Module 1.8.2

European Union Risk Management Plan (EU-RMP) for Omjjara (momelotinib)

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ACVR1	activin A receptor type 1
ADR	adverse drug reaction
ALK2	activin receptor-like kinase-2
AML	acute myeloid leukaemia
BAT	best available therapy
BCRP	breast cancer related protein
CALR	calreticulin
COVID-19	coronavirus disease of 2019
DAN	danazol
DIPSS	Dynamic International Prognostic Scoring System
EEA	European Economic Area
EMH	extramedullary haematopoiesis
EPAR	European Public Assessment Report
ESA	erythropoiesis stimulating agent
ESRD	end-stage renal disease
ET	essential thrombocythaemia
EU	European Union
FDA	Food and Drug Administration
HGB	haemoglobin
HSCT	haematopoietic stem cell transplantation
ISS	Integrated Summary of Safety
JAK1/JAK2	Janus associated kinase 1 and 2
JAK	Janus associated kinase
JAKi	JAK inhibitor
MACE	major adverse cardiovascular event
MF	myelofibrosis
MPN	myeloproliferative neoplasm
MPL	myeloproliferative leukaemia
NK	natural killer
PL	package leaflet
PK	pharmacokinetic
PMF	primary myelofibrosis
PV	polycythaemia vera
PY	person years
QTcF	QT interval corrected using Fridericia's formula
RMP	risk management plan
RT	randomised treatment
RUX	ruxolitinib
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SMAD	suppressor of mothers against decapentaplegic
SmPC	summary of product characteristics
SOC	system organ class
STAT	signal transducer and activator of transcription
TD	transfusion dependent
WHO	World Health Organization
WOCBP	women of child-bearing potential
XAP	Extended Access Protocol

Trademark Information

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PART I: PRODUCT(S) OVERVIEW

Table 1 Product Overview

Active substance(s) **(INN or common name)**	Momelotinib dihydrochloride monohydrate
Pharmacotherapeutic group(s) (ATC Code)	L01EJ04
Marketing Authorisation Holder/ Applicant	GlaxoSmithKline Trading Services Limited
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Omjjara
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class** Janus-associated kinase (JAK) inhibitors
	Summary of mode of action Momelotinib is an inhibitor of Janus Kinase 1 and 2 (JAK1/JAK2) and activin A receptor, type 1 (ACVR1), also known as activin receptor-like kinase 2 (ALK2). JAK1/2 inhibition has been shown to reduce the abnormal cytokine production in myelofibrosis (MF), which reduces constitutional symptoms, and to also reduce splenomegaly. Momelotinib's inhibition of ACVR1 down-regulates production of hepcidin in the liver, thereby increasing iron availability for erythropoiesis. Improved erythropoiesis reduces the anaemia associated with MF.
	Important information about its composition Momelotinib ($C_{23}H_{22}N_6O_2$) is a benzamide obtained by formal condensation of the carboxy group of 4-{2-[4-(morpholin-4-yl) anilino]pyrimidin-4-yl}benzoic acid with the primary amino group of

	aminoacetonitrile. It is an aminopyrimidine, a member of morpholines, a secondary amino compound, a tertiary amino compound, a member of benzamides and a nitrile.
Reference to the Product Information	Please refer to the product information (section 1.3.1 of the eCTD).
Indication(s) in the EEA	Current: Omjjara is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with moderate to severe anaemia who have primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis and who are Janus Kinase (JAK) inhibitor naïve or have been treated with ruxolitinib.
Dosage in the EEA	Current: The recommended dosage of Omjjara is 200 mg once daily.
Pharmaceutical form(s) and strengths	Current: Omjjara is available as film-coated tablets containing 100 mg, 150 mg, or 200 mg of momelotinib (free base equivalent) in the form of momelotinib dihydrochloride monohydrate.
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1 Myelofibrosis

Omjjara is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with moderate to severe anaemia who have primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis and who are Janus Kinase (JAK) inhibitor naïve or have been treated with ruxolitinib.

Myelofibrosis (MF) may occur de novo as PMF or evolve from a pre-existing myeloproliferative neoplasm (MPN), primarily post polycythaemia vera (PV) or post essential thrombocythaemia (ET). Primary myelofibrosis (PMF) is considered the most aggressive of the BCR-ABL1-negative MPNs (Newberry, 2014). The revised 2016 World Health Organization (WHO) classification system distinguishes PMF as “prefibrotic” (characterised by megakaryocytic proliferation and atypia, without significant reticulin fibrosis, increased age-adjusted bone marrow cellularity, and granulocyte proliferation) and from “overtly fibrotic”, characterised by grade 2 or 3 bone marrow fibrosis (Barbui, 2018; Garmezy, 2021; Tefferi, 2018). Once PV or ET reach an overtly fibrotic stage, they are virtually clinically indistinguishable from PMF.

PMF is a rare MPN characterised by stem cell-derived clonal myeloproliferation that is often but not always accompanied by JAK2, calreticulin (CALR), or myeloproliferative leukaemia (MPL) mutations. Additional disease features include bone marrow stromal reaction including reticulin fibrosis, abnormal cytokine expression, anaemia, hepatosplenomegaly, extramedullary haematopoiesis, constitutional symptoms, cachexia, leukemic progression, and shortened survival (Tefferi, 2018).

Incidence

Myelofibrosis is a rare MPN of primarily older adults, occurring more frequently in males than females (Lim, 2016; Roaldsnes, 2017). There is very limited published literature reporting the incidence and prevalence of MF. Available data show that the incidence is very low, with an estimated global annual crude incidence of 1.0 per 100,000 individuals (Orphanet, 2019). In the EU, the estimated age-adjusted incidence rate of MF, including primary and secondary MF, ranges from 0.41 to 0.6 per 100,000 individuals (Roaldsnes, 2017; Hultcrantz, 2020; Solans, 2022; HMRN, UK). Overall, the incidence rates are similar across geographic regions which include Europe, North America, and Australasia (Garmezy, 2021; Mehta, 2014; Titmarsh, 2014; Deadmond, 2015; Srour, 2016; Verstovsek, 2022; Cameron, 2022). A peak incidence generally occurs in the sixth decade of life (Garcia-Fortes, 2022).

Prevalence

The estimated global prevalence of PMF is 1.76 to 4.05 cases per 100,000 individuals (Titmarsh, 2014). The estimated EU annual prevalence of MF is 0.5 to 9 cases per 100,000 individuals. (Moulard, 2012).

SI.1.1 Demographics of the population in the proposed indication and risk factors for the disease

Although MF affects both females and males, it tends to be more common in males for PMF and post-PV MF, but more females are diagnosed with post-ET MF. The rate of PMF diagnosis increases with age, with most cases occurring between age 50 and 74 (median age 70), and more frequently among White and non-Hispanic patients (Garmezy, 2021). The disease rarely affects people under age 30.

Myelofibrosis manifests with three main hallmark features: 1) chronic anaemia and transfusion dependency; 2) constitutional symptoms due to aberrant cytokine production and inflammation; and 3) organomegaly, principally of the spleen, due to extramedullary haematopoiesis. A combination of clinical and laboratory features including bone marrow biopsy and cytogenetic and molecular studies provide the basis for diagnosing PMF. Presence of JAK2, CALR, or MPL mutation is estimated in 90% of patients with PMF and are also common in patients with PV and ET (Dos Santos, 2011; Tefferi, 2016). The clinical utility in testing for these mutations is supportive but not essential for diagnosis (Tefferi, 2021). However, genetic markers in PMF influence survival and are now part of some of the formal prognostic systems (Tefferi, 2018).

In 83% to 89% of newly diagnosed PMF patients, a palpable spleen is present, approximately one-third have at least grade 2 anaemia (i.e., haemoglobin [Hgb] values <10 g/dL), and about one-fourth are burdened by constitutional symptoms (Barraco, 2019). Thrombocytopenia, and specifically a platelet count $\leq 100 \times 10^9$/L, is present in approximately 15% of MF patients at diagnosis and is less common in secondary myelofibrosis (Barraco, 2019). Furthermore, all these features tend to be progressive over the disease course, with anaemia, constitutional symptoms, and thrombocytopenia, carrying an independent negative prognostic weight (Barraco, 2019; Gangat, 2011). For example, the median survival was reported to be 4.9, 3.4, and 2.1 years in PMF patients with mild, moderate, or severe anaemia, respectively, compared with 7.9 years in PMF patients without anaemia (Nicolosi, 2018).

The clinical features of MF and the patient's assigned prognostic group guide therapeutic decisions (Bassiony, 2020). The Dynamic International Prognostic Scoring System (DIPSS) uses five clinical risk variables to stratify by prognostic score: age, Hgb level, white blood cell counts, prevalence of circulating blast cells, and presence of constitutional symptoms (Passamonti, 2010). Symptomatic intermediate and high risk DIPSS patients are indicated for JAKi treatment, with median survival inversely correlated with risk category. DIPSS Plus, a redefined DIPSS for PMF, incorporates prognostic information from karyotype, platelet count, and red blood cell (RBC) transfusion dependence status to predict overall survival in this population (Gangat, 2011).

SI.1.2 The main existing treatment options

Allogeneic hematopoietic stem cell transplantation (HSCT) is the only curative treatment for MF. However, older patients tend to have one or more comorbidities which may increase the risk of transplant related mortality or preclude a transplant approach (Bacigalupo, 2021). For those who do not undergo HSCT, treatment remains mostly palliative and targeted at clinical aspects of the disease, such as cytopenias, splenomegaly, and constitutional symptoms (Harrison, 2020).

In terms of the main existing therapeutic options, the current standard of care for MF includes targeted therapies with approved JAKis. Ruxolitinib, the first approved drug in this class, has been reported to improve splenomegaly or constitutional symptoms such as fever, pruritus, and night sweats. Ruxolitinib has been the main therapy for patients with MF for nearly a decade (2011), until the approval of fedratinib in 2019. Fedratinib is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with PMF, post-PV MF or post-ET MF who are JAKi naïve or have been treated with ruxolitinib.

Although currently approved JAKi therapies for MF may provide benefits to patients in the areas of spleen volume reduction and symptom improvement, they are not indicated in patients with platelet counts <50 x 10^9/L (Bose, 2020), and can further exacerbate anaemia (Barraco, 2019; Verstovsek, 2022; Harrison, 2020). Pacritinib was recently approved in 2022 by the US FDA based on spleen volume reduction in MF patients with platelet counts below 50 x10^9/L. Overall, management of the clinical manifestations of MF in patients who present with or develop anaemia and/or thrombocytopenia remain ongoing challenges (Naymagon, 2017).

There is a high medical need in patients with MF who experience worsening anaemia and thrombocytopenia. Anaemia and RBC transfusion dependence constitute key adverse prognostic factors in MF that are inversely associated with quality of life and survival (Elena, 2011).

Physicians and patients must balance the control of symptoms and splenomegaly with safety risks and reduced quality of life associated with frequent RBC transfusions in patients with MF and anaemia who have limited options for MF therapy. Individualised therapies with a differentiated benefit-risk profile, including improved anaemia-specific outcomes, have the potential to address a high medical need for patients with MF and anaemia.

SI.1.3 Natural history of the indicated condition in the (untreated) population, including mortality and morbidity

Myelofibrosis can transform to acute myeloid leukaemia (AML), with transformation occurring in 8% to 23% of patients during the first decade after diagnosis (Mesa, 2005). The prognosis for overall survival of patients with MF differs depending on their baseline characteristics. Methods that use risk factors to classify the prognosis of individuals have evolved over time. Based on the DIPSS, the median survival for all patients with MF is approximately six years but is considerably worse for intermediate-2 and high-risk patients at four years and 2.25 years, respectively (Passamonti, 2010; Verstovsek, 2022). Whereas the stratification into the “intermediate-1” risk category has been reported to predict a 7.9-year median overall survival (Verstovsek, 2022; Tefferi, 2018).

Approximately 64% of MF patients are anaemic and 45% are transfusion dependent (TD) within one year of diagnosis (Tefferi, 2017). Despite treatment with currently approved JAK inhibitors, virtually all patients with MF eventually develop TD anaemia, a condition that is captured by several of the factors in the DIPSS Plus.

Anaemia and transfusion dependency are among the most important negative prognostic factors for survival in MF, having both acute and chronic complications including iron overload, and carrying twice as much impact as the other core variables in the DIPSS Plus. Severe anaemia (Hgb of <8 g/dL in women and <9 g/dL in men) in MF patients is associated with a greater than 1.5-fold increase in risk of death compared with moderate anaemia (Hgb of 8 g/dL to 9.9 g/dL in women and of 9 g/dL to 10.9 g/dL in men) (Verstovsek, 2022; Chifotides, 2022).

The pathophysiology of anaemia in patients with MF is multifactorial, most notably both an iron-restricted anaemia secondary to chronic inflammation which results from the activation of the JAK-signal transducer and activator of transcription (STAT) and ACVR1-suppressor of mothers against decapentaplegic (SMAD) pathways, as well as the progressive displacement of bone marrow by fibrosis and failure that leads to extramedullary hematopoiesis and splenomegaly. Hepcidin in chronic inflammatory disease causes an iron-restricted anaemia, characterised by decreased iron uptake from the gut, increased iron sequestration in macrophages, and reduced iron availability for erythropoiesis (Pardanani, 2013).

Besides causing disease-related morbidity, MF may additionally result in premature death from disease complications including:

- leukemic progression, that occurs in 15 - 20% of PMF patients (Parenti, 2021)
- infections (Gangat, 2011)
- thrombosis (Gangat, 2011)
- bleeding (Gangat, 2011)
- portal hypertension (Gangat, 2011)

SI.1.4 Important co-morbidities

The co-morbidity burden is an important risk factor for overall survival (Garcia-Fortes, 2022).

In an observational prospective study of the MF patient population at diagnosis, the most common co-morbidities included hypertension (42.2%), smoking (24.1%), diabetes (18.6%), dyslipidaemia (16.0%), cardiovascular disease (15.7%), renal dysfunction (8.7%), pulmonary disease (8.2%), other neoplasms (8.2%), and hepatic disease (6.2%) (Garcia-Fortes, 2022). The pathophysiology of vascular complications in patients with MPNs is complex, involving multiple factors such as inflammation, age, high blood counts, cardiovascular risk factors, and genetics. Notably, MPN patients with driver mutations have a 1.3 to 3.7 times increased rate of a new arterial and venous vascular disease compared to the general population (Frederiksen, 2019).

Additionally, due to a state of chronic inflammation and a dysregulated immune system associated with the disease, patients with MF have an increased risk of infections (Landtblom, 2021). A two-fold increased risk of serious infections, distributed over a wide range of infection types and infectious agents (bacterial/viral), has been observed in the MF patient population (Landtblom, 2021; Newberry, 2014).

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies and relevance to human usage:

Table 2 Key safety findings (from non-clinical studies)

Key Safety findings (from non-clinical studies)	Relevance to human usage
Toxicity including: **Key issues identified from acute or repeat-dose toxicity studies:** The single-dose and repeat-dose toxicity of momelotinib was evaluated in mice, rats, and dogs for treatment periods of up to 39 weeks. Principal findings consistent with the immunomodulatory effects of JAK inhibitors (JAKis) included decreases in total leukocytes, lymphocytes, eosinophils, and/or basophils, indicative of lymphoid and myeloid suppression. These findings correlated with lymphoid depletion in the spleen, lymph node, thymus, and/or gut-associated lymphoid tissue (GALT), and reduced bone marrow cellularity. Additional findings were observed in the eyes (cataracts in dogs only after 39 weeks of dosing), peripheral nerves (reversible slowing of conduction velocity in rats without histologic correlation), kidneys (tubular degeneration / regeneration), heart, and liver. Effects in peripheral nerves and cataracts were only observed in chronic studies at supratherapeutic dose levels.	In the randomised treatment (RT) pooled analysis and among the Blood and Lymphatic Disorders System Organ Class (SOC), the frequency of thrombocytopenia was very common and the frequency of neutropenia was common in subjects exposed to momelotinib, ruxolitinib and danazol. Thrombocytopenia and neutropenia are known adverse drug reactions (ADRs) of other marketed JAK inhibitors used in the treatment of MF. Thrombocytopenia and neutropenia are considered ADRs and identified risks not considered important for momelotinib. Terms in the Lymphatic Disorders SOC and anaemia are not considered ADRs or risks for momelotinib. Reports of vision blurred were common in the RT pooled analysis among the Eye Disorders SOC for momelotinib and numerically higher than ruxolitinib and danazol. Blurred vision is considered an ADR and an identified risk not considered important for momelotinib. In subjects exposed to momelotinib, reports of cataract nuclear were common, while cataract cortical, cataract subcapsular and cataract were uncommon. Cataract is not considered an ADR or risk for momelotinib. In the RT pooled analysis, peripheral neuropathy was common in subjects exposed to momelotinib, ruxolitinib and danazol. However, these events were observed at a higher rate among subjects exposed to momelotinib compared to ruxolitinib or danazol. The mechanism for peripheral neuropathy with momelotinib is unknown. Peripheral neuropathy is considered an ADR

	and an identified risk not considered important for momelotinib. Based on review of the RT pooled data in the Renal and Urinary Disorders SOC, there are no renal ADRs or risks identified for momelotinib. Momelotinib has not been studied in patients with end-stage renal disease (ESRD) or patients receiving dialysis. Based on the results of a phase 1 pharmacokinetic (PK) study of momelotinib in subjects with moderate and severe renal impairment, no dose adjustment is required for patients with renal impairment as described in the Summary of Product Characteristics (SmPC). Based on the RT pooled analysis in the Cardiac Disorders SOC, including an analysis of major adverse cardiovascular events (MACE), a causal relationship was not observed. A causal association with MACE has been identified with other JAKi's used in the treatment of chronic inflammatory disorders, hence MACE is included as an important potential risk for momelotinib. Based on the results of a phase 1 study of momelotinib in subjects with hepatic impairment, no dose adjustment is recommended for patients with mild or moderate hepatic impairment. The recommended starting dose is reduced in patients with severe hepatic impairment (Child-Pugh Class C) as described in the SmPC. Based on the RT pooled analysis, events of the Hepatobiliary disorders SOC are not considered ADRs or risks for momelotinib. Under the Investigations SOC, 'alanine transaminase increased' and 'aspartate transaminase increased' are ADRs included in the SmPC and identified risks not considered important for momelotinib.
Developmental and Reproductive Toxicology: In fertility studies, momelotinib was administered orally to male and female rats.	Momelotinib use during pregnancy and lactation has not been studied in humans and no cases of pregnancy or breastfeeding were

In males, momelotinib reduced sperm concentration and motility and reduced testes and seminal vesicle weights at doses of 25 mg/kg/day and greater (exposures 13-times the recommended dose of 200 mg daily based on combined momelotinib and M21 AUC) resulting in reduced fertility at 68 mg/kg/day. Observations in females included reduced ovarian function at 68 mg/kg/day and decreased number of pregnancies, increased pre- and post-implantation loss with total litter loss in most animals at 25 and 68 mg/kg/day. Exposures at the no adverse effect level in male and female rats at 5 mg/kg/day were approximately 3 times the recommended dose of 200 mg daily (based on combined momelotinib and M21 AUC).	reported during the momelotinib clinical development program. As per the SmPC, momelotinib is contraindicated in pregnancy and breast-feeding. Women of childbearing potential should not become pregnant during treatment and should use effective contraception during treatment and for at least 1 week after the last dose of momelotinib. Momelotinib must not be used during breast-feeding.
Genotoxicity/Carcinogenicity: Momelotinib was negative for genotoxicity in a battery of *in vitro* and *in vivo* studies, and for potential carcinogenicity testing in a transgenic mouse model. An increased incidence of testicular interstitial (Leydig) cell adenomas in rats during a two-year carcinogenicity study was considered a possible class effect since Leydig cell tumours have been associated with off-target effects of other JAK inhibitors. This effect is potentially related to inhibition of prolactin signalling pathways.	There were no findings from genetic toxicity studies that indicate a risk of genotoxicity for administration of momelotinib to patients. An increase in Leydig cell adenomas in a two-year rat carcinogenicity study was confined to the highest dose tested and considered related to inhibition of prolactin signalling pathways (Chapin, 2017). However, a human health risk is considered unlikely as human Leydig cells lack similar prolactin dependence for normal function. A causal association with secondary malignancies has been identified with other JAKi's used in the treatment of chronic inflammatory disorders. A causal association has not been observed with momelotinib and secondary malignancy is not an ADR. Secondary malignancy is included as an important potential risk for momelotinib.
General Safety Pharmacology: Momelotinib had no observed effects on the respiratory and central nervous systems of rats at the highest dose tested, with exposures (C_{max}) greater than 30-fold than that achieved in humans.	Based on the RT pooled analysis and among the Respiratory, Thoracic and Mediastinal Disorders SOC, cough was very common among subjects exposed to momelotinib and common among subjects exposed to ruxolitinib and danazol. Cough is considered

In nerve conduction studies, momelotinib at 3 µM did not inhibit voltage-gated sodium (hNav1.6, hNav1.7 and hNav1.8), potassium (hHCN2), or Shaker family potassium (Kv1.1 and Kv1.2) channels at a momelotinib concentration of 1.1 mM. This concentration was approximately three-fold the maximum free momelotinib concentration measured in the 26-week rodent toxicity study, in which a reversible, mild slowing of caudal and digital nerve conduction velocity was observed. The mechanism for the effect on nerve conduction velocity is unknown. *In vitro* and *in vivo* cardiovascular safety pharmacology studies indicate that momelotinib does not significantly affect cardiovascular parameters at clinically relevant doses. A dose of 100 mg/kg decreased arterial blood pressure (with a concurrent increase in heart rate) in dogs. At this supra-therapeutic dose in dogs, exposure (C_{max}) was approximately four-fold of that in humans. No prolongation in the QTc interval was observed.	an ADR and an identified risk not considered important for momelotinib. In the RT pooled analysis, in the Nervous System Disorders SOC, dizziness and headache were very common among subjects exposed to momelotinib. Peripheral neuropathy, paraesthesia and syncope were common among subjects exposed to momelotinib. The incidence of each of these events was higher in the subjects exposed to momelotinib compared to danazol. The incidences of dizziness, peripheral neuropathy, and paraesthesia were higher in the subjects exposed to momelotinib compared to ruxolitinib; however, the incidence of headache was higher in the subjects exposed to ruxolitinib compared to momelotinib. Syncope was only reported for momelotinib and not reported for either ruxolitinib or danazol. Dizziness and headache are known ADRs of other marketed JAK inhibitors used in the treatment of MF. Peripheral neuropathy, paraesthesia, dizziness, headache, and syncope are ADRs and identified risks not considered important for momelotinib. A thorough QT study documented no effect of momelotinib or its metabolites on corrected QT (QTc) interval using the Fridericia method (QTcF) in 48 healthy volunteers. Based on the RT pooled analysis in the Cardiac Disorders SOC, including an analysis of MACE, these events are not considered ADRs nor risks for momelotinib. Within the Vascular Disorders SOC, hypotension, haematoma and flushing were common among subjects exposed to momelotinib. The incidence for each event was higher among subjects exposed to momelotinib compared to either ruxolitinib or danazol. These vascular disorder events are ADRs and identified risks not considered important for momelotinib. A causal association with thromboembolism has been identified with other JAK inhibitors used in the treatment of chronic inflammatory

	disorders; however, a causal association has not been observed with momelotinib. Thromboembolism is included as an important potential risk for momelotinib.
Other toxicity-related information or data In *ex vivo and in vitro* studies to support occupational exposure to momelotinib during manufacturing, momelotinib drug substance was classed as corrosive to the skin, and as a severe eye irritant. At the limit of solubility, momelotinib was not phototoxic *in vitro* in the 3T3-NRU assay and momelotinib did not have skin sensitisation potential *in vivo*.	Momelotinib is formulated as a film-coated tablet intended for oral administration. There is no expectation for drug substance contact with the eyes or prolonged contact with the skin. Photosensitivity has not been observed in clinical trials to date. Phototoxicity and skin sensitisation are not expected with human use.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

As of the 17 May 2022 data-cut, momelotinib has been evaluated in 18 clinical studies, including nine studies in MF, with more than 1000 MF subjects administered oral doses as a single agent. The maximum duration of exposure to momelotinib is up to 11+ years in subjects originating from phase 1-2 studies. The subjects enrolled in these studies represent a continuum of experience with MF from early to late stages of this rare disease, including no prior JAK inhibitor treatment in Study GS-US-352-0101 (SIMPLIFY-1), prior treatment with ruxolitinib in Study GS-US-352-1214 (SIMPLIFY-2), and prior treatment with an approved JAK inhibitor (ruxolitinib and/or fedratinib) in subjects with the most advanced baseline disease characteristics in Study SRA-MMB-301 (MOMENTUM). The MOMENTUM study was conducted during the Coronavirus Disease of 2019 (COVID-19) global pandemic.

The completed clinical studies of momelotinib in subjects with PMF or post-PV/ET MF include five phase 1 and phase 2 open-label studies (CCL09101, CCL09101E, YM387II02, GSUS3521672, GSUS3521154) and three phase 3 randomised controlled studies, MOMENTUM, SIMPLIFY-1 and SIMPLIFY-2, all with available clinical study reports.

The safety analyses for this risk management plan (RMP) are based on 726 unique adults (a total of 1333.28 PY) who received at least one dose of momelotinib study drug in the following four studies:

- MOMENTUM: completed phase 3 randomised controlled study; momelotinib vs. danazol (DAN)
- SIMPLIFY-1: completed phase 3 randomised controlled study; momelotinib vs. ruxolitinib
- SIMPLIFY-2: completed phase 3 randomised controlled study; momelotinib vs. best available therapy (BAT; 88.5% ruxolitinib in BAT)
- Extended Access Protocol (XAP): ongoing open-label long-term extension safety and survival study for subjects from phase 3 studies

The 24-week RT periods by study include 195 treated subjects from MOMENTUM (130 MMB, 65 DAN), 430 treated subjects from SIMPLIFY-1 (214 MMB, 216 RUX), and 156 treated subjects from SIMPLIFY-2 (104 MMB, 52 BAT [46 RUX]).

The 24-week RT period for the integrated phase 3 studies includes 448 subjects treated with momelotinib, 262 subjects treated with ruxolitinib, and 65 subjects treated with DAN. The open-label treatment period for the integrated phase 3 studies include data from all 606 subjects who received open-label treatment with momelotinib including the subjects who crossed over to momelotinib treatment after ruxolitinib, BAT, or danazol The pooled group of momelotinib overall includes 726 subjects treated with momelotinib from the three phase 3 studies, including RT and the additional open-label treatment data. This pooled group is representative of the patient population with MF that is likely to be treated with the licensed product.

The baseline characteristics of the 3 phase 3 studies represent the spectrum of MF with intermediate-1 risk to high-risk prognostic scores and overlapping severities of symptoms, anaemia, and splenomegaly (see Table 3). The greatest proportions of subjects (approximately half) were transfusion dependent (TD) at baseline in MOMENTUM and SIMPLIFY-2 (JAK inhibitor experienced populations) and approximately two-thirds were transfusion independent (TI) in SIMPLIFY-1 (JAK inhibitor naïve population).

Table 3 Summary of Baseline Characteristics during RT Period (Safety Population)

	MOMENTUM		SIMPLIFY-1		SIMPLIFY-2	
Characteristic	momelotinib (N=130) n (%)	danazol (N=65) n (%)	momelotinib (N=214) n (%)	ruxolitinib (N=216) n (%)	momelotinib (N=104) n (%)	BAT (N=52) n (%)
Prognostic Risk Group, n (%)						
Intermediate-1	8 (6.2)	3 (4.6)	45 (21.0)	42 (19.4)	23 (22.1)	16 (30.8)
Intermediate-2	71 (54.6)	40 (61.5)	76 (35.5)	67 (31.0)	62 (59.6)	28 (53.8)
High	50 (38.5)	19 (29.2)	93 (43.5)	107 (49.5)	19 (18.3)	8 (15.4)
Not Reported	0	1 (1.5)	0	0	0	0
Baseline Transfusion Status, n (%)						
Transfusion Dependent	63 (48.5)	34 (52.3)	53 (24.8)	52 (24.1)	58 (55.8)	27 (51.9)
Transfusion Independent	17 (13.1)	10 (15.4)	146 (68.2)	151 (69.9)	32 (30.8)	19 (36.5)
Transfusion Requiring	50 (38.5)	21 (32.3)	15 (7.0)	13 (6.0)	14 (13.5)	6 (11.5)

Source: Table 14.1.3.2, Table 2.7.4.1.2.1, Table 114.1.3.1

The enrolled MF study population was largely moderately to severely anaemic (Hgb < 10 g/dL and < 8 g/dL) at baseline in MOMENTUM and SIMPLIFY-2 and the majority had at least mild anaemia based on Hgb < 12 g/dL in SIMPLIFY-1. Thrombocytopenia was also highly prevalent at baseline, likely due to underlying disease and prior JAK inhibitor treatment; proportions of subjects with baseline platelet counts < 150×10^9/L were balanced between treatments within each study and were greater in MOMENTUM and SIMPLIFY-2 compared with SIMPLIFY-1 (see Table 4).

Table 4 Summary of Baseline Haemoglobin and Baseline Platelets during RT Period (Safety Population)

	MOMENTUM		SIMPLIFY-1		SIMPLIFY-2	
Characteristic	momelotinib (N=130)	danazol (N=65)	momelotinib (N=214)	ruxolitinib (N=216)	momelotinib (N=104)	BAT (N=52)
Baseline Haemoglobin (g/dL)						
n	129	65	214	215	104	52
Mean (SD)	8.06 (1.140)	7.86 (0.825)	10.60 (2.027)	10.70 (2.248)	9.60 (1.810)	9.61 (1.524)

	MOMENTUM		SIMPLIFY-1		SIMPLIFY-2	
Characteristic	momelotinib (N=130)	danazol (N=65)	momelotinib (N=214)	ruxolitinib (N=216)	momelotinib (N=104)	BAT (N=52)
Median	8.00	8.00	10.50	10.30	9.20	9.25
Q1, Q3	7.50, 8.80	7.30, 8.40	9.10, 12.00	9.30, 11.90	8.35, 10.70	8.60, 10.05
Min, Max	3.8, 10.7	5.7, 9.7	5.6, 15.8	6.0, 19.1	5.9, 16.1	7.5, 13.7
Baseline Platelets (x10^9/L)						
n	128	64	210	210	102	49
Mean (SD)	151.7 (130.90)	130.7 (100.97)	298.5 (206.35)	303.7 (258.92)	173.2 (148.22)	127.2 (97.50)
Median	97.0	94.0	239.5	250.0	119.0	91.0
Q1, Q3	60.0, 195.5	53.5, 175.0	155.0, 376.0	146.0, 399.0	71.0, 236.0	64.0, 160.0
Min, Max	24, 733	26, 459	50, 1165	54, 2865	11, 777	27, 509
Baseline Platelets Group (x10^9/L), n (%)						
< 150	81 (62.3)	43 (66.2)	47 (22.0)	55 (25.5)	65 (62.5)	35 (67.3)
>= 150	47 (36.2)	21 (32.3)	163 (76.2)	155 (71.8)	37 (35.6)	14 (26.9)
Not Reported	2 (1.5)	1 (1.5)	4 (1.9)	6 (2.8)	2 (1.9)	3 (5.8)

Source: Table 2.7.4.1.2.1

Data from subjects originating from the phase 1 and phase 2 studies were not included in the Integrated Summary of Safety (ISS) population because of differences in their study designs, drug formulations, doses and dose regimens, treatment duration, and study eligibility. All of these studies had an open-label non-randomised study design and enrolled adult subjects with MF.

The integrated analyses of subjects treated with momelotinib overall (RT and open-label/extended treatment periods of each study, combined with XAP), allow further characterisation of the longer-term safety profile of the dosing regimen in this population. Exposure adjusted data are provided to assess cumulative toxicity, adjusted for the duration of exposure.

The mean duration of exposure for the pooled momelotinib group during the 24-week RT period was 20.7 weeks (range, 0.3-26.7 weeks), during momelotinib open-label treatment was 96.2 weeks (range, 0.3-383.9 weeks) and overall was 93.1 weeks (range, 0.3-407.7 weeks). The maximum duration of momelotinib overall exposure was 407.7 weeks (approximately 7.8 years), with 12.1% of subjects treated ≥ 60 months (≥ 5 years) as of the 17May2023 safety update data cut-off date (see Table 5).

Table 5 Duration of Exposure to Momelotinib

Exposure	Momelotinib Overall (N=726)
Duration of exposure (weeks)	
N	726
Mean (SD)	93.1 (100.74)
Median (Q1, Q3)	55.9 (22.1, 119.3)
Min, Max	0.3, 407.7

Duration of exposure	n (%)
Any Duration (> 0 weeks)	726 (100)
>= 4 weeks	690 (95.0)
>= 8 weeks	647 (89.1)
>= 12 weeks	614 (84.6)
>= 24 weeks	532 (73.3)
>= 48 weeks	410 (56.5)
>= 96 weeks	217 (29.9)
>= 36 months	134 (18.5)
>= 48 months	103 (14.2)
>= 60 months	88 (12.1)
>= 84 months	9 (1.2)
Total person years (PY)	1295.33

Source: Table 2.7.4.2.1

The mean daily dose for the pooled momelotinib group was 187.5 mg (starting dose 200 mg daily) during RT period, 175.4 mg during open-label period, and 178.8 mg overall. The mean dose intensity relative to the 200 mg starting dose of momelotinib remained above 85% throughout treatment (93.8% RT, 87.7% open-label, 89.4% overall) (see Table 6).

Table 6 Dose Relative to 200 mg Dose

Exposure	Momelotinib Overall (N=726)
Average Daily Dose (mg)	
N	726
Mean (SD)	178.8 (34.95)
Median (Q1, Q3)	194.0 (167.7, 199.8)
Min, Max	0, 494
Relative Dose Intensity (%)	
N	726
Mean (SD)	89.4 (17.47)
Median (Q1, Q3)	97.0 (83.8, 99.9)
Min, Max	0, 247

Source: Table 2.7.4.2.1

Subject characteristics (age groups, gender, race, and ethnicity) in the momelotinib overall group are summarised in Table 7 and Table 8.

Table 7 Age Group and Gender

Characteristic	Momelotinib Overall (N=726)
Age (years)	
n	726
Mean (SD)	66.4 (9.15)
Median (Q1, Q3)	68.0 (62.0, 73.0)
Min, Max	25, 92
Age group (years)	**n (%)**
18 to 64	266 (36.6)
>=65	460 (63.4)
Sex	**n (%)**
Male	423 (58.3)
Female	303 (41.7)

Source: Table 2.7.4.1.2

Table 8 Race and Ethnic Origin

Characteristic	Momelotinib Overall (N=726)
Race	**n (%)**
White	592 (81.5)
Black or African American	13 (1.8)
Asian	53 (7.3)
Other	14 (1.9)
Not Permitted	51 (7.0)
Not Reported	2 (0.3)
Ethnicity	**n (%)**
Hispanic or Latino	26 (3.6)
Not Hispanic or Latino	624 (86.0)
Not Reported	75 (10.3)

Source: Table 2.7.4.1.2

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Presented and discussed below are exclusion criteria from the pivotal clinical studies. While subjects with these conditions were excluded from study participation, subjects who developed any of these conditions after study enrolment were permitted to remain in the study and continue assessments.

Table 9 Exclusion Criteria

Criterion	Reason for exclusion	Is it considered to be included as missing information? (YES/NO)	Rationale
Active uncontrolled infection	To minimise the risk to subjects and to reduce interference with the assessment of safety and efficacy of momelotinib.	No	This exclusion was a safety precaution. It was not a stopping criterion. Infection is considered an ADR per the SmPC and serious infections are an important identified risk for momelotinib. Per the SmPC, momelotinib should not be initiated in patients with an active infection.
Known clinically significant anaemia requiring treatment with erythropoiesis stimulating agents (ESAs), due to iron, vitamin B12, or folate deficiencies, autoimmune or hereditary haemolytic anaemia, gastrointestinal bleeding, or thalassemia	To minimise the risk to subjects and to reduce interference with the assessment of safety and efficacy of momelotinib. Anaemia is a disease feature of MF, so anaemia and its treatment (e.g., transfusion) due to conditions other than MF could increase anaemia-associated risks and confound hematologic assessments.	No	Momelotinib is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with moderate to severe anaemia who have MF. Other causes of anaemia, such as anaemia due to iron, vitamin B12, or folate deficiencies, autoimmune or hereditary haemolytic anaemia, gastrointestinal bleeding, or thalassemia are not intended indications for momelotinib.

Criterion	Reason for exclusion	Is it considered to be included as missing information? (YES/NO)	Rationale
Patients with Severe Thrombocytopenia	To minimise the risk to subjects and to reduce interference with the assessment of safety and efficacy of momelotinib. Thrombocytopenia is present in approximately 15% of MF patients at diagnosis and carries an independent negative prognostic weight (Barraco, 2019; Gangat, 2011). Subjects with a platelet count <50 x 10^9/L were excluded from the SIMPLIFY-1 study due to prescribing information for the active comparator ruxolitinib, whereas the MOMENTUM study which had an active comparator of danazol (which does not have labelling restrictions for thrombocytopenia) excluded subjects with a platelet count <25 x 10^9/L). The SIMPLIFY-2 study did not exclude subjects with severe thrombocytopenia as there were no minimum platelet count requirements.	No	Thrombocytopenia is an ADR and an identified risk not considered important for momelotinib. Per the SmPC, dose interruption or reduction may be required for clinically significant worsening of thrombocytopenia.
Chronic active or acute viral hepatitis A, B, or C infection, hepatitis B or C carrier, and HIV	To minimise the risk to subjects and to reduce interference with the assessment of safety and efficacy of momelotinib. Hepatitis B virus reactivation in patients with hematologic malignancies treated with immunosuppressive therapy is a well-known risk. Approved JAK inhibitors impair dendritic cell and T cell functions, leading to reduced cytokine production that results in impaired control of silent infections and an increased risk of reactivation of viruses, such as herpes zoster	No	Infection is considered an ADR per the SmPC and serious infections are an important identified risk for momelotinib. Per the SmPC, momelotinib should not be initiated in patients with an active infection.

Criterion	Reason for exclusion	Is it considered to be included as missing information? (YES/NO)	Rationale
	and hepatitis B (Garcia-Horton, 2021; Duan, 2021).		
Presence of peripheral neuropathy ≥ Grade 2 per CTCAE	To minimise the risk to subjects and to reduce interference with the assessment of safety and efficacy of momelotinib. In a pre-clinical rat study, reversible slowing of conduction velocity in rats without histologic correlation was observed at supratherapeutic dose levels. Peripheral neuropathy was reported in Phase 2 clinical trials with momelotinib. Subsequently, subjects with moderate to severe neuropathy were excluded from phase 3 clinical trials with momelotinib to mitigate risk of worsened peripheral neuropathy and avoid confounding the safety analysis of the study results.	No	Per the SmPC, peripheral neuropathy is an ADR and an identified risk not considered important for momelotinib.
Use of Breast cancer resistance protein (BCRP) substrates including rosuvastatin	To minimise the risk to subjects and to reduce interference with the assessment of safety and efficacy of momelotinib. Momelotinib is an inhibitor of BCRP *in vitro*. Rosuvastatin is a known BCRP substrate. Coadministration of a single dose of rosuvastatin at 10 mg (a BRCP substrate) with multiple doses of momelotinib (200 mg once daily) increased rosuvastatin C_{max} by 3.2-fold and AUC by 2.7-fold which may increase the risk of adverse reactions of rosuvastatin. T_{max} and $t_{1/2}$ of rosuvastatin remained unchanged. Momelotinib may inhibit P-gp in the gut and increase exposure to P-gp substrates.	No	Per the SmPC, patients should be monitored for adverse reactions when BCRP substrates are co-administered with momelotinib. Caution is advised when administering momelotinib with P-gp substrates with a narrow therapeutic index. Caution is advised when administering momelotinib with sensitive substrates of OCT1, MATE1 and MATE2-K (e.g., metformin).

Criterion	Reason for exclusion	Is it considered to be included as missing information? (YES/NO)	Rationale
	Momelotinib may inhibit organic cation transporter (OCT)1. The active metabolite of momelotinib, M21, may inhibit multidrug and toxic compound extrusion transporter (MATE)1. Momelotinib and M21 have not been evaluated for MATE2-K inhibition.		
Pregnancy and Lactation	There are no data from the use of momelotinib in pregnant women. Studies in animals have shown embryo-foetal toxicity at exposures was lower than human exposure at the recommended dose (see section 5.3). Based on its mechanism of action, momelotinib may cause foetal harm. Momelotinib belongs to a class of drugs, JAK inhibitors, that has been shown to cause embryo-foetal mortality and teratogenicity in pregnant rats and rabbits at clinically relevant exposures. There are no data on the presence of momelotinib in human milk. Momelotinib was present in rat pups following nursing from treated dams with adverse events in the offspring (see section 5.3). A risk to the breast-fed child cannot be excluded.	No	Per the SmPC, momelotinib is contraindicated in pregnancy and breast-feeding. Women of childbearing potential should not become pregnant during treatment and should use effective contraception during treatment and for at least 1 week after the last dose of momelotinib. If the patient becomes pregnant while taking momelotinib, the patient should discontinue treatment and be advised of the potential hazard to the foetus. Momelotinib must not be used during breast-feeding.
Patients under 18 years of age	No data are available for this population.	No	Momelotinib is only intended for use in adults. The median age at diagnosis of PMF is 70 years (Garmezy, 2021) and rarely diagnosed in the paediatric population (Mughal, 2019). Per the SmPC, the safety and efficacy of momelotinib in children and adolescents less than 18 years of age have not been established. No data are available.

SIV.2 Limitations to detect adverse reactions in clinical trial development program

The clinical development program is unlikely to detect certain types of ADRs such as rare ADRs, ADRs with a long latency, or those caused by prolonged or cumulative exposure.

The momelotinib clinical development program had inherent limitations to detect ADRs as outlined below. MF patients have a median survival of approximately six years, which decreases to 2.25 and 4 years for the high risk and intermediate-2 patients, respectively (Verstovsek, 2022).

Table 10 Limitations to detect adverse reactions in clinical trial development program

Ability to detect adverse reactions	Limitation of trial program	Discussion of implications for target population
Which are rare	726 subjects were exposed to momelotinib in the phase 3 studies, MOMENTUM, SIMPLIFY-1, and SIMPLIFY-2, and in XAP.	The clinical trials MOMENTUM, SIMPLIFY-1, SIMPLIFY-2, and XAP, included 1295.33 PY of exposure. Based on available data and duration of exposure, there is no theoretical associated risk to cumulative exposure to momelotinib.
Due to prolonged exposure	In the integrated analysis of the three phase 3 studies (MOMENTUM, SIMPLIFY-1 and SIMPLIFY-2), the maximum duration of momelotinib overall exposure was approximately 7.8 years, with 12.1% (n=88) and 1.2% (n=9) of subjects treated ≥ 60 months and ≥ 84 months, respectively, as of the safety update data cut-off date of 17 May 2022.	Momelotinib has been administered in more than 1400 subjects, including more than 1000 MF patients, and has a total exposure of 1295.33 person-years. With a median survival of approximately six years for patients with MF, long term or chronic use would be limited. Based on available data and duration of exposure, there is no theoretical associated risk to prolonged exposure to momelotinib
Due to cumulative effects	In the integrated analysis of the three phase 3 studies (MOMENTUM, SIMPLIFY-1 and SIMPLIFY-2), the maximum duration of momelotinib overall exposure was approximately 7.8 years, with 12.1% (n=88) and	Momelotinib has been administered in more than 1400 subjects, including more than 1000 MF patients, and has a total exposure of 1295.33 person-years.

	1.2% (n=9) of subjects treated ≥ 60 months and ≥ 84 months, respectively, as of the safety update data cut-off date.	Based on available data and duration of exposure, there is no theoretical associated risk to cumulative exposure to momelotinib.
Which have a long latency	Subjects in the MOMENTUM, SIMPLIFY-1 and SIMPLIFY-2 studies were evaluated at periods ranging from ≤ 6 months (616 subjects) to greater than three years (317 subjects).	Momelotinib has been administered in more than 1400 subjects, including more than 1000 MF patients, and has a total exposure of 1295.33 person-years. Based on available data and duration of exposure, there is no theoretical associated risk of ADRs with a long latency to momelotinib.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development program

Table 11 Exposure of special populations included or not in clinical trial development program

Type of special population	Exposure
Pregnant women	Pregnant women were not included in the momelotinib clinical development program.
Breast-feeding women	Breast-feeding women were not included in the momelotinib clinical development program.
Patients with relevant comorbidities: • Patients with severe hepatic impairment or severe renal impairment (also based on laboratory results) were excluded • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Hepatic impairment: Ten non-MF subjects with moderate hepatic impairment (Child-Pugh-Turcotte (CPT) score 7-9) and ten non-MF subjects with severe hepatic impairment (CPT score 10-15) were included in the momelotinib clinical development program. Renal impairment: Ten non-MF subjects with moderate renal impairment (eGFR 30-59 mL/min/1.73m2) and ten non-MF subjects with severe renal impairment (eGFR 15-29 mL/min/1.73m2), were included in the momelotinib clinical development program. Cardiovascular impairment: Patients with unstable angina pectoris, symptomatic congestive heart failure or uncontrolled cardiac arrhythmia within six months

Type of special population	Exposure
	prior to randomisation, or with progressive thrombosis were not included in the momelotinib clinical development program. Immunocompromised: Patients with a prior or concurrent malignancy and patients with a positive HIV status were not included in the momelotinib clinical development program. Disease severity different from inclusion criteria: Patients with low-grade MF were not included in the momelotinib clinical development program.
Population with relevant different ethnic origin	No ethnicities were excluded from the momelotinib clinical development program. See Table 8 (Ethnic origin) in PART II: Module SIII.
Subpopulations carrying relevant genetic polymorphisms	Genetic analyses are ongoing and there are no known relevant genetic polymorphisms in the momelotinib clinical development program.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation exposure

There are no data for this section as momelotinib has not yet been marketed in any country.

SV.1.1 Method used to calculate exposure

Not applicable.

SV.1.2 Exposure

Not applicable.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

Momelotinib does not have a known potential for misuse for illegal purposes.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMP submission

Identification of safety concerns was based on analysis of data from the randomised treatment group of the integrated safety analysis and on risks reported for other JAK inhibitors used in chronic inflammatory disorders.

SVII 1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

Table 12 Risks with minimal impact on patients

System Organ Class (SOC)	Risk
Nervous system disorders	Dizziness Headache Paraesthesia
Ear and labyrinth disorders	Vertigo
Eye disorders	Vision blurred
Vascular disorders	Flushing
Respiratory, thoracic and mediastinal disorders	Cough
Gastrointestinal disorders	Constipation
Musculoskeletal and connective tissue disorders	Arthralgia Pain in extremity
General disorders and administration site conditions	Asthenia Fatigue

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorised):

Table 13 Known risks that require no further characterisation and are adequately communicated in the Product Information

System Organ Class (SOC)	Risk
Nervous system disorders	Peripheral neuropathy
Gastrointestinal disorders	Diarrhoea Nausea Abdominal pain Vomiting

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

Table 14 Adverse reactions with a low frequency and considered acceptable in relation to the severity of the indication treated

System Organ Class (SOC)	Risk
Investigations	Alanine transaminase increased Aspartate transaminase increased
Blood and lymphatic system disorders	Neutropenia
Metabolism and nutrition disorders	Vitamin B1 deficiency
Nervous system disorders	Syncope
Vascular disorders	Haematoma Hypotension
General disorders and administration site conditions	Pyrexia
Injury, poisoning and procedural complications	Contusion

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risks

Important Identified Risk: Serious Infections

A two-fold increased risk of serious infections, distributed over a wide range of infection types and infectious agents (bacterial/viral), has been observed in the MF patient population (Landtblom, 2021; Newberry, 2014). The risk of infections is primarily related to a state of chronic inflammation and a dysregulated immune system associated with MF (Landtblom, 2021). The JAK-STAT pathway has a critical role in the development and function of immune cells. Loss-of-function mutations in JAKs or STATs are associated with immune deficiencies or enhanced susceptibility to infections (Klein, 2021). The suppressive effects of JAK inhibitors on immune responses may increase the risk of serious infections.

In the pooled analysis, the frequency of serious infections during RT was 9.8% for momelotinib, 4.6% for ruxolitinib, and 16.9% for danazol. The risk of serious infections is consistent with clinical experience with other marketed JAK inhibitors, as reflected in the corresponding relevant warnings and precautions in the product information for these products.

Although the frequency of serious infections during RT was highest in the danazol group, serious infections were reported more frequently in the momelotinib group compared to the ruxolitinib group.

The risk of serious infections is considered an important identified risk for momelotinib.

Risk-Benefit impact:

Infections can be serious medical conditions and may also be life-threatening or fatal.

There are instructions in the Product Information to not initiate treatment with momelotinib in patients with an active infection and to observe patients receiving momelotinib for signs and symptoms of infection and to initiate appropriate treatment promptly.

Important Potential Risk: Major Adverse Cardiovascular Events (MACE)

The potential risk of MACE is based on the clinical experience of other JAK inhibitors used in chronic inflammatory indications. Although the exact mechanism for increased risk of MACE is not fully understood, several factors may contribute to the development of MACE. Patients treated with JAK inhibitors may experience elevated levels of total cholesterol, LDL cholesterol, and triglycerides, which could contribute to the development of MACE (Czókolyová, 2022). Additionally, the JAK-STAT pathway has been implicated in the regulation of platelet activation and aggregation, and its inhibition could lead to an imbalance that predisposes patients to MACE (Kotyla, 2021).

Myelofibrosis can be associated with an increased risk of MACE due to disease characteristics including abnormal production of platelets which can facilitate the formation of clots, chronic inflammation which can contribute to atherosclerosis, and anaemia which can increase the heart's workload. (Leiva, 2022).

In the momelotinib clinical development program during the RT period, the frequency of MACE was 3.1% (momelotinib), 2.7% (ruxolitinib) and 6.2% (danazol).

Risk-Benefit impact:

The mechanism for the risk of MACE is unknown. This risk does not impact the risk-benefit of momelotinib in treating MF, a condition with equally serious outcomes, when used in line with recommendations in the SmPC.

Important Potential Risk: Thromboembolism

The potential risk of thromboembolism (TE) is based on the clinical experience of other JAK inhibitors used in the treatment of chronic inflammatory conditions. The mechanism for thromboembolism in other JAK inhibitors is unknown. There is an increased risk of venous thromboembolism in MF, however, the exact mechanism is not understood (Saliba, 2020).

In the momelotinib clinical development program during the RT period, the frequency of TE was 3.3% (momelotinib), 0.8% (ruxolitinib), and 9.2% (danazol).

Risk-Benefit impact:

Thromboembolism may be life-threatening or fatal depending on the anatomical location and rapidity of treatment.

The mechanism for thromboembolism is unknown with other JAKis for the treatment of chronic inflammatory conditions. This risk is not expected to impact the risk-benefit of momelotinib in treating MF, a condition with potentially serious outcomes.

Important Potential Risk: Secondary Malignancies

The potential risk of secondary malignancies is based on the clinical experience of other JAK inhibitors used in the treatment of chronic inflammatory conditions. The mechanism for secondary malignancies is unclear but may be related to the immunomodulating mechanism of JAK inhibitors (Polverelli, 2021).

In the momelotinib clinical development program during the RT period, the frequency of overall malignancies was low in the momelotinib group (momelotinib 5.6%, ruxolitinib 5.7%, danazol 7.7%). AML/malignant transformation and non-melanoma skin cancer occurred in 3.0% and 5.5%, respectively in the overall momelotinib group.

Risk-Benefit impact:

Based on the information available to date, it is not expected that this potential risk impacts the risk-benefit of momelotinib in treating MF, when used in line with recommendations in the SmPC.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

Important Identified Risks

Important Identified Risk: Serious Infections

Potential mechanism:

JAK inhibitors are known to inhibit regulatory T cells (Tregs), dendritic cells and natural killer (NK) cells, as well as cause off-target effects of JAK1-mediated cytokine inhibition. These mechanisms may, individually or collectively, contribute to an increased risk of infections. However, the high incidence of background infections due to MF-related immunocompromise makes the effect of momelotinib difficult to assess.

Evidence source(s) and strength of evidence:

In animal studies, haematologic findings at all dose levels included dose-dependent decreases in white blood cell counts.

In the integrated analysis of safety, the frequency of serious infections during RT was higher for momelotinib compared to ruxolitinib, however, the frequency of serious infections was highest in the danazol group. An imbalance in serious COVID-19 events in the momelotinib group compared to the danazol group was noted in the MOMENTUM study. The risk of serious infections is considered an important identified risk for momelotinib.

Characterisation of the risk:

Characterisation of this risk mainly derives from three phase 3 randomised trials (MOMENTUM, SIMPLIFY-1, SIMPLIFY-2) of 448 subjects treated with momelotinib during the RT phase, and 726 subjects in the momelotinib overall group, which also included XAP.

Given the common association with neutropenia, and due to a state of chronic inflammation and a dysregulated immune system associated with the disease, patients with MF are at a significantly higher risk of severe infections compared to population controls (Landtblom, 2021). A two-fold increased risk of serious infections, distributed over a wide range of infection types and infectious agents (bacterial/viral), has been observed in this population (Landtblom, 2021; Newberry, 2014).

In the pooled analysis of subjects during RT, the Infections and Infestations SOC frequencies during RT were 39.7% momelotinib, 42.7% ruxolitinib, and 35.4% danazol. The danazol group had the highest proportion of subjects with grade ≥ 3 infections (10.5% momelotinib, 4.2% ruxolitinib, 16.9% danazol) and serious infections (9.8% momelotinib, 4.6% ruxolitinib, 16.9% danazol). The frequency of fatal infections was 2.2% momelotinib, 1.1% ruxolitinib, and 0

danazol. The most reported serious infection across groups was pneumonia (2.2% momelotinib, 1.1% ruxolitinib, 9.2% danazol).

Opportunistic Infections

Adverse events of opportunistic infections were retrospectively identified after review of all PTs reported in the Infections and Infestations SOC.

Serious opportunistic infections were reported for the pooled momelotinib group in 0.4% of subjects during RT, 1.0% open-label, and 1.1% overall. Bronchopulmonary aspergillosis was the only serious opportunistic infection reported in more than one subject and these events occurred in the momelotinib group (0 RT, 0.3% open-label, 0.3% overall). There was one serious report of herpes zoster which occurred in the ruxolitinib group. None of the identified serious opportunistic infections were reported in the danazol group.

Table 15 Integrated Overall Summary of the Infections and Infestations SOC and Subgroups of Serious Infections and Serious Opportunistic Infections by Study Period and Treatment (Safety Population)

	Randomised Treatment			Open-Label	Overall
Important Event, n (%)	momelotinib (N = 448)	ruxolitinib (N = 262)	danazol (N = 65)	momelotinib (N = 606)	momelotinib (N = 726)
Infections and Infestations	178 (39.7%)	112 (42.7%)	23 (35.4%)	319 (52.6%)	418 (57.6%)
Serious Infections	44 (9.8%)	12 (4.6%)	11 (16.9%)	119 (19.6%)	155 (21.3%)
Serious Opportunistic Infections	2 (0.4%)	1 (0.4%)	0	6 (1.0%)	8 (1.1%)

Source: Table 2.7.4.2.2; Table 2.7.4.2.3.15

Shading indicates adverse events ≥ 5 percentage points higher than 1 or more comparator group during randomised treatment.

COVID-19 Infections
Two momelotinib studies (MOMENTUM and XAP, in part) were conducted during the COVID-19 pandemic.

Summary
As of 01 November 2022 in the MOMENTUM study, COVID-19 events were reported for 26 subjects, including 14 during RT and 12 during momelotinib open-label treatment. During RT, 14 of 195 subjects (7.2%) had COVID-19 events with preferred terms of COVID-19, COVID-19 pneumonia, and asymptomatic COVID-19, including 13 subjects (10%) in the momelotinib group and one subject (1.5%) in the danazol group. In the momelotinib group, 6 subjects had serious COVID-19 events, all fatal, and 7 subjects had nonserious COVID-19 adverse events. Four subjects from the momelotinib open-label group had a serious COVID-19 event that recovered or resolved with sequelae, and there were no new fatal events.

None of the 6 subjects with fatal events were vaccinated against COVID-19 and all except one subject were from Europe. These fatal events occurred between August 2020 and March 2021, before broad availability of COVID-19 vaccines and coincided with the original severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) strain and alpha (B.1.1.7) variant lineage waves of the pandemic. None of the 12 COVID-19 cases which occurred between November 2020 and August 2022 during the MOMENTUM open-label period had a fatal outcome, and 11 of these 12 subjects had been vaccinated with at least 1 dose of COVID-19 vaccine. Cumulatively during long term momelotinib treatment in XAP, 22 subjects (9.8%) had COVID-19 events, including eight subjects (3.6%) with serious adverse events and 14 subjects (6.3%) with nonserious adverse events. Three subjects (1.3%) had fatal events in the XAP, 2 of which occurred in December 2021, while the other 2 events occurred in June 2022.

Table 16 Cumulative Summary of Treatment-Emergent Adverse Events of COVID-19 Infection and Deaths in the MOMENTUM and Ongoing XAP Studies

	MOMENTUM			XAP [1]
COVID-19 Event, n (%)	**MMB RT Period N=130**	**DAN RT Period N=65**	**MMB OL/ET Period N=134**	**MMB N=224**
Infection TEAE	13 (10.0%)	1 (1.5%)	12 (9.0%) [2]	22 (9.8%)
Serious TEAE	6 (4.6%)	0	4 (3.0%) [3]	8 (3.6%)
Grade 5 TEAE	6 (4.6%)	0	0	3 (1.3%)

The data cutoff date was 01 Nov 2022.
COVID-19 preferred terms include COVID-19, COVID-19 pneumonia and asymptomatic COVID-19.
[1] XAP includes subjects from MOMENTUM, SIMPLIFY-1, SIMPLIFY-2 and the MMB phase 2 clinical study GS-US-352-1154.
[2] 11 MMB→MMB, 1 DAN→MMB.
[3] All 4 subjects MMB→MMB
DAN, danazol; MMB, momelotinib; OL/ET, open-label/extended treatment; RT, randomized treatment
Source: Internal data

The majority of subjects with adverse events of COVID-19 were from European countries, consistent with the highest study enrolment in that region, and had one or more additional risk

factor (e.g., age > 65 years, diabetes, hypertension) or other predisposing risk factors for poor outcome with COVID-19. Acquired immunity following COVID-19 vaccination may be reduced in patients with MF, including those treated with JAK inhibitors (Chowdhury, 2021; Fiorino, 2021; Guglielmelli, 2021).

Risk factors and risk groups:

Immunocompromised individuals, including MF patients and the elderly population are at risk for infections, including COVID-19 infections (Barbui, 2021). A two-fold increased risk of serious infections has been observed in the MF patient population (Landtblom, 2021; Newberry, 2014).

Preventability:

All MF patients should be assessed holistically for infection risk, as is the case for all immunocompromised individuals. Momelotinib should not be initiated in patients with active infections. Physicians are guided to carefully observe patients receiving momelotinib for signs and symptoms of infections in the SmPC. MF patients should be offered vaccines and medications, including those licensed for SARS-CoV-2 according to local guidelines. These measures represent standard practice for MF, and additional risk mitigation measures are not required for momelotinib treatment.

Impact on the risk-benefit balance of the product:

No significant impact is expected, compared with the overall benefit-risk balance of momelotinib use in MF patients.

Public health impact:

There is no anticipated public health concern.

Important Potential Risks

Important Potential Risk: Major Adverse Cardiovascular Events (MACE)

Potential mechanisms:

The mechanism(s) for this risk is not clear.

Evidence source(s) and strength of evidence:

There is no established relationship between momelotinib and major adverse cardiovascular events (MACE). MACE is an important potential risk due to data seen with another JAKi (tofacitinib) in patients of elevated cardiovascular risk with rheumatoid arthritis (RA). Momelotinib is not indicated for use in the RA population.

Characterisation of the risk:

Cardiovascular comorbidities are common in MF (Newberry, 2014).

Adverse events of MACE were based on 16 preferred terms including acute myocardial infarction, myocardial infarction, cerebellar stroke, cerebral infarction, cerebral ischemia, cerebrovascular accident, cardiac failure, cardiac failure congestive, cardiogenic shock, coronary artery disease, coronary artery stenosis, haemorrhagic stroke, subarachnoid haemorrhage, aortic dissection, ischemic stroke, and lacunar infarction. These preferred terms were selected based on the FDA guidance for MACE endpoints in clinical trials (Hicks, 2018).

Adverse events of MACE were reported for the pooled MMB group in 3.1% of subjects during RT, 8.7% open-label, and 8.8% overall. The worst severity grade for the largest proportion of subjects was grade ≥3 (2.7% RT, 7.1% open-label, 7.3% overall) and most had events considered serious (2.9% RT, 6.8% open-label, 7.3% overall).

Cardiac failure was the most commonly reported MACE (1.1% RT, 3.0% open-label, 3.0% overall) and the most commonly reported serious MACE (1.1% RT, 2.0% open-label, 2.3% overall) (Table 2.7.4.2.3.15, SN0001 Table 2.7.4.2.3.15).

The proportion of subjects who discontinued study drug due to adverse events of MACE was low (0.7% MMB, 1.7% open-label, 1.8% overall).

After adjusting for exposure, the event rate for MACE during RT of 9.2 events per 100 personyears decreased to 5.8 events per 100 personyears during open-label treatment, suggesting no cumulative toxicity of treatment with longer exposure.

In the by-study analysis, across the MOMENTUM, SIMPLIFY-1, and SIMPLIFY-2 studies during RT, adverse events of MACE were 1.5% momelotinib, 6.2% danazol; 3.7% momelotinib, 2.3% ruxolitinib; and 3.8% momelotinib, 3.8% BAT, respectively.

During RT, adverse events of MACE were reported for 3.1% momelotinib, 2.7% ruxolitinib, and 6.2% danazol; most events were grade ≥ 3 (2.7% momelotinib, 1.5% ruxolitinib, 6.2% danazol) and serious (2.9% momelotinib, 1.1% ruxolitinib, 6.2% danazol). Adverse events of MACE were fatal in 0.4% momelotinib and 4.6% danazol. The most reported serious MACE across groups was cardiac failure (1.1% momelotinib, 0.8% ruxolitinib, 0 danazol).

During RT, no category of MACE was ≥ 5 percentage points higher for momelotinib over ruxolitinib or danazol or for ruxolitinib over momelotinib or danazol. Serious adverse events of MACE were ≥ 5 percentage points higher for danazol over ruxolitinib.
Adverse events of MACE led to study drug discontinuation in 0.7% momelotinib, 0 ruxolitinib, and 3.1% danazol.

After adjusting for exposure, event rates for MACE during RT were 9.2 events per 100 personyears for momelotinib, 7.7 events per 100 personyears for ruxolitinib, and 25.7 events per 100 personyears for danazol. Event rates for MACE decreased from

momelotinib RT to open-label treatment (from 9.2 to 5.6 events per 100 personyears), suggesting no cumulative toxicity of treatment.

Table 17 By-Study Overall Summary of Adverse Events of MACE During Randomised Treatment (Safety Population)

	MOMENTUM		SIMPLIFY-1		SIMPLIFY-2	
Important Event, n (%)	momelotinib (N = 130)	danazol (N = 65)	momelotinib (N = 214)	ruxolitinib (N = 216)	momelotinib (N = 104)	BAT (N = 52)
MACE	2 (1.5%)	4 (6.2%)	8 (3.7%)	5 (2.3%)	4 (3.8%)	2 (3.8%)

Source: Table 2.7.4.2.3.13.1

BAT, best available therapy, MACE, major adverse cardiovascular events.

Table 18 Integrated Summary of Adverse Events of MACE by Study Period and Treatment (Safety Population)

	Randomised Treatment			Open-Label	Overall
Important Event, n (%)	momelotinib (N = 448)	ruxolitinib (N = 262)	danazol (N = 65)	momelotinib (N = 606)	momelotinib (N = 726)
MACE	14 (3.1%)	7 (2.7%)	4 (6.2%)	53 (8.7%)	64 (8.8%)

Source: Table 2.7.4.2.2

MACE, major adverse cardiovascular events.

Table 19 Integrated Summary of Adverse Events of MACE by Study Period and Severity Grade (Safety Population)

Adverse Event Category	Randomized (N = 448)	Open-Label (N = 606)	Overall (N = 726)
Any adverse event, n (%)	14 (3.1%)	53 (8.7%)	64 (8.8%)
Worst severity grade			
Grade 1	0	5 (0.8%)	5 (0.7%)
Grade 2	2 (0.4%)	5 (0.8%)	6 (0.8%)
Grade 3	9 (2.0%)	28 (4.6%)	35 (4.8%)
Grade 4	1 (0.2%)	5 (0.8%)	6 (0.8%)
Serious	13 (2.9%)	41 (6.8%)	53 (7.3%)
Grade ≥ 3	12 (2.7%)	43 (7.1%)	53 (7.3%)
Fatal	2 (0.4%)	10 (1.7%)	12 (1.7%)
Leading to study drug discontinuation	3 (0.7%)	10 (1.7%)	13 (1.8%)

Source: Table 2.7.4.2.3.9, Table 2.7.4.2.3.13, Table 2.7.4.2.3.14, Table 2.7.4.2.3.15, Table 2.7.4.2.3.16, Table 2.7.4.2.18 and Module 2.7.4, Table 51 (SN0001)

The momelotinib RT group was pooled from MOMENTUM, SIMPLIFY1, and SIMPLIFY2

Risk factors and risk groups:

Certain JAK inhibitors are associated with MACE in chronic inflammatory disorders, such as RA (Ytterberg, 2022). The patient population for MF is different in terms of background risks, co-morbidities, and life expectancy compared to immune-mediated inflammatory disorders.

Although the exact mechanism for increased risk of MACE is not fully understood, there are several factors that may contribute to the development of MACE.

Preventability:

Preventability of MACE in MF patients treated with momelotinib is currently unknown. Prior to initiating or continuing therapy with momelotinib, the benefits and risks for the individual patient should be considered, particularly in patients 65 years of age and older, patients who are current or past long-time smokers, and patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors.

Impact on the risk-benefit balance of the product:

There is insufficient evidence to suggest a causal association between momelotinib and MACE and the exact mechanism for MACE is not fully understood. GSK will monitor reported events of MACE in the context of exposure to momelotinib through routine pharmacovigilance activities. The SmPC will guide clinicians on considering the benefit-risk balance in patients with risk factors of developing MACE. In the context of the proposed risk management approach, it is considered the overall benefit-risk balance of momelotinib use in MF patients remains favourable.

Public health impact:

There is no anticipated public health concern.

Important Potential Risk: Thromboembolism

Potential mechanisms:

The mechanism(s) for this risk is not clear.

Evidence source(s) and strength of evidence:

JAK inhibitors have been associated with an increased risk of thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis (compared to those treated with TNF blockers) in patients with RA.

There is not an established relationship between momelotinib and thrombosis based on review of data in the momelotinib clinical development program. Thrombosis is considered an important potential risk due to the association of thrombosis with JAKi in patients with RA. Momelotinib is not indicated for use in the RA population.

Characterisation of the risk:

Patients with MPNs, especially PV and ET but also PMF, are at higher risk of arterial and venous thrombosis compared to the general population (Kelliher 2021).
Adverse events of thromboembolism were summarised based on the SMQ, Embolic and Thrombotic Events.

Adverse events of thromboembolism were reported for the pooled MMB group in 3.3% of subjects during RT, 9.6% open-label, and 9.6% overall. The most reported adverse events of thromboembolism (≥ 1% overall) were the following:

- Acute myocardial infarction: 0.9% RT, 1.0% open-label, 1.4% overall
- Splenic infarction: 0.7% RT, 1.3% open-label, 1.4% overall
- Pulmonary embolism: 0.2% RT, 1.3% open-label, 1.2% overall
- Deep vein thrombosis: 0.4% RT, 1.0% open-label, 1.1% overall.

Among subjects with adverse events of thromboembolism, or approximately half of subjects experienced grade ≥3 event during RT and for most subjects during open-label treatment and overall (1.6% RT, 6.1% open-label, 6.1% overall).
The proportion of subjects with SAEs of thromboembolism was 1.8% during RT, 6.8% during open-label treatment, and 6.6% overall. The most reported serious adverse events of thromboembolism (≥ 1% overall) were the following (Table 2.7.4.2.3.15, SN0001 Table 2.7.4.2.3.15):

- Acute myocardial infarction: 0.7% RT, 0.8% open-label, 1.1% overall
- Splenic infarction: 0.4% RT, 1.2% open-label, 1.1% overall
- Pulmonary embolism: 0.2% RT, 1.2% open-label, 1.1% overall

Fatal thromboembolism events were reported in 0.4% of subjects during RT, 1.0% open-label, and 1.1% overall.

The proportion of subjects who discontinued study drug due to adverse events of thromboembolism was 0.4% during RT, 0.8% during open-label treatment, and 1.0% overall. After adjusting for exposure, the event rate for thromboembolism during RT of 11.9 events per 100 person-years decreased to 6.7 events per 100 person-years during open-label treatment, suggesting no cumulative toxicity of treatment with longer exposure (Table 2.7.4.2.3.13, SN0001 Table 2.7.4.2.3.13).

In the by-study analysis, across the MOMENTUM, SIMPLIFY-1, and SIMPLIFY-2 studies during RT, AEs of thromboembolism were 3.8% momelotinib, 9.2% danazol; 3.7% momelotinib, 0.9% ruxolitinib; and 1.9% momelotinib, 0% BAT, respectively.
In the integrated analysis of 24 weeks of treatment with momelotinib, adverse events of thromboembolism were reported for 3.3% momelotinib, 0.8% ruxolitinib, and 9.2% danazol.

Adverse events of thromboembolism were grade ≥3 in 1.6% momelotinib, 0 ruxolitinib, and 6.2% danazol; serious in 1.8% momelotinib, 0 ruxolitinib, and 6.2% danazol; and fatal in 0.4%

momelotinib, 0 ruxolitinib, and 1.5% danazol. Adverse events of thromboembolism led to study drug discontinuation in 0.4% momelotinib, 0 ruxolitinib, and 1.5% danazol.

After adjusting for exposure, event-rates for thromboembolism decreased from 11.9 events per person-years during RT to 6.5 events per person-years during momelotinib open-label treatment, suggesting no cumulative toxicity of treatment.

In the momelotinib overall group, there were 2 (0.3%) reported events of treatment-related pulmonary embolism, both of which had an outcome of recovered.

Table 20 By-Study Overall Summary of Adverse Events of Thromboembolism During Randomised Treatment (Safety Population)

	MOMENTUM		SIMPLIFY-1		SIMPLIFY-2	
Important Event, n (%)	momelotinib (N = 130)	danazol (N = 65)	momelotinib (N = 214)	ruxolitinib (N = 216)	momelotinib (N = 104)	BAT (N = 52)
Thromboembolism	5 (3.8%)	6 (9.2%)	8 (3.7%)	2 (0.9%)	2 (1.9%)	0

Source: Table 2.7.4.2.3.13.1

Shading indicates adverse events ≥ 5 percentage points higher than the comparator of each study.

BAT, best available therapy.

Table 21 Integrated Summary of Adverse Events of Thromboembolism by Study Period and Treatment (Safety Population)

	Randomised Treatment			Open-Label	Overall
Important Event, n (%)	momelotinib (N = 448)	ruxolitinib (N = 262)	danazol (N = 65)	momelotinib (N = 606)	momelotinib (N = 726)
Thromboembolism	15 (3.3%)	2 (0.8%)	6 (9.2%)	58 (9.6%)	70 (9.6%)

Source: Table 2.7.4.2.2

Shading indicates adverse events ≥ 5 percentage points higher than 1 or more comparator group during randomised treatment.

Table 22 Integrated Summary of Adverse Events of Thromboembolism by Study Period, Treatment, and Severity Grade (Safety Population)

Adverse Event Category Thromboembolism	Randomised Treatment			Open-Label	Overall
	momelotinib (N = 448)	ruxolitinib (N = 262)	danazol (N = 65)	momelotinib (N = 606)	momelotinib (N = 726)
Any adverse event, n (%)	15 (3.3%)	2 (0.8%)	6 (9.2%)	58 (9.6%)	70 (9.6%)
Worst severity grade					
Grade 1	2 (0.4%)	1 (0.4%)	1 (1.5%)	4 (0.7%)	5 (0.7%)
Grade 2	5 (1.1%)	1 (0.4%)	0	17 (2.8)	20 (2.8)
Grade 3	3 (0.7%)	0	3 (4.6%)	25 (4.1)	28 (3.9)
Grade 4	2 (0.4%)	0	0	6 (1.0)	8 (1.1)
Serious	8 (1.8%)	0	4 (6.2%)	41 (6.8%)	48 (6.6%)
Grade ≥ 3	7 (1.6%)	0	4 (6.2%)	37 (6.1%)	44 (6.1%)
Fatal	2 (0.4%)	0	1 (1.5%)	6 (1.0%)	8 (1.1%)
Leading to study drug discontinuation	2 (0.4%)	0	1 (1.5%)	5(0.8%)	7 (1.0%)

Source: Table 2.7.4.2.3.9, Table 2.7.4.2.3.13, Table 2.7.4.2.3.14, Table 2.7.4.2.3.15, Table 2.7.4.2.3.16, Table 2.7.4.2.18

Shading indicates adverse events ≥ 5 percentage points higher than 1 or more comparator group during randomised treatment (excluding severity grades 1, 2).

Risk factors and risk groups:

Myelofibrosis is associated with an elevated risk of thromboembolism (Saliba, 2020).

Preventability:

Thrombosis is difficult to identify before a patient exhibits signs and symptoms and, is largely not preventable. In patients with known venous thromboembolism (VTE) risk factors other than cardiovascular or malignancy risk factors, momelotinib should be used with caution. VTE risk factors other than cardiovascular or malignancy risk factors include previous VTE, patients undergoing major surgery, immobilisation, use of combined hormonal contraceptives or hormone replacement therapy, and inherited coagulation disorder.

Patients should be re-evaluated periodically during Omjjara treatment to assess for changes in VTE risk. Promptly evaluate patients with signs and symptoms of VTE and discontinue Omjjara in patients with suspected VTE, regardless of dose.

Impact on the risk-benefit balance of the product:

There is not an established relationship between momelotinib and thrombosis based on review of data in the momelotinib clinical development program. Patients with MPNs, especially PV and ET but also PMF, are at higher risk of arterial and venous thrombosis compared to the general population (Kelliher 2021).

When used in line with warnings and precautions in the SmPC, overall benefit-risk balance of momelotinib in MF patients is considered to be favourable.

Public health impact:

There is no anticipated public health concern.

Important Potential Risk: Secondary Malignancies

Potential mechanisms:

The mechanism(s) for this risk is not clear. However, JAK inhibitors inhibit a number of cytokines, including interferons, and also down-regulate NK cells. It is suggested that reduced immune surveillance with long-term treatment increases the risk of other secondary malignancies (Polverelli, 2021).

Evidence source(s) and strength of evidence:

There is not an established relationship between momelotinib and secondary malignancies based on review of data in the momelotinib clinical development program. Secondary malignancies are considered an important potential risk because of the data seen with another JAKi in patients with RA. Momelotinib is not indicated for use in the RA population.

Characterisation of the risk:

Patients with MF are known to have a higher incidence of nonhaematological second primary malignancies compared to the general population (Mora, 2019). Leukaemic transformation to AML is known to occur in up to 20% of MF patients (Iurlo, 2019).

Adverse events of malignancies were summarized based on a clinical review of preferred terms in the SOC Neoplasms Benign, Malignant, and Unspecified (Including Cysts and Polyps).

Malignancies were reported for the pooled momelotinib group in 5.6% of subjects during RT, 13.5% open-label, and 14.0% overall. The worst severity grade for the greatest proportion of subjects was grade 2 (2.2% RT, 5.3% open-label, 5.2% overall). Among the most reported malignancies were the following:

- Basal cell carcinoma: 0.7% RT, 3.6% open-label, 3.3% overall
- Squamous cell carcinoma of the skin: 0.9% RT, 3.1% open-label, 2.9% overall
- AML: 1.1% RT, 1.7% open-label, 1.9% overall
- Transformation to AML: 0.4% RT, 0.3% open-label, 0.7% overall

Serious adverse events of malignancies were reported for the pooled MMB group in 2.2% of subjects during RT, 5.1% open-label, and 5.5% overall. The most reported serious malignancy was squamous cell carcinoma of the skin (0 RT, 0.8% open-label, 0.7% overall) (Table 2.7.4.2.3.15, SN0001 Table 2.7.4.2.3.15).

The proportion of subjects who discontinued study drug due to malignancies was low (2.5% RT, 3.3% open-label, 4.3% overall).

After adjusting for exposure, the event rate for malignancies during RT of 18.9 events per 100 person-years decreased to 13.2 events per 100 person-years during open-label treatment, suggesting no cumulative toxicity of treatment with longer exposure (Table 2.7.4.2.3.13, SN0001 Table 2.7.4.2.3.13).

Table 23 By-Study Overall Summary of Adverse Events of Malignancies During Randomised Treatment (Safety Population)

	MOMENTUM		SIMPLIFY-1		SIMPLIFY-2	
Important Event, n (%)	**momelotinib (N = 130)**	**danazol (N = 65)**	**momelotinib (N = 214)**	**ruxolitinib (N = 216)**	**momelotinib (N = 104)**	**BAT (N = 52)**
Malignancies	7 (5.4%)	5 (7.7%)	10 (4.7%)	12 (5.6%)	8 (7.7%)	5 (9.6%)
AML/malignant transformation	4 (3.1%)	3 (4.6%)	1 (0.5%)	2 (0.9%)	3 (2.9%)	1 (1.9%)
Nonmelanoma skin cancer	0	0	4 (1.9%)	7 (3.2%)	2 (1.9%)	2 (3.8%)

Source: Table 2.7.4.2.3.13.1

Shading indicates adverse events ≥ 5 percentage points higher than the comparator of each study.

BAT, best available therapy; AML, acute myeloid leukaemia.

Table 24 Integrated Summary of Adverse Events of Malignancies by Study Period and Treatment (Safety Population)

	Randomised Treatment			Open-Label	Overall
Important Event, n (%)	**momelotinib (N = 448)**	**ruxolitinib (N = 262)**	**danazol (N = 65)**	**momelotinib (N = 606)**	**momelotinib (N = 726)**
Malignancies	25 (5.6%)	15 (5.7%)	5 (7.7%)	82 (13.5%)	102 (14.0%)
AML/malignant transformation	8 (1.8%)	3 (1.1%)	3 (4.6%)	14 (2.3%)	22 (3.0%)
Nonmelanoma skin cancer	6 (1.3%)	8 (3.1%)	0	36(5.9%)	40 (5.5%)

Source: Table 2.7.4.2.2

AML, acute myeloid leukaemia.

Risk factors and risk groups:

Risk factors or risk groups have not been established in patients on momelotinib.

Preventability:

Preventability of secondary cancers and tumour progression in patients with MF on momelotinib treatment is currently unknown.

Impact on the risk-benefit balance of the product:

There is no established relationship between momelotinib and secondary malignancies based on review clinical trial data. It is possible that secondary malignancies are rare occurrences that cannot be detected in randomised trials. However, rare incidences of secondary malignancies as a potential safety concern do not impact the overall risk-benefit ratio of momelotinib in the context of the efficacy and overall survival data available.

Public health impact:

There is no anticipated public health concern.

PART II: MODULE SVIII – SUMMARY OF THE SAFETY CONCERNS

Table 25 Summary of safety concerns

Summary of safety concerns	
Important identified risk	Serious Infections
Important potential risk	Major Adverse Cardiovascular Events (MACE)
	Thromboembolism
	Secondary Malignancies
Missing information	None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST AUTHORISATION SAFETY STUDIES)

III.1 Routine pharmacovigilance activities

No routine PV activities beyond adverse reaction reporting and signal detection activities are required.

Specific adverse reaction follow-up questionnaires

Not applicable

Other forms of routine pharmacovigilance activities

Not applicable

III.2 Additional pharmacovigilance activities

None proposed.

III.3 Summary Table of additional Pharmacovigilance activities

This section is not applicable to this application.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

There is no post-authorisation efficacy study proposed for this product.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table 26 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Serious Infections	**Routine risk communication:** SmPC sections 4.4 and 4.8 Package Leaflet (PL) sections 2 and 4 **Routine risk minimisation activities recommending specific clinical measure to address the risk:** Recommendations on patient selection, patient observation, and initiating appropriate treatment promptly are all included in SmPC section 4.4. **Other routine risk minimisation measures beyond the Product Information:** Legal status: Prescription only medicine

Safety concern	Routine risk minimisation activities
MACE	**Routine risk communication:** SmPC section 4.4 **Routine risk minimisation activities recommending specific clinical measure to address the risk:** Recommendation on patient selection included in SmPC section 4.4. **Other routine risk minimisation measures beyond the Product Information:** Legal status: Prescription only medicine

Safety concern	Routine risk minimisation activities
Thromboembolism	**Routine risk communication:** SmPC section 4.4 **Routine risk minimisation activities recommending specific clinical measure to address the risk:** Recommendation on patient selection included in SmPC section 4.4. **Other routine risk minimisation measures band 4eyond the Product Information:** Legal status: Prescription only medicine

Safety concern	Routine risk minimisation activities
Secondary Malignancies	**Routine risk communication:** SmPC section 4.4 **Routine risk minimisation activities recommending specific clinical measure to address the risk:** Recommendation on patient selection included in SmPC section 4.4. **Other routine risk minimisation measures beyond the Product Information:** Legal status: Prescription only medicine

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimisation Measures

Table 27 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Serious Infections	Routine risk minimisation measures: SmPC sections 4.4 and 4.8 SmPC section 4.4 – recommendation on patient selection, patient observation and initiating appropriate treatment promptly. PL sections 2 and 4 Legal status: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
MACE	Routine risk minimisation measures: SmPC section 4.4 Legal status: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Thromboembolism	Routine risk minimisation measures: SmPC section 4.4 Legal status: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Secondary Malignancies	Routine risk minimisation measures: SmPC section 4.4 Legal status: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Omjjara (momelotinib)

This is a summary of the risk management plan (RMP) for momelotinib. The RMP details important risks of Omjjara, how these risks can be minimised, and how more information will be obtained about risks and uncertainties (missing information).

The Omjjara Summary of Product Characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how the product should be used.

This summary of the RMP for momelotinib should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current risks will be included in updates of the RMP for momelotinib.

1. The medicine and what it is used for

Omjjara is indicated for the treatment of disease-related splenomegaly or symptoms, and moderate to severe anaemia in adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis, who are Janus Associated Kinase (JAK) inhibitor naïve or have been treated with a JAK inhibitor (see SmPC for the full indication). Omjjara contains momelotinib dihydrochloride monohydrate as the active substance and it is given by the oral route.

Further information about the evaluation of the benefits can be found in Omjjara EPAR, including in its plain language summary, available on the EMA website, under medicine's webpage.

2. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of momelotinib, together with measures to minimise such risks are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size - the amount of medicine in a pack is chosen to ensure

that the medicine is used correctly;

- The medicine's legal status - the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation measures*.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including periodic safety update report assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A. List of important risks and missing information

Important risks of Omjjara are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Omjjara. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not yet been established and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., use of the medicine in children or adolescents).

List of Important Risks and Missing Information	
Important Identified Risk:	Serious Infections
Important Potential Risks:	Major Adverse Cardiovascular Events (MACE)
	Thromboembolism
	Secondary Malignancies
Missing Information:	None

II.B. Summary of important risks

Important Identified Risk: Serious Infections	
Evidence for linking the risk to the medicine	In animal studies, haematologic findings at all dose levels included dose-dependent decreases in white blood cell counts. In the integrated analysis, during RT, serious infections were higher in the momelotinib group compared to the ruxolitinib group. The danazol group had the highest rate of serious infections (9.8% momelotinib, 4.6% ruxolitinib, 16.9% danazol), but had no fatal infections (2.2% momelotinib, 1.1% ruxolitinib, 0 danazol). The most reported serious infection across groups was pneumonia (2.2% momelotinib, 1.1% ruxolitinib, 9.2% danazol). Grade 3, grade ≥ 3, and serious infections were all ≥ 5 percentage points higher for momelotinib over ruxolitinib and for danazol over momelotinib. Further, an imbalance in COVID-19 events in the momelotinib group was noted. Therefore, the risk of serious infections is considered an important identified risk for momelotinib.
Risk factors and risk groups	Immunocompromised individuals, including MF patients as well as the elderly population are at risk for infections including COVID-19 infections (Barbui, 2021).
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4 and 4.8 SmPC section 4.4 – recommendations on patient selection, patient observation, and initiating treatment promptly. PL sections 2 and 4 Legal status: Prescription only medicine Additional risk minimisation measures**:** None

Important Potential Risk: MACE	
Evidence for linking the risk to the medicine	In a large randomised active-controlled study of tofacitinib (another JAK inhibitor) in rheumatoid arthritis patients 50 years and older with at least one additional cardiovascular risk factor, a higher rate of MACE, defined as cardiovascular death, non-fatal myocardial infarction (MI) and non-fatal stroke, was observed with tofacitinib compared to TNF inhibitors. Events of MACE have been reported in patients receiving JAK inhibitors, however, a causal relationship has not been established for momelotinib. In momelotinib clinical trials with MF, event rates for MACE decreased from momelotinib RT to open-label treatment (from 9.2 to 5.8 events per 100 person-years), suggesting no cumulative toxicity of treatment.
Risk factors and risk groups	Patients with MF are at an increased risk of other comorbidities such as cardiovascular disease.
Risk minimisation measures	Routine risk minimisation measures: Prior to initiating or continuing therapy with momelotinib, the benefits and risks for the individual patient should be considered, particularly in patients 65 years of age and older, patients who are current or past long-time smokers, and patients with a history of atherosclerotic cardiovascular disease or other cardiovascular risk factors. SmPC section 4.4 - recommendation on patient selection Legal status: Prescription only medicine Additional risk minimisation measures**:** None

Important Potential Risk: Thromboembolism	
Evidence for linking the risk to the medicine	In a large randomised active-controlled study of tofacitinib (another JAK inhibitor) in rheumatoid arthritis patients 50 years and older with at least one additional cardiovascular risk factor, a dose dependent higher rate of venous thromboembolic events (VTE) including deep venous thrombosis (DVT) and pulmonary embolism (PE) was observed with tofacitinib compared to TNF inhibitors. Events of deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving JAK inhibitors, however, a causal relationship has not been established for momelotinib. In momelotinib clinical trials with MF, event rates for thromboembolism decreased from momelotinib RT to open-label treatment (from 11.9 to 6.7 events per 100 person years), suggesting no cumulative toxicity of treatment.
Risk factors and risk groups	Given the median age of MF diagnosis as well as the pathophysiology of the underlying disease, patients with MF are at an increased risk of other comorbidities such as thromboembolic disease.

Risk minimisation measures	Routine risk minimisation measures: Prior to initiating or continuing therapy with momelotinib, the benefits and risks for the individual patient should be considered, particularly in patients with cardiovascular factors. In patients with known VTE risk factors other than cardiovascular or malignancy risk factors, momelotinib should be used with caution. VTE risk factors other than cardiovascular or malignancy risk factors include previous VTE, patients undergoing major surgery, immobilisation, use of combined hormonal contraceptives or hormone replacement therapy, and inherited coagulation disorder. Patients should be re-evaluated periodically during momelotinib treatment to assess for changes in VTE risk. Promptly evaluate patients with signs and symptoms of VTE and discontinue momelotinib in patients with suspected VTE, regardless of dose. SmPC section 4.4 - recommendation on patient selection Legal status: Prescription only medicine Additional risk minimisation measures**:** None

Important Potential Risk: Secondary Malignancies	
Evidence for linking the risk to the medicine	In a large randomised active controlled study of tofacitinib (another JAK inhibitor) in rheumatoid arthritis patients 50 years and older with at least one additional cardiovascular risk factor, a higher rate of malignancies, particularly lung cancer, lymphoma and non-melanoma skin cancer (NMSC) was observed with tofacitinib compared to TNF inhibitors. Lymphoma and other malignancies have been reported in patients receiving JAK inhibitors, however, a causal relationship has not been established for momelotinib.
Risk factors and risk groups	Given the median age of MF diagnosis, patients with MF are at an increased risk of secondary malignancies.
Risk minimisation measures	Routine risk minimisation measures: Prior to initiating or continuing therapy with momelotinib, the benefits and risks for the individual patient should be considered, particularly in patients 65 years of age and older, and patients who are current or past long-term smokers. SmPC section 4.4 - recommendation on patient selection Legal status: Prescription only medicine Additional risk minimisation measures**:** None

II.C. Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Omjjara.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Omjjara.

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable.

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable.