exposure levels of filgotinib, decreases in RBC parameters (red blood cells, haemoglobin, and haematocrit) and reticulocytes, which are consistent with JAK2 inhibition, were also observed. In the long-term dog study (9 months), Demodex infection was confirmed in all animals in the high dose group (about clinical exposure) and considered secondary to immunosuppression. Effects on male reproduction organs (testes and epidiymidis) and decreased spermatogenesis with a 2.7-fold exposure margin between the no observed adverse effect level (NOAEL) in dogs (the most sensitive species) and clinical exposure were also observed, although not found to be related to JAK inhibition.

Filgotinib was not genotoxic and there was no evidence of tumorigenicity of filgotinib or GS-829845 in a 6-month rasH2 transgenic mouse study. In a 2-year rat study, filgotinib but not GS-829845, caused an increased incidence of testicular Leydig cell adenomas at an exposure approximately 4.2-fold clinical exposure. The clinical relevance of these benign LH-related tumors is considered low.

2.2.3. Olumiant (baricitinib)

Baricitinib is a selective and reversible inhibitor of JAK1 and JAK2. In isolated enzyme assays, baricitinib inhibited the activities of JAK1, JAK2, TYK2 and JAK3 with IC_{50} values of 5.9, 5.7, 53 and >400 nM, respectively.

In off-target screens, baricitinib showed moderate binding affinity for CaMK2d and CaMK2g (IC_{50} 170 nM and 150 nM, respectively), both isoforms have been ascribed a role in synaptic plasticity. In addition, the potential off-target binding of baricitinib and tofacitinib was investigated by Faquetti et al (2021), using two computational methods with the aim to identify targets related to thrombosis or viral infection/reactivation. No potential non-JAK targets related to an increased risk of thrombosis or viral infection/reactivation were identified neither for baricitinib nor for tofacitinib.

In repeat-dose toxicity studies in mice, rats and dogs, decreases in lymphocytes, eosinophils and basophils as well as lymphoid depletion in organs/tissues of the immune system were observed. Decreases in red blood cell parameters were observed in mice, rats and dogs at exposures approximately 6 to 36 times the human exposure. In chronic dog studies, opportunistic infections

related to demodicosis were observed in dogs at exposures approximately 7 times the human exposure.

Baricitinib was not genotoxic, and there was no evidence of tumorigenicity in a 6-month rasH2 transgenic mouse study or in a 2-year rat study at AUC exposures about 27 times the clinical AUC.

2.2.4. Rinvoq (upadacitinib)

Upadacitinib is reported to preferentially inhibit signalling by JAK1 or JAK1/3 with functional selectivity over cytokine receptors that signal via pairs of JAK2 in cellular assays.

Upadacitinib showed inhibitory activity at two non-JAK kinases, Rho kinase 1 and 2, with IC_{50}s of 1 µM and 0.42 µM, respectively. Activities via these off-targets are considered unlikely at clinically relevant exposures.

The main organs affected in the repeat-dose toxicity studies were primarily those related to JAK inhibition, that is the immune and haematopoietic system. Findings consistent with the inhibition of JAK1/3 were observed (i. e. decreases in circulating lymphocytes and lymphoid depletion in spleen, thymus and lymph nodes) but also effects consistent with JAK2 inhibition such as decreases in RBC parameters and reticulocytes that were observed in rats and dogs at multiples of the clinical exposure. In the long-term dog study (9 months), Demodex infection was confirmed in all animals in the high dose group (about 2-fold clinical exposure) and considered secondary to immunosuppression.

Upadacitinib was not genotoxic and there was no evidence of tumorigenicity in a 6-month rasH2 transgenic mouse study or in a 2-year rat study at AUC exposures about 10 times the clinical AUC.

2.2.5. Xeljanz (tofacitinib)

Tofacitinib is reported to inhibit JAK1, JAK2, JAK3 and to a lesser extent TYK2 in enzymatic assays. In human cells, tofacitinib preferentially inhibits signalling by heterodimeric cytokine receptors that associate with JAK3 and/or JAK1 with functional selectivity over cytokine receptors that signal via pairs of JAK2.

Tofacitinib showed off-target inhibition of VEGFR1, MT3, Cam kinase 2α and LynA kinase with IC_{50}s of 3.7, 5.3, 12 and 2.3 µM respectively. Off-target activities at clinically relevant exposures seem unlikely.

In repeat-dose toxicity studies, effects consistent with the inhibition of JAK1/3 were observed (i. e. decreases in circulating lymphocytes and NK cells, and lymphoid depletion in spleen, thymus and lymph nodes). Effects consistent with JAK2 inhibition such as decreases in RBC parameters (red blood cells, haemoglobin, and haematocrit) and reticulocytes were observed in rats and monkeys at multiples of the clinical exposure. Secondary effects from immunosuppression, such as bacterial and viral infections and lymphoma were observed in monkeys at clinically relevant doses.

Tofacitinib was not genotoxic and there was no evidence of tumorigenicity in a 6-month rasH2 transgenic mouse study. In a 2-year rat study, tofacitinib caused benign testicular interstitial (Leydig) cell tumours, and in female rats hibernomas (malignancy of brown adipose tissue) were observed at exposures greater than or equal to 83 or 41 times the clinical exposure level at 5 mg or 10 mg twice daily. Benign thymomas were also observed in female rats at 187 or 94 times the clinical exposure level at 5 mg or 10 mg twice daily.

2.2.6. Discussion on non-clinical aspects

Selectivity and effect in humans at therapeutic exposure are dependent on the pattern of inhibition on individual JAKs in pairs and degree of inhibition of downstream signals via STATs. Comparison of potency and evaluation of selectivity between different JAKis should therefore preferably be performed in the same study based on their impact on activation of specific signaling pathways in whole blood assays rather than in biochemical assays performed on purified and isolated kinases.

Three scientific articles have studied the pharmacodynamic activity of several JAKis head-to-head in *in vitro* cellular assays taking the clinical efficacious exposure into account:

- Traves et al (2021) studied the *in vitro* inhibition of cytokine responses of whole blood peripheral blood mononuclear cell combined with clinical pharmacokinetics to model the daily pharmacodynamic profiles of tofacitinib, upadacitinib, baricitinib and filgotinib. The main conclusion was that all examined JAKis potently inhibited JAK1-dependent pathways (IFN-α induced JAK1/TYK2 and IL-6 induced JAK1/JAK2/TYK2) at doses that have similar efficacy in RA. Modest differences were observed in other JAK1-dependent pathways (IFN-γ induced JAK1/JAK2), JAK2(G-CSF, IL-12 or IL-23 induced JAK2/TYK2 and GM-CSF induced JAK2/JAK2)- and JAK3(IL-2, IL-15 or IL-4 induced JAK1/JAK3)-dependent signalling. Filgotinib showed a lower inhibitory effect on JAK2- and JAK3-dependent activity in comparison with the other JAKis. It was concluded that JAK inhibition is context-dependent and influenced by parameters such as cytokine stimulus, STAT substrate and cell type.
- McInnes et al (2019), studied baricitinib, upadacitinib and tofacitinib, and reported that tofacitinib and upadacitinib were the most potent inhibitors of the JAK1/3-dependent cytokines tested (IL-2, IL-4, IL-15 and IL-21). All 3 JAKis were inhibitors of JAK1/2-dependent cytokines (IL-6 and IFN-γ), the JAK1/TYK2-dependent cytokines IL-10 and IFN-α, the JAK2/2-dependent cytokines IL-3 and GM-CSF, and the JAK2/TYK2-dependent cytokine G-CSF, but often to significantly differing degrees. The authors concluded that different JAKis modulated distinct cytokine pathways to varying degrees, and no JAKi potently or continuously inhibited an individual cytokine signalling pathway throughout the dosing interval.
- Dowty et al (2019) also studied the *in vitro* potency of several JAKis (tofacitinib, upadacitinib, baricitinib and filgotinib) in the context of clinical efficacious exposures. While some numeral differences were observed, the authors concluded that the different effects of tofacitinib, upadacitinib, baricitinib, and filgotinib on the signalling of various cytokines at therapeutic doses were minor, suggesting that the claimed selectivity of these compounds may not take place in patients.

Overall, the 5 JAKis under review share a similar pharmacodynamic profile with greatest inhibition of JAK pairs involving JAK1, an isoform predominantly involved in regulation of inflammatory and innate immune responses, at therapeutic concentrations. There are also *in vitro* differences in their selectivity for the existing pairs of the 4 isoforms. However, it remains unclear whether this translates into clinically meaningful differences of the safety profiles. Therefore, based on the available data and lacking evidence on the role of specific JAK pathways in the adverse events of interest, the PRAC concluded that these safety events are considered class effects. Given that JAK inhibition seems to involve a complex interplay between JAK pairing, cell type, cytokine stimuli and STAT substrate, it seems unlikely that further *in vitro* data can provide meaningful insights on detailed mechanisms behind the adverse events of interest.

Effects on cardiovascular function have been assessed in standard *in vitro* and *in vivo* safety pharmacology studies and in repeat dose toxicology studies. There were no prominent findings with any of the JAKis in these studies. In pivotal repeat-dose studies with the 5 JAKis, the cardiovascular

system was not a target organ of toxicity. Neither were there any prominent alterations in clinical pathology parameters of relevance for MACE and VTE, such as platelet counts, coagulation tests, cholesterol or triglycerides.

In repeat-dose toxicity studies in healthy rodents (rats) and non-rodents (dogs or monkeys), dose- and duration-dependent decreases in circulating lymphocytes, lymphocyte subsets and lymphoid depletion in tissues of the immune system were observed following treatment with tofacitinib and the 4 other JAKis. These effects are consistent with inhibition of the JAK1/JAK3 pathway and would generally suggest an increased risk for infection and potentially tumour development. Findings interpreted as secondary to immune suppression were also observed in toxicology and/or carcinogenicity studies with all 5 JAKis. Thus, from a non-clinical perspective, a risk for infections seems plausible for all 5 JAKis. Since a compromised immune system is a risk factor for human carcinogenicity, an increased risk for malignancy seems plausible for the JAKis. The risk seems rather similar for all 5 JAKis, thus being a class effect.

The 5 JAKis under review are unique active substances with differences in their JAK isoform selectivity that may affect clinical efficacy and safety. It is also evident that there are great similarities between tofacitinib and the other JAKis such as a shared pharmacodynamic mode of action. There are currently no data available on the role of specific JAK pathways in the adverse events of interest, therefore the occurrence of these events cannot be ascribed to a specific JAK isoform. Thus, the PRAC concluded that the events of MACE, VTEs, serious infections and malignancies are considered general JAKi class effects.

2.3. Data on clinical efficacy

Comprehensive summaries of efficacy data for the products included in this referral, based on the clinical study results for the initial marketing authorisation and subsequent extensions of indications, are included in Section 5.1 of approved SmPC for the respective products. For all indications, except atopic dermatitis and alopecia aerata, the MAHs were asked to provide available efficacy data for their respective JAKi in patients previously treated with TNFi, or for the atopic dermatitis indication, in patients previously treated with systemic therapy. A summary of these data is provided hereafter.

2.3.1. Cibinqo (abrocitinib)

Efficacy of abrocitinib 100 mg QD and 200 mg QD versus placebo was demonstrated in short-term (12 week) monotherapy studies of both co-primary efficacy endpoints (Investigator Global Assessment for Atopic Dermatitis [IGA] and Eczema Area and Severity Index 75% reduction; [EASI-75]). Across all treatment groups, about 41% - 69% of patients had received prior systemic treatment for atopic dermatitis. A dose-response relationship was shown, with the highest level of efficacy obtained for the dose 200 mg QD. The key secondary efficacy endpoints on itch (PP-NRS-4 and PSAAD) showed a dose-dependent efficacy of abrocitinib which was superior to placebo and supported the efficacy results obtained with the primary endpoints.

In the active control combination therapy study, the efficacy of abrocitinib 100 mg QD and 200 mg QD was compared with that of dupilumab 300 mg/ml while all subjects were on medicated topical therapy. A placebo control was also included. Efficacy was similar for abrocitinib 100 mg QD and dupilumab, while in the first 12 weeks of treatment abrocitinib 200 mg QD was superior to dupilumab. The efficacy of itch was also dose-dependent and could be noted earlier with abrocitinib than with dupilumab. Treatment effects in subgroups (e.g. weight, age, sex, race and prior systemic immunosuppressant treatment) in 12-week monotherapy and 16-week combination therapy were consistent with the results in the overall study population, as described in the approved SmPC section 5.1.

The MAH has conducted a randomised withdrawal study to evaluate whether a short duration of 200 mg QD could be used to achieve rapid disease control followed by long-term maintenance with 100 mg QD to minimise cumulative exposure. Long-term prevention of AD flare was achieved in a majority of patients with the induction-maintenance regimen.

2.3.2. Jyseleca (filgotinib)

Efficacy data in RA were obtained from 3 completed Phase 3 trials including a total of 3452 patients with RA. FINCH 1 included patients with an inadequate response to methotrexate, FINCH 2 included patients with an inadequate response or intolerance to bDMARDs, and FINCH 3 included methotrexate-naïve RA patients. Patients who completed either of these trials could roll-over to FINCH 4 long term extension (LTE) trial. When compared to placebo in the FINCH 2 study, both doses of filgotinib (i.e., 100 mg and 200 mg) showed superiority over placebo for the primary endpoint and all key secondary endpoints. Additionally, data from the FINCH 4 LTE trial showed sustainability of response to filgotinib 200 mg *and* 100 mg over period of 48 weeks.

Efficacy data in UC were obtained from the phase 2b/3 trials, SELECTION consisting of two induction studies and one randomized maintenance study. In the induction studies, Cohort A (n=660) included biologic-naïve patients and Cohort B (n= 691) included biologic-experienced patients. In the maintenance study filgotinib-responders (n=571) from the induction studies were re-randomized into a maintenance study (Week 11 to 58). Non-responders from the induction phase or patients who experienced disease worsening or completed the maintenance study could roll-over to the long-term extension trial SELECTION LTE. In SELECTION, the primary endpoint was met for filgotinib 200 mg but failed to reach statistical significance for filgotinib 100 mg. In the SELECTION maintenance study, the primary endpoint was met for both filgotinib 200 mg and 100 mg at week 58.

Efficacy in subjects with RA with inadequate response to bDMARDs was evaluated in FINCH 2 demonstrating superiority of filgotinib (in both doses) over placebo for the primary endpoint (i.e., the American College of Rheumatology 20% improvement (ACR20) response rate at week 12): filgotinib 200 mg 66.0% versus placebo 31.1% (difference in response rates: 34.9%, $p < 0.001$) and for filgotinib 100 mg 57.5% versus placebo 31.1% (difference in response rates: 26.4% $p < 0.001$).

Efficacy in subjects with UC with inadequate response to TNFi or to vedolizumab was evaluated in cohort B of the SELECTION trial where the primary endpoint (i.e., proportion of subjects achieving endoscopy, rectal bleeding, and stool frequency remission at Week 10) was met for filgotinib 200 mg; 11.5% versus placebo 4.2% (difference in proportions: 7.2%, $p = 0.0103$). For filgotinib 100 mg, the corresponding figure was 9.5% versus placebo 4.2% (difference in proportions: 5.2%, $p = 0.0645$). Thus, for the 100 mg dose the result did not reach statistical significance.

2.3.3. Olumiant (baricitinib)

Three studies in approximately 2,500 patients with **RA** showed that baricitinib improves symptoms, in patients with inadequate response to DMARDs. Results from 12 weeks evaluation within these three studies showed that in patients previously treated with methotrexate, 70% of patients on baricitinib achieved at least a ACR20 response, compared with 61% of patients on adalimumab and 40% on placebo. In patients previously treated with DMARDs, 62% of patients on baricitinib achieved at least ACR20 response, compared with 40% of patients on placebo. In patients previously treated with TNF-inhibitors, 55% of patients on baricitinib achieved at least ACR20, compared with 27% of patients on placebo.

Three main studies in around 1,600 patients with **AD** for whom local treatments were insufficient or were not suitable showed that baricitinib improved AD symptoms. In 2 studies, 14 to 17% of patients

treated with baricitinib had skin clear or almost clear of inflammation after treatment for 16 weeks compared with 5% of the placebo patients. In a study where baricitinib or placebo were added to local corticosteroid treatment, the figures were 31% with baricitinib and 15% with placebo.

The MAH provided data that was considered to support efficacy in patients with inadequate response to TNFi, or for whom such treatments may not be appropriate. This is based on data of a subsample of patients from the All BARI **RA** data set and discussed by Tanaka et al, 2019. In this study, improvements were seen in disease activity, physical functioning, and pain 12 weeks after switch from adalimumab to baricitinib (n = 40), while adverse events remained the same. Of note, in the 35 patients with an initial inadequate response to baricitinib but who still continued its use, these improvements were also observed except for inflammatory markers C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Smolen at al., 2017 reported that patients with RA who had an inadequate response to biological DMARDs including at least one TNFi, and who were subsequently randomized to baricitinib, achieved better outcome at several PRO's compared to those randomized to placebo. As such, treatment with baricitinib after failure on TNFi is effective.

Regarding efficacy in **AD** patients treated with systemic therapy prior to baricitinib, the development programme of baricitinib comprised patients who were candidates for systemic therapy only. In the All BARI AD data set, 51% of the patients received prior treatment, and one study was performed in patients previously treated with ciclosporin. In this study, the proportion of patients reaching EASI75 at week 16 was significantly larger than in placebo and secondary outcomes supported these findings. The effects lasted at least until 52 weeks.

Baricitinib was approved in June 2022 for the treatment of severe AA. This approval was based on two main studies in 1200 adults with severe AA (experiencing loss of at least 50% of scalp hair), in which baricitinib was shown to reduce hair loss compared to placebo. After 36 weeks of treatment, the extent of hair loss improved from over 50% to under 20% of scalp hair in 34% of the participants taking 4 mg of baricitinib and in 20% of the participants taking 2 mg of baricitinib, compared with 4% of the participants taking placebo. The benefits of baricitinib appeared to continue with longer-term treatment.

2.3.4. Rinvoq (upadacitinib)

In **RA,** data was provided from two phase 3 studies M13-542 and M15-925 which enrolled subjects with prior exposure to bDMARDs, where approximately 90% and 88% respectively had previous exposure to at least one TNFi. In both studies, at week 12 upadacitinib 15mg showed greater efficacy when compared to placebo or active comparator. Further, the MAH provided long-term efficacy analyses in the TNF-IR subgroups of studies M13-542 and M15-925 up to week 260 and week 156 respectively. Data from these studies showed continued improvement or maintenance of efficacy in patients on upadacitinib 15mg.

The efficacy of upadacitinib in patients with **PsA** was evaluated in 2 studies that are still ongoing. Study M15-554 enrolled 642 patients with inadequate response to at least one bDMARD, while study M15-572 enrolled 1705 patients with inadequate response to at least one non-biological DMARD. In study M15-554, around 78% of patients were previously exposed to TNFi. Primary and secondary endpoints were greater with upadacitinib 15mg once daily compared to placebo at Week 12. Long term data up to Week 104 also continued to show improvement or maintenance in efficacy. Data from study M15-572, which involved an adalimumab arm, showed comparable results between upadacitinib 15mg and adalimumab 40mg with maintenance of clinical response up to week 104.

In **AS**, data was provided for Study M19-944, which included patients with AS who had inadequate response to bDMARD. At week 14, statistically significantly greater percentage of subjects achieved primary endpoint in upadacitinib 15mg group compared to placebo. All 14 multiplicity-controlled

secondary endpoints were also met. Efficacy data were consistent in post-hoc analysis of subgroup of patient with previous exposure to TNFi (approximately 87% of 420 total subjects).

Regarding **AD**, subgroup results of the co-primary efficacy endpoints ([IGA and EASI 75] at Week 16) for subjects with or without prior use of systemic therapy for AD shows that, across each treatment arm, the response rates were similar between subjects with or without prior use of systemic therapy. For all three studies, subjects with or without prior use of systemic therapy receiving upadacitinib 15 mg or 30 mg QD had higher response rates compared to placebo. The upadacitinib 30 mg QD dose consistently resulted in numerically higher proportions of IGA responders and EASI 75 responders than the upadacitinib 15 mg QD dose for subjects with or without prior use of systemic therapy for AD.

An indication in **UC** was approved in July 2022. To support this indication, efficacy and safety were evaluated in three multicentre, double-blind, placebo-controlled Phase 3 clinical studies, two replicate induction studies, and one maintenance study. In the induction studies, the primary endpoint was clinical remission at week 8; which was reached by 26 % (study UC1) or 33.5 % (UC2) of patients treated with 45 mg upadacitinib, and by 4-5 % of placebo patients in both studies. In the UC-3 study, maintenance treatment was evaluated in 451 patients who achieved clinical response with 8-week upadacitinib 45 mg induction treatment, and thereafter were randomised to upadacitinib 15 mg, 30 mg or placebo once daily for up to 52 weeks. The primary endpoint was clinical remission at 52 weeks, which was reached by 12.1% (placebo), 42.3% (upa 15 mg) and 51.7% (upa 30 mg). Efficacy was also seen in patients with prior biologic failure.

Further, an indication in **nr-axSpA** was approved in July 2022. The efficacy and safety of upadacitinib 15 mg once daily were assessed in a randomised, double-blind, multicentre, placebo-controlled study in patients 18 years of age or older with active non-radiographicaxial spondyloarthritis. Study SELECT-AXIS 2 (nr-axSpA) was a 52-week placebo-controlled trial in 314 patients with active non-radiographic axial spondyloarthritis with an inadequate response to at least two NSAIDs or intolerance to or contraindication for NSAIDs. In SELECT-AXIS 2 (nr-axSpA), a significantly greater proportion of patients treated with upadacitinib 15 mg achieved an ASAS40 response compared to placebo at week 14.

2.3.5. Xeljanz (tofacitinib)

Six studies in over 4,200 patients with **RA** have shown that Xeljanz is effective at reducing signs of disease and well reducing joint damage, mainly studied in patients previously treated with other DMARDs, and mainly in combination with methotrexate.

Xeljanz, in combination with methotrexate, was shown to be effective at improving symptoms of **PsA** in two main studies; one in comparison with adalimumab or placebo, and the other compared with placebo; all in patients with inadequate response to other treatments. In the first study, symptoms improved substantially in 50 and 52% of patients on tofacitinib or adalimumab, compared with 33% on placebo. Also in the second study, tofacitinib was more effective than placebo at improving symptoms (50% vs 24%).

Three studies were undertaken in **UC**. In one of these, 18% of tofacitinib 10 mg BID treated patients had mild or no symptoms after eight weeks vs 8% of placebo patients. In the second study, similar effects were seen in 17% on tofacitinib and 4 % of placebo patients at week 8. In the third study, 34% in the tofacitinib 5 mg BID group had mild or no symptoms after one year vs 11% of placebo patients.

Tofacitinib versus placebo was studied in one study in patients with **AS** with inadequate response to previous treatment. ASAS20 / ASAS 40 were reduced in about 56% / 40 % of tofacitinib patients versus 29% / 13% of patients on placebo.

Tofacitinib was also more effective than placebo at reducing symptoms of **JIA** both in combination with methotrexate and alone; studied in 173 patients between 2 and 17 years old, and where 28% of tofacitinib treated patients experienced flare-ups after 26 weeks compared with 53% of placebo-treated patients.

Regarding **RA**, evidence for the efficacy of tofacitinib in patients previously treated with TNFi mainly comes from study 1132 (ORAL Step). In that study, it was shown in RA patients with inadequate response to TNFi, that tofacitinib 5 mg + MTX was more effective than placebo + MTX in ACR50 at month 3 (26% versus 8%, p<0.0001). Favourable effects were also shown in disability (HAQ-DI). This result was reflected in the pooled data of the RA phase 2/3 studies (1032, 1044, 1046 and 1064), where it was shown that in patients who were previously treated with TNFi, tofacitinib 5 mg is more effective than placebo in ACR50 response at month 3 (27% versus 9%, p<0.0001) and that this response was similar in patients who were naïve to TNFi (30% versus 8%, p<0.0001).

Regarding **PsA,** the efficacy of tofacitinib in patients with PsA who were previously treated with TNFi has been shown in study 1125 (OPAL Beyond). In that study, it was shown in PsA patients with inadequate response to TNFi, that tofacitinib 5 mg was more effective than placebo in ACR50 at month 3 (30% versus 15%, p<0.05). Tofacitinib also had a favourable effect on the level of disability (HAQ-DI).

Regarding **UC**, for the primary endpoint of remission, superiority was shown to placebo for tofacitinib 10 mg BID for 8 weeks; in induction treatment in subjects with moderately to severely active UC who failed or were intolerant to at least 1 protocol specified UC treatment, either corticosteroids, AZA/6-MP, or TNFi therapy. Benefit was further supported by the relevant secondary endpoints.

For the pivotal maintenance study A3921096, the primary endpoint presented was remission at 52 weeks. The proportion of subjects in sustained corticosteroid-free remission among subjects in remission at baseline was statistically significantly greater in both the tofacitinib 5 mg BID group and the tofacitinib 10 mg BID group compared with the placebo group. Tofacitinib 5 mg BID and tofacitinib 10 mg BID were also superior to placebo for the primary endpoint of remission at week 52, and other relevant secondary endpoints. **The incremental benefit of 10 mg BID maintenance dosing over the 5 mg BID maintenance dosing was particularly pronounced in patients who have failed previous TNFi therapy.**

As for **AS**, efficacy of tofacitinib in patients with AS who were previously treated with TNFi was analysed in subgroup analysis of study 1120, performed in patients who were naïve to biological DMARDs (~80%) and in patients who did use TNFi previously (~20%). In that study, it was shown in AS patients with inadequate response to TNFi, that tofacitinib 5 mg was more effective than placebo in ASAS40 at week 16 with a treatment effect (tofacitinib 5 mg versus placebo) of 19% (p<0.05). The treatment effect in patient naïve to biological DMARDs was 31% (p<0.05).

Regarding JIA, efficacy of tofacitinib in patients with polyarticular course JIA who were previously treated with TNFi was analysed in subgroup analysis of randomised withdrawal study 1104, performed in JIA patients who were randomised if they had at least some response (JIA ACR30). Included patients were naïve to biological DMARDs (62%) or had used TNFi previously (38%). In patients who were naïve to TNFi, the treatment effect in ACR50 response at week 44 was 14% (p=0.15), while the treatment effect was 35% (p=0.023) in patients who were TNFi experienced.

2.3.6. Discussion on clinical efficacy

Cibingo

Abrocitinib has proven to be efficacious for the treatment of **AD**; both in monotherapy and combination studies. Effects in patients having received prior systemic immunosuppressant treatment are consistent with the results in the overall study population. Long-term prevention of AD flares was achieved in a majority of patients with the induction-maintenance regimen.

The results from a randomised withdrawal study support the feasibility of using abrocitinib 200 mg QD induction to rapidly achieve disease control followed by dose reduction to 100 mg QD for maintenance treatment.

Jyseleca

With respect to the established benefit of filgotinib, the available data support that filgotinib is an effective treatment for **RA** and **UC.** Additionally, overall data presented by the MAH support that for patients with RA or UC, who failed to achieve therapeutic response to a TNFi, could still benefit from using filgotinib.

Rinvoq

The overall benefit of upadacitinib treatment is considered unchanged by the current review and thus consistent with the presentation of efficacy data in section 5.1 of the approved SmPC. The data presented by MAH support benefits of upadacitinib also in patients with RA, PsA and AS who previously failed to achieve therapeutic response to TNFi.

Olumiant

The efficacy data submitted during this procedure are consistent with the information in SmPC Section 5.1 of the approved SmPC. Thus, the benefits of Olumiant are considered unchanged.

Data that was considered to support efficacy in patients with inadequate response to TNFi, or for whom such treatments may not be appropriate were provided.

With regards to the AD indication, efficacy data are available in patients treated previously with systemic therapy from the studies conducted in patients who were candidates for systemic therapy. Indeed, these studies included patients who received prior systemic therapies. The main data derive from a study where patients were previously treated with ciclosporin and suggest that treatment with baricitinib is effective in these patients.

The AA indication was approved in June 2022, baricitinib has been shown to be efficacious against placebo. There are no other systemic therapies approved for this indication.

Xeljanz

The efficacy data submitted during this procedure are consistent with the information in section 5.1 of the approved SmPC. Thus, the benefits of tofacitinib are considered unchanged.

The efficacy data in RA, PsA, AS and JIA patients previously treated with TNFi indicate that treatment with tofacitinib in such patients is effective.

Regarding UC, efficacy data support a 10 mg BID maintenance schedule that might be considered if the patient experiences a decrease in response on tofacitinib 5 mg twice daily and failed to respond to alternative treatment options such as TNFi.

The PRAC concluded that no new data have emerged that would question the efficacy of the JAKis in their approved indications.

2.4. Data on clinical safety

The MAHs were requested to discuss data for their respective product(s) regarding MACE, MI, malignancy, VTE (such as DVT/PE), serious infections, and all-cause mortality per indication from completed and ongoing clinical studies, and observational studies stratified by dose. These results are presented respectively in Sections 2.4.1. and 2.4.2.

The MAHs were also asked to discuss whether the safety outcomes of the ORAL Surveillance study as observed in patients with RA can be considered class effects of JAKis, across all indications in inflammatory diseases, these discussions are presented in Section 2.4.3.

2.4.1. Safety Data from clinical trials

2.4.1.1. Cibinqo (abrocitinib)

The safety data from clinical studies were provided in the following datasets:

- Short-term controlled data that included data from 2 sources: the placebo-controlled short-term safety pool (STSP) and the active-controlled short-term pools (ACSP).
- Longer-term safety, including data from 2 sources: the Long-term Dose-Controlled Pool (LTDCPsNDA) and Regimen Randomized Long-term Safety Pool (RRLTPsNDA). Data from the Full Cumulative Pool 2020 (FCP2020), the long-term data included in the approved SmPC, were provided for reference.

Short-term controlled data

In a 16-week study with abroticinib 100 mg, 200mg, dupilumab and placebo, there were 0 or 1 event in each of treatment group for all events of interest except for serious infections and all-cause mortality. Regarding serious infections, no clear-cut increase of the EAIRs for abrocitinib 100 mg and 200 mg in comparison with placebo was seen in some data pools, while for one data pool, higher exposure adjusted incidence rates (EAIRs) were seen for both abrocitinib groups (EAIRs for 100 mg and 200 mg d.d. were 2.80 (0.34, 10.12) and 1.24 (0.25, 3.61), respectively) in comparison with placebo (0.00 (0.00, 9.48)) and dupilumab 0.00 (0.00, 1.46)). Regarding all-cause mortality, from the STSP there was one death in abrocitinib group and no deaths in other groups, and from the ASCP there were 2 deaths in abrocitnib 200 mg group and no deaths in other groups.

Longer-term safety data

For MACE, a low number of cases for both abrocitinib 100 mg and 200 mg was reported. However, regarding risk factors for MACE, the IR for MACE was higher in the older subgroup (1.16/ 100PY for baseline age ≥65 years) compared to younger adults (0.28/ 100PY for baseline age 18 - <65 years). In the analysis of MACE by smoking status, IR was higher for current or former smokers (0.38) compared to non-smokers (0.22).

Regarding malignancies (excluding NMSC (non-malignant skin cancer)), there was a higher rate of malignancies (excluding NMSC) observed with abrocitinib 200 mg (0.27 (0.10, 0.58)) compared to abrocitinib 100 mg (IR 0.13 (0.02, 0.46)) For NMSC, EAIR for abrocitnib 100 mg was 0.39 (0.14, 0.84), and for abrocitinib 200 mg 0.13 (0.03, 0.39). The EAIRs for NMSC were consistent with the background rates for cohorts of patients with AD from the Danish Registry (0.1/100 PY (95% CI: 0.24, 0.29)) and among patients ≥12-years with moderate-to-severe AD in the Kaiser Permanente Northern California database (0.40/ 100 PY (95% CI: 0.34, 0.47)).

A higher rate of VTE was observed with abrocitinib 200 mg compared to abrocitinib 100 mg. EAIR for abrocitinib 200 mg was higher in comparison with abrocitinib 100 mg (0.22 (0.07, 0.52) vs 0.13 (0.02,

0.46)). In the RRLTP, the EAIR for VTE was 0.13 (0.02, 0.46). Overall, in LTDCPsNDA and RRLTPsNDA, there were 7 events of VTE in subjects who were on abrocitinib 200 mg in the time of the event, while there were 2 events of VTE in subjects on abrocitinib 100 mg.

The most frequent serious infections in the LTDCPsNDA were those related to herpes zoster, herpes simplex, and pneumonia.

In the LTDCP, there was a trend toward a dose-response for all-cause mortality (EAIRs were 0.13 (0.02, 0.46)) and 0.22 (0.07, 0.52) for abrocitinib 100 mg and abrocitinib 200 mg, respectively). All deaths were related either to MACE, serious infections or malignancy. Out of 7 fatal cases, there was a case with diagnosis of multi-organ failure due to Staphylococcal sepsis with aortic valve endocarditis after septic arthritis of the left knee joint on day 704, in which the event was considered related to study drug by the investigator. Following PRAC's request, the MAH provided an analysis of cases of sepsis as well of infections with fatal outcome.

In total 6 cases of sepsis were reviewed. According to the MAH, five of these did not fulfil a definition of sepsis, but were other serious infections, including severe herpes zoster infections or other bacteraemia, including one case of tuberculosis.

The review of the case of tuberculosis indicated that a causal relationship to abrocitinib is possible.

In total 6 fatal infections (5 after COVID-19 and one septic shock) were reported. All five deaths due to COVID-19 were in patients with comorbidities known to be associated with a worse Covid-19 outcome. However, the role of abrocitinib in the disease progression could be possible, due to the immunosuppressive effect of the medicine. The septic shock was reported in a patient diagnosed with multi-organ failure due to Staphylococcus sepsis with aortic valve endocarditis after septic arthritis of the left knee joint. It is not possible to conclude on the role of abrocitinib in this case.

2.4.1.2. Jyseleca (filgotinib)

The MAH presented data from 5 completed clinical trials for **RA** (DARWIN 1 (GLPG0634-CL-203), DARWIN 2 (GLPG0634-CL-204), FINCH 1 (GLPG0634-CL-301), FINCH 2 (GLPG0634-CL-302), FINCH 3 (GLPG0634-CL-303)), and 2 ongoing long-term extension (LTE) trials (DARWIN 3 (GLPG0634-CL-205) and FINCH 4 (GLPG0634-CL-304)). For **UC,** the clinical trials include one completed clinical trial (SELECTION (induction and maintenance trial, GLPG0634-CL-306)) and one ongoing LTE trial (SELECTION LTE (GLPG0634-CL-307)). Data from subjects with UC included in the ongoing MANTA trial (GLPG0634-CL-228) were also included.

The analysis sets consisted of data from the placebo-controlled trials and the active controlled trials as well as a pooled data set including parent plus LTE trials. EAIRs were presented for all ages, <65 versus ⩾65 years of age, and for RA also for <75 versus ⩾75 years of age. For the age group ⩾75 years the sample sizes were however too low to draw meaningful conclusions; these data are not further discussed.

In addition, an exploratory post-hoc analysis was performed using inclusion criteria **mimicking** those used for the **ORAL Surveillance study,** i.e., subjects with RA ⩾50 years of age with one or more cardiovascular (CV) risk factor**.**

<u>RA</u>

For all age groups, the EAIRs of **MACE, MI, VTE, malignancies (excluding NMSC) and NMSC,** were comparable between filgotinib and placebo, and filgotinib and adalimumab, as was the incidence rates by dose of filgotinib in the 24 weeks placebo-controlled trials and the 52 weeks active-controlled trials. The same was observed for the pooled parent plus LTE trials.

Among subjects aged ⩾65 years of age, the EAIRs of filgotinib in pooled parent plus LTE trials were higher for MACE, malignancies (excluding NMSC) and NMSC for both dose groups of filgotinib versus all ages, as expected in an older patient population. For VTE, the EAIRs in pooled parent plus LTE trials were comparable in the 100 mg group but higher in 200 mg group versus all ages, however based on few (⩽3) events. For malignancies (excluding NMSC) the EAIR was numerically higher in the filgotinib 200 mg group (2.0/100 PY; 95% CI 1.3,3.0) than in the filgotinib 100 mg group (1.0/100 PY; 95% CI 0.5,2.0). For NMSC, the same was seen; the EAIR for 200 mg was 1.4/100 PY (95% CI 0.8,2.2) and for 100 mg 0.5/100 PY (95% CI 0.1,1.2). For MACE and VTE, the numerical differences between the 2 filgotinib dose groups were small with largely overlapping CIs and for MI there was no difference by dose. An important aspect highlighted by the MAH is that in general the numbers of events were few, making assessment of differences in incidence by group, including potential dose effects, difficult.

For all age groups, the EAIRs of **serious infections** were higher (with overlapping 95% CIs) for both dose groups of filgotinib versus placebo in the 24-week pooled trials. In the 52-week poled active-controlled trial, the EAIRs of serious infections were similar for adalimumab and both dose groups of filgotinib. In the 65 years and older group, EAIRs of serious infections were higher for 200 mg filgotinib in comparison with the 100 mg group in all datasets, however, CIs were overlapping.

For all age groups, **TEAEs leading to death** were low in the clinical trials in all groups (n⩽3). For all age groups and for those 65 years and older, the EAIRs for TEAEs leading to death in pooled parent plus LTE trials, was slightly higher for 200 mg versus 100 mg with overlapping 95% CIs. Of note, the EAIR for TEAEs leading to death was numerically higher in the pooled filgotinib clinical trials than in the ORAL Surveillance study with tofacitinib or TNFi. However, as highlighted by the MAH about 28% of the TEAEs leading to death in the pooled short-term and long-term RA clinical trials with filgotinib were related to COVID-19. By contrast the ORAL Surveillance study was conducted between 2014 and July 2020, i.e., mainly before the start of the COVID-19 pandemic. In addition, between study comparisons of aspects as this are highly uncertain.

UC

There were too few events of **MACE, MI, VTE, malignancies (excl. NMSC)** and **NMSC** in the 11-week placebo-controlled induction trials and the 47-week maintenance UC trial to draw meaningful conclusions. The EAIRs were however comparable for **MACE, MI and VTE** in both dose groups and placebo from pooled UC dataset, including LTE trial, whereas the EAIRs of **malignancies** and **NMSC** were higher for both dose groups of filgotinib in comparison with placebo. However, there were overlapping CIs and concerning all malignancies the CIs were also wide.

Regarding **serious infections,** from the pooled UC dataset, including LTE trial, slightly higher EAIRs were noted for both filgotinib dose groups in comparison with placebo. From the 47-week maintenance trail, no conclusion could be drawn, as only few events were reported across all groups.

There was a total of 8 **deaths** in the filgotinib 200 mg group (n treated=1055), no deaths in the filgotinib 100 mg (n=583) and placebo groups (n= 534) from the pooled UC dataset, including LTE trial.

For UC, the number of subjects 65 years and older constituted less than 10% of all subjects. For this age group the EAIRs of the AEs of interest were as expected generally higher than in the all-ages group. Although numerical differences between the groups, the numbers of events were few and the 95% CIs wide and largely overlapping.

Across both indications, the MAH was requested to review all cases of sepsis as well as cases of infections with a fatal outcome. A total of 27 cases of sepsis were identified, in 11 cases, causality was assessed as related or cannot be ruled out by the investigator. Of 27 cases, in 20 cases filgotinib was discontinued due to the event. Regarding fatal infections (non-COVID-19), the MAH provided details of

13 cases, of which 8 cases reported sepsis with fatal outcome. Of 13 cases, in 9 cases, causality was assessed as related by the investigator and the majority of cases reporting sepsis (7 cases of sepsis, 1 case of pneumonia and 1 meningitis meningococcal in which causality cannot be ruled out).

2.4.1.3. Olumiant (baricitinib)

Additional safety data for both the **RA** and **AD** indications have been provided during the referral compared to the data available for the initial marketing authorisation applications. Furthermore, safety data within the recently approved treatment of severe AA were also provided.

The initial marketing authorisation of baricitinib for **RA** (2017) was based on safety analysis of 3492 patients (5134.4 PY) exposed to baricitinib; clinical data in this referral were provided for 3770 patients (14 443 PY). For **AD**, the approval of the indication (2020) was based on 2531 patients exposed to baricitinib (2247 PY); clinical data in this referral were provided for 2562 patients (2804 PY).

For **RA**, data on a direct comparison with TNFi were available from the clinical trials, and preliminary data from the ongoing *JAJA/JAJD* trials, two ongoing randomised, active-controlled clinical trials in patients with active RA, comparing baricitinib (2 and 4 mg) with TNFi (adalimumab or etanercept) with respect to VTE (preliminary data were still blinded).

For **AD**, no trial data with an active comparator (systemic treatment) were available.

Increased risks for VTE and serious infections in baricitinib versus TNFi (adalimumab) were already known during the initial marketing authorisation application. The new data from clinical trials indicated an increasing risk for malignancy with prolonged exposure to baricitinib as compared to the incidence reported in the placebo-controlled clinical trial period, which may partially be ascribed to increasing age, and a decreased risk for serious infections with prolonged exposure, which is likely to be due to survivor bias. Of note, lower IRs were found for each safety events in AD and AA versus RA; this can be ascribed to differences in demographic (especially younger age with lower risk profiles in AA and AD versus RA) and disease characteristics (systemic disease in RA versus more localized disease in AD and AA). Furthermore, data sets for AD and AA were incomplete and not all identified cases were integrated in the calculation of IRs.
Regarding treatment of AA, safety data were evaluated, and no new safety concerns were identified.

2.4.1.4. Rinvoq (upadacitinib)

Analyses were performed with pooled data for each indication for upadacitinib by dose and active comparator treatment groups. Subgroup analysis included subjects < 65 years versus ⩾ 65 years for both pooled data by indication and individual study data. To mimic the ORAL Surveillance (OS) study analysis, an additional subgroup analysis of subjects ⩾ 50 years of age with at least one cardiovascular risk factor was also performed for RA Study M14-465, which has both upadacitinib 15 mg and adalimumab treatment arms. The previous assessment of MACE, VTE, malignancy excluding NMSC, and mortality submitted to PRAC in the 4th PSUR responses was performed with the latest data cut-off as of 15 August 2021. The cumulative data included in the current analyses are based on a cut-off date of 15 February 2022.

Safety data from individual studies were provided for the comparisons of upadacitinib versus adalimumab (RA Study M14-465 and PsA Study M15-572) and upadacitinib monotherapy versus MTX monotherapy (RA Study M13-545).

Data from the adalimumab-controlled study (M14-465) in RA indicates that the incidence of **MACE** in all subjects as well as subgroups of subjects < 65 and ⩾ 65 years of age was similar between upadacitinib 15 mg and adalimumab. In MTX Controlled Study M13-545, a higher EAIR was noted for upadacitinib 30 mg monotherapy compared to MTX monotherapy. In the PsA adalimumab-controlled study (M15-572), the incidences of adjudicated MACE were similar between upadacitinib 15 mg and adalimumab. When comparing the upadacitinib doses, the incidence of adjudicated MACE was numerically higher with 30 mg compared to 15 mg in the RA, PsA and UC program.

In AD, the incidence of adjudicated MACE were lower with upadacitinib 30 mg compared to 15 mg. Regarding **MI**, no events were reported in the AD, UC, and AS indications. In RA Study M14-465, 4 adjudicated MI events were reported for upadacitinib 15 mg (none for adalimumab), although the incidence rate was low (0.1 n/100 PYs). When comparing 15 mg and 30 mg in RA overall, the EAIR of adjudicated MI was 0.16 and 0.28 per 100PY for 15 mg and 30 mg, respectively [HR 1.45, 95% CI (0.53, 3.93)]. In the PsA indication there was no dose-dependent pattern.

Regarding **malignancy**, long-term data from the RA studies have recently been assessed within EMEA/H/C/004760/II/0014, noting an imbalance between the 15 and 30 mg dose. This imbalance includes both NMSC and malignancy other than NMSC.

VTE occurred with a similar frequency with MTX, upadacitinib 15 mg and upadacitinib 30 mg in RA Study M13-545, and also in the upadacitinib 15 mg and adalimumab arms in RA Study M14-465. In PsA study M15-572, the adjudicated VTE EAIRs were comparable across adalimumab, upadacitinib 15 mg and 30 mg. In the overall PsA data, the EAIR was slightly higher for 30 mg than for 15 mg, with the difference most prominent in the >65 age group.

In the **AD** and **UC** indications, the adjudicated VTE EAIR rates were similar between upadacitinib 15 and 30 mg groups in all patients, and in the < 65 years of age population. However, in UC patients ≥ 65 years, the event incidence was higher for upadacitinib 30 mg than for 15 mg.

Across the indications (RA, PsA, AD, and UC), the rates of the overall **serious infections** were higher with upadacitinib 30 mg compared to 15 mg.

For the recently approved **nr-axSpA** indication, the safety profile observed was consistent with the safety profile observed in previously approved indications.

2.4.1.5. Xeljanz (tofacitinib)

The MAH provided data from Study A3921133 ORAL Surveillance in RA patients 50 years of age and older and with at least one additional CV risk factor and from the pooled clinical trial programme in RA, PsA and UC. For the AS and JIA indications, there were a limited number of serious events of interest and the events are therefore presented separately.

2.4.1.5.1. Study A3921133 ORAL Surveillance

Study A3921133 was a prospective, randomized, open-label, event-driven, blinded endpoint study in adult patients aged ⩾50 years with moderate to severe RA and at least one additional cardiovascular risk factor evaluating the safety of tofacitinib 5 mg twice daily (BID) and tofacitinib 10 mg BID compared to a TNFi (adalimumab or etanercept), randomized in a 1:1:1 ratio, with approximately 1400 patients in each treatment arm. These cardiovascular risk factors (of which the study subjects were required to have at least one at screening) were:

- Current cigarette smoker.
- Diagnosis of hypertension.

- High density lipoprotein (HDL) <40 mg/dL.
- Diabetes mellitus.
- Family history of premature coronary heart disease (CHD)
- Presence of extra-articular disease associated with rheumatoid arthritis, which may include nodules, Sjögren's syndrome, anemia of chronic disease and pulmonary manifestations.
- History of coronary artery disease including a history of revascularization procedure, coronary artery bypass grafting, MI, cardiac arrest, unstable angina, acute coronary syndrome

Interim study results of some secondary safety outcomes and final study results of the co-primary outcomes of study A3921133 have been previously submitted and were assessed by the PRAC in the **Article 20 referral procedure** in 2019 and the **signal procedure** in 2021, respectively.

Interim data of the following topics have been reviewed during the Article 20 referral procedure in 2019:

- Thrombotic events.
- Mortality.
- Serious infections.

Final study results of the following primary outcomes have been reviewed in the signal procedure:

- MACE (incl MI).
- Malignancies excl NMSC.

Following these earlier procedures, VTE (PE and DVT), MI, lymphoma and lung cancer have been considered as causally associated with use of tofacitinib and were included as ADRs in section 4.8. To minimise these risks, SmPC Sections 4.2 and 4.4 were updated with warnings that tofacitinib should only be used in patients with certain risk factors if no suitable treatment alternatives are available, i.e., in patients >65 years of age, patients who are current or past smokers, patients with other cardiovascular risk factors, and patients with malignancy risk factors. Tofacitinib should be used with caution in patients with known risk factors for VTE.

The final study results of Study A392113 are provided in Table 1.

Table 1 Unfavourable Effects Table for Xeljanz in Study A392113, final results.

Effect	Short description	Unit	TNFi	Tofacitinib 5 mg	Tofacitinib 10 mg	Uncertainties / Strength of evidence
Unfavourable Effects						
n=	Evaluable subjects		1451	1455	2911	
AEs	Subjects with ⩾1 AE	%	90	92	92	
SAEs		%	21	24	27	
Death	All-cause	IR n/100PY (95%CI)	0.34 (0.20–0.54)	0.50 (0.33-0.74)	0.80 (0.57-1.09)	Tofa 10mg vs TNFi: HR (95%CI) = 2.4 (1.3 – 4.2). Tofa 5mg vs TNFi: HR (95%CI) = 1.5 (0.8 – 2.6).
- Fatal CVD		IR n/100PY (95%CI)	0.20 (0.10-0.36)	0.25 (0.13-0.43)	0.41 (0.25-0.63)	Tofa 10mg vs TNFi: HR (95%CI) =2.1 (1.0, 4.4) Tofa 5mg vs TNFi: HR (95%CI) =1.3 (0.6 - 2.9)
- Fatal		IR	0.02	0.10	0.00	Tofa 10mg vs TNFi:

Effect	Short description	Unit	TNFi	Tofacitinib 5 mg	Tofacitinib 10 mg	Uncertainties / Strength of evidence
malignancy		n/100PY (95%CI)	(0,00-0.11)	(0.03-0.23)	(0.00-0.08)	0 Tofa 5mg vs TNFi: HR (95%CI) =4.9 (0.6 – 41.7)
- Fatal infections		IR n/100PY (95%CI)	0.06 (0.01-0.17)	0.08 (0.02-0.20)	0.18 (0.08-0.35)	Tofa 10mg vs TNFi: HR (95%CI) = 3.1 (0.8, 11.5) Tofa 5mg vs TNFi: HR (95%CI) = 1.3 (0.3, 5.8)
MACE		IR n/100PY (95%CI)	0.73 (0.52-1.01)	0.91 (0.67-1.21)	1.05 (0.78-1.38)	Tofa 10mg vs TNFi: HR (95%CI) = 1.4 (0.9 – 2.2). Tofa 5mg vs TNFi: HR (95%CI) = 1.2 (0.8 – 1.9).
- Non-fatal MI		IR n/100PY (95%CI)	0.16 (0.07 – 0.31)	0.37 (0.22-0.57)	0.33 (0.19-0.53)	Tofa 10mg vs TNFi: HR (95%CI) = 2.1 (0.9 – 4.9). Tofa 5mg vs TNFi: HR (95%CI) = 2.3 (1.0 – 5.3).
Malignancy (non-NMSC)		IR n/100PY (95%CI)	0.77 (0.55-1.04)	1.13 (0.87-1.45)	1.13 (0.86-1.45)	Tofa 10mg vs TNFi: HR (95%CI) = 1.5 (1.0 – 2.2). Tofa 5mg vs TNFi: HR (95%CI) = 1.5 (1.0 – 2.2).
NMSC		IR n/100PY (95%CI)	0.32 (0.18-0.52)	0.61 (0.41-0.86)	0.69 (0.47-0.96)	Tofa 10mg vs TNFi: HR (95%CI) = 2.2 (1.2 – 3.9). Tofa 5mg vs TNFi: HR (95%CI) = 1.9 (1.0 – 3.5).
VTE		IR n/100PY (95%CI)	0.20 (0.10— 0.37)	0.33 (0.19-0.53)	0.70 (0.49-0.99)	Tofa 10mg vs TNFi: HR (95%CI) = 3.5 (1.7 – 7.1). Tofa 5mg vs TNFi: HR (95%CI) = 1.7 (0.8 – 3.6).
- PE		IR n/100PY (95%CI)	0.06 (0.01-0.17)	0.17 (0.08-0.33)	0.50 (0.32-0.74)	Tofa 10mg vs TNFi: HR (95%CI) = 8.3 (2.5, 27.4) Tofa 5mg vs TNFi: HR (95%CI) = 2.9 (0.8, 10.8)
- DVT		IR n/100PY (95%CI)	0.14 (0.06-0.29)	0.21 (0.11-0.38)	0.31 (0.17-0.51)	Tofa 10mg vs TNFi: HR (95%CI) = 2.2 (0.9, 5.4) Tofa 5mg vs TNFi: HR (95%CI) = 1.5 (0.6, 4.0)
Serious infections		IR n/100PY (95%CI)	2.44 (2.02-2.92)	2.86 (2.41-3.37)	3.64 (3.11-4.23)	Tofa 10mg vs TNFi: HR (95%CI) = 1.5 (1.2 – 1.9). Tofa 5mg vs TNFi: HR (95%CI) = 1.2

Effect	Short description	Unit	TNFi	Tofacitinib 5 mg	Tofacitinib 10 mg	Uncertainties / Strength of evidence
						(0.9 – 1.5).
- Fatal serious infections		IR n/100PY (95%CI)	0.08 (0.02-0.20)	0.12 (0.04 - 0.25)	0.27 (0.14-0.46)	Tofa 10mg vs TNFi: HR (95%CI) = 3.3 (1.1 – 10.3). Tofa 5mg vs TNFi: HR (95%CI) = 1.5 (0.4 – 5.2).
- Herpes Zoster		IR n/100PY (95%CI)	0.26 (0.14-0.44)	0.66 (0.46-0.93)	0.66 (0.45-0.94)	Tofa 10mg vs TNFi: HR (95%CI) = 2.6 (1.3 – 4.9). Tofa 5mg vs TNFi: HR (95%CI) = 2.6 (1.4 – 4.9).
Hepatic events		IR n/100PY (95%CI)	0.70 (0.49-0.97)	0.90 (0.66-1.20)	1.51 (1.8- 1.91)	Tofa 10mg vs TNFi: HR (95%CI) = 2.1 (1.4 – 3.2). Tofa 5mg vs TNFi: HR (95%CI) = 1.3 (0.8 – 2.0).

Abbreviations: PY=Patient years;
Notes: Efficacy was a secondary endpoint of study A3921133; no Type I error control was applied to efficacy endpoints. Co-primary safety outcomes were MACE and malignancies (without NMSC).

2.4.1.5.2. Clinical trial programme

RA, PsA, UC

MACE and MI were not frequent in RA, PsA and UC clinical trials. There was no indication that their occurrences would be more frequent with tofacitinib 5 mg as compared to adalimumab in RA and PsA studies.

Malignancies (excluding NMSC) and NMSC occurred more frequently in absolute numbers in the larger RA studies, than in the PsA and UC studies. In RA, over 0-24 months, malignancies were more frequent for tofacitinib 10 mg (IR=0.65) and 5 mg (IR=0.35) than for adalimumab (IR=0.18). In RA over that same time period, NMSC did not appear to be more frequent for tofacitinib 10 mg (IR=0.45) and 5 mg (IR=0.43) than for adalimumab (IR=0.54).

VTE (PE and DVT) was most frequent in the RA studies and was numerically more frequently seen in tofacitinib 10 mg (IR=0.25) and 5 mg (IR=0.27) compared to adalimumab (IR=0.18).

Serious infections were numerically more frequent in RA and PsA patients treated with tofacitinib 10 mg and 5 mg as compared to adalimumab.

Mortality figures over the period 0-24 months and a 28-day window were not clearly different for tofacitinib 5 mg and 10 mg in RA, PsA and UC, but the number of cases was low. A comparison with adalimumab for RA and PsA was made in the previous referral procedure. In RA, it showed higher IRs for mortality in RA tofacitinib 5 mg (IR=0.31) and 10 mg (IR=0.20) compared to adalimumab (IR=0.18) or methotrexate (IR=0).

JIA, AS

For JIA and AS, no cases of MACE or other cardiovascular safety events, VTE, malignancies including NMSC, or death, were reported in the clinical trial programme. Serious infections were reported, but only a limited number of events.

The overview of the pooled clinical trial data sets in RA (non-A3921133), PsA, and UC patients shows lower occurrence of events compared to study A3921133, and no clear signals for the safety events in scope of this referral had emerged from completed clinical trials. For the largest study population from pre-registration clinical trials (RA), numerically (but not statistically) higher IRs for malignancy, VTE (PE/DVT), serious infections, mortality were observed for tofacitinib versus comparator arms in completed clinical trials.

2.4.2. Safety data from observational studies

2.4.2.1. Cibinqo (abrocitinib)

Observational studies to estimate extent of risks are planned for abrocitinib but no results are available yet.

2.4.2.2. Jyseleca (filgotinib)

There is one ongoing prospective, non-interventional MAH-initiated observational study in RA (FILOSOPHY, GLPG0634-CL-401) evaluating effectiveness, safety, and health-related outcomes of filgotinib in patients from European countries with moderate to severe active RA. One of the secondary objectives is to assess the rates of serious and opportunistic infections (including herpes zoster), MACE, VTE, hyperlipidemia, malignancies, NMSC, and gastrointestinal perforation. The trial aims to recruit a total of approximately 1500 patients. Enrolment started in May 2021. As of 23 February 2022, a total of 214 subjects have been enrolled. As of 17 February 2022, no events of MACE, VTE, malignancy, or death have been reported**.**

2.4.2.3. Olumiant (baricitinib)

Interim results of the ongoing multi-database observational cohort Study B023 in **RA** patients suggest an increased risk for MACE and a trend for an increased VTE risk in baricitinib users as compared to TNFi users.

The overall risk of **MACE** was statistically significantly greater in baricitinib users than in TNFi users (IRR = 1.92; 95% CI 1.27, 2.91). The France administrative healthcare SNDS database contributed most to person time. From the SNDS data, the IRR for MACE was 2.33 (95% CI 1.15, 4.74), and HR was 2.33 (95%: 1.14, 4.77).

A trend was observed with an overall 34% greater risk of **VTE** (IRR = 1.34; 95% CI 0.84, 2.14) in baricitinib users as compared to TNFi users. The France SNDS database contributed most to person time. From the SNDS data, the IRR for VTE was 1.59 (95% CI: 0.79, 3.21), and HR was 1.57 (95% CI: 0.78, 3.18).

The interim analysis included data from 13 of 16 eligible data sources with a total exposure of ~3558 PY.

The final study results of study B023 show a statistically increased risk of VTE, and trends for increased risks of MACE and serious infections for baricitinib compared to TNFi.

Regarding the remaining safety concerns under review, no conclusions can be made based on the interim findings from B023, nor from the Japan Post-Marketing Safety Study. Two further studies are ongoing in the RA indication (14V-MC-B011 and 14V-MC-B012, both in EU). No data from observational studies are available for the **AD** or **AA** indications. AD will be added to ongoing study 14V-MC-B011.

2.4.2.4. Rinvoq (upadacitinib)

No data from observational studies are available for upadacitinib. There are two ongoing observational studies in RA (P19-150 in EU, and P19-141 in US), and one ongoing prospective cohort study in AD (P20-390).

2.4.2.5. Xeljanz (tofacitinib)

Observational study data are currently only available for the **RA indication**. In the main analysis of the completed Corrona RA PASS, there was a trend for increased crude IRs for tofacitinib compared to biologic (b)DMARDs, but comparative analyses did not show differences between tofacitinib and bDMARD initiators apart from an increased risk of herpes zoster. In a post-hoc sensitivity analysis, the HR for malignancies (excl NMSC) was 1.34 (0.94-1.93) compared to 1.04 (0.68-1.61) in the primary analysis. The RA Corrona PASS was designed with 80% power to detect an HR of 2.05 for MACE and 2.2 for malignancies. These HRs have not been reached in study A3291133.

Results of the first 2-year interim reports of the 4 ongoing studies in EU RA registries (BIOBADASAR, BSRBR-RA, RABBIT, ARTIS) showed higher crude incidence rates for serious infections for the tofacitinib cohort compared to bDMARDs. Comparative analyses provided from the ARTIS registry showed increased adjusted HRs for hospitalized infections (1.22, 95% CI 0.73-2.04) and VTE (2.31, 95% CI 0.89-5.98) for tofacitinib compared to biologic DMARDs. For the other safety outcomes of interest, no consistent pattern was observed across the 4 studies. However, follow-up time is still limited, and analyses were not adjusted for confounders. The final study report of these 4 ongoing studies (expected in September 2026) will include a follow-up of up to 7 years to allow evaluation of long-term safety outcomes (e.g. malignancy, mortality).

There are 4 ongoing studies in the UC indication (A3921329 Corrona and A3921347 DUS and active surveillance in US, and A3921344 SWIBREG registry and A3921352 UR-CARE registry in EU), 1 ongoing LTE follow-up study in the JIA indication (A3921145), and 4 planned studies in the JIA and juvenile PsA indications (BIKER/JuMBO registry, Swedish JIA clinical registry, UK JIA registry, long-term observational safety study in JIA patients).

2.4.3. Relevance of ORAL surveillance study

Cibinqo

The ORAL Surveillance study was specifically designed to compare incidence of ADRs after treatment of RA patients with cardiovascular risk factors, with tofacitinib or adalimumab. A comparable RCT is not available or planned for abrocitinib. Results from observational studies on long-term safety will be available only in next decade. Nevertheless, as outlined above, it is concluded that the main safety events are JAKi class effects for the substances included in this review. Therefore, the main findings from the ORAL Surveillance study are relevant and important on further characterisation of the safety profile of abrocitinib.

Jyseleca

Regarding extrapolation of the ORAL Surveillance data on tofacitinib to filgotinib, the MAH provided an exploratory post-hoc analysis applying inclusion criteria mimicking those of the ORAL Surveillance study, i.e., in subjects with RA ≥50 years of age with at least one cardiovascular risk factor. Data were grouped according to the treatment received in the induction trials: filgotinib 200 mg, filgotinib 100 mg, and placebo. The PRAC acknowledged the limitations of such indirect comparison, and that the interpretation of the results should be done with caution given differences in the populations,

composition of datasets, inclusion criteria, trials designs (randomized versus non-randomized), regions, and trial periods.

EAIRs for MACE, VTE, and serious infections in this RA population at higher risk for cardiovascular events, were numerically lower in the pooled filgotinib clinical trials than in the ORAL Surveillance study with tofacitinib and closer to the rates with TNFi. The EAIR for malignancies (excluding NMSC) was in the range of tofacitinib. The EAIR for TEAEs leading to death was numerically higher in the pooled filgotinib clinical trials than in the ORAL Surveillance study with tofacitinib or TNFi. About 28% of the TEAEs leading to death in the pooled short-term and long-term RA clinical trials with filgotinib were related to COVID-19.

Additionally, numerical differences in the EAIRs for malignancies (excluding NMSC), NMSC, serious infections, and deaths *between* the 2 filgotinib dose groups were seen, in favour of the low dose (100 mg), while 95% CIs were overlapping. For MACE the incidence was numerically lower in the high dose group than the low dose group, and for VTE the incidence was the same for both dose groups, with largely overlapping CIs.

In conclusion, the findings from filgotinib post-hoc analyses did not overall indicate a dose-related effect in the selected patient population. However, the PRAC considered that these findings are not sufficiently robust to disregard the findings reported in the ORAL Surveillance study.

Olumiant

The ORAL Surveillance study included an arthritis-population selected based on high CV-risk, still the ORAL Surveillance study population is considered sufficiently similar to the overall RA population to allow extrapolation of data. Furthermore, it is reasonable to assume that also for the AD population, although at lower risk for MACE and malignancy, these are clinically important risks in the long term.

Regarding treatment of severe AA, it is acknowledged that this patient group generally has less risk factors for the main serious safety outcomes compared with e.g. RA patients, as they are at least not inherent to the underlying disease. Nevertheless, for patients with risk factors for the main safety concerns, it is considered that the same risks apply.

Rinvoq

The MAH has presented an in-depth discussion on the applicability of ORAL Surveillance data to Rinvoq. This includes a discussion on the prevalence of risk factors across different patient populations based on data from the Optum health claims database. In these data, patients with RA had the highest occurrence of at least one CV risk factor: 79.1%. The risk factors were very similar in the RA and PsA populations, but also among patients with atopic dermatitis, 64.8% had at least one CV risk factor. The UC population had the lowest occurrence of at least one CV risk factor; 56.2%. Incidence rates of safety events among adult patients with moderate to severe disease were provided across the indications RA, PsA, AS, UC and AD based on data from the Claims database. For MI/stroke, malignancy excluding NMSC, and serious infections, the incidence rate in adult RA patients was higher than that in adults with any other evaluated conditions, indicating that patients with inflammatory diseases other than RA might be at lower risk for these events.

The ORAL Surveillance study included an arthritis-population selected based on high CV-risk, still the ORAL Surveillance study population is considered sufficiently similar to the populations covered by the adult arthritis indications RA and PsA to allow extrapolation of data. According to the MAH, for diseases with lower background risks of a particular AE compared to RA (such as AD), any potential incremental risk associated with JAKis use would result in a smaller absolute increase in risk compared to that observed in ORAL Surveillance. This was acknowledged by the PRAC, although it is reasonable to assume that also for the AD population, although at lower risk for MACE and malignancy, these are

clinically important risks in the long term. A similar line of thinking would apply to the other recently approved indications.

Xeljanz

From the ORAL Surveillance study, only data in a group of RA patients with higher background CV risk are available. Tofacitinib overall performed numerically or statistical significantly worse than TNFi. The safety outcomes under review are established ADRs for tofacitinib. The PRAC therefore considered that these risks can be generalised to other diseases in the auto-immune spectrum, since no differences in terms of ADRs that are due to the mechanism of action of tofacitinib are expected across the indications. The main factors driving differences between indications presumably are age and co-morbidity.

2.4.4. Discussion on clinical safety

All JAKis under review are unique active substances with differences in their JAK isoform selectivity that at least theoretically may affect clinical efficacy and safety, but it is evident that there are also great similarities between tofacitinib and the other JAKis such as a shared pharmacodynamic mode of action (see Section 2.2.). Until more data has been identified, in particular on the role of specific JAK pathways in the adverse events of interest, it is not possible to ascribe the occurrence of any of these events to a specific JAK isoform. Thus, the PRAC considered the main safety events as general JAKi class effects.

Nevertheless, the extent to which the tofacitinib ORAL Surveillance data on MACE, VTE, serious infections, malignancies and mortality are applicable to all JAKis approved for chronic inflammatory conditions, across the target populations, depends also on the similarities of the respective populations.

The extrapolation of the results of the ORAL Surveillance study results to the JAKis in their approved indications was discussed within this procedure. No results from randomised controlled studies comparable to the ORAL Surveillance study with tofacitinib are available for the other JAKis.

It is acknowledged that the ORAL Surveillance study included a RA population selected based on high cardiovascular risk and with a mean disease duration of more than 10 years (Ytterberg et al. 2022) which influences the degree of generalisability of the study results to the EU populations covered by the approved JAKi indications. The ORAL study population however is considered to constitute a sensitive model to be able to identify potential differences between TNFi (adalimumab or etanercept was administered in the study) and JAKi (tofacitinib). To show these differences in a population with lower baseline risk, would likely have required a substantially larger study size. Overall, the ORAL Surveillance Study population is considered sufficiently similar to the populations covered by the adult arthritis indications RA and PsA to allow extrapolation of data. Also, for the other indications for which JAKis are approved in the EU, the target populations are considered to be sufficiently similar, with regards to important disease characteristics and baseline risk factors, for the ORAL Surveillance data to be relevant.

Therefore, the PRAC recommended in general to implement class warnings related to the final study results of the ORAL surveillance study already implemented in the product information of tofacitinib to the product information of all JAKis used in inflammatory disorders. This wording of the warning recommending the use of tofacitinib if no suitable treatment alternatives are available for patients with certain risk factors was previously considered by the PRAC during assessment of the final study results of the primary study outcomes on MACE and malignancy (EMA/PRAC/333216/2021) of the ORAL Surveillance Study and was implemented in tofacitinib SmPC. The PRAC acknowledged that there is no new data that would warrant changes to the recommendation to use only if no suitable treatment

alternatives are available for patients with risk factors for MACE or malignancy and in patients 65 years and older. The MAHs proposed to complement the warning to state that *[medicine] should only be initiated or continued after careful consideration of the risks and an evaluation that [medicine] represents the best therapeutic alternative for the patient*. This was not considered necessary by the PRAC since such assessment is considered standard clinical practice and would not provide specific actionable recommendations beyond what already is to be included into the product information.

However, based on the data submitted during the procedure, the PRAC recommended some updates to the risk factors included in the existing warning for tofacitinib:

- In the ORAL surveillance study, the majority (more than 90%) of tofacitinib patients who were current or past smokers had a smoking duration of more than 10 years and a median of 35.0 and 39.0 smoking years, respectively. The warnings on MACE and malignancy in SmPC Section 4.4 were updated to reflect the long-term duration of smokers in the ORAL Surveillance Study so that the warning applies to current and past *long-time* smokers.
- Post-hoc analyses of ORAL Surveillance study showed that history of atherosclerotic cardiovascular disease (ASCVD, i.e., a composite of coronary artery disease, cerebrovascular disease, or peripheral artery disease) is a risk factor accounting for higher relative risk in adverse events of special interest between tofacitinib and TNFi. Therefore, the warning on MACE is updated to include *history of atherosclerotic cardiovascular disease* as risk factor.
- In light of the results of the ORAL Surveillance Study, all-cause mortality is added as a risk for patients 65 years of age and older

In addition, during the review, an inconsistency was raised on the warnings of VTE and malignancy and MACE. The existing list of VTE risk factors in tofacitinib SmPC includes risk factors overlapping with CV and malignancy risk factors for which a different recommendation applies since use with caution is recommended for VTE and use only if no suitable treatment alternatives are available is recommended for CV and malignancy risk factors. The warning on VTE was therefore updated to specify VTE risk factors other than CV or malignancy risk factors and including a cross reference to the CV and malignancy warnings.

Therefore, the PRAC recommended the use of the JAKis only if no suitable treatment alternatives are available in patients 65 years of age and older, with history of atherosclerotic CV disease or other CV risk factors, who are current or past long-time smoker and with other malignancy risk factors (e.g. current, or history of malignancy). Cautious use is recommended in patients with known risk factors for VTE.

Given that these risks are considered class effects, the SmPC Section 4.4 and the corresponding PL section for all products in this review were updated accordingly. In order to specifically highlight the most important considerations for prescribers before and during use of these JAKis, the PRAC recommended the addition of a boxed warning in SmPC Section 4.4 to describe the groups of patients for whom JAKis should be only used if no other treatment alternatives are available.

Cibinqo

For MACE, due to a low number of cases for both abrocitinib 100 mg and 200 mg, no final conclusion could be drawn. However, regarding risk factors for MACE, the IR for MACE was higher in the older subgroup compared to younger adults. In the analysis of MACE by smoking status, IR was higher for current or former smokers compared to non-smokers. The warning on MACE in SmPC Section 4.4 is complemented with information that cases of MACE have been observed in clinical studies with abrocitinib in addition to the class warning described above. The warning on lipids is updated to remove guidance on a risk benefit consideration against other available therapies in patients with high

burden of cardiovascular risk factors since the use of abrocitinib in these patients is now only recommended if no suitable treatment alternatives are available.

There was a higher rate of malignancies (excluding NMSC) observed with abrocitinib 200 mg compared to abrocitinib 100 mg and a dose relationship is possible. These long-term safety data from clinical trials, indicate a class effect based on extrapolation of results from the ORAL Surveillance study. Therefore, in addition to the implementation of the class warning on malignancies, SmPC Section 4.4 is updated to inform on the higher rate of malignancies with abrocitinib 200mg compared to abrocitinib 100mg, and that NMSC has been reported in patients treated with abrocitinib.

A higher rate of VTE was observed with abrocitinib 200 mg compared to abrocitinib 100 mg. Although limited data, the MAH commented that a dose-response cannot be ruled out for VTE. This is agreed by the PRAC. The warning on VTE in SmPC section 4.4 is updated to reflect the higher rate of VTE observed with abrocitinib 200 mg compared to abrocitinib 100 mg, and the warning is revised to align it with the class warning which also takes the ORAL Surveillance study results into account. The adverse reaction thrombotic events including thromboembolism in SmPC Section 4.8 is renamed venous thromboembolism.

The most frequent serious infections in the LTDCPsNDA were those related to herpes zoster, herpes simplex, and pneumonia. In the approved SmPC it is stated that among all patients treated with abrocitinib, including the long-term extension study, the rate of serious infections was 2.18 per 100 patient-years treated with 100 mg and 2.11 per 100 patient-years treated with 200 mg. The MAH commented that IRs for serious infection in the LTDCPsNDA and the RRLTPsNDA were consistent with that in the FCP2020 and that there remained no dose-response for serious infections. However, it was noted that in LTDCPsNDA there was higher EAIR for abrocitinib 200 mg (2.69 (2.05, 3.46)) in comparison with abrocitinib 100 mg (2.20 (1.53, 3.08)).

Following the PRAC's request, the MAH provided an analysis of cases of sepsis as well of infections with fatal outcome. In total 6 cases of sepsis were reviewed. According to the MAH, five of these did not fulfil a definition of sepsis, but were other serious infections, including severe herpes zoster infections or other bacteraemia, including one case of tuberculosis. Herpes zoster is listed in the product information; both as an ADR (SmPC section 4.8) and in SmPC section 4.4.

The review of the case of tuberculosis indicated that a causal relationship to abrocitinib is possible, the SmPC Section 4.4 states that tuberculosis was observed in clinical studies with abrocitinib, therefore no update is warranted.

The review of the 6 fatal infections did not point to a need for updating the product information.

The MAH submitted updated safety data (data cut-off of 25 September 2021) requiring updates of the SmPC Section 4.8 including changes not included in the scope of the referral. As part of the MAH's obligation, the MAH should therefore submit these changes in another regulatory procedure.

In addition, since the safety events of MACE, VTE and malignancy observed in the ORAL Surveillance study are dose dependent the PRAC recommended updates to SmPC Section 4.2 to lower the dose in patients with certain risk factors. A starting dose of 100 mg once daily is thus recommended for patients at higher risk of VTE, MACE and malignancy. In addition, the PRAC recommended the use of the lower dose of 100mg in patients 65 years of age and older.

A dose of 200 mg once daily can be considered in patients who would benefit the most from a higher dose i.e. those with high disease burden but not at higher risk for MACE, VTE and malignancy or for patients with an inadequate response to 100 mg.

The results from the randomised withdrawal study (see Clinical Efficacy Section 2.3.1. support the feasibility of using abrocitinib 200 mg once daily induction to rapidly achieve disease control followed

by dose reduction for maintenance treatment. Therefore, the updated posology recommends a dose decrease to 100 mg once daily upon disease control for all patients.

Jyseleca

The EAIRs of malignancies and NMSC were higher for both dose groups of filgotinib in comparison with placebo. However, there were overlapping CIs and concerning all malignancies the CIs were also wide. Since most cancers were detected in the first year after start of treatment, and as most cancers typically take several years to develop and to be diagnosed, the MAH states that a causal association between filgotinib treatment and cancers detected within the first year of filgotinib treatment seems biologically implausible. This is acknowledged by the PRAC. However, it is noted that 4 subjects were diagnosed with a malignancy in the second year of the treatment and 5 were diagnosed after 2 or more years of the filgotinib treatment, while no events were noted in placebo group during the whole period of exposure. Taking these data into account, together with the conclusion of class effects based on extrapolation of results from the ORAL Surveillance study, it is concluded that malignancy is a safety concern applicable to filgotinib. The SmPC Section 4.4 is therefore updated to implement the class warning on malignancies.

Regarding serious infections, from the pooled UC dataset, including LTE trial, slightly higher EAIRs were noted for both filgotinib dose groups in comparison with placebo. In view of the available data on sepsis from clinical trials including cases with a plausible temporal relationship, and in view of a plausible mechanism of action, a causal relationship between filgotinib and sepsis is considered established. Sepsis (frequency: uncommon) is therefore added as an adverse reaction in the SmPC Section 4.8.

There was a total of 8 deaths in the filgotinib 200 mg group (n treated=1055), no deaths in the filgotinib 100 mg (n=583) and placebo groups (n= 534) from the pooled UC dataset, including LTE trial. The MAH stated that this should be interpreted in the context of the much longer average exposure duration in the filgotinib 200 mg group compared to the other groups. While indeed higher number of subjects were exposed to filgotinib 200 mg for longer periods of time, 8 reported deaths in the 200 mg dose groups versus 0 in the other groups however remains an observation. Overall, 5 deaths were related to COVID-19, while the remaining three died of left ventricular failure, MI and UC (one each).

Since data from the ORAL Surveillance study suggest that the risks for the major safety outcomes of MACE, VTE and malignancy increase with dose, and currently available safety data for filgotinib also suggest dose relationships for certain risks (namely death for RA and UC (regardless of age), VTE, malignancy and NMSC for RA (in patients 65 years and older)), the MAH was requested to comment on the possibility of posology amendments in both approved indications (RA and UC). The MAH provided a comprehensive analysis of the efficacy in RA and UC. For RA, both doses (i.e, 100 mg and 200 mg) showed superiority over placebo for the primary endpoint and all key secondary endpoints (FINCH 2 study). Additionally, data from the FINCH 4 LTE study showed sustainability of response to filgotinib 200 mg *and* 100 mg over a period of 48 weeks. Likewise, efficacy in UC was evaluated from the SELECTION +SELECTION LTE trial. The primary endpoint was met for filgotinib 200 mg but failed to reach statistical significance for filgotinib 100 mg. However, in the SELECTION maintenance study, the primary endpoint was met for both filgotinib 200 mg and 100 mg at week 58. Based on the available data, the PRAC recommended a dose of 100 mg once daily for the treatment RA and maintenance phase of UC, in patients at increased risk for VTE, MACE, malignancy and in patients 65 years and older. The dose may be escalated to 200 mg once daily in case of insufficient disease control. For long term treatment, the lowest dose should be used.

Olumiant

The amount of new data compared to the initial application is more extensive for RA than for AD; safety conclusions are thus mainly based on results in the RA populations. The new data from clinical trials indicated an increasing risk for malignancy with prolonged exposure to baricitinib as compared to the incidence reported in the placebo-controlled clinical trial period, which may partially be ascribed to increasing age, and a decreased risk for serious infections with prolonged exposure, which may be due to survivor bias. Lower IRs were found for each safety events in AD versus RA which can be ascribed to differences in demographic (especially younger age with lower risk profiles in AD versus RA) and disease characteristics (systemic disease in RA versus more localized disease in AD). Furthermore, data sets for AD were incomplete and not all identified cases were integrated in the calculation of IRs. Trial data with a direct comparison between baricitinib and TNFi was limited in patient numbers as well as in duration of follow-up; the increased risks for VTE and serious infections in baricitinib versus TNFi (adalimumab) were already known during the initial MA application. The final results of the JAJA/JAJD studies will provide valuable data on this comparison, also elucidating specific risk factors for the five safety conditions in baricitinib versus TNFi.
The main source of data on the comparison of safety between baricitinib and TNFi currently stems from the observational B023 study. Regarding Study B023, the MAH explained that current interim results include data up to 09 February 2022. The final study report for the B023 study was finalized internally by the MAH on 30 June 2022, which is in line with the study milestones. The MAH submitted a summary overview of the final results of Study B023. It is acknowledged that the results in the final study report are generally consistent with the results provided in the updated interim analysis. The final study results of study B023 show a statistically increased risk of VTE, and trends for increased risks of MACE and serious infections for baricitinib compared to TNFi. However, the final study results will be assessed after submission of the final study report in a separate regulatory procedure.

Regarding treatment of AA, safety data were evaluated, and no new safety concerns were identified. For AA, no alternative treatment is currently approved. During the procedure, it was discussed whether a specific warning to the AA indication should be considered since although severe AA is recognized as a significant autoimmune condition with emotional and psychosocial distress, AA is not associated with a comparable level of loss of function or life-threatening symptoms as some of the other JAKi treatment indications (if left untreated/suboptimally treated), whereas the safety concerns under review are life threatening. The PRAC agreed with the MAH that there is no need to include a specific AA warning since the proposed warnings are applicable for all indications of baricitinib, including AA indication.

The review of safety data for baricitinib do not warrant SmPC update beyond the implementation of the safety warnings applicable to the class of JAKis.

In addition, since the safety events of MACE, VTE and malignancy observed in the ORAL Surveillance study are dose dependent and relevant to the class of JAKis and following a reassessment of the relevant data and consultation with the MAH further to observations received on the dosing recommendations, the PRAC recommended updates to SmPC Section 4.2 to lower the dose in patients with certain risk factors. The lower dose of 2 mg is recommended to be used in patients at higher risk for MACE, VTE and malignancy, with the possibility of a dose escalation to 4mg once daily in case of inadequate response. In addition, the current recommendation to use the lower dose of 2 mg once daily in patients ≥75 years is updated to recommend the use of the lower dose of 2mg once daily for patients ≥65 years, with the possibility of a dose escalation to 4mg once daily in case of inadequate response.

Rinvoq

The incidence of adjudicated MACE was numerically higher with 30 mg compared to 15 mg in the RA, PsA and UC clinical programme, whereas adjudicated MACE was lower with upadacitinib 30 mg compared to 15 mg in AD. Events of **MI** were reported only in the RA and PsA indications. In AD, adjudicated MI was higher with upadacitinib 30 mg compared to 15 mg, whereas, in the PsA indication there was no dose-dependent pattern.

Regarding **malignancy**, long-term data from the RA studies have been reviewed in another procedure EMEA/H/C/004760/II/0014, noting an imbalance between 15 and 30 mg. Within this referral, the MAH proposed to include a statement in the PI that a higher incidence of malignancies, driven by NMSC, was observed with upadacitinib 30 mg compared with 15 mg. However, this imbalance is not driven by NMSC only, as also malignancy excluding NMSC was higher for upadacitinib 30 mg compared with 15 mg. The SmPC Section 4.4 is therefore updated to include this information. Based on available data, NMSC is considered causality related to upadacitinib, with a dose dependent relationship observed in clinical studies. NMSC is therefore added to SmPC Section 4.8 with a frequency common based on occurrence in clinical studies.

Regarding **VTE**, events of deep venous thrombosis (DVT) and pulmonary embolism (PE) were observed in clinical trials for upadacitinib. The SmPC Section 4.4 is therefore updated to include this information.

Across the indications (RA, PsA, AD, and UC), the rates of the overall **serious infections** were higher with upadacitinib 30 mg compared to 15 mg, the SmPC Section 4.4 is also updated with this information.

In addition, SmPC Section 4.4 is updated to mention that cases of sepsis have been reported in patients receiving upadacitinib. Given that infection including serious ones, is an established risk for upadacitinib, there is at least a reasonable possibility for a causal relationship. SmPC Section 4.8 is therefore updated with the term sepsis with a frequency of uncommon based on clinical study data.
In light of the dose dependency of the safety events of MACE, VTE and malignancy observed in the ORAL Surveillance study that are considered relevant to the class of JAKis, the PRAC recommended to update the posology for atopic dermatitis and the maintenance of UC to recommend a dose of 15 mg once daily in patients with risk factors for VTE, MACE and malignancy. A dose of 30 mg once daily can be considered in patients who would benefit the most from a higher dose i.e. those with high disease burden but not at higher risk for VTE, MACE and malignancy, or for patients with an inadequate response to 15 mg. For AD and the maintenance phase of UC, the lowest effective dose is recommended to be used.

Xeljanz

The final study report of Study A392113 submitted during this procedure provide a complete overview of all safety outcomes, as well as efficacy outcomes, for tofacitinib compared to TNFi.

The final results of Study A392113 show a consistent pattern of worse safety outcomes for a number of serious risks of tofacitinib compared to TNFi. For tofacitinib 5 mg twice daily, there was a statistically significant higher risk, compared to TNFi, for: non-fatal MI (HR=2.3), malignancy (HR=1.5), NMSC (HR=1.9), and a non-significant increased risk of considerable size for pulmonary embolism (HR=2.9) and death (HR=1.5). In addition, increased risks for tofacitinib as compared to TNFi, although not significant, were also observed for MACE, VTE, serious infections (including Herpes Zoster), and hepatic events. This pattern of worse safety outcomes compared to TNFi was observed for both approved tofacitinib doses (i.e. tofacitinib 5 mg BID and tofacitinib 10 mg BID). Dose-dependency was observed for several safety outcomes, with increased risks of all-cause mortality, thromboembolic events and serious infections in tofacitinib 10 mg BID compared to tofacitinib 5 mg BID and TNFi.

In the ORAL Surveillance Study A3921133, the risks were generally consistently higher in patients with identified single outcome-specific risk factors (e.g. age ≥65 years of age, male sex, smoking history) for the safety events of interest. Similarly, risks were higher in patients with common risk factors considered relevant for all safety events of interest (i.e. 'age ≥65 years or ever smoked' or 'age ≥65 years or ever smoked or history of diabetes or history of CAD or male sex') compared to patients who did not have the above mentioned common risk factors. However, post hoc analyses of the final study results also show numerically or statistically significant disadvantages for tofacitinib compared to TNFi for other outcomes than CV, also in patients without strong risk factors for these types of events (e.g. malignancy and serious infections).

Patients with a previous history of malignancy were excluded from the ORAL study population, but there was still an increased risk of malignancy among tofacitinib treated patients as compared to the TNFi treated group. Similarly, in patients ≤65 years of age, incidence rates for malignancy, NMSC, all-cause mortality, serious infections and PE were higher for tofacitinib compared to TNFi. Also, for CV outcomes such as MI, univariate analyses showed that patients without the specific CV risk factors included in the analysis (eg without atherosclerotic disease but with another CV risk factor) still had increased risk for CV outcomes as compared to TNFi. Finally, in patients *without* common composite risk factors the incidence rates of MACE, pulmonary embolism, serious infections, malignancy (excluding NSMC), NMSC and all-cause death were numerically higher in patients treated with tofacitinib 5 mg as compared to TNFi. This may indicate that although the absolute risk of most safety outcomes is higher in patients with strong risk factors, the risk of these outcomes may not be absent in patients with less strong risk factors or in the absence of the risk factors (eg for malignancy).

Study A3291133 was an event driven study, in which patient follow-up was continued until a pre-specified number of events was observed. Considering the longer follow-up and the relevant design of study A3291133, these study results are considered an important source of data in the referral evaluation. No clear signals of these serious safety outcomes were identified in the pre-registration trials, although numerically (but not statistically) higher IRs for malignancy, VTE (PE/DVT), serious infections, mortality were observed for tofacitinib versus comparator arms in completed RA clinical trials (largest study population from pre-registration clinical trials). In general, these clinical studies at the time of marketing authorisation included a more selected population, and follow-up varied between 3-24 months (versus up to 78 months for study A3291133 with median follow-up time 4 years). This follow-up period was insufficient to describe the overall long-term safety profile in particular for events of long latency time since in study A3291133, it took approximately 24 months to observe a difference between tofacitinib and TNFi in the occurrence of the primary safety outcomes MACE (MI) and malignancy.

The existing warnings in SmPC Section 4.4 on VTE, MACE and malignancies were updated as discussed above. The SmPC Sections 4.8 and 5.1 were updated to reflect the updated data from the ORAL Surveillance Study A3921133**.**

Of note, the dosing recommendation in SmPC Section 4.2 limiting the use of 10 mg BID for the maintenance treatment of UC patients with VTE only if there is no suitable alternative was agreed during the 2019 referral procedure (EMEA/H/A-20/1485). The PRAC recommended to update the posology recommendation on the 10 mg BID maintenance dose in UC patients to align with the warnings on MACE and malignancies in SmPC sections 4.4.

3. Expert consultation

The PRAC consulted the ad-hoc expert group on 19 September 2022 which provided advice on a number of issues. The input given by the experts is provided below:

Question 1, extrapolation

Given the comparable mechanism of action of the products under review and the increased risks for venous thromboembolism (VTE), major adverse cardiovascular events (MACE), serious infections, malignancy and all-cause mortality observed for tofacitinib as compared to TNFi in the ORAL Surveillance study[1] in patients with rheumatoid arthritis that can be considered class effects of the Janus Kinase inhibitors (JAKis), do you agree that these risks are relevant across all approved indications (i.e. treatment of rheumatic disorders (rheumatoid arthritis (RA)/psoriatic arthritis (PsA)/ ankylosing spondylitis (AS)/ juvenile idiopathic arthritis (JIA) / non radiographic axial spondyloarthritis (nr-AxSpA)), ulcerative colitis (UC), atopic dermatitis (AD), and alopecia areata (AA))?

The experts agreed that based on the limited clinical data currently available from the ORAL Surveillance study with tofacitinib and Study B023 with baricitinib which are the main sources of evidence, a class effect on the safety findings of MACE, VTEs, malignancy, serious infections, and all-cause mortality cannot be ruled out and hence should be considered as relevant across all approved indications.

The experts agreed that these safety findings observed in RA patients are relevant across all the indications approved for the JAKis under review. However, the experts consider that the relevance of these safety findings differs across the approved indications and population of patients, which is different in terms of baseline risk profile.

The experts pointed out to the fact that a high-risk population was enrolled into the ORAL Surveillance study i.e. moderate to severe MTX-IR RA patients who were ≥ 50 years of age and with at least one additional cardiovascular risk factor (i.e. current cigarette smoker, hypertension, HDL<40 mg/dL, diabetes mellitus, history of coronary artery disease, family history of premature coronary heart disease, extra-articular manifestations of RA).

The experts highlighted important differences between the RA population which is at increased risk for CV disorders or malignancies due to the underlying disease compared to the paediatric population or patients with UC, AA and AD who present a different risk profile background. Nevertheless, if a patient has risk factors in any of the authorised indications, the patient would be equally at risk of the above safety findings. The experts mentioned the established CV risk for the other rheumatic disorders but highlighted that those were not as prominent as in the RA population.

Question 2, restriction of indications

a) **Would you support the restriction of indications (i.e. rheumatic disorders (RA/PsA/AS/JIA/ nr-AxSpA), UC, and AD) that are currently proposed by the EMA?**

   For the AD indication, in your opinion, what would be the most relevant restriction of the indication: limiting treatment with JAKis to patients who responded inadequately or are intolerant to at least one prior systemic therapy, or limiting treatment to patients who responded inadequately or who are intolerant to at least one prior systemic therapy, including at least one biologic treatment?

   Should different considerations be given for the restrictions in the paediatric populations?

b) **For the AA indication, in your opinion, what would be the most relevant restriction of the indication considering that no approved systemic treatments are available for the AA indication?**

[1] Ytterberg SR, Bhatt DL, Mikuls TR, Koch GC, Fleischmann R, Rivas JL, Germino R, Menon S, Sun Y, Wang C, Shapiro AB, Kanik KS, Connel CA (2022). Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis. The New England Journal of Medicine 386 (4): 316-326

For each of the above questions, you are invited to discuss possible differences between the different JAKis.

a) In light of the data presented to the experts, the panel overall did not support the restrictions of the rheumatic and UC indications as currently proposed by the PRAC; nevertheless they considered that strengthening of the warnings on MACE, malignancies, VTEs, serious infections already implemented for Xeljanz (tofacitinib) would be more appropriate, since individual patients with risk factors may still benefit from JAKIs. It was proposed to implement the safety warnings for the other JAKis to recommend cautious use in patients with risk factors and above 50 years of age. The experts recommended to list these relevant risk factors based on ORAL Surveillance study. In patients with no existing risk factors, the experts considered that no specific restrictions, change or warning should be applied.

For the UC indication, the experts pointed out the fast onset of action of JAKis as an important therapeutic advantage in patients with disease exacerbations and may prevent them from further complications of the disease.

For the paediatric population, the experts recognised that none of the risk factors would apply or at least it would be very difficult to formulate these risks, and no safety signals have been identified so far in the absence of long-term data. Therefore, the experts agreed that no restriction to the paediatric population would be necessary. One expert expressed that from a clinical perspective, JAKis used in the treatment of JIA should be recommended after TNFi use in the absence of comparative efficacy data that JAKis perform better than the TNFis. It was also noted that there are no safety data available to support that there are less risks with the use of TNFis compared to JAKis in this paediatric patient population.

Regarding the dermatological indication of atopic dermatitis, the experts considered that no specific restriction can be applied; statement on cautious use in patients with increased risks could be added. The experts discussed that currently systemic treatment includes the use of cyclosporine or other corticosteroids that are associated with safety issues particularly on the long term use, thus treatment should be limited in time. Other immunomodulators are used off label (MTX, azathioprine). Biologics treatments have recently been approved but there is currently not enough evidence or experience to limit treatment to patients who responded inadequately or who are intolerant to at least one prior systemic therapy, including at least one biologic treatment both in the adult and paediatric populations. The experts and a patient representative recognised the quick onset of response achieved with the JAKis.

b) Regarding the treatment of severe alopecia areata, the experts noted that baricitinib is the only approved medicinal product in this indication as a systemic treatment. Overall, the experts were not in favour of limiting the use of the product to a second line treatment; in case risk factors are known or identified, the product should rather be used with caution in these patients and appropriate warning would be recommended.

Possible differences between the different JAKis have been discussed by the experts, but this did not lead to specific recommendation at the product level.

The experts and patients' representatives were not in favour of any prescriptive/mechanistic restrictions underlining the need to have access to broad treatment choices and possibility of having informed decision and a dialogue with their doctors. The panel mentioned that, across the indications, individualised benefit/risk evaluation should be discussed with the patient and a shared decision making between the patient and the treating physician is preferred.

Question 3, further risk minimisation measures

a) **Please comment on the further measures proposed beyond restriction of indications, such as dose reductions and safety warnings limiting the use in patients with known risk factors for MACE, myocardial infarction (MI), VTE (such as DVT/PE), malignancy or serious infections to minimise the risks associated with JAKis treatment. You are invited to discuss possible differences for the different JAKis and indications.**

b) **For the AA indication, are there specific patient populations in whom baricitinib should not be prescribed, for example through contra-indication(s)? You are invited to comment if further risk minimization measures for the AA indication (e.g. dose reduction, warnings), than those proposed already, should be considered in patients with known risk factors for MACE, myocardial infarction (MI), VTE (such as DVT/PE), malignancy, or serious infections.**

c) **Which further risk minimisation measures would you consider, in addition to those already proposed, for use of JAKis in children and adolescents?**

d) **Do you have any further suggestions for measures to minimise the risks, not already discussed above?**

a) Regarding the further measures proposed, the experts recommended to lower the warning age threshold from above 65 years of age to above 50 years of age in SmPC section 4.4. 'Special warnings and precautions for use' of tofacitinib based on the RA population included in the ORAL surveillance study who were above 50 years of age. The experts were of the view that these warnings would also be applicable across all inflammatory indications including AA where the JAKi baricitinib is the only effective treatment approved so far. Further, the experts indicated that the starting dose should not be decreased to ensure rapid onset of action but considered that efforts should be made to use the lowest effective dose to maintain response for all indications, when possible. This position was also supported by all patients' representatives.

b) For the AA indication, the experts did not identify any specific population in whom baricitinib should not be prescribed. As mentioned in question 2b), the experts recognised that baricitinib is the only effective systemic drug approved in AA. Hence, the experts did not recommend restricting its use, however caution and appropriate warnings should be applied for patients with known risk factors as also outlined in point a) above.

c) The experts considered that no further RMMs would be needed for use of JAKis in children and adolescents. The experts also highlighted that the identified risks factors would, in general, not necessarily apply to the paediatric population.

d) The experts mentioned the need for further data in the post-marketing setting. Two types of analyses were suggested to be conducted; one concerted analysis across all JAKis authorised in the treatment of inflammatory disorders to confirm whether the extrapolation of safety findings to all JAKis is reasonable; and another analysis with an a priori risk stratifications to ensure that there are no variations in effects size going in opposite directions to the currently known safety profile of the JAKis under review. In addition, the experts stressed the importance of reducing the risk factors in patients when possible (e.g. avoid/reduce smoking, exercise, etc.).

4. Benefit-risk balance

This referral procedure concerns JAKis approved for inflammatory disorders:

- Xeljanz (tofacitinib): rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), ulcerative colitis (UC) and juvenile idiopathic arthritis (JIA).
- Olumiant (barcitinib): RA, alopecia areata (AA) and atopic dermatitis (AD)
- Cibinqo (abrocitinib): AD
- Jyseleca (filgotinib): RA and UC
- Rinvoq (upadacitinib): RA, PsA, AS, non-radiographic axial spondyloarthritis (nr-axSpA), UC and AD

These medicinal products inhibit different JAK isoforms which attenuates signalling of interleukins and interferons, resulting in modulation of the immune and inflammatory response.

The background to this referral procedure is based on data from the ORAL Surveillance study A3921133. This is a Phase 3b/4 randomized study that evaluates the safety of tofacitinib at two doses (5 mg and 10 mg BID) versus TNFi. The study is a post marketing commitment to assess the risk of cardiovascular events in subjects 50 years of age and older with at least one cardiovascular risk factor with moderately or severely active RA.

Interim results from the ORAL Surveillance study were assessed in 2019 in an Article 20 referral procedure (EMEA/H/A-20/1485) and a preliminary analysis of the final results were included in signal procedure (EPITT 19382) which concluded in June 2021. The PRAC concluded that tofacitinib is associated with an increased risk of venous thromboembolism (VTE) and that there is a potential risk regarding increased mortality. This was partly driven by a higher mortality rate due to serious infections for tofacitinib and was particularly apparent for patients aged 65 years and above. Further, there was an increased incidence of major adverse cardiovascular events (MACE) and higher risk of malignancy with tofacitinib compared to TNFi. The PI of tofacitinib, but not the other JAKis, was updated accordingly.

The final results of the completed ORAL Surveillance study confirmed the findings observed in the preliminary analysis. No randomised controlled studies have been concluded with the other JAKis to specifically evaluate the safety concerns of interest. However, preliminary results on baricitinib were made available from the observational Study I4V-MC-B023 (B023) showed an increased rate of MACE and VTE with baricitinib compared to TNFi in RA patients. A safety referral was therefore triggered to assess whether the safety concerns on MACE, VTEs, serious infections, malignancies and mortality observed in rheumatoid arthritis patients with tofacitinib are a class effect and to assess its impact on the benefit risk balance of the JAKis used in the treatment of chronic inflammatory disorders.

Following assessment of the currently available mechanistic data, together with current knowledge of the safety profiles of these substances, the PRAC considered the main safety events observed during tofacitinib treatment in the ORAL Surveillance study as general JAKi class effects. This view was also supported by the Ad Hoc Expert Group.

It is acknowledged that the extent to which the tofacitinib ORAL Surveillance data on MACE, VTE, serious infections, malignancies and mortality are applicable to all JAKis approved for inflammatory conditions, across the target populations, depends also on the similarities of the respective populations including presence of risk factors for occurrence of the observed adverse events. Overall, the ORAL Surveillance study population is considered sufficiently similar to the populations covered by the adult arthritis indications RA and PsA to allow extrapolation of data. The target populations of the other rheumatic disorders and UC are considered to be sufficiently similar, with regards to important disease characteristics and baseline risk factors, for the ORAL Surveillance data to be relevant.

For the AD population, the prevalence of risk factors (including age and co-morbidities) is different compared to a RA population, mainly explained by lower age and disease specific differences. Patients with AD are already due to their underlying disease at increased risk for cardiovascular comorbidities compared to the general population (e.g. Ivert et al., 2019), which supports extrapolation of the findings in RA in the ORAL surveillance study to AD. Regarding treatment of severe AA, the PRAC acknowledged that this patient group generally has less risk factors for the main serious safety outcomes compared with e.g. RA patients, as they are at least not associated to the underlying disease.

Nevertheless, as also pointed out by the Ad Hoc Expert Group, if a patient has risk factors in any of the authorised indications, the patient would be equally at risk for the safety findings being the focus of this review. JAKis are used for indications requiring chronic treatment, potentially exposing patients without risk factors for prolonged periods of time. Thus, even a small increase in absolute risk of serious adverse events may be clinically relevant. These risks are monitored and will be further characterised in ongoing PASSes.

Therefore, since the safety events are considered class effects and because the risk factors for these events can emerge in populations treated with any of the JAKis, the PRAC concluded that these important safety concerns are relevant to all approved indications including the AD and AA populations.

4.1.1. Impact of class effects on the benefit-risk balance of all JAKis under review

With regards to the benefits of the JAKis, no new data has emerged within this review. Importantly, in general, their benefits seem clinically relevant also for subjects not responding to anti-TNF (in the non-dermatological indications) or previous systemic AD-treatment, respectively.

Since data from the ORAL Surveillance study suggest that the risks for the major safety outcomes increase with dose, current dosing advice (SmPC section 4.2) is recommended to be revised for all products to lower the dose in patients with risk factors for MACE, VTEs, or malignancy and in patients 65 years of age and older, as applicable.

The special warnings and precautions (SmPC section 4.4) were updated for all products to align with the current recommendations for use for tofacitinib based on the ORAL Surveillance study. Currently, it is recommended that tofacitinib should be used only if no suitable treatment alternatives are available in patients over 65 years of age, in patients who are current or past smokers, and patients with other cardiovascular risk factors. Cautious use is recommended in patients with known risk factors for VTE.

The Ad Hoc Expert Group (AHEG) also recommended to strengthen the existing warning of Xeljanz to state that the product should be used with caution in patients with risk factors and being above 50 years of age, in accordance with the inclusion criteria of the ORAL Surveillance study. However, patients with similar risk factors as those included in the ORAL Surveillance study are already targeted by the existing warning of tofacitinib, as outlined above.

The warnings recommended during this review still included some updates to the existing warning for tofacitinib:

- The warning on MACE is updated to include *history of atherosclerotic cardiovascular disease* as risk factor, as supported by a post hoc analysis of the Oral Surveillance Study.
- The warnings on MACE and malignancies were updated to indicate that the risk factors apply to *long-time* smokers in accordance with the long duration of smoking for patients of the ORAL Surveillance study.

- All-cause mortality is added a risk for patients 65 years of age and older.
- The risk factors for VTE were updated to exclude those overlapping with malignancy and MACE, to avoid discrepant information across the warnings since different recommendations are given.

In order to specifically highlight the most important considerations for prescribers before and during use of these JAKis, the PRAC recommended the addition of a boxed warning in SmPC Section 4.4 to indicate the groups of patients for whom JAKis should be only used if no other treatment alternatives are available.

The impact of the safety concerns identified in the ORAL Surveillance study across all approved indications for all JAKis under review, were considered. The PRAC acknowledged the fact that, as also outlined by the AHEG, the ORAL Surveillance population constitutes a high CV-risk population which did not include individuals with low CV risk, based on inclusion criteria. This enriched population with respect to CV risk had a mean RA disease duration of more than 10 years (Ytterberg et al. 2022), which could in many aspects differ from the EU populations targeted by the approved JAKis indications. The PRAC also noted that the magnitude of the absolute risks observed in the ORAL Surveillance study likely is lower in populations with lower baseline risk. The main challenge is to estimate the magnitude of the absolute risks in different patient groups with lower baseline risk, and disease characteristics to weigh these risks against the observed/expected benefits and conclude on proportionate risk mitigation measures. For this evaluation, some guidance can be derived from the post hoc analysis of subgroups in the ORAL Surveillance study but there are also uncertainties deriving from e.g. the degree of generalisability of the ORAL Surveillance data to all populations targeted by the approved JAKi indications.

Taking all data available and the AHEG's view into account, the PRAC considered that an approach aiming at more precision and focus on readily identifiable individual risk factors, instead of limiting use across the respective target populations, is the preferred option to retain a positive benefit-risk balance without depriving patients with low risk of adverse events of an effective treatment option. Therefore, the PRAC recommended to implement warnings applicable to patients with certain risk factors in SmPC Section 4.4 of *all* approved JAKis to aid the prescribers in their assessment of benefits and risks for the individual patient.

For all products, the PRAC recommended also updates of the key elements of the existing educational materials according to the risk minimisation measures recommended during this procedure, to update the existing PASSes in place to monitor the new risks identified and to update the existing drug utilisation studies (DUSs), or to implement new DUS, in case none are in place to evaluate the effectiveness of the newly recommended risk minimisation measures. The PRAC acknowledged the recommendation from the AHEG to consider additional pharmacovigilance activities. However, the PRAC did not consider such additional activities necessary as there are a number of on-going PASS for the 5 JAKis. The PRAC agreed that a DHPC should be distributed to the HCP in order to inform on the recommended risk minimisation measures.

Overall, the PRAC concluded that the benefit risk balance of Cibinqo, Jyseleca, Olumiant, Rinvoq and Xeljanz remains positive subject to changes to the product information and implementation of risk minimisation measures recommended by the PRAC.

4.1.2. Benefit-risk balance of individual JAKis under review

Cibinqo (abrocitinib)

Cibinqo has recently been approved, for the treatment of AD. With regards to the benefit, abrocitinib has proven to be efficacious for the treatment of **AD**; both in monotherapy and combination studies. Effects in patients having received prior systemic immunosuppressant treatment were consistent with the results in the overall study population. Long-term prevention of AD flare was achieved in a majority of patients with the induction-maintenance regimen. The product is currently approved with a posology to use 200 mg QD as induction treatment, with an aim to rapidly achieve disease control followed by dose reduction to the lowest effective dose for maintenance treatment for most patients. A starting dose of 100 mg once daily is recommended for patients 65 years of age and older, and there is a reference to SmPC sections 4.4 and 4.8 for other patient groups who may benefit from a starting dose of 100 mg.

Regarding the established risks, the available long term safety data are limited. Nevertheless, thromboembolic events including pulmonary embolism are already listed as uncommon ADRs. Furthermore, herpes zoster including ophthalmic zoster (common), and pneumonia (uncommon) are already listed as ADRs. For MACE, although currently available data are still not mature for final conclusion, there is a trend for a dose dependency, and a higher occurrence than in the comparative arm in studies.

Considering the results from the ORAL Surveillance study, showing that increased risks for some of the key safety concerns only became apparent until after more than 2 years treatment, there are uncertainties regarding the long-term safety with abrocitinib. Nevertheless, as results from this study are considered relevant for all substances covered by this referral, the main outcomes are considered safety concerns also for abrocitinib. Therefore, product information updates were recommended by the PRAC to implement warnings across the class of JAKis (see Section 4.1.1.). Further revisions of the warnings on malignancies and VTEs (SmPC section 4.4) were also made following review of abrocitinib specific data during this procedure.

In addition, since data from the ORAL Surveillance study suggest that the risks for the major safety outcomes of MACE, VTE and malignancy increase with dose, the PRAC recommended to update the posology (SmPC Section 4.2) to recommend a starting dose of 100 mg in patients at higher risks of VTE, MACE and malignancy and that the use of the 200 mg dose may be considered in patients who would benefit the most from a higher dose i.e. those with high disease burden but not at higher risk for MACE, VTE and malignancy or patients with an inadequate response to 100 mg. The dose should be decreased to 100 mg once daily upon disease control. In addition, the PRAC recommended the use of 100 mg once daily in patients 65 years of age and older.

Jyseleca (filgotinib)

With respect to the established benefit of filgotinib, the available data support that filgotinib is an effective treatment for **RA** and **UC.** Additionally, overall data presented by the MAH support that for patients with RA or UC, who failed to achieve therapeutic response to a TNF inhibitor, could still benefit from using filgotinib. The currently recommended dose for Jyseleca is 200 mg once daily, a starting dose of 100 mg is recommended in patients 75 years of age and older.

Overall, the main safety outcomes of the ORAL Surveillance study with increased risk for VTE, MACE, serious infections and malignancy with tofacitinib versus TNFi) are considered class effects relevant to all JAKis in their approved indications, and the SmPC Section 4.4 is updated to implement class warnings (see Section 4.1.1.). Further, SmPC section 4.8 is updated following review of filgotinib specific data during this procedure, to add sepsis as an ADR (frequency: uncommon).

Since data from the ORAL Surveillance study suggest that the risks of MCAE, VTE and malignancy increase with dose, the PRAC recommended the use of 100 mg once daily for the treatment RA and for maintenance treatment of UC, in patients at increased risk of VTE, MACE, malignancy and in patients

65 years and older. The dose may be escalated to 200 mg once daily in case of insufficient disease control. For long term treatment, the lowest effective dose should be used.

Olumiant (baricitinib)

With respect to the established benefits of baricitinib, the available data support that baricitinib is an effective treatment in its approved indications.

For **AD**, the benefit/risk balance of baricitinib was considered positive in patients treated with systemic therapy (ciclosporin) prior to baricitinib, based on clinical studies. Dupilumab was the second available approved systemic therapy at the time of the application of baricitinib. No head-to-head comparison studies with ciclosporin or dupilumab have been performed. Regarding efficacy in AD patients treated with systemic therapy prior to baricitinib, the developmental programme comprised patients who are candidates for systemic therapy only. In the All BARI AD data set 51% of the patients received prior treatment, and one study was performed in patients previously treated with ciclosporin. In this study, the proportion of patients reaching EASI75 at week 16 was significantly larger than in placebo and secondary outcomes supported these findings. The effects lasted at least until 52 weeks.

For **AA**, two main studies in 1200 adults with severe alopecia areata showed that baricitinib was effective at reducing hair loss compared to placebo. In these studies, after 36 weeks of treatment, the extent of hair loss improved from over 50% to under 20% of scalp hair in 34% of the participants taking 4 mg of baricitinib and in 20% of the participants taking 2 mg of baricitinib, compared with 4% of the participants taking placebo.

The main source for comparison of safety between baricitinib and TNFi currently stems from the observational B023 study in **RA**, which suggests an increased risk for MACE (IRR 0.92; 1.27 – 2.91) and VTE (IRR 1.34; 0.84 – 2.14) for baricitinib versus TNFi. This higher risk for VTE was also found in a clinical trial directly comparing baricitinib and TNFi. VTE is already listed/known ADR for baricitinib and is included in the PI. Furthermore, the observed increased risks of MACE and VTE seem consistent across tofacitinib and baricitinib and taking the assumed JAKi class effect into account; the main safety outcomes of the ORAL Surveillance study are considered relevant also for baricitinib. Finally, there are data showing that baricitinib has a clinically relevant effect also in patients with previous inadequate response to adalimumab (TNFi).

Overall, the main safety outcomes of the ORAL surveillance study (increased risk for VTE, MACE, serious infections and malignancy (excluding NMSC) with tofacitinib versus TNFi) are considered class effects of all JAKis. Additionally, the available clinical study data on baricitinib show trends of increased incidence of some of the adverse events of interests also with baricitinib. Therefore, product information updates were recommended by the PRAC to implement warnings across the class of JAKis, and to apply to all indications of baricitinib, including the AA indication.

Since data from the ORAL Surveillance study suggest that the risks for the major safety outcomes of MACE, VTE and malignancy increase with dose, the current recommendation to use the 2mg dose in patients ≥75 years is updated to recommend the use of lower dose of 2mg once daily for patients 65 years and older and in patients at higher risk of VTE, MACE and malignancy. A dose of 4 mg once daily may be considered in case of inadequate response.

Rinvoq (updadacitinib)

The overall benefit of upadacitinib treatment is considered unchanged by the current procedure and thus consistent with the presentation of efficacy data in section 5.1 of the approved SmPC. The data presented by MAH support benefits of upadacitinib also in patients with RA, PsA and AS who previously failed to achieve therapeutic response to TNF inhibitors.

Regarding **AD**, upadacitinib has a clinically relevant efficacy, with short onset, and it is given via oral administration. Furthermore, long-term safety of upadacitinib is presently not established, which is an additional uncertainty.

For the recently approved indications i.e. UC and nr-axSpA, the safety profile and concerns regarding the benefit/risk are consistent with those of the other approved indications.

As concluded in the current review, the main safety outcomes of the ORAL Surveillance study data are considered class effects of all JAKis. Additionally, the available clinical study data on upadacitinib further support these being main safety concerns. Therefore, product information updates were recommended by the PRAC to implement warnings across the class of JAKis (see Section 4.1.1.). Further revisions of the wording of warnings on serious infections and malignancy in SmPC Sections 4.4 and SmPC Section 4.8 were made following review of upadacitinib specific data to add sepsis (frequency: uncommon) and NMSC (frequency: common) as ADRs.

In light of the dose dependency of the safety events of MACE, VTE and malignancy observed in the ORAL Surveillance study that are considered relevant to the class of JAKis, the PRAC recommended to update the posology (SmPC Section 4.2) of Rinvoq to recommend for treatment of AD and maintenance treatment of UC, use of 15 mg once daily in patients with risk factors for VTE, MACE and malignancy. A dose of 30 mg once daily can be considered in patients who would benefit the most from a higher dose i.e. those with high disease burden but not at higher risk for VTE, MACE and malignancy, or for patients with an inadequate response to 15 mg. Lowest effective dose during maintenance treatment of both settings is also recommended (see Section 5.1.2.1.).

Xeljanz (tofacitinib)

With respect to the established benefits of tofacitinib, the available data support that tofacitinib is an effective treatment in its approved indications. The MAH has now provided support also for the efficacy of tofacitinib in patients previously treated with TNFi.

The final results of the ORAL Surveillance study (A3921133) show an increased incidence for major safety risks that are known ADRs of tofacitinib, including MACE, MI, VTE, malignancy and death, NMSC and serious infections in patients treated with tofacitinib compared to TNFi, and this pattern was observed for both approved tofacitinib doses (i.e. 5 mg BID and 10 mg BID). Dose-dependency was observed for several safety outcomes, with increased risks of all-cause mortality, thromboembolic events and serious infections in tofacitinib 10 mg BID compared to tofacitinib 5 mg BID and TNFi.

The SmPC of tofacitinib is updated to include the final results of the ORAL Surveillance study in SmPC Sections 4.8 and 5.1.

The existing warning on VTE, malignancies and MACE in SmPC Section 4.4 is updated as described in Section 4.1.1.

Further, the PRAC recommended to update the posology recommendation on the 10 mg BID maintenance dose in UC patients in SmPC Section 4.2 to align with the warnings on MACE and malignancies in SmPC Section 4.4.

5. Summary of new activities and measures

5.1. Risk management

The MAHs should operate a risk management system described in Risk Management Plans which have been endorsed as part of the current review procedure.

The following RMPs are agreed by the PRAC: Cibinqo RMP v 3.2, Jyseleca RMP v 6.0, Olumiant RMP v 18.2, Rinvoq RMP v 12.4 and Xeljanz RMP v 30.2.

5.1.1. Safety concerns

The safety specification of **Cibinqo** is updated to include all-cause mortality as an important potential risk. The important identified risk of thrombotic events including pulmonary embolism is renamed venous thromboembolism.

The safety specification of **Rinvoq** is updated to add NMSC as an important identified risk. The important potential risk of malignancy is renamed malignancy excluding NMSC.

No changes were made to the safety specification of **Jyseleca, Olumiant** and **Xeljanz**.

5.1.2. Risk minimisation measures

5.1.2.1. Routine risk minimisation measures

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 of MACE, VTE, serious infections, malignancies and mortality associated with the use of Cibinqo, Jyseleca, Olumiant, Rinvoq and Xeljanz. These changes include amendments to SmPC Sections 4.2, 4.4, 4.8 and 5.1 (Xeljanz only).

For SmPC Section 4.2, the PRAC recommended the use of the respective lower doses in groups of patients with risk factors.

Further warnings and precautions of use relating to the risks associated with the use of Cibinqo, Olumiant, Jyseleca, Rinvoq and Xeljanz were also included in SmPC Section 4.4 to:

- Use only if no suitable treatment alternatives are available in patients
    - 65 years of age and older;
    - history of atherosclerotic CV disease or other CV risk factors;
    - who are current or past long-time smoker;
    - with malignancy risk factors (e.g. current, or history of malignancy)
- Use with caution in patients with known risk factors for VTE

The following changes were made to the adverse drug reactions of the products in SmPC Section 4.8:

- For Jyseleca, sepsis was added (frequency: uncommon).
- For Rinvoq, sepsis (frequency uncommon) and NMSC (frequency: common) were added.

The Package Leaflets were amended accordingly.

5.1.2.2. Additional risk minimisation measures

The existing educational materials were updated to reflect the risk minimisation measures recommended during the referral.

For **Cibinqo**, the prescriber brochure is updated:

- To include a section about abrocitinib and describe the indication and posology

- To include information on the use in patients 65 years and older with description of the risks in these patients and use of 100mg dose
- To update the information on the risk of infections recommending to consider risk factors when prescribing abrocitinib, including elderlies and patients with diabetes
- To update the information on the risk of VTE to recommend cautious use in patients with known risks of VTEs and to provide examples of risk factors. Further, recommendation is added for periodic re-evaluation of changes in VTE risk and on the response if clinical features of VTE occur including prompt evaluation and the need for discontinuation of Cibinqo.
- To update the information on the risk of malignancy to recommend the use in patients at high risk for malignancy only if no other suitable treatment alternatives are available and to remind on the need for periodic skin examination.
- To update the information on the risk of MACE to recommend the use in patients at high risk for cardiovascular risk only if no other suitable treatment alternatives are available, with examples who may be at risk.

The patient card is updated:

- To include a section about abrocitinib and describe the indication and posology
- To include information on the risk of heart disease describing the signs/symptoms of heart disease that the patient needs to be aware of, so that they can seek attention from their HCP
- To include a reminder on the risk of cancer and a reminder on the risk of skin cancer to let their doctor know if they notice any new growth on the skin.

For **Jyseleca**, the guide for HCP is updated:

- To include a section about the approved indications and posology
- To update the information on MACE to recommend the use in patients at high risk for cardiovascular risk only if no other suitable treatment alternatives are available.
- To update the information on the risk of malignancy to recommend the use in patients at high risk for malignancy only if no other suitable treatment alternatives are available and to remind on the need for periodic skin examination.
- To update information on patients 65 years and older with information on the risks in these patients.

The patient card is updated:

- To include information on the risk of heart disease describing the signs/symptoms of heart disease that the patient needs to be aware of, so that they can seek attention from their HCP
- To include a reminder on the risk of cancer and a reminder on the risk of skin cancer to let their doctor know if they notice any new growth on the skin.

For **Olumiant**, the guide for HCP is updated:

- To include a section about the approved indications and posology
- To recommend cautious use in the elderly and diabetic populations as there is a higher risk of infections and to recommend the use in patients 65 years and older if no suitable treatment alternative are available.

- To remind on the risk of VTE and PE to recommend cautious use in patients with known risk factors for DVT/PE.
- To inform on the potentially increased risk of MACE in patients using JAKi treatment. In patients over 65 years of age, patients who are current or past long-time smokers, and patients with other cardiovascular risk factors, baricitinib should only be used if no suitable treatment alternatives are available.
- To inform on Lymphoma and other malignancies been reported in patients receiving JAKis, including baricitinib and to indicate that in patients over 65 years of age, patients who are current or past smokers, or with other malignancy risk factors (e.g. current malignancy or history of malignancy) baricitinib should only be used if no suitable treatment alternatives are available.

The PAC is updated:

- To inform on the risk of infections and viral reactivation, which can become serious if not treated.
- To recommend patients to seek immediate medical attention if signs and symptoms of myocardial infarction or stroke occur.
- To inform on the risk of NMSC and to tell their doctor if they notice any new skin lesion.

For **Rinvoq**, the guide for HCP is updated:

- To include a section on the approved indications and posology
- To include information on the use in patients 65 years and older with description of the risks in these patients and use of 15mg dose
- To update the information on the risk of VTE to recommend cautious use in patients with known risks of VTEs and to provide examples of risk factors. Further, recommendation is added for periodic re-evaluation of changes in VTE risk and on the response if clinical features of VTE occur including prompt evaluation and the need for discontinuation of Rinvoq.
- To update the information on the risk of MACE to recommend the use in patients at high risk for MACE only if no other suitable treatment alternatives are available, with examples of who may be at risk.
- To update the information on the risk of malignancy to recommend the use in patients at high risk for malignancy only if no other suitable treatment alternatives are available and to remind on the need for periodic skin examination.

For the 30 mg dose in atopic dermatitis and maintenance treatment of UC:

- To inform on the dose-dependent increase in NMSC and malignancy
- To recommend the use of the lowest effective dose
- To inform on the dose-dependent increase in serious infections and herpes zoster. This is added only to maintenance treatment of UC since already implemented for AD.

The patient card is updated:

- To include information on the risk of heart disease describing the signs/symptoms of heart disease that the patient needs to be aware of, so that they can seek attention from their HCP

- To include a reminder on the risk of cancer and a reminder on the risk of skin cancer to let their doctor know if they notice any new growth on the skin.

For **Xeljanz**, the Guide for HCP and the prescriber checklist were updated:

- To include all-cause mortality as a specific risk to patients 65 years and older
- To extend the recommendation of not using 10 mg in UC maintenance treatment to patients with risk factors of MACE and malignancy.

5.1.3. Pharmacovigilance activities

5.1.3.1. Additional pharmacovigilance activities

Cibinqo

The additional pharmacovigilance activities were updated as follows:

- All-cause mortality is added as an endpoint of the safety surveillance Study B7451084.
- The objectives of the long-term extension Study B7451015 were updated to include all-cause mortality.
- The drug utilisation study (B7451085) is updated to align with the updated RMM to assess the adherence to consideration of risk factors prior to treatment with abrocitinib. The risk factors of MACE and malignancy are added.

Olumiant

The RMP is updated with the addition of the two ongoing randomized active-controlled clinical trials as category 3 PASSs:

- Study I4V-MC-JAJA (JAJA): A Randomized Active-Controlled Parallel-Group Phase 3b/4 Study of Baricitinib in Patients with Rheumatoid Arthritis
- Study I4V-MC-JAJD (JAJD): A Randomized, Controlled Pragmatic Phase 3b/4 Study of Baricitinib in Patients with Rheumatoid Arthritis

The primary inferential statistical analyses will include data from both studies. Study JAJD shares primary, secondary, and safety-related exploratory objectives with Study JAJA, as well as similarly adjudicated endpoints. Study JAJD is designed to capture one-third and may potentially capture one-half of the planned total VTE events to be observed between these 2 safety trials. Study JAJD will complement Study JAJA by collecting information from a real-world setting. This will broaden the generalisability of results to RA patients receiving treatment with baricitinib who might not have participated in traditional clinical trials.

These studies are aimed at addressing the important identified risk of VTE and the important potential risks of MACE, opportunistic infection, serious infection and malignancy.

The final study report is expected by 31 March 2028.

Studies I4V-MC-B003 and I4V-MC-B004, conducted in the US using US CorEvitas RA registry, are removed from the RMP, since the results of these studies are not expected to provide further decision relevant data. Data from the CorEvitas RA registry from baricitinib-treated patients were also included in Study B023 which uses multiple data sources to increase power, interim results of this study have been reviewed in the current Article 20 referral and provides relevant safety information prompting an update of the product information. The removal is also justified because of the low enrolment numbers,

due to low market uptake of baricitinib in the US. In Study B0003, within 3.5 years a total of 324 patients (including 112 baricitinib-treated patients in the matched cohort) have been enrolled in the propensity score-matched cohorts with very low number of events (<n=5). In study B004, 445 new users of baricitinib have been enrolled after more than 3 years with also a low number of events (n≤10), while the required sample size is over 1000. The MAH expects that in the future no sufficient number of patients will be reached considering the current US Product Information and position of baricitib in the therapeutic work-up.

The RMP is updated with the addition of a new drug utilization study (DUS) study. This DUS aims to measure the effectiveness of the newly proposed prescribing recommendations. This will be accomplished by evaluating prescribing behaviours after implementation of the recommended changes in prescribing following the current referral procedure and will be addressed by describing the characteristics of patients with a dispensing of baricitinib for RA, AD, or AA specifically with respect to the characteristics of the treated populations per revised SmPC. The DUS protocol will be submitted by 25 April 2023.

Study B025 which was a survey to assess the effectiveness of baricitinib risk minimisation in prescribers (dermatologists) in atopic dermatitis is updated to extend the survey to all indications, hence to rheumatologists as well. The survey will, in addition, address the important potential risk of malignancy. The amended protocol will be submitted by 25 April 2023. The due date for final study report submission is delayed to an estimated date of 30 April 2025.

Rinvoq

The objectives of the PASSes in RA (Study P19-150 and Study P19-141), in AD (Study P20-390) and the planned study in UC (Study P23-480) were updated to include all-cause mortality.

The objective of the DUS in AD (P21-825) and in UC (P23-479) were updated to evaluate changes to aRMM following the 2022 Article 20 Referral after feasibility assessment.

A DUS is planned to evaluate the effectiveness of the aRMMs for upadacitinib in RA.

Xeljanz

The objectives of the DUS A3921321 were updated to include the description of changes in the utilization of tofacitinib following the updated recommendations on the UC maintenance treatment dosage for patients with MACE and malignancy risks after the 2022 Article 20 referral.

5.2. Direct Healthcare Professional Communications and Communication plan

The Committee adopted the wording of a DHPC, to inform HCP of the outcome of the review and associated risk minimisation measures for Cibinqo, Rinvoq, Jyseleca, Olumiant and Xeljanz. The Committee also agreed on a communication plan. This communication should be distributed to allergologists, dermatologists, gastroenterologists, rheumatologists, paediatricians and, if applicable, other relevant target groups to be defined at the national level.

6. Grounds for Recommendation

Whereas,

- The PRAC considered the procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data for the JAKis used in the treatment of inflammatory disorders. The concerned products are Cibinqo, Jyseleca, Olumiant, Rinvoq and Xeljanz.

- The PRAC considered the totality of the data submitted during the referral in relation to the risks of major adverse cardiovascular events (MACEs), venous thromboembolism (VTE), malignancy, serious infections and all-cause mortality. This included the responses submitted by the marketing authorisation holders in writing and during oral explanations as well as the outcome of an Ad hoc expert group meeting.
- The PRAC concluded that, based on the currently available data, the increased risk for MACE, VTE, malignancy, serious infections and all-cause mortality observed in the ORAL Surveillance study with tofacitinib compared with TNF-inhibitors are considered JAKis class effects. The PRAC also concluded that these safety findings observed in patients with rheumatoid arthritis apply to all approved indications for the JAKis used in the treatment of chronic inflammatory disorders. However, the magnitude of the absolute risk depends on the background risk in the respective populations.
- To minimise these risks, the PRAC recommended implementing warnings for all JAKis included in this review that these products should only be used in patients 65 years of age and older, who are current or past long-time smoker, with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors, or with other malignancy risk factors (e.g. current, or history of malignancy) if no suitable treatment alternatives are available. Cautious use is recommended in patients with known risk factors for VTE, other than those listed above.
- The PRAC recommended to revise current dosing advice to lower the dose in certain patient groups with risk factors since the occurrence of MACEs, VTEs, malignancies, serious infections and all-cause mortality have been observed in a dose dependent manner.
    - For Cibinqo, a lower starting dose is recommended in patients at higher risk for VTE, MACE, and malignancy with the possibility of a dose escalation in case of inadequate response. The lower dose is recommended for use in patients 65 years and older.
    - For Jyseleca, in the treatment of RA and for maintenance treatment of UC, a lower dose is recommended in patients at higher risk for VTE, MACE, and malignancy and in patients 65 years and older, with the possibility of a dose escalation in case of inadequate response.
    - For Olumiant, a lower dose is recommended for patients at higher risk of VTE, MACE and malignancy, for patients 65 years and older and for patients with history of chronic and recurrent infections, with the possibility of a dose escalation in case of inadequate response.
    - For Rinvoq, in the treatment of AD and maintenance treatment of UC, a lower dose is recommended in patients at higher risk for VTE, MACE, malignancy and in patients 65 years and older, with the possibility of a dose escalation in case of inadequate response.
    - For Xeljanz, the high dose is no longer recommended for the treatment of ulcerative colitis patients with CV and malignancy risk factors, unless there is no suitable alternative treatment available.
- Based on the clinical data presented, the PRAC recommended to include new adverse reactions for Jyseleca with the addition of sepsis (frequency: uncommon) and for Rinvoq with the addition of sepsis (frequency uncommon) and non-malignant skin cancer (frequency: common).
- The PRAC recommended an update of the key elements of the educational materials accordingly.

- PRAC recommended updates of the risk management plans including studies of drug utilisation accordingly.
- The 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 Cibinqo, Jyseleca, Olumiant, Rinvoq and Xeljanz remains favourable subject to the agreed amendments to the product information and other risk minimisation measures.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for Cibinqo, Jyseleca, Olumiant, Rinvoq and Xeljanz.

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Appendix 1 - Divergent positions

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

Janus Kinase inhibitors (JAKi)

Xeljanz (tofacitinib) EMEA/H-A20/1517/C/004214/0048

Cibinqo (abrocitinib) EMEA/H-A20/1517/C/005452/0003

Olumiant (baricitinib) EMEA/H-A20/1517/C/004085/0032

Rinvoq (upadacitinib) EMEA/H-A20/1517/C/004760/0017

Jyseleca (filgotinib) EMEA/H-A20/1517/C/005113/0014

Divergent statement

The below named PRAC Members consider that some restriction of indications of above mentioned products is necessary to maintain their Benefit/Risk balance positive, based on the following grounds:

- ORAL is a Phase 3b/4 randomized study specifically designed to evaluate safety of tofacitinib at two doses (5 mg and 10 mg BID) vs TNFi and methodologically represents the strongest possible base for conclusion. Results of this study showed higher incidence on MACE, malignancies, VTEs, serious infections, and most importantly mortality in patients treated with tofacitinib vs TNFi.
- Preliminary results of I4V-MC-B023 (B023) observational study, including data from several healthcare databases of RA patients, showed an increased rate of MACE and VTE with baricitinib vs TNFi in RA patients.
- Safety concerns under review are identified ADRs class effect for JAKi and are therefore expected in both patients *with* and *without* risk factors.
- In patients *without* risk factors, absolute risk of serious safety outcomes is expected to be low but is not negligible. In patients without risk factors (e.g. children, adolescents), the serious safety outcomes of JAKis under review are of great concern, especially in the view of the expected long-term treatment.
- Restriction of indication as proposed by the Co-Rapporteurs in the updated AR and below is needed to ensure positive benefit/risk balance also in patients without risk factors in view of potentially fatal ADRs under review, in addition to the risk minimisation measures for patients *with* risk factors.
- Restriction of indications is considered the most effective measure in affecting factual prescription behaviour.
- The inclusion of a mention, in the therapeutic indications, that JAKi may be prescribed also if TNFi is *inappropriate* (leaving sufficient room to not consider a treatment by TNFi in specific patients) does not hamper adequate clinical judgement and allows for prescribing JAKi to patients who truly need this treatment.

- There may be long-term unintended consequences of PRAC decision to implement warning only for patients with risks factors without restriction of indications. The use of the JAK inhibitors may be channeled to indications where patients have less risk factors for MACE and malignancy, however higher doses may be used. These populations include children and adolescents and that is of concern particularly due to risk of malignancy with this treatment (including lymphoma) in these populations.

Based on the presented evidence in their totality, we are of the following opinion:

To ensure a positive B/R balance for the concerned products, next to the warning for patients 65 years of age or older and patients with risk factors for MACE and malignancy, the indications should be restricted to patients who:

- responded inadequately or are intolerant to TNFi or for whom TNFi is inappropriate (RA, PsA, UC, AS, JIA indications)
- responded inadequately or are intolerant to at least one prior systemic therapy or for whom alternative systemic therapies are inappropriate (AD indication)
- responded inadequately or are intolerant to alternative treatment options or for whom alternative treatment options are inappropriate (see section 5.1) (AA indication).

PRAC Members expressing a divergent opinion:

- Menno van der Elst (Netherlands)
- Nikica Mirošević Skvrce (Croatia)
- Amelia Cupelli (Italy)
- Tiphaine Vaillant (France)
- Eva Jirsová (Czechia)
- Annalisa Capuano (independent scientific expert)