09 November 2023
EMA/548646/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Omjjara

International non-proprietary name: momelotinib

Procedure No. EMEA/H/C/005768/0000

Note

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

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List of abbreviations

Quality

AS	Active substance
BCS	Biopharmaceutics classification system
CHMP	Committee for Medicinal Products for Human use
CQA	Critical quality attribute
DoE	Design of experiments
EC	European Commission
EI	Elemental impurity
EMA	European Medicines Agency
EU	European Union
FP	Finished product
FT-IR	Fourrier transform infrared spectroscopy
GC	Gas chromatography
HDPE	High density polyethylene
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IR	Infrared spectroscopy
KF	Karl Fischer titration
LDPE	Low density polyethylene
MO	Major objection
NMR	Nuclear magnetic resonance
NOR	Normal operating range
PAR	Proven acceptable range
PDE	Permitted daily exposure
Ph. Eur.	European Pharmacopoeia
RH	Relative humidity
SDS	Sodium dodecyl sulfate
SmPC	Summary of product characteristics
TSE	Transmissible spongiform encephalopathy
UPLC	Ultra-high performance liquid chromatography
XRPD	X-ray powder diffraction

Non-clinical; Clinical

ACVR1/ALK2	Activin A receptor type 1/activin receptor-like kinase-2
AML	Acute myeloid leukemia
AUC	Area under the plasma concentration-time curve
BAT	Best available therapy
BID	Twice daily
C_{max}	Maximum plasma concentration
CHMP	Committee for Medicinal Products for Human Use
CL/F	Apparent clearance
CYP	Cytochrome P450
DAN	Danazol
DIPSS	Dynamic International Prognostic Scoring System

eGFR	Estimated glomerular filtration rate
ELN	European LeukemiaNet
EMA	European Medicines Agency
E-R	Exposure-response
ESMO	European Society for Medical Oncology
ET	Essential thrombocythemia
EU	European Union
FDA	Food and Drug Administration
FLT3	FMS-like tyrosine kinase 3
Hgb	Hemoglobin
HSCT	Hematopoietic stem cell transplantation
IPSS	International Prognostic Scoring System
ISS	Integrated Summary of Safety
ITT	Intent-to-treat
JAK	Janus kinase
LFS	Leukemia-free survival
LS	Least squares
MAA	Marketing Authorisation Application
MACE	Major adverse cardiovascular events
MCT	Meaningful change threshold
MF	Myelofibrosis
MFSAF	Myelofibrosis Symptom Assessment Form
MMB	Momelotinib
MMRM	Mixed model for repeated measures
MOMENTUM	Study SRA-MMB-301
MPN	Myeloproliferative neoplasm
MPN-SAF	Myeloproliferative Neoplasm Symptom Assessment Form
OS	Overall survival
P-gp	P-glycoprotein
PK	Pharmacokinetics
PMF	Primary myelofibrosis
PV	Polycythemia vera
RBC	Red blood cell
RUX	Ruxolitinib
SIMPLIFY-1	Study GS-US-352-0101
SIMPLIFY-2	Study GS-US-352-1214
SmPC	Summary of product characteristics
SRR	Splenic response rate
STAT	Signal transducer and activator of transcription
TD	Transfusion dependence or transfusion dependent
TI	Transfusion independence or transfusion independent
T_{max}	Time to C_{max}
TR	Transfusion requiring
TSS	Total symptom score
US	United States
XAP	Study SRA-MMB-4365

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Glaxosmithkline Trading Services Limited submitted on 9 November 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Omjjara, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 15 October 2020.

Omjjara, was designated on 05 August 2011 as an orphan medicinal product EU/3/11/886 in the following condition: post-polycythemia vera myelofibrosis; EU/3/11/887 in the following condition: post-essential thrombocythemia myelofibrosis and EU/3/11/888 in the following condition: primary myelofibrosis.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Omjjara as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/omjjara

The applicant applied for the following indication:

Omjjara is indicated for the treatment of disease-related splenomegaly or symptoms, and 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.

1.2. Legal basis and dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) EMEA-001656-PIP01-14 and EMEA-001656-PIP02-19 on the granting of a (product-specific) waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.4.2. New active substance status

The applicant requested the active substance momelotinib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.5. Protocol assistance

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
19 July 2012	EMEA/H/SA/2368/1/2012/PA/SME/III	Dr Andre Elferink, Dr Christoph Unkrig and Dr Rembert Elbers
19 September 2013	EMEA/H/SA/2368/1/FU/1/2013/PA/II	Dr Joao Manuel Lopes de Oliveira and Dr Ferran Torres
28 February 2019	EMEA/H/SA/2368/1/FU/2/2019/SME/II	Dr Adriana Andrić and Dr Karin Janssen van Doorn
19 September 2019	EMEA/H/SA/2368/1/FU/3/2019/PA/SME/II	Dr Karin Janssen van Doorn, Dr Juha Kolehmainen and Dr Armando Magrelli

The Protocol assistance pertained to the following non-clinical and clinical aspects:

EMEA/H/SA/2368/1/2012/PA/SME/III:

- The adequacy of the non-clinical study package with regards to metabolism studies, identification of metabolites and toxicology studies, to support clinical investigation
- The conduct of comparative bioavailability studies to support a proposed switch from capsule to tablet formulation for the phase III clinical trials
- The design and timing of the TQT study
- Elements of the proposed phase III clinical studies YM387-III-01 and YM387-III-02, including eligible population, sample size, design, comparators, primary and secondary endpoints and related measuring instruments.
- The appropriateness of the clinical program to support the sought indication and to justify significant benefit in the context of the orphan medicinal product designation.

EMEA/H/SA/2368/1/FU/1/2013/PA/II

- The design and key elements of study GS-US-352-0101 including population, sample size, endpoints and statistical analysis plan, in order to support a regulatory approval in the sought indication.

EMEA/H/SA/2368/1/FU/2/2019/SME/II

- The design and key elements of study SRA-MMB-301 including patient population, comparator, primary and secondary endpoints and related PRO instruments, as well as statistical analysis.

EMEA/H/SA/2368/1/FU/3/2019/PA/SME/II

- The potential of the available clinical data, in particular considering studies SIMPLIFY-1 and SIMPLIFY-2, to support an application for conditional marketing authorization in the sought indication.
- The relevance of the revised clinical study SRA-MMB-301 to provide comprehensive data post-approval in the context of a conditional marketing authorization.
- The adequacy of the clinical program to support the sought indication as well as to generate data to justify significant benefit in the context of the orphan medicinal product designation

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Christophe Focke Co-Rapporteur: Alexandre Moreau

The application was received by the EMA on	9 November 2022
The procedure started on	1 December 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	21 February 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	2 March 2023
The CHMP Co-Rapporteur's assessment was circulated to all CHMP and PRAC members on	3 March 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	30 March 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	14 July 2023
The CHMP and PRAC Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	25 August 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	31 August 2023
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	14 September 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	9 October 2023
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	25 October 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Omjjara on	9 November 2023

The CHMP adopted a report on similarity of Omjjara with Inrebic on	9 November 2023
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product	9 November 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Myelofibrosis (MF) is a rare Philadelphia chromosome (Ph1)-negative myeloproliferative neoplasm (MPN) that may occur de novo as primary MF (PMF) or as secondary MF (SMF) when it evolves from other pre existing MPNs polycythaemia vera (PV) or essential thrombocythemia (ET) (post PV/ET MF). SMF is clinically indistinguishable from PMF and develops due to fibrotic transformation and progressive bone marrow fibrosis (Sangle, 2014).

2.1.2. Epidemiology

MF has an incidence of about 0.58 new cases per 100,000 person-years, but a higher prevalence of 6 per 100,000 person-years because of its chronic and disabling course. Median age at diagnosis is 67 years, without any significant difference in distribution between the sexes (Iurlo, 2017; Visser et al, 2021). The median survival for all patients with MF is approximately 6 years (Zahr, 2016). Median survival is considerably worse for patients with PMF with intermediate 2 risk (4 years) or high risk disease (1.5 -2.5 years) (Passamonti, 2010; Cervantes, 2009). The most frequent cause of death in patients with MF is transformation to acute myeloid leukaemia (20%). Most patients die because of other disease-related events, such as progression without transformation, infections, and thrombo-haemorrhagic complications.

2.1.3. Aetiology and pathogenesis

MF is a rare, chronic, progressive disease caused by clonal proliferation of hematopoietic stem cells in the bone marrow that leads to cytokine release, myeloid hyperproliferation, bone marrow fibrosis, and over time, characteristic clinical features (O'Sullivan, 2018; Iurlo, 2017). The etiology of anemia in MF is multifactorial, that could be distinguished as MF-associated anemia with contributions from bone marrow fibrosis, direct effects of inflammation on the bone marrow microenvironment, splenomegaly with splenic sequestration; treatment-related anemia (eg, following treatment with JAK inhibitors), and anemia due to other causes, such as indirect effects due to elevated hepcidin or concomitant factors or deficiencies that contribute to anemia.

Regardless of whether myelofibrosis is primary or secondary, the disease is characterized by a clonal haemopoietic stem cell proliferation associated with reactive bone marrow fibrosis, osteosclerosis, angiogenesis, extramedullary haematopoiesis (EMH) and abnormal cytokine expression. MPNs are considered to arise from a somatic mutation of a pluripotent haematopoietic progenitor cell, but the exact cause of pathogenesis is unknown.

Almost all patients with PV and about one half of patients with ET and PMF have a Janus kinase 2 (JAK2) mutation, typically JAK2V617F mutation. Increased JAK2 signaling, evidenced by constitutively phosphorylated signal transducer and activator of transcription (STAT3), is not strictly dependent on the presence of JAK2V617F mutation. Other mutations in patients with PMF include calreticulin (CALR) and myeloproliferative leukemia virus oncogene (MPL) (Tefferi, 2012). About 10% of patients with PMF have no detectable mutation in JAK2, CALR, or MPL and are termed "triple negative" (Tefferi, 2016). Mutations in JAK2, CALR, and MPL activate the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathway (Romano, 2017), resulting in cell proliferation and inhibition of cell death and clonal expansion of myeloproliferative malignant cells.

It is less clear how the driver mutations that are present in earlier myeloproliferative neoplasms, such as essential thrombocythemia or polycythemia vera, evolve to the more advanced phases of myelofibrosis. Factors may include epigenetic changes; additional somatic mutations in other genes, such as additional sex combs like 1 (ASXL1), ten-eleven translocation–2 (TET2), and isocitrate dehydrogenase 1 (IDH1) and 2 (IDH2); and contributions of the bone marrow microenvironment, particularly regarding inflammation. Cytokine elevations in MF occur regardless of mutational status or disease subtype and MF is considered to be a condition with a considerable inflammatory potential (Lussana, 20175).

2.1.4. Clinical presentation, diagnosis and prognosis

MF manifests with complex clinical features that differ from patient to patient. Up to 30% of patients may be asymptomatic at the time of MF diagnosis, which may follow a routine blood test or physical examination revealing splenomegaly (O'Sullivan, 2018). As the disease progresses, all patients become symptomatic due to bone marrow fibrosis/failure, systemic inflammation, and/or organomegaly. Key clinical features include constitutional symptoms, anemia, and organomegaly, principally of the spleen, which can cause associated symptoms (eg, abdominal pain, early satiety). Patients may experience constitutional symptoms such as fatigue, night sweats, fever, cachexia, bone pain, and pruritus (Tefferi, 2021).

Overall, MF is an aggressive, chronic disease with symptomology that is often debilitating.

A diagnosis of MPN is based on the 2016 World Health Organization (WHO) diagnostic criteria and requires a combination of clinical, laboratory, cytogenetic, and molecular testing (O' Sullivan, 20186). This includes the presence of 1 of the 3 driver mutations (JAK2, CALR and MPL). In patients with triple-negative disease, the detection of one of the associated somatic mutations (eg, EZH2, TET2, IDH1/2, ASXL1, SRSF2, or SF3B1) suffices as the presence of a clonal marker for diagnostic purposes. Because the natural course of secondary MF (post-PV MF and post-ET MF) may differ from that of PMF, the diagnosis of post-PV or post-ET MF should adhere to criteria published by the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) (Barosi, 2008).

Several prognostic scoring systems have been developed to facilitate risk assessment for patients with MF. The prognostic scorings were originally developed for primary MF, but the same models and parameters are applied in post-PV and post-ET MF, partly because the therapeutic approach is quite similar. The International Prognostic Scoring System (IPSS) is used to predict survival at diagnosis, and the Dynamic International Prognostic Scoring System (DIPSS) is used to predict survival at any time during the disease. The IPSS, DIPSS, and DIPSS plus prognostic models for PMF used to stratify patients into risk groups for survival and to guide treatment decisions all include Hgb < 10 g/dL as a risk factor. Transfusion dependence (TD) is included as an additional risk factor in the DIPSS plus model. Variables are included with a defined number of points in different scoring systems (with moderate and anaemia with haemoglobin level < 10 g/dL scored as 1 or 2 points). IPSS included

variables of age > 65 years, constitutional symptoms, haemoglobin level < 10 g/dL, white blood cell (WBC) counts > 25 x 109/L and circulating blast frequency ≥1%. DIPSS puts more emphasis on anaemia. DIPSS Plus incorporates 3 additional independent risk factors: platelet count < 100 x 109/L, red blood cell (RBC) transfusion need, and unfavourable karyotype (Gangat, 2011). A strong association between DIPSS Plus risk category and overall survival (OS) for MF patients has been reported; intermediate-1, intermediate-2, or high-risk disease has been associated with median survival of 6.5, 2.9, and 1.3 years, respectively (Gangat, 2011; Tefferi, 2016). Approximately 90% of individuals with MF are in the intermediate or high-risk categories according to DIPSS Plus (Gangat, 2011), comprising a large population with symptomatic disease and shortened survival and representing the greatest unmet medical need.

An increased risk of leukemic transformation and shortened survival are serious concerns for patients with MF (O'Sullivan, 2018; Gangat, 2011). Although transformation to acute myeloid leukemia (AML) is the most frequent cause of death for patients with MF (20%; Iurlo, 2017), survival is more commonly shortened because of other disease related events such as complications from progressive bone marrow failure, infections, thrombohemorrhagic complications, portal hypertension, or cardiovascular complications.

Anemia in MF

The etiology of anemia is multifactorial with contributions from bone marrow fibrosis, direct effects of inflammation on the bone marrow microenvironment, splenomegaly with splenic sequestration, treatment effects, and indirect effects due to elevated hepcidin (anemia of inflammation) and other causes. Anemia and RBC TD are major negative prognostic factors for survival in patients diagnosed with MF. Elevated hepcidin levels have also been correlated with poor survival in patients with PMF (Pardanani, 2013). Many of the disease related conditions contributing to early death are exacerbated by anemia, RBC transfusion associated iron overload, or both (Naymagon, 2017). Anemia and associated RBC transfusion need are also risk factors for leukemic transformation in MF (Dunbar, 2020).

The presence of TD assigns a patient to at least intermediate 2 risk in the DIPSS plus model. All grades of anemia have been shown to adversely affect survival among patients with PMF (Nicolosi, 2018). Severe anemia (defined as Hgb < 8 mg/dL or TD) was associated with a > 1.5 fold increase in the risk of death compared with moderate anemia (defined as Hgb 8 to < 10 mg/dL) at the time of diagnosis.

In a study of 1000 consecutive patients with PMF, 38% had Hgb level < 10 g/dL and 24% required RBC transfusions at the time of diagnosis (Tefferi, 2012). Within 1 year after diagnosis, 58% had Hgb level < 10 g/dL and 46% required transfusions. Nearly all patients with MF eventually require RBC transfusions. In addition to predicting poor survival, anemia and TD are inversely associated with quality of life (Naymagon, 2017). Finally, RBC transfusions are associated with risk of acute and chronic complications (eg, infection, fluid overload, infusion reactions, iron overload), and they substantially burden patients, their families, and health care systems (Semple, 2019; Naymagon, 2017; Bartoszko, 2015; Shander, 2009). Therefore, all grades of anemia have been associated with shortened survival in patients with PMF (Nicolosi, 2018).

There is currently insufficient data to allow conclusion on prognosis worsening in patients with anemia post-JAK inhibitors exposure.

). RBC transfusions are associated with risk of acute and chronic complications (eg, infection, fluid overload, infusion reactions, iron overload), reduced quality of life, and reduced survival, and they substantially burden patients, their families, and health care systems (Semple, 2019; Naymagon, 2017; Bartoszko, 2015; Shander, 2009).

2.1.5. Management

Treatment of PMF and SMF is similar and requires an individualized approach, considering each patient's age, comorbidities, symptom profile, prognostic risk category, performance status, treatment preference, and other factors. The selection of appropriate treatment is based on the risk score and presence of symptoms (European LeukemiaNet (ELN), Barbui, 2018; the European Society for Medical Oncology (ESMO) clinical practice guidelines, Vannucchi 2015).

- Allogeneic HSCT is the only curative therapy for MF (Robin, 2019). However, the procedure is associated with high morbidity and mortality, particularly in older adults, and is thus generally considered for only a limited subset of patients aged < 70 years with suitable donors, lack of significant comorbidities, and good performance status (Tiribelli, 2020). Allogeneic stem-cell transplantation (SCT) is the only treatment that is potentially curative and can induce long-term remission in patients with MF (Barbui, 2018; Vannucchi, 2015). However, the majority of MF patients are not eligible for the procedure due to age, comorbidities and an overall frail condition (Stahl, 2017; Vannucchi, 2015). Therefore, the existing treatment options are primarily symptom oriented. Treatment goals include reduction of spleen size, improvement of cytopenias and symptom burden, reduction of bone marrow fibrosis, restoration of transfusion-independence, and prevention and delay of progression to acute myeloid leukemia (AML) (Stahl, 2017; Vannucchi, 2015).

- For many patients who are ineligible for allogeneic HSCT, the current standard of care includes treatment with an approved JAK inhibitor:

- Ruxolitinib. RUX is a JAK1 and JAK2 inhibitor indicated for the treatment of disease related splenomegaly or symptoms in adult patients with PMF, post PV MF, or post ET MF (Jakavi SmPC, 2017). RUX has been incorporated into international treatment guidelines, including the ESMO Practice Guidelines for Philadelphia chromosome negative chronic MPNs (Vannucchi, 2015), and has become the standard of care for patients with MF. RUX reduces splenomegaly and MF associated symptoms in patients with MF and has been associated with improved OS. Development/exacerbation of thrombocytopenia and anemia was common with RUX, necessitating frequent RUX dose modifications and/or RBC transfusions (Harrison, 2012; Verstovsek, 2012). Mean Hgb levels were decreased from baseline with RUX. After RUX discontinuation, patients experience relapse of symptoms, worsening splenomegaly, and poor survival. For patients with intermediate-risk 2 or high-risk score and not eligible for alloSCT, ruxolitinib is the core treatment of MF. Ruxolitinib (Jakavi), a JAK1/2 inhibitor, which is centrally approved drug in the EU for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis. It improves splenomegaly symptoms in patients with intermediate-2–risk and high-risk myelofibrosis (COMFORT-II study Cervantes, 2013). It is also used in patients with symptomatic intermediate-1–risk myelofibrosis who are not responding or are intolerant to hydroxyurea. Whether ruxolitinib improves survival is uncertain, as meta-analyses have not been able to conclude on estimates of survival advantage of ruxolitinib and the benefit of ruxolitinib is currently seen as controlling splenomegaly and constitutional symptoms (Barbui, 2018).

- Fedratinib. Fedratinib is a JAK2 and FLT3 inhibitor indicated for the treatment of disease related splenomegaly or symptoms in adult patients with PMF, post PV MF, or post ET MF who are JAK inhibitor naïve or have been treated with RUX (Inrebic SmPC, 2021). Fedratinib reduces splenomegaly and symptom burden in patients with MF but similar to RUX, does not provide anemia benefit and can cause or exacerbate cytopenias. In the registrational phase 3 study JAKARTA, encephalopathy, including Wernicke encephalopathy, occurred in some patients treated with fedratinib (Pardanani, 2015). Thus, thiamine levels are assessed in patients before and throughout fedratinib treatment to mitigate the risk of encephalopathy (Inrebic SmPC, 2021).

- Other treatments. Before JAK inhibitors were available for MF, treatment options were limited.

– Hydroxycarbamide (hydroxyurea), a cytoreductive agent, has been widely used to reduce constitutional symptoms and symptomatic splenomegaly. However, responses are not durable and exacerbation of anemia is common (Iurlo, 2017; Martínez Trillos, 2010).

– Other supportive treatments for splenomegaly include splenectomy, splenic irradiation, and partial splenic artery embolization (Tremblay, 2020). However, these treatments are limited to select patients.

– Supportive therapies for MF associated anemia include androgens (eg, testosterone, DAN), corticosteroids (eg, prednisone), immunomodulators (eg, lenalidomide), erythropoiesis stimulating agents, and RBC transfusion (Iurlo, 2017; Naymagon, 2017). However, the efficacy, durability, and tolerability of these therapies are limited. Notably, the ELN could not issue any evidence-based recommendations for treating MF associated anemia (Barbui, 2018). Other therapeutic options for MF include erythropoiesis-stimulating agents (ESAs), corticosteroids, danazol, and immunomodulatory drugs (thalidomide, lenalidomide, and pomalidomide) for improvement of anaemias and hydroxyurea and interferon for the treatment of splenomegaly and/or constitutional symptoms (Stahl, 2017). Hydroxyurea (HU) is the only approved on a national basis in a few countries (e.g. France, Italy, Sweden and Spain) in the EU. Splenectomy and splenic irradiation are treatment options in refractory disease and disease specific complications (Tefferi 2016).

Unmet medical need in MF patients with anemia

The approved JAK inhibitors for MF do not improve anaemia, a cardinal feature of this progressive disease and an important risk factor for poor survival. RUX and fedratinib can exacerbate cytopenias (thrombocytopenia, anemia, neutropenia) due to myelosuppressive effect attributed to JAK2 inhibition, necessitating dose modification, interruption, or discontinuation. Compromised dose intensity can limit treatment effects on disease related splenomegaly and symptoms.

Although ruxolitinib and fedratinib are not contraindicated in patients with anemia and TD, anaemia is a common reason for discontinuation or one of the factors considered at the initiation of JAK inhibitors. Consequently, management of the clinical manifestations of MF in patients who present with or develop anemia and/or thrombocytopenia remains an ongoing challenge (Naymagon, 2017 There is currently no approved JAK inhibitors specifically for management of anaemia along with other disease manifestations, such as symptoms and splenomegaly.

2.2. About the product

Momelotinib is a potent, orally bioavailable, small molecule inhibitor of the Janus kinases (JAK) JAK1 and JAK2 and the activin A receptor type 1 (ACVR1)/activin receptor like kinase 2 (ALK2).

It belongs to the pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors.

Like other JAK inhibitors (eg, ruxolitinib, fedratinib), MMB interferes with the JAK STAT (signal transducers and activators of transcription) signaling pathways, which are dysregulated in MF as a key component in the pathogenesis and clinical manifestations of the disease. Distinct from other molecules in its class, MMB also inhibits the ACVR1 SMAD (mothers against decapentaplegic) signaling pathway resulting in reduced hepcidin expression in the liver, thereby increasing iron availability for erythropoiesis. This unique attribute of MMB confers a differentiated benefit on anaemia and red blood cell (RBC) transfusion dependence, which are important negative prognostic factors for MF and inversely correlate with quality of life. Further, transfusion independence has been shown to be associated with improved overall survival in MMB treated patients with MF.

The initially proposed indication is as follows:

"Omjjara is indicated for the treatment of disease related splenomegaly or symptoms, and anaemia in adult patients with primary myelofibrosis (MF), 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."

The recommended dose of Omjjara is 200 mg once daily.

A complete blood cell count must be performed before initiating treatment with Omjjara, periodically during treatment, and as clinically indicated.

Note: Momelotinib is also known as CYT387, GS-0387, SRA 0387, MMB

2.3. Type of application and aspects on development

Several rounds of scientific advice have been sought for momelotinib development (see section 1.5).

With regards to paediatric requirements, momelotinib was granted a product-specific waiver for primary myelofibrosis indication (EMEA-001656-PIP02-19) and for treatment of essential thrombocythaemia, post-essential thrombocythaemia myelofibrosis, polycythaemia vera and post-polycythaemia vera myelofibrosis (EMEA-001656-PIP01-14) on the grounds that the disease or condition for which the specific medicinal product is intended occurs only in adult populations.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as film-coated tablets containing 100, 150 and 200 mg of momelotinib (as momelotinib dihydrochloride monohydrate) as active substance.

Other ingredients are:

Tablet core: propyl gallate, microcrystalline cellulose, lactose monohydrate, sodium starch glycolate (type A), colloidal anhydrous silica and magnesium stearate.

Tablet coating: polyvinyl alcohol, macrogols, titanium dioxide, talc, iron oxide yellow and iron oxide red.

The product is available in white, high-density polyethylene (HDPE) bottles with child-resistant polypropylene cap and induction-sealed, aluminium faced liner. Each bottle contains a silica gel desiccant and polyester coil.

2.4.2. Active substance

2.4.2.1. General information

The INN of the active substance (AS) is momelotinib and the chemical name is *N*-(cyanomethyl)-4-(2-{[4-(morpholin-4-yl)phenyl]amino}pyrimidin-4-yl)benzamide. The structure is shown in Figure 1.

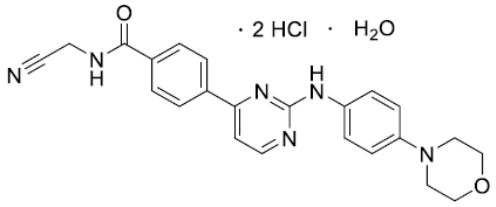


Figure 1. active substance structure

The molecular formula of the free base is $C_{23}H_{22}N_6O_2$; The molecular formula of the active substance is $C_{23}H_{22}N_6O_2 \bullet 2HCl \bullet H_2O$.

The relative molecular mass of the free base is 414.47. The relative molecular mass of the active substance is 505.40.

The chemical structure of momelotinib dihydrochloride monohydrate (MMB diHCl) was elucidated by a combination of elemental analysis, mass spectrometry, ^{1}H- and ^{13}C-NMR spectroscopy, FT-IR spectroscopy, UV, counter ion content and X-ray crystallography. The solid-state properties were investigated by XRPD, melting point, thermogravimetric analysis and dynamic vapour sorption.

MMB diHCl appears as light yellow to brown to reddish-brown not hygroscopic crystalline solid which may contain differently coloured solids within the same colour range. In its base form is practically insoluble in water. The equilibrium aqueous solubility of momelotinib dihydrochloride monohydrate cannot be accurately assessed due to disproportionation of the dihydrochloride salt in non-acidified aqueous media. The salt form shows an initial kinetic solubility of > 60 mg/mL in water at 25 °C followed by a decrease in solubility over 30 to 45 minutes along with formation of a monohydrochloride salt form in the solid phase.

No chiral centres exist in the molecule.

One polymorphic form for momelotinib dihydrochloride monohydrate (GS-0387-01, Form II) has been observed. MMB diHCl Form II is the most thermodynamically stable form of the dihydrochloride salts under all conditions relevant to drug product manufacturing and storage.

2.4.2.1. Manufacture, characterisation and process controls

MMB diHCl is synthesized in five main steps using well defined starting materials with acceptable specifications. In the sequential procedure narrative, quantities/ranges of materials (starting materials, intermediates, solvents, catalysts and reagents) are included. The intended commercial scale is defined.

Critical steps, critical process parameters (with their ranges), process controls and yields for each stage are defined. Tests and acceptance criteria performed at critical steps are described and justified. Isolated intermediates are characterized and controlled by suitable specifications. There is no alternative processing, non-routine reprocessing or reworking.

The starting materials comply with ICH Q11 requirements. For each starting material, the following information was included: name and address of the manufacturer, flow chart of the synthetic process (including reagents, solvents and catalysts), discussion of carry-over of impurities from the starting material and specification. The parameters included in the specifications are sufficient for controlling the starting materials. The justification of the specification includes an evaluation of the risks and the ability of the subsequent steps to adequately control and/or purge impurities.

For each reagent, solvent or other material, a specification is also provided. In summary, the specifications for starting materials, solvents and reagents are deemed adequate.

The development of the AS manufacturing process utilized 5 sites. Similar specifications and synthetic routes were used at all manufacturing sites, including the same regulatory starting materials and intermediates. The synthesis has progressed through different processes which used different reagents and solvents. For each of the five manufacturing steps, the process development activities were summarized.

A comparability study of AS manufactured at development sites vs. the proposed commercial site shows that there are no significant differences in quality.

The active substance is packaged in two low-density polyethylene (LDPE) bags secured with a plastic or wire tie. These LDPE bags are placed in a suitable high-density polyethylene drum sealed with a gasket line lid and fitted with a tamper-evident seal for shipment. The primary packaging material which complies with Commission Regulation (EU) 10/2011, as amended.

2.4.2.2. Specification

The active substance specification includes tests for: appearance, identification (IR, UPLC) identification of crystalline form (X-RPD), water content (KF), residual solvents (GC), assay (UPLC), related substances (UPLC), hydrochloride content (titration), particle size (laser light scattering) residue on ignition/sulphated ash (Ph. Eur.) and microbial limits (Ph. Eur.).

Parameters included in the specification cover all the critical aspects for ensuring the quality of the AS. The proposed limits have been justified considering batch data and stability results and the relevant guidelines and Pharmacopoeia requirements. Impurity levels above the ICH Q3A thresholds have been toxicologically evaluated and qualified.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis data of 8 commercial scale batches manufactured by the proposed commercial site were provided. The results are within the specifications and consistent from batch to batch. In addition, batch data from 14 batches of varying batch sizes manufactured at the development sites were also presented. The results were generated according to analytical procedures in place at the time of product release and met the specification of the time.

2.4.2.3. Stability

Stability studies were conducted on multiple AS batches manufactured at development sites as well as by the proposed manufacturer.

Stability data from commercial scale batches of active substance stored in the intended commercial container closure system for up to 60 months under long term conditions (25ºC / 60% RH, 6 batches and 30°C/75% RH, 4 batches) and for up to 6 months under accelerated conditions (40ºC / 75% RH, 12 batches) according to the ICH guidelines were provided.

The following parameters were tested: appearance, water content, assay, related substances, HCl content, particle size, microbiological examination (annually) and XRPD (annually). The analytical methods used were the same as for release and were stability indicating. Although the batches were manufactured and tested at different times, all of them meet the currently proposed specification.

Photostability testing following the ICH guideline Q1B was performed on a commercial scale batch. The active substance is photostable. Additional forced degradation studies were conducted under acid hydrolysis, alkaline hydrolysis, oxidation, elevated heat and humidity conditions.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 60 months with storage condition "store below 30°C", in the proposed container.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The finished product (FP) is presented as film-coated tablets containing 100, 150 or 200 mg of momelotinib (as dihydrochloride monohydrate salt).

The description of momelotinib film-coated tablets is presented Table 2.

Different tablet strengths are distinguishable by size, shape and debossing.

Table 1. Description of momelotinib, film-coated tablets

Strength (units/dosage form)	Description
100 mg, tablet	Momelotinib Tablets, 100 mg, are brown, round, film-coated tablets, debossed with an underscored M on one side and 100 on the other side.
150 mg, tablet	Momelotinib Tablets, 150 mg, are brown, triangle-shaped, film-coated tablets, debossed with an underscored M on one side and 150 on the other side.
200 mg, tablet	Momelotinib Tablets, 200 mg, are brown, capsule-shaped, film-coated tablets, debossed with an underscored M on one side and 200 on the other side.

All strengths are manufactured from a common powder blend and differ only in the mass of powder compressed into tablets.

Key physicochemical characteristics of the solid-state form of the AS, such as particle size, solubility, and stability were adequately evaluated and the potential effect on the relevant properties was considered according to the ICH Q8 Guideline.

The used crystalline Form II of momelotinib diHCl, is maintained under all conditions relevant to FP manufacturing and storage as demonstrated in stability studies by XRPD analysis of finished product.

Momelotinib diHCl.H_2O is considered a BCS Class 2 compound. In aqueous solution, it undergoes hydrolytic and oxidative degradation and so exposure to moisture should be minimized during manufacture and storage.

An investigation on degradation products by hydrolysis and oxidative degeneration was carried out. To address the oxidative degradation of MMB, the impact of different antioxidants at different concentrations on the stability of the formulation was assessed in order to determine the antioxidant for the final formulation.

The choice, characteristics and function of the excipients have been discussed. Compatibility of the drug substance with the excipients has been demonstrated in formulation development studies and long-term stability studies. The levels of the different excipients were optimized in development studies.

Several AS manufacturers have been used throughout development. A study has been carried out on the material from different manufacturers. No difference in the quality of the FP was observed for any tablet strength. The selected manufacturing process produces a powder blend with equivalent characteristics, irrespective of any minor differences in the incoming AS.

Different formulations have been used for different clinical trials phases. An overview of the formulations employed in clinical trials throughout the development of momelotinib was provided.

MMB diHCl Form II was selected to progress to the development of an immediate release tablet formulation to support Phase 3 studies.

The development of the manufacturing process has been adequately described and reflects the considerations in ICH Q8. The process is conventional for production of film coated tablets.

The applicant conducted risk assessments to identify steps and parameters that could impact the finished product critical quality attributes (CQAs). Design of Experiments (DoE) studies were conducted on these steps and the process optimized accordingly. However, no design space is claimed.

In order to select a suitable dissolution method for the finished product, medium pH, surfactant type and quantity, paddle speed and discriminatory power were studied. The low solubility of the AS necessitated the use of a surfactant. The chosen surfactant has been justified.

The selected dissolution method was demonstrated to be discriminatory with respect to tablet hardness and disintegrant levels and is adequately justified.

A bulk hold time study was conducted to assess the physiochemical and microbiological properties of the final powder blend, cores and coated tablets cumulatively during storage. Bulk hold times in defined containers were established for these intermediates.

The FP is packaged in HDPE bottles fitted with a child-resistant polypropylene screw cap with an aluminum-faced liner and induction sealed packed with one 3 g canister of silica gel desiccant and polyester coil. The primary components were selected based on their intended use in the packaging of commonly marketed products of dry solid oral dosage form in compliance with *European Commission Regulation (EU) No. 10/2011.*

The effectiveness of desiccant at reducing MMB degradation was assessed in a stability study performed under accelerated conditions (40 °C/75% RH for up to 6 months) in sealed bottles containing varying amounts of silica gel desiccant. Based on these results, cannisters of 3 g silica gel are used as a component of the primary packaging for momelotinib tablets.

2.4.3.2. Manufacture of the product and process controls

The applicant has provided sufficient information regarding all sites for the manufacturing site, including packing and batch release site and the relevant GMP certificates.

A clear narrative description of the manufacturing process was included as was a flow-chart which also shows the in-process controls. The process is considered a standard manufacturing process and includes blending, granulation, compression and film coating.

The commercial batch size for the manufacture of momelotinib common powder blend and of each strength was stated.

A table listing the process parameters and their target, NOR and PAR values was provided. It was also mentioned that if parameter changes are required during manufacturing, only one parameter per step may be varied within its PAR, the others being kept at their NOR values.

For each stage of the FP manufacturing, the critical process parameters that impact the product characteristics were summarized. The proposed in-process controls are acceptable.

A holding time study has been carried out to support the proposed holding times for tablet cores and coated tablets; the proposed holding times are accepted. The applicant has confirmed that expiration period of a batch will be calculated in accordance with the *Note for Guidance on Start of Shelf-Life of the Finished Dosage Form (CPMP/QWP/072/96).*

Validation of Momelotinib Tablets, 100 mg, 150 mg and 200 mg, is being performed via a continuous process verification approach in accordance with the *EMA Guideline on process validation for finished products - information and data to be provided in regulatory submissions (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1,Corr.1 – Nov 2016)*.

Process qualification of Momelotinib Tablets, 100 mg, 150 mg and 200 mg followed a matrixed approach which included manufacture of 3 consecutive batches of common powder blend with subsequent manufacture of 2 lots each of the 100 mg and 150 mg tablets and 3 lots of 200 mg tablets for a total of 7 tablet lots. The validation plan was described in detail and tests results submitted.

Process qualification has been completed, and the results indicate that the manufacturing process is well-controlled, robust and is capable of routinely yielding product of consistent quality.

The commercial manufacturing process for momelotinib tablets is therefore considered sufficiently validated at the commercial site and scale.

2.4.3.3. Product specification

The finished product release and shelf life specifications include appropriate tests for this kind of dosage form: appearance, identification (UV, UPLC), water content (KF), assay (UPLC), degradation products (UPLC), uniformity of dosage units (Ph. Eur.), dissolution (Ph. Eur.), propyl gallate content (UPLC) and microbial limits (Ph. Eur.).

The FP specifications comprise of sufficient tests and appropriate limits to ensure the batch-to-batch quality of the product. The parameters and acceptance criteria for appearance, identification, assay, uniformity of dosage units, water content, dissolution and microbiological control are acceptable.

Regarding degradation products, impurities in the FP have been qualified at appropriate levels. Therefore, specifications for known impurities at release and at shelf-life can be considered justified.

The potential presence of elemental impurities (EIs) in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. An overall risk assessment for elemental impurities has been presented, considering the sum of all contributions of relevant sources to elemental impurities in the FP. The assessment is based on actual maximum levels of EIs per component and show that none is likely to be present in the drug product above the control threshold (i.e. 30 % of the established PDE). The analytical method has been correctly described and suitably validated for its intended purpose. Based on the risk assessment and the presented batch data, it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment to evaluate the potential for nitrosamine impurities in the drug product considering all suspected and actual root causes was performed in accordance with the latest guideline *EMA Questions and Answers on Information on nitrosamines for marketing authorization holders* (*EMA/409815/2020*). In response to a major objection by the CHMP, the applicant documented the risks associated with nitrosamine formation in both AS and FP and provided it in a standard template.

The major objection was thus resolved. No risk has been identified for the presence of potential nitrosamine impurities. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Analytical method validation studies for non-pharmacopoeial analytical methods have been conducted and, accordingly, the validation reports are provided, as per *ICH Q2*.

Moreover, forced degradation studies for assay and related substances methods have been carried out. These methods are considered stability indicating.

Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis results are provided for three commercial scale batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. In addition, batch data generated according to analytical procedures in place at the time from numerous batches used throughout the development program have been presented. Results met the specification of the time.

2.4.3.4. Stability of the product

Stability data from a total of 14 commercial scale batches of finished product covering all three strengths stored for up to 60 months under long term conditions (25ºC / 60% RH) and under intermediate conditions (30°C/75% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of the medicinal product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, water content, assay, degradation products, dissolution, propyl gallate and microbial limits. The analytical procedures used are stability indicating. The results comply with the proposed specification limits. No significant changes have been observed.

The batches subject to stability studies include FP made using AS lots manufactured from the proposed commercial supplier using the formulation, process parameters, in-process controls, and equipment that is representative of commercial production. The registration stability package also includes FP data using AS batches from a previous manufacturer.

FP lots manufactured using AS from the previous manufacturer are considered equivalent to batches manufactured by the proposed commercial AS manufacturer and are thus appropriate for shelf-life determination.

A photostability study was conducted as per ICH Q1B. The results confirm that the tablets are not sensitive to light and the packaging does not need to be light protective.

An in-use stability study was performed at 30°C/75% RH and 40°C/75% RH with induction seals broken and tested at 7, 14, 21 and 30 days on two batches of 100 and 200 mg tablets and one batch of 150 mg tablets. The results met specifications. Tablets remain stable in conditions designed to mimic worst-case patient use and thus defining an in-use shelf life is not required.

Additional temperature excursion studies were conducted at 60°C/ambient RH for 1 and 2 weeks and at -20°C/ambient RH for 1 month for one batch each of 100 mg and 200 mg tablets. Results demonstrates the tablets remain stable in extreme conditions that mimic a worst-case shipping temperature excursion.

Based on available stability data, the proposed shelf-life of 3 years with the storage conditions "store in the original bottle in order to protect from moisture. Do not remove the desiccant. Do not swallow the desiccant. This medicinal product does not require any special temperature storage conditions" as stated in the SmPC (section 6.3 and 6.4) is acceptable.

2.4.3.5. Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. A MO raised during the procedure concerning the information regarding the risk assessment on the potential presence of nitrosamine impurities has been resolved by provision of additional data. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

The nonclinical development program was designed to support the use of MMB in the treatment of patients with myelofibrosis. The overall nonclinical program was conducted in accordance with the Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical trials and Marketing Authorisation for Pharmaceuticals [ICH M3(R2)] in addition to other relevant ICH guidances related to the development of a small molecule.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

The development of MMB has involved several companies, and therefore study reports from different companies for the potency and selectivity of MMB and metabolites on JAK family enzymes are available. The IC_{50} and Kd data from the different study reports are summarized in the Tables 1 and 2 below.

Table 2. In vitro biochemical potency of MMB against JAK family enzymes

System	Source		IC50 Values (nM)				
			JAK1	**JAK2**	**JAK2V 617F**	**JAK3**	**TYK2**
Alphascreen kinase assay	Pardanani *et al.*, 2009 & Tyner *et al.*, 2010	**MMB**	11 (ATP = 80 µM)	18 (ATP = 80 µM)		155 (ATP = 80 µM)	17 (ATP = 80 µM)
LanthaScreen TR-FRET enzymatic assay	PC-352-2005	**MMB**	30 (ATP =70 µM)	3.8 (ATP =25 µM)			
Alphascreen kinase assay	CRB09001	**MMB**	70 (ATP= 80 µM)	5.7 (ATP= 80 µM)		270 (ATP = 80 µM)	260 (ATP = 635 µM)
Alphascreen kinase assay	CRB09001	**MMB**		6.6 (ATP= 80 µM)	2.8 (ATP= 80 µM)		
Alphascreen kinase assay: batch to batch comparison #1	CRB09001	**MMB**		15.2 (n=8; ATP= 80 µM)		77.7 (n=8; ATP= 80 µM)	
Alphascreen kinase assay: batch to batch comparison #2	CRB09001	**MMB**	21.5 (n=9; ATP= 80 µM)	19.4 (n=20; ATP= 80 µM)		155.4 (n=19; ATP= 80 µM)	
Z'-LYTE FRET kinase assay: potency validation	CRB09002	**MMB**		22.3 (ATP = Km app)			
Z'-LYTE FRET kinase assay	CRB09002	**MMB**	21 (ATP = 87 µM)	4.3 (ATP = 49 µM)		17.1 (ATP = 14 µM)	5.0 (ATP = 23 µM)
Millipore KinaseProfiler	CRB09003	**MMB**		5.0 (ATP = 45 µM)			
Commercial kinase potency screen	Asshoff et al, 2017	**MMB**	26.9	1.4		6.1	19.9

The *in vitro* IC50 inhibition of MMB on JAK family enzymes were evaluated with different assays based on phosphorylation and in the presence of ATP. In general, at clinically relevant exposures, MMB appeared to have higher inhibitory activity on JAK2 with IC50 values ranging from 1.4 – 18 nM over the other JAK family members (JAK2 > JAK1, 11-70 nM > TYK2, 5-260 nM > JAK3, 6-270 nM). However IC50 values were highly variable for JAK3 and TYK2 depending of the ATP concentration (see

table above). MMB has also potent activity at clinically relevant exposures on the MPN-associated JAK2V617F mutant (IC50=2.8 nM), almost equivalent to the activity on wild-type JAK2.

Table 3. In vitro biophysical potency of MMB and metabolites against JAK family enzymes

System	**Source**		**K_D (nM)**			
			JAK1	**JAK2**	**JAK3**	**TYK2**
KINOMEscan	WIQ002-01-s-00001	**MMB**	28	0.13		
		M21	53	0.79		
KINOMEscan	PC-352-2006	**M21**	150	1.1	8	1.2
		M19	> 10000	280	190	1200
KINOMEscan	WIQ001-01-s-00001	**M19**	>30000	530	240	1700

The *in vitro* Kd potency of MMB and the metabolites M21 and 19 were also investigated in several studies with KINOMEscan assay which do not require the presence of ATP. MMB was more potent on JAK2 (0.13 nM) compared to JAK1 (28 nM), but no Kd values were available on JAK3 and TYK2, although this has been investigated for the metabolites M21 and M19. The applicant has been requested to clarify the selectivity of MMB and M21 for JAK 2 and JAK1 over other JAK family members (JAK 3, TYK2), as a post-approval commitment within two years after approval. The major metabolite M21 had inhibitory activities on JAK family members (JAK2 > TYK2 > JAK 3 > JAK 1), but with lower inhibitory activity compared to the parent compound MMB. The metabolite M19 (minor in human and major in animal species) had low or no *in vitro* Kd potency on JAK family members, and is therefore not considered as an active metabolite.

In ATP-dependent kinase assays, MMB inhibited ACVR1 (ALK2) with IC50 values ranged from 6.8 to 8.4 nM. In ATP-independent competitive binding assays, MMB and metabolite M21 inhibited ACVR1 (ALK2) at clinically relevant exposures with low Kd values of 8.6-25 nM and 38-99 nM, respectively, compared to the metabolite M19 (1700-5300 nM).

Based on the binding mode, MMB and M21 are expected to be type 1, ATP-competitive kinase inhibitors.

The inhibitory activities of MMB, metabolites M21 and M19 on panel of kinases were investigated, and are summarized below in Table 4 (Reports PC-352-2006, CRB09001 CRB09002, and CRB09003).

Table 4. Summary of biophysical and biochemical potency for MMB, M21, and M19 against various kinases

DiscoverX Assays with no ATP										Enzymatic Assays Containing ATP			
		MMB		M21			M19				MMB		[ATP]
	Value (units)	Kd (nM)	Fold-JAK2	Kd (nM)	M21/MMB	Fold-JAK2	Kd (nM)	M19/MMB	Fold-JAK2	Value (units)	IC50 (nM)	Fold-JAK2	(μM)
Merged enzyme list	Enzyme name									Enzyme name			
JAK2	**JAK2 (JH1 domain-catalytic)**	**0.13**	**1.0**	**0.95**	**7.3**	**1.0**	**405**	**3115.4**	**1.0**	**JAK2**	**17**	**1.0**	**80, Km app, 49 (Km)**
JAK2(h)										JAK2(h)	5.0	0.29	45
IKK-β	IKK-beta	1.9	15	1.7	**-1.1**	1.8				IKK-β(h)	144	8.2	10
JAK1	JAK1 (JH1 domain-catalytic)	28	220	102	**3.6**	110	>10000		>25	JAK1	26	1.5	80, 87 (Km)
JNK3	JNK3	24	190	4.8	**-5.0**	5.1	55	**2.3**	0.14	MAPK10 (JNK3)	1720	98	100
TBK1	TBK1	29	220	63	**2.2**	67	1200	**41.4**	3.0	TBK1	90	5.1	Km app
JAK3	JAK3 (JH1 domain-catalytic)			8		8.5	215		0.53	JAK3	133	7.6	80, 14 (Km)
Tyk2	TYK2(JH1domain-catalytic)			1.2		1.3	1450		3.6	Tyk2	133	7.6	23 (Km), 625
ACVR1	ACVR1	16.8	130	68.5	**4.1**	72	3500	**208.3**	8.6	Not Tested			
ACVR1B	ACVR1B	520	4000	540	**1.0**	570							
ALK	ALK	>10000	>77000	>10000		>11000	>10000		>25				
AURKA	AURKA	140	1100	300	**2.1**	320	200	**1.4**	0.49				
AURKC	AURKC	140	1100	430	**3.1**	460	450	**3.2**	1.1				
BMPR1A	BMPR1A	1000	7700	2400	**2.4**	2500	>10000		>25				
BMPR1B	BMPR1B	19	150	8.7	**-2.2**	9.2	65	**3.4**	0.16				
BMPR2	BMPR2	40000	>310000	8000	**-5.0**	8500	2700	**-14.8**	6.7				
IKK-α	IKK-α	0.69	5.3	0.425	**-1.6**	0.45							
IKK-ε	IKK-ε	26	200	33	**1.3**	35							
IRAK1	IRAK1	5.8	45	7.45	**1.3**	7.9							
IRAK4	IRAK4	930	7200	1400	**1.5**	1500							
JAK1	JAK1 (JH2 domain-pseudokinase)						1800		4.4				
JNK1	JNK1	35	270	11	**-3.2**	12	91	**2.6**	0.22				
JNK2	JNK2	200	1500	67	**-3.0**	71	480	**2.4**	1.2				
PDGFRB	PDGFRB	47	360	92	**2.0**	97	>10000		>25				
TGFBR1	TGFBR1	670	5200	650	**-1.0**	690							
CDK1/cyclinB	Not Tested									CDK1/cyclinB(h)	51	2.9	45
CDK2/cyclinA										CDK2/cyclinA(h)	181	10	45
CDK2/cyclinE										CDK2/cyclinE(h)	887	51	120
CDK9/cyclin T1										CDK9/cyclin T1(h)	199	11	45
FLT3										Flt3	180	10	80, Km app
JAK2 (JH1-JH2)										JAK2 (JH1-JH2)	6.6	0.38	80
JAK2 (JH1-JH2) V617F										JAK2 (JH1-JH2) V617F	2.8	0.16	80
JNK1a1										JNK1a1(h)	802	46	45
MAPKAPK2										MAPKAPK2	2370	140.0	Km app
PDGFRA										PDGFRA	160	9.1	Km app
PKCb1										PKCb1(h)	1899	110	10
PKCg										PKCg(h)	1823	100	15
PKCm										PKCm(h)	113	6.5	45
PRKCN (PKD3)										PRKCN (PKD3)	109	6.2	Km app
ROCK2										ROCK2	179	10	100

Key: h=human; Km=the concentration providing half of enzyme maximal activity; km app=Apparent Km.

Based on these *in vitro* data, MMB may inhibit IKKα and CDK1/cyclin B, and the metabolite M21 may inhibit IKK family members. However, additional biochemical (e.g. containing physiologically relevant levels of ATP), cell mechanistic, or potentially translational studies would be necessary to establish the clinical relevance of the inhibitory activity of MMB, M21, or M19 on other kinases. The applicant has been requested to clarify the selectivity of MMB and M21 over other targets as a post-approval

commitment within two years after approval. Given the apparent loss of potency of M19 against JAK2 and the limited exposure of M19, the binding observed on other targets is unlikely to contribute to the clinical activity of MMB.

In primary human PBMCs, MMB had around 5-fold higher inhibitory activity on the JAK2-mediated phosphorylation of STAT5 with EC50 values of 59.6 nM, compared to JAK1/2-mediated phosphorylation of STAT3 (259 nM) and JAK1/3-mediated phosphorylation of STAT6 (235 nM). The metabolite M21 had lower inhibitory activities on these three pathways with EC50 ranged from 689 to 724 nM. In the U937 cell line, MMB inhibited IFNγ- or IFNα-mediated phosphorylation of STAT1 with IC50 values of 182 nM and 145 nM, respectively. Based on the biochemical IC50 values of JAK2 and TYK2 (5 and 133 nM, respectively) below the clinical free Cmax, inhibition of the IL-12-mediated phosphorylation of STAT4 is possible at clinically relevant doses. In conclusion, MMB demonstrated higher inhibitory activities on the signaling pathway involved for the targeted indication of myelofibrosis (myelopoiesis, erythropoiesis, thrombopoiesis, …), but inhibitory activities on other JAK signaling pathway are also possible at clinically relevant doses.

In cellular proliferation assays, MMB inhibited proliferation of JAK2-dependent BA/F3 murine myeloid cells (IC50=798 nM vs 1430 nM for parental cells and IC50 value of 2425 nM in JAK3-dependent cells), as well as JAK2V617F mutant HEL92.1.7 cells (IC50=1805 nM). In contrast, growth inhibition was minimal at an MMB concentration of 3 µM in a selection of 10 diverse tumor cell lines that were not dependent on the JAK pathway for proliferation. In Tyner et al. (2010), between 0.5 and 1.5 µM MMB caused growth suppression of JAK2-dependent hematopoietic cell lines with similar sensitivity between wild-type JAK2 and JAK2V617F, as well as in CMK cells which are dependent on both JAK1 and JAK3 due to an activating mutation of JAK3 (JAK3A572V). However, significant growth inhibition was observed in Molm14 cells which carry an internal tandem duplication of FLT3 and in cell lines engineered to express BCR-ABL. Overall, the data from panel of cell lines are consistent with growth inhibition of JAK2, but possibly on other JAK family-dependent cell lines and on other diverse tumor cell lines that do not depend on the JAK pathway for proliferation (e.g. FLT3, BCR-ABL) at clinically relevant doses.

MMB and M21 treatment resulted in a concentration-dependent reduction in BMP6-stimulated hepcidin RNA transcription in the HepG2 hepatoma cell line with EC50 values of 652 nM and 1420 nM, respectively. These data suggest that MMB and to a lesser degree, M21, may restore iron homeostasis via regulation of ACVR1-mediated hepcidin expression.

MMB and M21 were also shown to inhibit TNFα-induced NF-κB signaling with IC50 of 600 nM and 2900 nM, respectively. These data are in line with the observed binding to upstream NF-κB regulators IKK-α, IKK-β, and/or IKK-ε with potency values ranging from well below to above the clinical free Cmax. This suggest that inhibition of this pathway could be expected to positively contribute to overall activity, however it is currently unknown whether these mechanisms contribute to the activity of MMB and/or M21 in myelofibrosis patients. MMB demonstrated similar potency against erythroid (IC50 range: 0.90–1.21 µM) and myeloid (IC50 range: 0.81–1.29 µM) progenitor proliferation, which is line with expected inhibition of JAK2-dependent signaling pathway.

The *in vivo* activities of MMB were evaluated in one mouse MPN model (myeloproliferative neoplasm) dependent on JAK2V617F, which is relevant for the proposed indications. MMB either partially or fully normalized white cell counts, hematocrit, spleen size, reduced extramedullary hematopoiesis and returned normal hematopoiesis to the bone marrow in a dose- and time-dependent manner, with higher efficacy observed at 50 mg/kg (= 240 mg Human Equivalent Dose for an adult of 60 kg). MMB also reduced the concentration of inflammatory cytokines IL-17, IL-3, and IP-10 relative to control animals. No change was observed in body weight. In this model, despite the hematologic responses and reduction of the JAK2V617F allele burden, JAK2V617F cells persisted and MPN recurred upon

cessation of treatment. This suggest that inhibition of proliferation is observed, but there are no induction of apoptosis of the JAK2V617F-expressing cells. In this study, the overall impact of MMB on the homeostasis of blood cells in naive mice were also assessed, and doses up to 100 mg/kg had little to no effect on peripheral blood counts over a period of 8 weeks (= 480 mg Human Equivalent Dose for an adult of 60 kg).

In a rat ACD model, MMB-mediated inhibition of the JAK/STAT and ACVR1/SMAD pathways caused a reduction of pSTAT3 and pSMAD1/5/8 levels in the liver as well as a reduction of hepatic hepcidin gene (Hamp) transcription, which was not seen with ruxolitinib. There was an accompanying decrease in serum hepcidin, increase in serum iron, and RBC production in the bone marrow. However, erythropoietic precursors (I, II, and II) declined with increasing MMB doses, which could be related to JAK2 inhibition. In this rat ACD model, MMB also reduced IL-6 mRNA levels in the spleen, consistent with previous findings of its inhibitory effects on proinflammatory cytokines.

2.5.2.2. Secondary pharmacodynamic studies

The activity of MMB (10 µM) was evaluated against a panel of 42 enzymes in the Adverse Reaction Enzymes assay. Only potential UGT1A1 inhibition was considered clinically relevant, with IC50 of 0.3 µM. Additional *in vitro* studies showed that MMB at 10 µM had no activity against a panel of enzymes and receptors (targets involved in drug dependence, vasoactive receptors, ion channels, …).

MMB did not inhibit thiamine transport in Caco-2 and THTR-overexpressing cells, and therefore is unlikely to contribute to encephalopathy similar to that reported with fedratinib.

2.5.2.3. Safety pharmacology programme

Safety pharmacology studies conducted showed no relevant effects on respiratory function or the central nervous system of rats at the highest dose tested with exposures at least 6-fold estimated MMB free drug Cmax in human with MF at the clinical dose of 200 mg. In the 26-week toxicity study in rats and 39-week toxicity study in dogs, functional observational battery testing showed no MMB-related adverse effects. In addition, in the 39-week study in dogs, no MMB-related adverse effects were observed in the peripheral nerves at the terminal necropsy. However, in the 26-week study in rats, the non-GLP neuro-electrophysiological evaluation done around Tmax showed at the highest dose of 50 mg/kg/day, reversible, mild slowing of caudal and digital nerve conduction velocity, but were not associated with any significant changes in the tibial motor responses or any changes in the amplitudes for either the caudal or digital nerves. These effects were observed at exposure margins of 6 and 11, based on MMB free Cmax and AUC, respectively, at the clinical dose of 200 mg. There were no safety margins for the metabolite M21. Additional non-GLP *in vitro* studies performed on ion channels associated with peripheral nerve function showed no inhibition at doses up to 3 µM (safety margin of 14 based on MMB free Cmax). Although there are sufficient safety margins based on free exposure for MMB, there were no safety margins for the major active metabolite M21 present at low levels in rats. In clinical trials, peripheral neuropathy was observed and therefore adverse effects observed on velocity in rats may be considered clinically relevant.

The cardiovascular *in vitro* studies showed that MMB was a weak inhibitor of hERG channel K+ current (IC50>10 µM), with no clinical relevance. Although this study was not considered with GLP compliance, this is considered acceptable taking into account the available GLP *in vivo* cardiovascular in dogs and the clinical data in thorough QT study. Cardiovascular safety parameters evaluated in dogs indicated that MMB did not significantly affect cardiovascular parameters at doses up to 30 mg/kg in the safety pharmacology study. On day 1 MMB decreased arterial blood pressure and concurrently increased HR at 100 mg/kg, which is approximately 4-fold above the estimated free drug Cmax in humans with MF.

The metabolite M21 was not detected in dog plasma, or at very low levels. In the 13-week study in dogs, dose-related increases in heart rate were observed at ≥ 8.5 mg/kg/day, correlated at 51 mg/kg/day with physiologic shortening of the PR interval (up to -13%) and QT intervals (up to -12 ms), but were not considered clinically significant. In human, no MMB-related adverse effects were observed in the thorough QT study.

2.5.2.4. Pharmacodynamic drug interactions

MMB is intended to be administered as monotherapy in line with SmPC. The absence of pharmacodynamic drug interactions studies is considered acceptable.

2.5.3. Pharmacokinetics

The analytical methods are well described in the respective bioanalytical and validation reports. For some pivotal GLP toxicology studies, toxicokinetics analysis were not performed in compliance with GLP (8283319 4-week in mice; 8336287 4-week impurities in rats ; WIL-604183 Juvenile DRF in rats ; WIL-604256 Juvenile in rats and 8283320 26-week study carcinogenicity in mice), but validation was conducted following the principles of GLP. For the other pivotal GLP studies, SOP deviations were acknowledged and documented in the raw data, but none of the analytical method or SOP deviations were considered to have affected the quality or integrity of the study. The analysis of thiocyanate levels, thiamine and thiamine diphosphate were not performed with GLP compliance.

The *in vitro* permeability studies indicates that the intestinal absorption of MMB in humans is likely to be high.

In mice after oral administration, MMB was absorbed with Tmax of 0.5 hours to 8 hours. The increases in MMB and M19 exposure were suprapropportional at lower doses (10 to 100 mg/kg), but subproportional at higher doses (from 100 to 300 mg/kg). The increases in M20 and M21 exposure were suprapropportional at lower doses (10 to 30 mg/kg), but subproportional at higher doses (from 30 to 300 mg/kg). The metabolite M19 was present at higher levels with mean metabolite to parent exposure ratios up to 0.189, compared to metabolites M20 and M21 with mean metabolite to parent exposure ratios up to 0.007. The exposures of MMB and its metabolites in the 500 mg/kg group were similar to the 300 mg/kg, which may be indicative of saturated absorption.

The PK of MMB was evaluated in rats with different formulation (free base, solution or suspension, 3 MMB salt forms). The formulation of MMB as a dihydrochloride salt in solution was selected for further non-clinical and clinical development. Following IV administration as a dihydrochloride salt, the systemic CL of MMB was low (0.47 L/h/kg) and the volume of distribution was 0.8 L/kg. MMB is therefore well distributed into tissues. The absolute oral bioavailability of MMB dihydrochloride was moderate (50 to 70.1%). The absorption of MMB following oral administration of the dihydrochloride salt was 1.7 to 3 hours postdose. The half-life of MMB dihydrochloride was short (1.7 to 2.2 hours). In rats, following oral administration of MMB dihydrochloride, the metabolites M19 and M21 were present at lower levels with mean metabolite to parent exposure ratios of 0.04 and 0.008, respectively.

Following a single IV dose of MMB dihydrochloride in dogs, a short half-life of 0.7 hours, a clearance of 1.8 L/h/kg and a volume of distribution of 2.4 L/kg were observed. Following a single oral dose of MMB dihydrochloride in dogs, higher absolute oral bioavailability of MMB (38% fed vs <21% fasted), delayed time to Cmax (3 hours fed vs 1 hour fasted) and higher AUC exposure (2-fold higher fed) were observed in fed status, compared to fasted status. The oral bioavailability of MMB in dogs was lower than in rats. No information about the metabolites are available for dogs in PK studies.

In human, as indicated in the SmPC, MMB is rapidly absorbed after oral administration with the maximal plasma concentration (Cmax) achieved within 3 hours post-dose. Following an oral dose of MMB 200 mg, the mean terminal half-life (t½) of MMB was approximately 4 to 8 hours; the half-life of M21 was similar. In both rats and dogs, following single oral administration of MMB dihydrochloride, like in human, rapid absorption of MMB was observed (up to 3 hours) with short half-life (up to 1.7 hours).

MMB, M8, M19, and M21 displayed moderate to high protein binding in plasma from all species, with higher protein binding in rat plasma compared with the other species. Unbound MMB was 11.8% in mouse, 2.5% in rat and 19.2% in dog and human. Unbound M8, M19 and M21 ranged from 0.9 to 66.6% across species. The plasma protein binding of MMB and metabolites has not been investigated in rabbits.

In vitro B/P concentration ratio for MMB was approximately 0.6-0.8 and 1.1 in rat and human blood, respectively, suggesting almost 2-fold higher distribution in the erythrocyte fraction in human. Because of the expected pharmacological activities of MMB on blood cells, in case of decreased in blood cells observed after administration of MMB, it will be difficult to determine whether this effect is due to the pharmacological activities or due to distribution in red blood cells.

Following a single oral dose (80 mg/kg; 100 µCi/kg) of ^{14}C-MMB to male SD (nonpigmented) and Long Evans (partially pigmented) rats, MMB was widely distributed in tissues with radioactivity in most tissues reaching a maximum concentration at 4 hours, with subsequent declining plasma concentrations through 120 hours post dose. MMB-associated radioactivity was similar in SD and Long Evans rats with wide tissue distribution and the highest concentrations of radioactivity in alimentary canals for both the nonpigmented and pigmented animals. Radioactivity was nonquantifiable in bone, brain, spinal cord, and testis at all sampling times suggesting low penetration of ^{14}C-MMB-derived radioactivity across the blood-brain and blood-testis barriers. Except for skin (pigmented) and eye uveal tract in Long Evans rats, where radioactivity was declining but still quantifiable at 168 hours post dose, radioactivity was cleared from tissues by 72 hours post dose, suggesting reversible binding. Consistent with low brain concentrations of ^{14}C-MMB in rats following oral dosing, brain uptake of MMB was low in Swiss mice following an IV injection at a 5 mg/kg dose level, with a brain:plasma ratio of approximately 0.215±0.036 at 60 minutes post dose.

In a prenatal and postnatal development study in SD rats, plasma MMB was not extensively converted to M19 or M21. Plasma AUC values of MMB in dams on Lactation Day 10 (LD10) were approximately 4- to 8-fold greater than in pups, while plasma M19 exposure in dams was approximately 2- to 3-fold lower than that of pups. Although the presence of MMB has not been quantified in milk, the presence of MMB and metabolites in plasma of the pups suggest that MMB may be present in milk.

The rates of MMB metabolism in liver microsomes and in hepatocytes from human and various animal species were low to moderate and showed no major species differences in the relative rate of metabolism. The *in vitro* studies on metabolism had limited success to detect metabolic products, and therefore species comparison could not be made. The *in vitro* studies using human hepatocytes demonstrated that multiple CYP enzymes are largely responsible for the metabolism of MMB (CYP3A> CYP2C8 ~ CYP2C19 ~ CYP2C9 > CYP1A2).

The *in vivo* studies in animal species (mouse, rat and dog) showed that the three most abundant metabolites across the species were M19 (an amide hydrolysis product of MMB), M20 (a morpholino cleavage metabolite), and M21 (a morpholino lactam metabolite). Other metabolites in lower abundance included M8, M16, and M17. The amount of M19 was 3 to up to 33-fold greater in dog and rat, respectively, than in pooled human samples, and the amount of M20 was 5 to 11-fold greater in the rat than in the human pool. The major active metabolite M21 in human plasma was present in rat plasma but at 0.2-0.5-fold lower levels and was not detected in the dog. M8 was a minor metabolite in

humans, detected at low abundance in one study in rat, and not detected in dog. There were no unique human metabolites. Rat is therefore a more relevant animal species than dog based on metabolism data, as the major active metabolite M21 is not present in dog.

The hydrolysis of MMB to M19 (major pathway in animal species but not in human) leads to the simultaneous formation of aminoacetonitrile, which can undergo further metabolism to form thiocyanate. The levels of thiocyanate in plasma were evaluated in rat and dog studies (see below in section "Repeat-dose toxicity studies"). In human, levels of thiocyanate were not considered clinically significant.

Following a single oral dose of ^{14}C-MMB to intact mice, rats and dogs, total radioactivity derived from ^{14}C-MMB was eliminated into feces (>70% in all nonclinical species), with minor clearance via urinary excretion (<15% in all animal species). Since the biliary excreted radioactivity were up to 33% and 42% in bile-cannulated rats and dogs, respectively, almost half of the radioactivity excreted in feces was from biliary excretion rather than incomplete absorption. Biliary excretion is therefore the major route of elimination of ^{14}C-MMB-derived radioactivity. Based on the radioactivity excreted in urine and bile after oral administration, a minimum of approximately 49% and 44% of the orally administered dose was absorbed in rats and dogs, respectively. Most of the radioactivity derived from ^{14}C-MMB was excreted after oral administration, within 24 to 48 hours after dosing in animal species. The excretion data in animal species are consistent with data from a human mass balance study where after oral administration of 200 mg ^{14}C-MMB, ^{14}C-MMB was primarily eliminated in the feces (~69.3%) versus urine (~27.5%).

2.5.4. Toxicology

The toxicology program was performed in line with ICH M3(R2) guideline. Sprague Dawley rat, Beagle dog, rasH2 mouse and New Zealand White rabbit were selected for the pivotal nonclinical toxicity studies. Biochemical and biophysical potency data for MMB or its metabolites against non-human orthologs of JAK family enzymes are not available, but the kinase domains of JAK1, JAK2, JAK3, TYK2, and ACVR1 are well conserved between human and animal species. The main toxicity findings in the animal species used in the MMB toxicology program (mice, rats, rabbits and dogs) are consistent with effects reported for modulating JAK1, JAK2 and ACVR1 kinases and subsequent downstream sequelae, which support the relevance of animal species used in the toxicology studies. For the repeat-dose toxicity studies, rat is a more relevant animal species from PK point-of-view, compared to dog.

2.5.4.1. Single dose toxicity

Single dose toxicity studies were performed with MMB free base or MMB bis-bisulfate. In mice, MMB was well tolerated at doses up to 50 mg/kg BID. In rats, single oral maximum tolerated dose of MMB was 500 mg/kg. Reversible hematology changes observed at ≥ 250 mg/kg were consistent with the on-target pharmacologic action of MMB on JAK family. In dogs, MMB was well tolerated at doses up to 500 mg/kg.

2.5.4.2. Repeat dose toxicity

In the repeat-dose toxicity studies in mice, rats and dogs, findings included reduced red cell mass (red blood cell count, hemoglobin, hematocrit), as well as lower white blood cell count correlated with dose-related cellular depletion in the bone marrow (femur and sternum) and with lymphoid depletion in the spleen, lymph node, thymus, and/or gut-associated lymphoid tissue. Recovery from the cellular and lymphoid depletion was noted but incomplete upon cessation of dosing. The leukopenia and

lymphopenia did not result in opportunistic infections or neoplasms in the repeat-dose toxicity studies in both rats and dogs, as well as in the mouse and rat carcinogenicity or rat, although in the clinical trials with MMB, infection was a very common adverse reaction reported, in line with the class effect reported with other JAK inhibitors. These findings are consistent with the pharmacological activity of MMB on janus kinases involved for hematopoiesis and immune response, and are clinically relevant.

Decreased testes and epididymal weights were noted in 13- and 26-week toxicity studies in rats, correlating with degeneration/atrophy of germinal epithelium within seminiferous tubules of the testes, and oligospermia/germ cell debris in the epididymis. Similar microscopic findings in the testes and epididymides were also noted in a 4-week rat study. These effects were more severe at ≥ 50 mg/kg/day and irreversible, and occurred at exposure margins of 93 and 12 based on MMB total and free AUC, respectively, at the clinical dose of 200 mg. However, no radioactivity was detected in the testes of SD or Long Evans rats after a single dose of dose of 80 mg/kg 14C-MMB. In dogs, mild spermatid/spermatocyte degeneration in the testes and a mild increase in germ cell debris in the epididymides in males was observed in all groups including control group, and were considered related to the stage of sexual maturity (recently mature).

Histopathology findings in the female rat reproductive system included an increased incidence of corpora hemorrhagica, luteal cysts, and follicular cysts in the ovaries after administration of ≥ 30 mg/kg/day in the 4-week toxicity study. Epithelial degeneration was observed in the cervix at ≥ 10 mg/kg/day. There were no alterations to the female reproductive organs in the 13- or 26-week rat repeat-dose toxicity studies where the high dose was 68 mg/kg/day and 50 mg/kg/day, respectively.

Dose-limiting toxicities in the dog studies was inappetence and decreased body weight gain and/or body weight in the 4-week study at 100 mg/kg/day and the 39-week study at 50 mg/kg/day (exposure margin of at least 2.8 based on MMB total/free AUC).

In the 39-week study in dogs, an increase in posterior subcapsular cataracts was noted in 2 males and 3 females administered the high MMB dose of 50 mg/kg/day (exposure margin of 2.8 based on MMB total/free AUC). The cataracts were present after a 6-week recovery period in 1 male and 2 females that were retained. In the rat tissue distribution study, no radioactivity was detected in the eyes or lens of SD rats or in the lens of Long Evans rats. There were low levels of radioactivity detected in the eyes of Long Evans rats 8 and 24 hours after a single dose of 80 mg/kg 14C-MMB. The significance of this finding is unknown, but the incidence of cataracts was not increased in MMB-treated subjects in clinical studies.

In the 26-week study in rats and in the repeat-dose toxicity studies, effects on peripheral and central nervous systems and on cardiovascular system were observed and has been further discussed above in section “Safety pharmacology”.

Histopathology findings in the 4-week rat toxicity study that were not observed in the longer duration studies or in dogs included hemorrhage in the gastrointestinal tract at ≥ 30 mg/kg/day, hemorrhage at the base of the heart in a few males administered 100 mg/kg/day, and a decreased incidence of minimal mononuclear infiltration in the liver at 100 mg/kg/day. The hemorrhage findings may be related to off-target effects toward VEGFR and/or FGFR family kinases and occurred at exposure margins of at least 58 and 7.6 based on MMB total and free AUC, respectively, at the clinical dose of 200 mg. In the clinical trials with MMB, haemorrhagic events were observed, but bleeding events are not uncommon in patients with myelofibrosis and may not be attributed to MMB.

Although the major active metabolite M21 is not considered qualified based on free exposure in animal species in line with the ICH M3(R2), it can be considered qualified based on pharmacodynamic activities similar to MMB. In addition, the adverse effects reported in the toxicology studies were consistent with those reported for other drugs in this class. Taking into account the clinical experience

with MMB, additional toxicology studies with administration of the metabolite M21 were not considered necessary.

The hydrolysis of MMB to M19 leads to the simultaneous formation of aminoacetonitrile, which can undergo further metabolism to form cyanide and further formation of thiocyanate. In animal species, MMB is mainly metabolized in M19, but not in human. In the 4-week study in rats and dogs, plasma thiocyanate analysis indicated dose-concordant increases in thiocyanate levels over the dosing period, but the levels were below than concentrations reported to cause toxicity. In human, levels of thiocyanate were not considered clinically significant.

Because inhibition of thiamine transporters has been proposed as a putative mechanism for the Wernicke encephalopathy reported during clinical development of the JAK inhibitor fedratinib, non-GLP additional studies were performed and showed no differences in mean plasma thiamine or thiamine diphosphate levels in the 39-week study in dogs. Such studies were not performed in rats.

2.5.4.3. Genotoxicity

The data from the standard battery of genotoxicity assessments, in line with ICH S2(R1), indicated that MMB does not present a genotoxic hazard to humans. No *in vitro* genotoxicity studies were performed with the major active metabolite M21. In the *in vivo* micronucleus test in rats, doses up to 1000 mg/kg of MMB were administered. Based on the TK data observed in the repeat-dose toxicity study in rats, the metabolite M21 should has been present at sufficient exposure levels to be considered as qualified.

2.5.4.4. Carcinogenicity

In the 104-week carcinogenicity study in rats, neoplastic findings were limited to an increased incidence of testicular interstitial (Leydig) cell adenomas in males at 15 mg/kg/day (18.33%), as well as at 5 mg/kg/day MMB plus 25 mg/kg/day M21 with lower incidence (10%). This finding was correlated with increased incidence of testicular enlargement and various testicular discolorations or foci observed macroscopically. This was considered most likely associated with JAK2-mediated inhibition of prolactin signaling pathways in the rat, while human health risk is considered unlikely as human Leydig cells lack similar prolactin dependence for normal function (Chapin, 2017). Except these findings with unlikely human relevance, no other tumorigenicity findings were observed at doses up to 15 mg/kg/day MMB, with exposure margins based on total and free AUC of 33 and 4.3 for MMB, respectively, at the clinical dose of 200 mg. There is no safety margin for the metabolite M21. In the 26-week carcinogenicity study in transgenic mice, there were no MMB-related neoplasms in animals administered up to 100 mg/kg/day, although there was a clear carcinogenic response in animals administered the positive control article. At the NOEL of 100 mg/kg/day, the safety margins are 26 and 16, based on MMB total and free AUC, respectively at the clinical dose of 200 mg. There is no safety margin for the active metabolite M21, as MMB was not converted extensively to M21.

2.5.4.5. Reproductive and developmental toxicity

Consistent with the MMB-related adverse effects observed on male reproductive system in the repeat-dose toxicity studies, MMB had adverse effects on male reproductive system at ≥ 25 mg/kg/day (reduced seminal vesicle weight and reduced sperm concentration and motility) and reduced fertility at 100/68 mg/kg/day in the fertility and early embryonic development study. These effects are consistent with a combination of MMB-related inhibition of ACVR1 (ALK2) resulting in reduced activin signaling during spermatogenesis and reduced JAK/STAT signaling in different stages of the spermatogenic

cycle. The NOAEL for male fertility was considered to be 5 mg/kg/day, and corresponds to safety margins of 10 and 1 based on MMB total and free AUC, respectively, at the clinical recommended dose of 200 mg. The clinical translational relevance is unknown. In the GLP fertility and early embryonic development study in female rats, effects on female reproductive system were observed at 100/68 mg/kg/day (reduced numbers of corpora lutea and mean number of estrous cycles, reduced mean ovarian and vagina weight) and reduced fertility was observed at ≥ 25 mg/kg/day (increase in early resorptions, increased post-implantation loss and decreased number of live fetuses). ACVR1 signaling is important in ovarian development and function along with folliculogenesis, and MMB inhibition of ACVR1 signaling was the likely mechanism for the adverse female reproductive effects observed. The NOEL for maternal toxicity and fertility was 5 mg/kg/day and the NOEL for early embryonic development was 5 mg/kg/day, and corresponds to safety margins of 22 and 3 based on MMB total and free AUC, respectively, at the recommended clinical intended dose of 200 mg. In the SmPC, it has been highlighted that MMB impaired fertility in rats in section 4.6, and effects of MMB observed in male and female fertility studies have been described in section 5.3. No specific recommendations regarding male and female fertilities in human have been included in the SmPC.

MMB, when administered orally to pregnant rats and rabbits during organogenesis showed evidence of embryo-fetal toxicities, but no teratogenicity. In rats, maternal toxicity was observed at 68 mg/kg/day and was associated with embryonic death, soft tissue anomalies, and decreased foetal weights and skeletal variations at 6 mg/kg/day and higher (approximately 8-fold and 1-fold the recommended dose of 200 mg daily based on total and free AUC, respectively). One visceral malformation (absent aortic arch) was reported in two fetuses from two different litters in the high dose group only, and may be related to ACVR1 inhibition as this receptor has a role in outflow tract development in response to BMP signaling. The NOEL for embryo-fetal effects at 2 mg/kg was approximately 2 and 0.2 times higher than the total and free AUC, respectively, observed at the recommended dose of 200 mg. There are no safety margins for any metabolites, including the major active metabolite M21. In rabbits, severe maternal toxicity and evidence of embryo-foetal toxicity (abortions, embryonic deaths, decreased foetal weights and/or decreased foetal skeletal ossification) were observed at 60 mg/kg/day and higher (exposure equivalent to the recommended dose of 200 mg based on AUC). The NOAEL at 30 mg/kg/day was lower than the AUC observed at the recommended dose of 200 mg daily. In the SmPC, the embryo-fetal toxicities observed in animal species have been highlighted in section 4.6, and the effects of MMB observed in EFD studies have been described in section 5.3. Based on the low or absence of safety margins at clinical exposures, the role of JAK2 in development described in the literature and the known class effects of other marketed JAK inhibitors, contra-indication for pregnancy has been included in the SmPC.

In an oral pre- and post-natal development study, rats received oral administration of MMB from gestation to end of lactation. Evidence of maternal toxicity, increases in embryonic and foetal death, and decreased birth weights were observed at doses of 6 mg/kg/day and higher. Pup survival was significantly reduced at 6 mg/kg/day or higher from birth to lactation and was therefore considered a direct effect of MMB via exposure through the milk. The free AUC exposure at the NOAEL for both maternal and F1 litters at 2 mg/kg/day was lower than the AUC observed at the recommended dose of 200 mg daily. Taking into account that exposure to momelotinib through the milk was observed at clinically relevant exposures and that potential toxic effects on fetal bone development have been observed with certain approved JAK inhibitors, contra-indication during breast-feeding has been included in the SmPC.

In the pivotal juvenile toxicity study in rats, reversible lower mean body weights and body weight gains (with corresponding lower mean food consumption) that resulted in shorter mean tibial lengths and femur lengths, a delay in the age of attainment in balanopreputial separation, and decreased forelimb grip strength during the FOB assessment occurred at 10 mg/kg/day from PND 7 through 56. Reversible

memory impairment was noted in males at 10 mg/kg/day during the Biel maze assessment during the dosing phase. There were no adverse MMB-related effects on reproductive endpoints or spermatogenic endpoints, but higher postimplantation loss resulting in lower mean number and litter proportion of viable embryos was noted at 10 mg/kg/day. The NOAEL for juvenile toxicity at 3 mg/kg was approximately 2.4 and 0.3 times higher than the total and free AUC, respectively, observed at the recommended dose of 200 mg.

2.5.4.6. Toxicokinetic data

In rats, the systemic MMB exposures (Cmax and AUC) increased generally in a greater than dose-proportional manner at doses below 30 mg/kg/day, and in a less than dose-proportional manner at higher doses. Systemic MMB exposure (Cmax and AUC0-24) was in general slightly higher in females than males. Low accumulation of MMB has been observed with repeating dosing, but generally less than 2-fold. In rats, MMB was mainly metabolized in M19 and less to M21, M20 and M17. Systemic exposures to all metabolites were lower than to MMB. The metabolites M17 and M19 appeared to be generally higher in females than males while the metabolites M20 and M21 appeared to be sex-independent.

In dogs, the systemic MMB exposure (Cmax and AUC) increased generally in an approximate dose-proportional manner or in a less than dose-proportional manner. Systemic MMB exposure (Cmax and AUC0-24) was in general similar between male and female dogs. Decreased systemic MMB exposure (Cmax and AUC) was observed overtime until week 13 (less than 2-fold in general), but MMB exposure at week 39 was in general similar than at day 1. In dogs, MMB was mainly metabolized in M19 but exposures were at lower levels than MMB. The metabolites M21, M20, M17 were barely or not present.

In mice, Systemic exposure to MMB, M19, M20, and M21 generally increased with the increasing MMB dose level with less than 2-fold differences in exposure between sexes and no accumulation. MMB was not converted extensively to M21, M20, or M8.

In rabbits, available AUC0-t metabolite to parent ratios indicated that MMB was not extensively converted to M21 but was extensively converted to M19. Systemic Cmax and AUC increases in MMB, M19 and M21 were generally greater than dose proportional, but no accumulation was observed.

2.5.4.7. Local Tolerance

In vitro studies showed that MMB is considered to be corrosive (UN Packing Group III category 1C) and to be a severe eye irritant (category 1).

2.5.4.8. Other toxicity studies

MMB did not show the potential to induce skin sensitization using the Local Lymph Node Assay in the Mouse. MMB is a chemical substance that will be administered orally, and there are no concerns for antigenicity.

In the toxicology studies in animal species, immunotoxicity was observed and is linked to the pharmacological activity of MMB (class effect of JAK inhibitors). In clinical trials with MMB, infections were very common adverse reactions. This has been highlighted in the SmPC. No additional non-clinical immunotoxicity studies are needed.

The absence of dependence studies for MMB is considered acceptable.

Two 4-week oral toxicity studies were conducted in rats to qualify impurities and potential impurities in the Good Manufacturing Practice material. The impurities spiked into the drug substance did not alter the NOAEL in rats. The impurities have been tested with two QSAR methodologies (prediction with Leadscope model applier (statistical-based), Derek Nexus (expert rule-based) and/or CASE Ultra (expert rule-based)). All the impurities tested in the 4-week toxicology studies are categorized as class 5 (non-mutagenic). During the manufacturing process, genotoxic impurities are formed, but control strategies are applied (see quality report).

MMB has no phototoxic potential.

2.5.5. Ecotoxicity/environmental risk assessment

Table 1. Summary of main study results

Substance (INN/Invented Name): momelotinib			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	Unknown, additional data should be provided	pH 7: 2.7	Potential PBT (additional data should be provided)
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.009	μg/L	> 0.01 threshold (N)
Other concerns (e.g. chemical class)			(N)

The Predicted Environmental Concentration in surface water (PECsurfacewater) has been calculated with a refined Fpen based on literature reference (Moulard, et al., 2012), which is considered acceptable taking into account that myelofibrosis is a rare disease. The Phase I assessment was completed based on a maximum daily dose of 200 mg active ingredient per inhabitant per day, daily consumption of 1 tablet for 365 days per year and a conservative prevalence of 9 cases of myelofibrosis per 100,000 individuals. Based on these input values, the conservative PECsurfacewater is calculated to be 0.009 µg/L, and is below the cut-off of 0.01 µg/L. MMB is not classified as endocrine active substances, parasitics or antibiotic. No Phase II assessment is required.

The applicant committed to conduct additional study for the calculation of the octanol/water partitioning coefficient (Kow) as a post-approval commitment (CHMP Recommendation), in line with guideline on the environmental risk assessment of medicinal products for human use (EMA/CHMP/SWP/44609/2010 Rev. 1). If the Kow value at any pH value between pH 5 and pH 9 meets the trigger values for PBT assessment (log Kow > 4.5), further PBT assessment is required. The updated ERA and the study reports should be provided within 2 years following approval.

2.5.6. Discussion on non-clinical aspects

Overall, the pharmacological studies provide evidence for inhibition of JAK family kinases and ACVR1 that support efficacy in humans. The applicant has committed to clarify the selectivity of MMB and M21 on JAK family kinases compared to other targets, as well as to discuss the clinical relevance, as a post-approval commitment (**CHMP Recommendation**) within two years after approval. The repeat-dose toxicological data showed adverse effects related to the pharmacological activity of MMB on JAK family kinases. The non-clinical findings are in line with adverse effects observed in the clinical program.

Based on the low or absence of safety margins at clinical exposures in the reproductive and developmental toxicity studies, the role of JAK2 in development described in the literature and the known class effects of other marketed JAK inhibitors, contra-indication during pregnancy and breast-feeding has been included in the SmPC.

With regards to the environmental risk assessment, momelotinib PEC $_{surfacewater}$ value is below the action limit of 0.01 μg/L and is not a PBT substance as log K_{ow} does not exceed 4.5. Therefore momelotinib is not expected to pose a risk to the environment. As a post-approval commitment (**CHMP Recommendation**) within two years after approval, the applicant should conduct additional studies for the calculation of the octanol/water partitioning coefficient (Kow), and further PBT assessment if needed.

2.5.7. Conclusion on the non-clinical aspects

From a non-clinical perspective, the MAA for Omjjara is approvable.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 5: Clinical Studies Contributing to the Clinical Pharmacology of MMB

Study Phase/Number	Key Clinical Pharmacology Objectives
Phase 1-2: Subjects With MF	
CCL09101	To determine the PK of MMB in subjects with PMF or post-PV/ET MF.
YM387-II-02	To determine the PK of BID, orally administered MMB in subjects with PMF or post-PV/ET MF.
Phase 2: Subjects With MF	
GS-US-352-1672	To evaluate MMB PK in transfusion-dependent subjects with MF. To assess biomarkers of inhibition of JAK1/2 and ACVR1 in transfusion-dependent subjects with MF treated with MMB.
Phase 3: Subjects With MF	
MOMENTUM (SRA-MMB-301)	Sparse blood samples were collected for PK evaluation at times corresponding to trough concentrations (predose and at the week 8, 16, and 24 visits).
SIMPLIFY-1 (GS-US-352-0101)	Sparse blood samples were collected for PK evaluation at times corresponding to trough concentrations (predose). In addition, rich PK sampling was performed in a subset of subjects to provide a more thorough evaluation of PK parameters.
SIMPLIFY-2 (GS-US-352-1214)	Sparse blood samples were collected for PK evaluation at times corresponding to trough concentrations (predose). In addition, rich PK sampling was performed in a subset of subjects for noncompartmental analysis and evaluation of PK parameters.
Phase 1: Subjects With Renal Impairment	
GS-US-352-1152	To evaluate the PK of MMB and its metabolites (GS-644603 [M21] and GS-642112 [M19]) in subjects with impaired renal function compared with matched healthy controls.
Phase 1: Subjects With Hepatic Impairment	

Study Phase/Number	Key Clinical Pharmacology Objectives
GS-US-352-1153	To evaluate the PK of MMB and its metabolites (GS-644603 [M21] and GS-642112 [M19]) in subjects with impaired hepatic function compared with matched healthy controls.
Phase 1: Healthy Subjects	
YM387-I-02 (Bioequivalence and food effect)	To evaluate relative bioavailability and bioequivalence of single oral doses of MMB tablet to capsule and food effect on MMB tablet.
GS-US-352-0102 (Food effect, Dose proportionality, Relative bioavailability, and DDI potential)	Primary objectives: To assess the relative bioavailability of a tablet formulation of MMB compared with the capsule To explore the effect of high-fat and low-fat meal types on the PK of MMB administered as a tablet formulation To evaluate the effect of omeprazole, a representative proton pump inhibitor, on the PK of MMB
GS-US-352-1150 (Thorough QT study)	To evaluate the effect of MMB at therapeutic (200 mg) and supratherapeutic (800 mg) doses on QTc interval and other cardiovascular parameters in a single-dose crossover design using a time matched, baseline-adjusted, and placebo-corrected approach
GS-US-352-0108 (Race/ethnicity)	To investigate the PK of MMB following single-dose administration in healthy Japanese and Caucasian subjects.
GS-US-352-1151 (DDI)	Primary objectives: To evaluate the effect of multiple doses of the strong CYP3A4 inhibitor ritonavir on the PK of MMB To evaluate the effect of multiple doses of the strong CYP3A4 inducer rifampin on MMB PK To evaluate the effect of a single dose of the OATP inhibitor rifampin on MMB PK To evaluate the effect of multiple doses of MMB on CYP3A enzyme activity using the probe substrate MDZ To evaluate the effect of multiple doses of MMB on BCRP using the probe substrate rosuvastatin
GS-US-352-1149 (Mass balance)	The primary objective was to determine the major routes of MMB elimination using a mass balance analysis following administration of a single oral dose of radiolabeled [^{14}C]-MMB. Secondary objectives: To evaluate the PK of MMB and metabolite(s), where possible To determine the metabolite profile of MMB in humans
ACVR1, activin A receptor type 1; BCRP, breast cancer resistance protein; BID, twice daily; CYP, cytochrome P450; DDI, drug drug interaction; ET, essential thrombocythemia; JAK, Janus kinase; MDZ, midazolam; MF, myelofibrosis; MMB, momelotinib; OATP, organic anion transporting polypeptide; PK, pharmacokinetics; PMF, primary myelofibrosis; PV, polycythemia vera; QTc, QT interval corrected.	

Table 6: Phase 2 and 3 Clinical Studies of MMB in Subjects With Myelofibrosis

Study ID / Acronym [1] Status First Subject Screened/ LSLV Regions	Patient population	Study Design	Dosing Regimen (MMB Tablets)	Planned / Actual Enrollment, Treated, Completed	Duration of Treatment [2]	Primary Endpoint
SRA-MMB-301 **MOMENTUM [3]** RT period completed; OL	Subjects with intermediate-1 intermediate-2 or high-risk (DIPSS or DIPSS-Plus) PMF, post-PV MF, or post-ET MF. Symptomatic (MFSAF TSS ≥	Phase 3, international, randomized, double-blind, active-controlled, followed by optional open-label MMB or DAN	RT period MMB or DAN (2:1) and matching placebo: MMB 200 mg QD and DAN-placebo BID or DAN 300 mg BID and MMB-placebo QD	Planned, ~180/ actual, 195 RT period Treated, 195 (130 MMB, 65 DAN) Completed 24 weeks, 132 (94 MMB, 38 DAN)	RT period 24.00 weeks MMB, 23.71 weeks DAN MMB overall (including DAN→MMB) 26.71 weeks	First MFSAF TSS response rate at week 24, assessed using the MFSAF v4.0 questionnaire Second

Study ID / Acronym [1] **Status** **First Subject Screened/ LSLV** **Regions**	**Patient population**	**Study Design**	**Dosing Regimen (MMB Tablets)**	**Planned / Actual Enrollment, Treated, Completed**	**Duration of Treatment [2]**	**Primary Endpoint**
treatment period ongoing; data cutoff 03 Dec 2021 for week 24 analysis Feb 2020/ Dec 2021 for week 24 analysis Europe, North America, Asia, Australasia	10) Splenomegaly (palpable spleen ≥ 5 cm below LCM or spleen volume ≥ 450 cm^3) **Anemic (Hgb < 10 g/dL)** **Prior JAK inhibitor**		<u>OL treatment period</u> MMB→MMB: dose received in RT period DAN→MMB: MMB 200 mg QD DAN→DAN: 400 mg (max total daily dose)	<u>OL treatment period</u> Treated, 132 (92 MMB→MMB, 40 DAN→MMB, 0 DAN→DAN) <u>MMB overall</u> Treated, 170 MMB (130 MMB, 40 DAN→MMB)	Planned maximum duration of participation was approximately 7 years, with possibility to continue in extension study	TI rate at week 24, defined as the proportion of subjects with TI in the terminal 12 weeks of the 24-week RT period
GS-US-352-0101 **SIMPLIFY-1** Completed Study termination by sponsor [4] Dec 2013/ May 2019 Europe, North America, Australia, Asia	Subjects with intermediate-2 or high-risk (IPSS) PMF, post-PV MF, or post-ET MF. Intermediate-1 (IPSS) MF patients are allowed if associated with symptomatic splenomegaly, hepatomegaly, anemia (Hgb < 10 g/dL), and/or unresponsiveness to available therapy Splenomegaly (palpable spleen ≥ 5 cm below LCM) **JAK inhibitor naive**	Phase 3, international, randomized, double-blind, active-controlled, followed by optional open-label MMB	<u>RT period</u> MMB or RUX (1:1) and matching placebo: MMB 200 mg QD and RUX-placebo BID or RUX BID [5] and MMB-placebo QD <u>OL treatment period</u> MMB→MMB: dose received in RT period RUX→MMB: dose matching the equivalent MMB-placebo dose	Planned, ~420/ actual, 432 <u>RT period</u> Treated, 430 (214 MMB, 216 RUX) Completed 24 weeks, 376 (175 MMB, 201 RUX) <u>OL treatment period</u> Treated, 368 (171 MMB→MMB, 197 RUX→MMB) <u>MMB overall</u> Treated, 411 (214 MMB, 197 RUX→MMB)	<u>RT period</u> 23.9 weeks MMB, 24.0 weeks RUX <u>MMB overall (including RUX→MMB)</u> 77.0 weeks Planned maximum duration of participation was approximately 5 years, with possibility to continue in extension study	SRR at week 24, defined as the proportion of subjects with a reduction in spleen volume ≥ 35% from baseline at week 24 as measured by MRI or CT scan
GU-US-352-1214 **SIMPLIFY-2** Completed Study termination by sponsor [4] Jun 2014/ Apr 2019 Europe, North America, Asia	Subjects with intermediate-2 or high-risk (DIPSS) PMF, post-PV MF, or post-ET MF. Intermediate-1 (DIPSS) MF patients are allowed if associated with symptomatic splenomegaly, and/or hepatomegaly Splenomegaly (palpable spleen ≥ 5 cm below LCM) **Prior ruxolitinib**	Phase 3, international, randomized, open-label, BAT-controlled, followed by optional extended treatment with MMB	MMB or BAT (2:1) MMB 200 mg QD or BAT (including RUX)	Planned, ~150/ actual, 156 <u>RT period</u> Treated, 156 (104 MMB, 52 BAT [46 RUX]) <u>MMB overall</u> Treated, 144 (104 MMB, 40 BAT→MMB)	<u>Randomized to MMB</u> 40.0 weeks <u>Randomized to BAT</u> 38.1 weeks <u>MMB overall (including BAT→MMB)</u> 40.0 weeks Planned maximum duration of participation was approximately 5 years, with	SRR at week 24, defined as the proportion of subjects with a reduction in spleen volume ≥ 35% from baseline at week 24 as measured by MRI or CT scan

Study ID / Acronym [1] Status First Subject Screened/ LSLV Regions	Patient population	Study Design	Dosing Regimen (MMB Tablets)	Planned / Actual Enrollment, Treated, Completed	Duration of Treatment [2]	Primary Endpoint
(Israel)					possibility to continue in extension study	
GU-US-352-1672 Completed Study termination by sponsor Jan 2016/ Aug 2017 North America	Subjects with intermediate-2 or high-risk (DIPSS) PMF, post-PV MF, or post-ET MF. Intermediate-1 (DIPSS) MF patients are allowed if associated with symptomatic splenomegaly, and/or hepatomegaly	Phase 2, multicenter, open-label, single-arm, translational biology study in transfusion-dependent subjects	MMB 200 mg QD	Planned, ~40/ actual, 41 Treated, 41	23.4 weeks	TI rate at week 24, defined as the proportion of subjects with TI in 12 week period during the 24-week treatment period
SRA-MMB-4365 XAP 03 May 2018 to ongoing Europe, North America, Asia, Australasia	Study eligibility defined in prior study	Phase 2, international, open-label, extension study for GS-US-352-0101, GS-US-352-1154, GS-US-352-1214, and SRA-MMB-301	MMB dose received in prior study.	Planned, ~400/ Actual, 170 • GS-US-352-0101, 96 • GS-US-352-1154, 19 • GS-US-352-1214, 22 • SRA-MMB-301, 33 Treated, 170 Ongoing, 110 Data cutoff date: 03 Dec 2021, study is ongoing	31.69 months (Q1, 7.98; Q3, 35.91) (Until MMB is commercially available in their region or development is discontinued)	[6]

[1] Protocol number and study acronym, as applicable. [2] Duration of treatment is provided as overall median exposure to study drug. [3] MOMENTUM was conducted during the COVID-19 pandemic. [4] Termination was planned after eligible ongoing subjects transitioned to study SRA-MMB-4365 (XAP) for long-term MMB treatment. [5] The starting dose (5-20 mg BID) was based on screening laboratory values outlined in the study protocol. [6] Objectives of study SRA-MMB-4365 (XAP): Extended access, long-term safety, OS, LFS in subjects with MF BID, twice daily; CT, computed tomography; DAN, danazol; ID, identification; LSLV, last subject last visit; MFSAF v4.0, Myelofibrosis Symptom Assessment Form version 4.0; max, maximum; MMB, momelotinib; MRI, magnetic resonance imaging; OL, open-label; QD, once daily; RT, randomized treatment; RUX, ruxolitinib; SRR, splenic response rate; TI, transfusion independence; TSS, total symptom score.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Momelotinib (MMB) has been developed for the treatment of adult patients with MF. MMB inhibits the JAK1/JAK2 kinases and the activin A receptor type 1 (ACVR1)/activin receptor-like kinase 2 (ALK2). The recommended dose according to the SmPC is 200 mg once daily, taken with or without food.

MMB has one major circulating metabolite, M21. The major metabolite M21 is active but less potent compared with MMB with a pharmacologic activity index of 34% for JAK1/2 inhibition and 40% for ACVR1 inhibition.

Fourteen clinical studies conducted in healthy volunteers and patients with myelofibrosis (MF) contributed to the characterization of the clinical pharmacology of MMB. Other than three early Phase 1 and 2 clinical studies (CCL09101, YM387-I-02, YM387-II-02) that were performed using powder-in-capsule formulation or tablet formulation of MMB dihydrochloride salt form I, and the mass balance study (GS-US-352-1149) in which an oral solution was used, all later Phase 1 and 2 studies and all Phase 3 studies were performed using a film-coated tablet formulation of MMB dihydrochloride monohydrate salt Form II. The commercial tablet formulation is identical to that used in the Phase 3 clinical studies.

Absorption

MMB is rapidly absorbed after oral administration with median Tmax ranging from 1.8 to 3 h following a single dose of MMB (100 to 800 mg) in healthy volunteers. In MF patients receiving 200 mg QD, the median Tmax was 1.75 h for MMB and slightly longer (i.e. 3 h) for the active metabolite M21.

MMB is a low-solubility drug and has pH-dependent solubility. MMB showed moderate to high *in vitro* permeability. Based on these characteristics, MMB is classified as a BCS class 2 compound. No absolute bioavailability study has been conducted.

MMB and M21 are substrates of P-gp and BCRP *in vitro*.

Relative bioavailability

Two dihydrochloride salt forms of MMB were evaluated in MMB clinical studies: MMB dihydrochloride salt Form I and MMB dihydrochloride monohydrate salt Form II, the latter being used in all phase 3 studies. The relative bioavailability between the tablet formulation (MMB Form II) and the capsule formulation (MMB Form I) was investigated under fasting conditions in part A of study GS-US-352-0102. Fifty eligible subjects were randomized to 1 of the 4 treatment sequences in which tablet doses (100, 150, 200 or 300 mg) in period 1 were compared to the target 300 mg capsule dose in period 2, separated by a 3 day wash-out. The MMB tablet formulation at 200 mg resulted in a comparable exposure (AUC and Cmax) to the 300-mg capsule and was therefore selected as the starting dose for Phase 3 studies in MF patients.

Table 7: MMB PK parameters Following Single Doses of 200-mg MMB Tablet (Test) versus 300-mg MMB Capsule (Reference)

Treatment Sequence	PK Parameter	Mean (%CV)		%GLSM Ratio (90% CI)
		Test	Reference	
III 200-mg Tablet (Test, n=12) vs. 300-mg Capsule (Reference, n=11)	C_{max} (ng/mL)	323.7 (58.2)	356.1 (54.9)	91.99 (78.98, 107.15)
	AUC_{inf} (h•ng/mL)	2549.7 (66.1)	2665.5 (74.9)	101.69 (87.45, 118.26)
	$AUC_{0\text{-last}}$ (h•ng/mL)	2324.5 (65.3)	2443.9 (71.3)	100.35 (86.73, 116.10)
	T_{max} (h)[a]	2.00 (1.75, 2.00)	2.00 (2.00, 3.00)	–
	$t_{1/2}$ (h)[a]	5.91 (4.83, 7.52)	5.80 (4.48, 7.10)	–

Comparisons were made relative to the reference 300-mg capsule.

a Median (Q1, Q3)

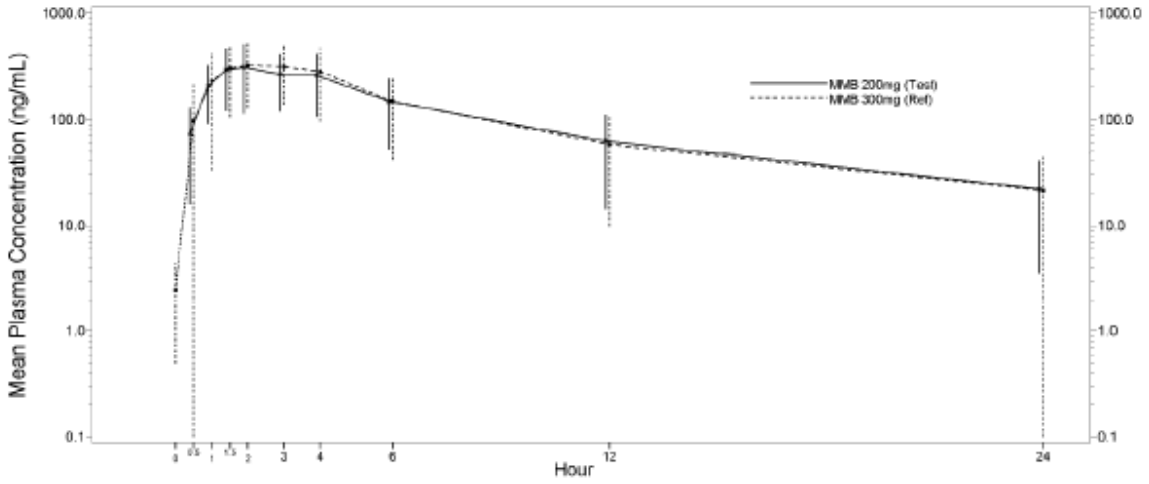


Figure 2: Mean (SD) Plasma Concentration-Time Profiles of MMB Following Single Doses of 200-mg MMB Tablet (Test) versus 300-mg MMB Capsule (Reference)

No further bioequivalence study was conducted since the commercial formulation is identical to the tablet formulation used in phase 3 clinical studies.

Food effect

Part C of study GS-US-352-0102 evaluated the effect of food (low-fat and high-fat meal) on the 200 mg MMB Form II tablet using a fixed-sequence, open-label, crossover design.

Table 8: MMB PK Parameters Following Single-Dose Administration with Various Meal Types

Part C (Food Effect) PK Parameter	200-mg Tablet Fasted (Reference) (N = 12)	200-mg Tablet Low-Fat Meal (Test) (N = 12)	200-mg Tablet High-Fat Meal (Test) (N = 12)
Median (Q1, Q3)			
T_{max} (h)	2.50 (1.50, 4.00)	4.00 (4.00, 4.00)	4.50 (3.00, 5.00)
$t_{1/2}$ (h)	6.79 (4.67, 7.19)	5.48 (5.10, 6.88)	5.76 (4.69, 6.98)
%GLSM Ratio (90% CI)			
C_{max} (ng/mL)	–	137.94 (119.21, 159.61)	127.63 (101.81, 160.00)
AUC_{inf} (h•ng/mL)	–	116.25 (101.07, 133.72)	127.71 (107.54, 151.66)
$AUC_{0\text{-}last}$ (h•ng/mL)	–	116.44 (100.83, 134.46)	127.80 (106.92, 152.76)

Food intake delayed the absorption of MMB (increase of tmax from 2.5h to 4.5h), and resulted in a modest increase in MMB exposure (Cmax increase 28% [high-fat meal] to 38% [low-fat meal] and AUC increased 16% [low-fat meal] to 28% [high-fat meal]) with minimal change to M21 exposure. These changes were not considered clinically relevant. MMB was administered to patients in all Phase 3 studies without instructions on food intake.

Distribution

In patients with MF receiving MMB 200 mg once daily, the mean apparent volume of distribution (Vz/F) of MMB at steady-state was 984 L, suggesting extensive tissue distribution (SIMPLIFY-1).

In the mass balance study, the blood to plasma ratio ranged from 0.73 to 0.87 indicating low association of MMB and its circulating metabolites with blood cells. The *in vitro* blood to plasma concentration ratio for MMB was approximately 1.

In the hepatic and renal impairment studies, ex vivo plasma protein binding for MMB and M21 was determined by equilibrium dialysis using plasma samples around Tmax (± 1 µM) and 24h following a single 200 mg MMB dose (GS-US-352-1153; GS-US-352-1152). In healthy control subjects, the free fraction of MMB and M21 at tmax was ± 9% and 8%, respectively. The observed slight decrease in free fraction for MMB (7% at 24h post-dose) with decreasing concentrations is not considered clinically relevant. Slight differences were also observed in plasma protein binding dependent on organ impairment status.

The protein binding data for MMB determined ex vivo are in line with a previous *in vitro* study using ultracentrifugation at concentrations of 0.5 and 5 µM (CDCO_Cytopia_07_006) showing free fractions of 8.5% and 12.7%. In an *in vitro* study using equilibrium dialysis (AD-352-2012), the free fraction at a concentration of 2 µM was 19.2% and 14.6% for MMB and M21, respectively. According to the applicant, the discrepancies between both studies were mostly caused by data variations as well as different methodologies applied.

Elimination

Based on the MMB PK substudy results from the Phase 3 study SIMPLIFY-1, steady-state MMB CL/F was found to be 103 L/h. Based on the population PK model, the elimination clearance for an oral dose of 200 mg MMB once daily was estimated at 83.1 L/h. T1/2 of MMB ranged from approximately 4 to 8 hours across studies.

Mass balance

Study GS-US-352-1149 was a single dose mass balance study conducted in 6 healthy subjects under fasting conditions. Subjects received 200 mg of unlabeled MMB and [^{14}C]-labeled MMB (~100 µCi) as a 200-mL solution. The overall mean recovery of radioactivity in urine and feces was 96.7% (range 93.9 to 98.0%) over the 264-hour study, with 69.3% of the dose recovered in feces and 27.5% in urine.

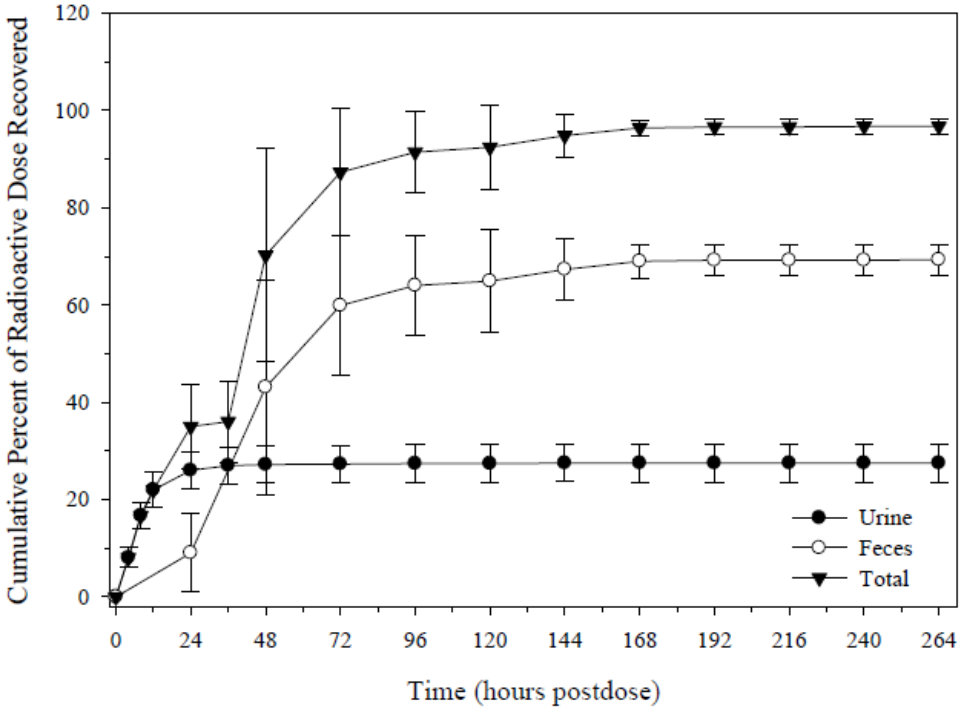


Figure 3: Mean (±SD) cumulative percent of radioactive dose recovered in urine and faeces

In total, 19 metabolites were characterized from plasma, urine, and faeces samples. In plasma, the major radioactivity peaks were the unchanged parent compound and M21, accounting for approximately 17.3 and 64.2 % of total radioactivity exposure (AUC0-24h). The other circulating metabolites (M5, M8, M19, M20, and M28) accounted for less than 6% of total radioactivity. The active metabolite M21 was the only major metabolite contributing to > 10% of total radioactivity and > 25% of parent exposure.

Approximately all radioactivity (27.3% and 74.2% of dose) could be identified in urine and faeces, respectively. Only 12.6% and 0.6% of the dose was retrieved as parent drug in faeces and urine, respectively. MMB was primarily eliminated as metabolites. M14 was the predominant metabolite excreted in faeces (21.4% of dose). The active metabolite, M21, was found both in faeces and urine (12.7% and 11.5% of dose, respectively).

Table 9: Percent of Radioactive Dose Present as [14C]-MMB and [14C]-Metabolites in Pooled Urine and Feces Samples From All Sampling Intervals by HPLC (PK Analysis Set)

	Mean % of radioactive dose*		
Metabolite	**urine (U)**	**feces (F)**	**U+F**
M22/M23**	1,7	1,4	3,1
M5	2,3	3,8	6,1
M26/27**	2,3	3,1	5,4
M8	0,7	2,5	3,2
M14	1,8	21,4	23,2
M29	1,3	2,6	3,9
M32	/	1,5	1,5
M31	/	2,3	2,3
M16	1,6	1,5	3,1
M19/M33	/	7,1	7,1
M20	/	1,7	1,7
M1/M3**	1,5	/	1,5
M28	1	/	1
M15	1	/	1
M21	11,5	12,7	24,2
MMB	0,6	12,6	13,2
Total	27,3	74,2	101,5

*Percent of dose (%) = Peak distribution x Total radioactivity excreted in the pooled time interval
** Coelution

Metabolism

In vitro metabolism data indicate that hepatic MMB metabolism is predominantly mediated by CYP enzymes. Based on the effect of selective enzyme inhibitors on the metabolism of MMB in human hepatocytes, CYP1A2, CYP2C8, CYP2C9, CYP2C19 and CYP3A4 are involved in the metabolism of MMB and formation of M21. The formation of M21 was also investigated in a separate experiment and indicated that this occurred in at least two steps with involvement of aldehyde oxidase following metabolism by CYP enzymes.

No MMB metabolism by flavin-containing monooxygenase (FMO) and monoamine oxidase (MAO) enzymes was detected using recombinant enzymes.

Enzyme	Normalized Fractional Metabolism (%)	
	MMB Metabolism	M21 Formation
CYP1A2	8.8	22.5
CYP2B6	0	0
CYP2C8	19.3	22.2
CYP2C9	16.7	8.4
CYP2C19	19.0	22.9
CYP2D6	0	0
CYP3A	36.2	24.1

The metabolism scheme proposed by the applicant is presented in Figure . MMB metabolism involved oxidation and scission of the morpholine ring, amide hydrolysis, N-dealkylation, nitrile hydrolysis, nitrile oxidation, and taurine conjugation of the cyanomethylamide. M14 likely arises from oxidation of M19, amide hydrolysis of M8, and/or amide hydrolysis of M21.

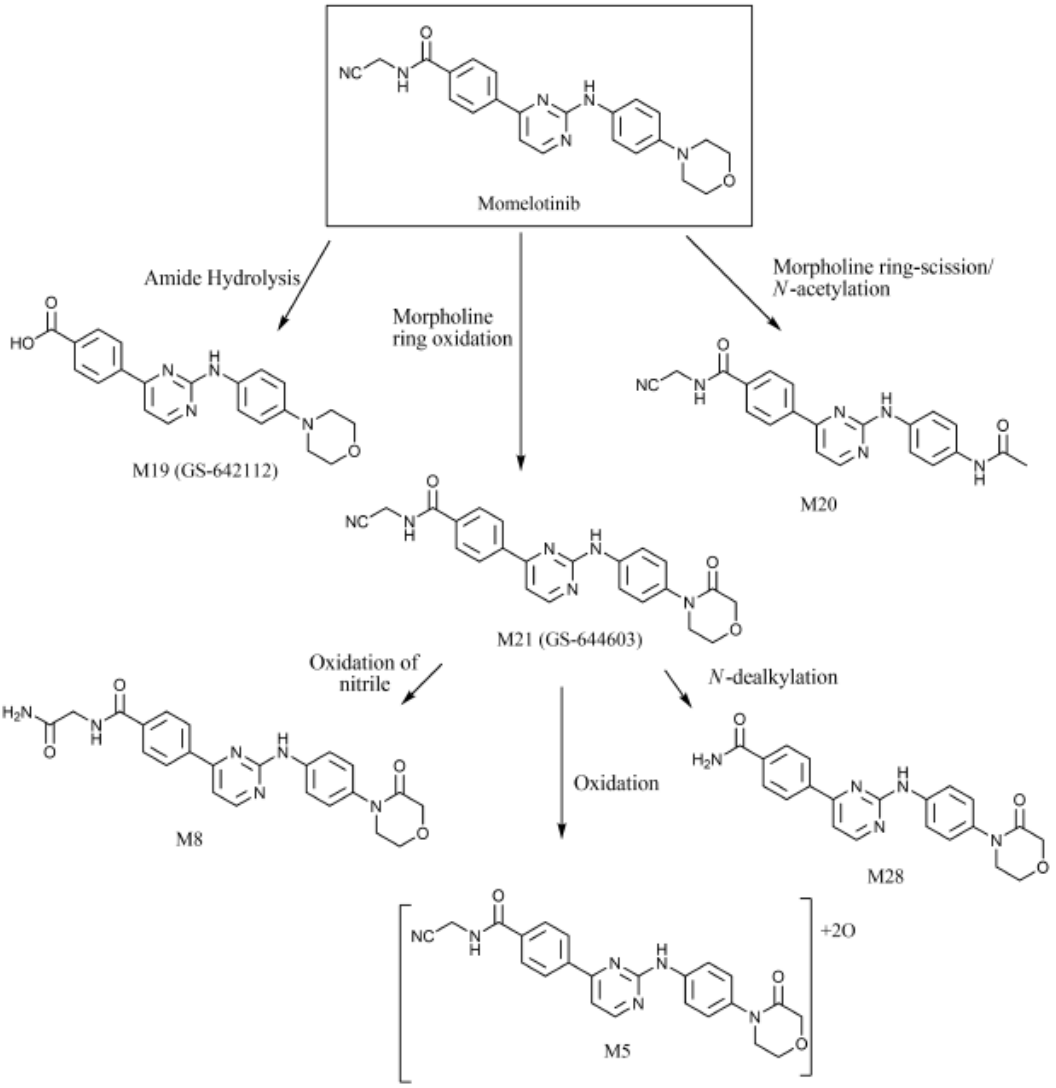


Figure 4. Proposed biotransformation pathways of MMB in humans

Pharmacokinetics of metabolites

Following a single oral dose of MMB from 150 to 800 mg under fasted conditions (GS-US-352-0102, part B), M21 had a slightly longer Tmax (median of 3.5 hours) and similar t1/2 (median range, 4.9-7.3 hours) compared to the parent MMB. The metabolite to parent ratio was in a similar range from 150 to 800 mg, with a mean molar ratio of M21 to MMB for AUCinf ranging from 1.4 to 2.1.

In the PK sub-study of the phase 3 SIMPLIFY studies in MF patients, PK parameters for M21 and MMB were measured at week 2 (steady state) of 200 mg MMB QD administration.

Table 10: PK parameters of MMB and M21 following MMB 200 mg QD in subjects with MF (SIMPLIFY-1, week 2 visit)

PK Parameters	Statistics	MMB	N	M21	N
AUC_{tau} (ng·h/mL)	Mean (%CV)	3288.3 (60.4)	19	4068.9 (39.0)	19
C_{max} (ng/mL)	Mean (%CV)	479.3 (61.4)	20	411.4 (53.1)	20
C_{tau} (ng/mL)	Mean (%CV)	27.4 (92.3)	16	55.8 (63.0)	16
T_{max} (h)	Median (Q1, Q3)	1.8 (1.0, 3.0)	20	3.0 (2.0, 3.7)	20
$t_{1/2}$ (h)	Median (Q1, Q3)	5.1 (4.5, 7.4)	19	7.6 (5.8, 9.9)	18

Table 11: PK parameters of MMB and M21 following MMB 200 mg QD in subjects with MF (SIMPLIFY-2, week 2 visit)

PK Parameters	Statistic	MMB	N	M21	N
AUC_{tau} (ng·h/mL)	Mean (%CV)	2153.6 (55.1)	6	4113.1 (23.2)	6
C_{max} (ng/mL)	Mean (%CV)	367.0 (33.2)	7	486.9 (29.5)	7
C_{tau} (ng/mL)	Mean (%CV)	11.1 (101.3)	5	35.3 (59.3)	5
T_{max} (h)	Median (Q1, Q3)	1.5 (1.0, 4.0)	7	3.0 (2.0, 6.0)	7
$t_{1/2}$ (h)	Median (Q1, Q3)	4.3 (3.8, 4.6)	6	5.5 (5.1, 6.8)	6

Compared to MMB and M21, the minor metabolite M19 had a relatively longer Tmax (5-8h) and terminal half-life (10.5-22.9h) across MMB doses of 150 to 800 mg in healthy volunteers.

Dose proportionality and time dependencies

Following a single oral dose of MMB from 100 to 800 mg (study GS-US-352-0102), MMB, M121 and M19 plasma exposures increased in a less than dose-proportional manner at doses above 200 mg. The metabolite to parent ratio is not dose-dependent for M21 and M19 (range of mean AUC ratio of M21 and M19 to MMB: 1.4-2.1 and 0.2 to 0.3, respectively).

Table 12: Dose proportionality of MMB

PK Parameter	C_{max}/Dose (ng/mL/mg)		AUC_{inf}/Dose (h•ng/mL/mg)	
Dose	GLSM	GLSM Ratio	GLSM	GLSM Ratio
100 mg (N = 12)	1.54	–	12.80	–
150 mg (N = 21)	1.81	118.13 (87.22, 159.99)	14.67	114.67 (81.96, 160.45)
200 mg (N = 36)	1.70	111.05 (83.98, 146.84)	14.47	113.11 (83.01, 154.12)
300 mg (N = 12-13)	1.28	83.11 (59.42, 116.25)	10.26	80.16 (54.88, 117.09)
400 mg (N = 8)	0.82	53.35 (36.39, 78.22)	6.49	50.73 (33.21, 77.48)
800 mg (N = 8)	0.70	45.40 (30.97, 66.56)	5.95	46.49 (30.44, 71.02)

GLSM ratios were comparisons made relative to the 100-mg tablet.

There was no significant accumulation of MMB and M21 after repeated daily dosing of 200 mg MMB in patients based on trough concentrations measured from week 2 up to week 24 in SIMPLIFY studies. Steady state seems to be reached by week 2 (no earlier measurements of trough concentrations available).

Table 13: Plasma Trough Concentrations of MMB and M21 Following MMB 200 mg Once Daily in Subjects with Myelofibrosis (SIMPLIFY-1)

Analyte	Sampling Time								
	Week 2 Predose	Week 4 Predose[a]	Week 4 Switch[b]	Week 8 Predose	Week 12 Predose	Week 16 Predose	Week 20 Predose	Week 24 Predose	Week 28 (OL Week 4) Predose
MMB									
N	124	111	44	99	87	87	76	61	46
Median (Q1, Q3) (ng/mL)	17.8 (5.6, 42.8)	16.5 (6.7, 41.2)	27.4 (11.2, 52.2)	21.7 (8.8, 47.6)	15.8 (6.8, 41.6)	15.7 (8.4, 32.2)	18.6 (8.5, 32.1)	17.9 (9.9, 41.8)	18.3 (6.3, 54.1)
GS-644603 (M21)									
N	124	112	44	99	88	87	77	61	47
Median (Q1, Q3) (ng/mL)	49.2 (20.2, 81.1)	42.4 (21.7, 81.9)	63.2 (37.2, 116)	49.9 (29.8, 82.6)	46.3 (25.5, 87.8)	46.8 (24.1, 69.8)	48.1 (26.1, 68.9)	54.3 (34.3, 93.6)	48.7 (22.9, 100)

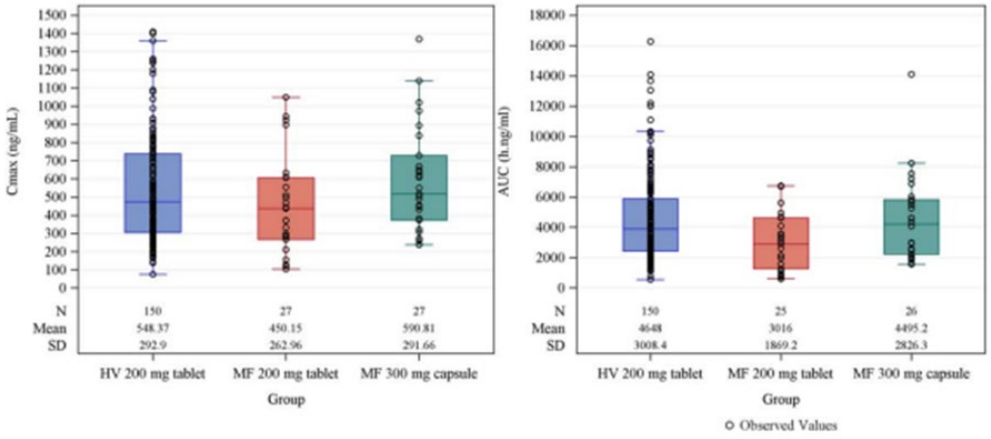
MMB = momelotinib; N = number of subjects; OL = open-label; Q1, Q3 = first and third quartiles; RUX = ruxolitinib

[a] MMB

[b] "Week 4 Switch" is the Switch (ruxolitinib to MMB) at open-label phase Week 4.

Target population

Exposures (Cmax and AUC) of MMB in healthy volunteers and subjects with MF were similar, as presented in the figure below:



Notes: Healthy volunteers included in the plot took 200 mg single-dose MMB tablet in studies CSR GS-US-352-0102, CSR GS-US-352-0108, CSR GS-US-352-1150, CSR GS-US-352-1151, CSR GS-US-352-1152, CSR GS-US-352-1153.

Subjects with MF included in the plot took 200 mg QD MMB tablet in studies CSR GS-US-352-0101 and CSR GS-US-352-1214 and participated in the intensive PK substudy (data at Week 2) or took 300 mg QD MMB capsule in study CSR CCL09101 (data on Day 1).

AUC is either AUC_{inf} for single dose (HV 200 mg tablet group and MF 300 mg capsule group) or AUC_{tau} (MF 200 mg tablet group) for multiple dose at steady state.

AUC, area under the plasma concentration-time curve; AUC_{inf}, area under the plasma concentration-time curve from time zero extrapolated to infinite time; AUC_{tau}, area under the plasma concentration-time curve over the dosing interval; C_{max}, maximum plasma concentration; HV, healthy volunteers; MF, myelofibrosis; MMB, momelotinib; PK, pharmacokinetics; QD, once daily.

Figure 5: Box Plots for MMB Exposures in Healthy Volunteers and Subjects With Myelofibrosis

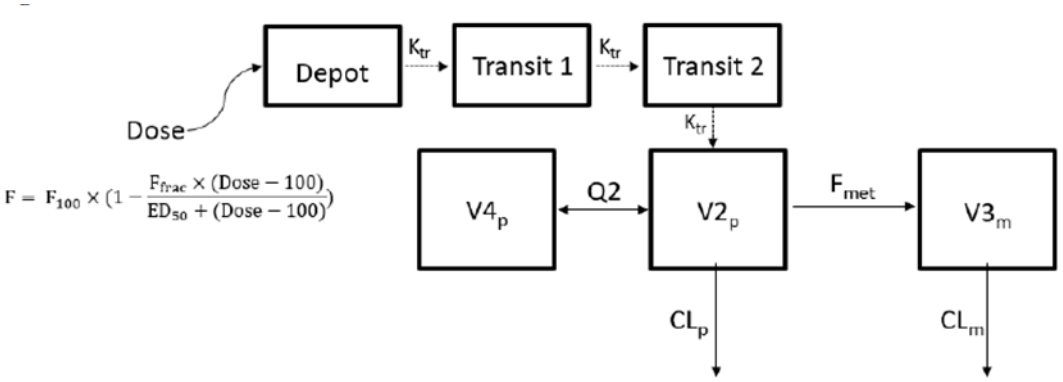
Rapid absorption (Tmax reached within 3 hours) and a short half-life (4 to 8 hours) were observed in both healthy volunteers and subjects with MF. The inter-subject variability is relatively high.

Population PK analysis

A population PK analysis was performed to develop a model to characterize the PK of MMB and its major metabolite, M21, and to evaluate the covariates including intrinsic and extrinsic factors that may explain the variability in the PK of MMB and M21.

The final model was used to simulate concentration-time profiles and predict daily average exposures of both MMB and M21 in patients with MF at 200 mg once daily with the consideration of dose adjustment and/or interruption during Phase 3 trials.

Data from the 5 clinical studies in phases 1 through 3 were included (CCL09101, YM387-II-02, SIMPLIFY-1, SIMPLIFY-2, MOMENTUM). A total of 3548 and 2223 observed concentrations of MMB and M21, respectively, were included from 616 subjects with MF.



F_{100} = F (relative bioavailability) for 100 mg, assumed to be 1; F_{frac} = maximum fractional change in F; ED_{50} = the dose corresponding to half of Ffrac; K_{tr} = Absorption transit rate constant; CL_p = apparent clearance of parent; CL_m = apparent clearance of metabolite; F_{met} = Fraction of metabolite in plasma, 0.64; Q2 = apparent inter-compartment clearances for the central and peripheral compartment; $V2_p$ = apparent volume of distribution of the central compartment; $V4_p$ = apparent volume of distribution of the peripheral compartment; $V3_m$ = apparent volume of distribution of the metabolite compartment

Note: The assumption that F_{met} = 0.64 is based on findings from Zheng (2018).

Figure 6: MMB and M21 model structure schematic

After discovery of dosing errors, the initial popPK models for MMB and M21 (base model for MMB and final model for MMB and M21) were updated using the corrected dataset by re-estimating the model parameters in different steps. The structural models were kept intact; no additional model development or exploration was performed.

Table 14: updated final population Pk model for MMB and Metabolite M21-Parameter Estimates

Parameter	Estimate	RSE%	95% CI	Shrinkage
Typical Values				
CL/F (L/h) of MMB	49.5 Fixed	-	-	-
Vc/F (L) of MMB	286 Fixed	-	-	-
Vp/F (L) of MMB	203 Fixed	-	-	-
Q/F (L/h) of MMB	30.6 Fixed	-	-	-
CL/F of M21 (L/h)	17.7	3.54	16.4 – 18.9	-
Vc/F of M21 (L)	41.7	13.2	31.0 – 52.5	-
Ktr (1/h)	0.649 Fixed	-	-	-
Dose on bioavailability, Ffrac	0.429 Fixed	-	-	-
Dose on bioavailability, ED50 (mg)	6.02 Fixed	-	-	-
Covariate Effects				
Capsule formulation on Ktr	4.93 Fixed	-	-	-
eGFR on CL/F of M21	0.525	13.1	0.390 – 0.660	-
AST on CL/F of M21	0.216	22.1	0.123 – 0.310	-
Between Subject Variability				
On CL/F of MMB	0.763	3.25	0.715 – 0.812	6.89%
On CL/F of M21	0.484	4.61	0.440 – 0.527	22.2%
Residual Error				
Prop. Error - CCL09101	0.638 Fixed	-	-	-
Prop. Error - YM-387-II-02	0.532 Fixed	-	-	-
Prop. Error - GS-US-352-0101	1.18 Fixed	-	-	-
Prop. Error - GS-US-352-1214 and SRA-MMB-301	0.731 Fixed	-	-	-
Prop. Error - M21 (all studies)	0.697	2.25	0.666 – 0.727	-

Estimation method: FOCEI; Objective function value: 55955.78

CL/F = apparent clearance; Vc/F = apparent central volume of distribution; Q/F = apparent inter-compartmental clearance; Vp/F = apparent peripheral volume of distribution; Ktr = absorption transit rate constant; Ffrac = maximum fractional change in relative bioavailability; ED50 = dose offset from 100 mg corresponding to half of Ffrac; eGFR = estimated glomerular filtration rate; AST = aspartate aminotransferase; %RSE = percent relative standard error of the estimate = 100%×(SE/parameter estimate); 95% CI = 95% confidence interval; SE = standard error of the estimate; Prop. = proportional.

However, systematic model misspecification (overprediction of the central tendency and the variability) was noted on the VPCs sparse concentration data from studies GS-US-352-1214 and GS-US-352-101, and per se for the tablet formulation. The model prediction for the disposition was highly questioned for this subset of data. In their responses, the applicant acknowledged that many dosing times were missing in the source data used in the initial submission, and needed to be imputed. The applicant noted that many trough data, especially in Phase 3 studies (SIMPLIFY-1, SIMPLIFY-2, and MOMENTUM) may have been subjected to such misclassification. A sensitivity analysis was conducted on the current popPK model (with Erlang absorption) with the suspect data excluded and additional data included (not pertaining to the PK-substudy). The sensitivity analysis dataset contained 2419 momelotinib concentrations from 459 subjects, whereas the model in Report Amendment 5382- PKPD001 included 2480 momelotinib concentrations from 359 subjects. In sensitivity analysis, a substantial improvement in the model fit for the tablet data was observed. The prediction-corrected visual predictive checks (pcVPC) for the sparse concentration data from studies SIMPLIFY-1 and SIMPLIFY-2 did not indicate the presence of systematic misspecification. In addition, the pcVPC for the rich data from studies SIMPLIFY-1 and SIMPLIFY-2 indicates that Erlang absorption structural model in sensitivity analysis #1 adequately capture the absorption of the tablet formulation without negative impact on the model fit for the capsule data.

At the CHMP's request, the comprehensive results using the new model were submitted and the updated model with better predictive performances for MMB and M21 was used for subsequent E-R analysis (see Discussion on Clinical Pharmacology).

Special populations

Renal impairment

The applicant provided the results of a dedicated study (Study GS-US-352-1152) of momelotinib and its main metabolites in patients with moderate and severe renal impairment. No patients with mild renal impairment were included in the study. Three cohorts of subjects were enrolled with moderate (Cohort 1), severe (Cohort 2), and mild (Cohort 3) renal impairment in addition to matched healthy subjects in all 3 cohorts.

The comparison of the PK parameters in subjects with moderate/severe renal impairment is summarised in the tables below:

Table *15*: Summary Statistics and Statistical Comparisons of Plasma PK Parameters in Subjects with Moderate Renal Impairment and Matched Healthy Subjects (MMB PK Analysis Set)

PK Parameter	Mean[a] (%CV)		%GLSM Ratio (90% CI)
	Moderate Renal Impairment (N = 10)	Normal Renal Function (N = 9)	
AUC_{inf} (h*ng/mL)	3731.4 (47.1)	4279.7 (44.1)	86.68 (54.48, 137.90)
AUC_{last} (h*ng/mL)	3651.8 (47.3)	4178.3 (43.6)	86.44 (54.42, 137.32)
C_{max} (ng/mL)	406.6 (56.9)	443.4 (41.9)	83.87 (53.56, 131.34)
CL/F (L/h)	71.7 (65.1)	63.3 (76.1)	–
V_z/F (L)	864.3 (85.8)	723.1 (71.6)	–
T_{max} (h)[b]	3.00 (3.00, 4.00)	4.00 (4.00, 4.00)	–
$t_{1/2}$ (h)[b]	7.55 (5.67, 9.37)	7.52 (6.69, 8.85)	–

GLSM = geometric least square mean
a Means presented are unadjusted
b Median (Q1, Q3)

Table 16: Summary Statistics and Statistical Comparisons of Plasma PK Parameters in Subjects with Severe Renal Impairment and Matched Healthy Subjects (MMB PK Analysis Sets)

PK Parameter	Mean[a] (%CV)		%GLSM Ratio (90% CI)
	Severe Renal Impairment (N = 10)	Normal Renal Function (N = 10)	
AUC_{inf} (h*ng/mL)	3502.9 (59.2)	3905.3 (42.6)	83.91 (53.34, 132.00)
AUC_{last} (h*ng/mL)	3416.1 (58.6)	3784.3 (40.6)	84.07 (53.79, 131.39)
C_{max} (ng/mL)	280.2 (53.4)	374.6 (36.0)	68.12 (45.62, 101.71)
CL/F (L/h)	81.8 (69.5)	65.5 (67.4)	–
V_z/F (L)	871.5 (74.9)	757.6 (60.4)	–
T_{max} (h)[b]	6.00 (4.00, 6.00)	4.00 (4.00, 4.00)	–
$t_{1/2}$ (h)[b]	7.18 (6.24, 8.23)	7.49 (6.85, 11.59)	–

GLSM = geometric least square mean
a Means presented are unadjusted
b Median (Q1, Q3)

Table 17: Plasma PK Parameters of MMB, GS-644603, and GS-642112 Following a Single Dose of MMB 200 mg in Subjects with Moderate or Severe Renal Impairment and Healthy Subjects as Determined by CLCr (PK Analysis Set)

Analyte	PK Parameter	Mean (%CV)		
		Moderate Renal Impairment by CL_{Cr} (N = 11)	Severe Renal Impairment by CL_{Cr} (N = 6)	Normal Renal Function by CL_{Cr} (N = 10)
MMB	AUC_{inf} (h*ng/mL)	4152.9 (48.8)	2561.7 (51.2)	4173.1 (42.8)
	C_{max} (ng/mL)	381.6 (51.6)	202.4 (48.5)	362.0 (32.5)
GS-644603	AUC_{inf} (h*ng/mL)	6776.1 (45.8)	4714.1 (55.4)	3852.8 (33.2)
	C_{max} (ng/mL)	416.5 (57.6)	263.0 (69.0)	283.4 (42.9)
GS-642112	AUC_{inf} (h*ng/mL)	1685.0 (78.8)	1794.2 (93.5)	1721.0 (75.5)
	C_{max} (ng/mL)	43.5 (57.1)	41.6 (62.2)	45.6 (25.6)

Creatinine Clearance (CLcr): Male = (140-Age[y])*Weight[kg]/(Creatinine[mg/dL]*72); Female = 0.85*(140-Age[y])*Weight[kg]/(Creatinine[mg/dL]*72).

A single dose study (GS-US-352-1152, 200mg) is deemed adequate to characterize the PK of momelotinib and its metabolites in subjects with renal impairment and to inform dosing recommendations in this population.

In the human mass balance study (GS-US-352-1149), renal excretion was a very minor route of clearance for momelotinib at therapeutic relevant exposures levels suggesting there is a low probability that renal impairment would affect exposure of momelotinib.

Study GS-US-352-0102 assessed the proportionality of exposure across the dose range of 100mg to 800mg for the tablet formulation and momelotinib's exposure was dose proportional between doses of 100 and 300mg. The observed less than proportional increase in exposure in doses above 300mg is attributed to saturation in absorption rather than an increase in the elimination rate of momelotinib (the half-life was comparable across doses).

Hepatic impairment

The effect of hepatic impairment on the PK and safety of MMB was evaluated in Phase 1 study GS-US-352-1153 following a single dose of 200 mg of MMB in a fed state. Cohort 1 enrolled subjects with moderate hepatic impairment and matched healthy controls, Cohort 2 enrolled subjects with severe hepatic impairment and matched healthy controls, and Cohort 3 enrolled subjects with mild hepatic impairment and matched healthy controls.

Table 18: GS-US-352-1153: MMB PK Parameters Following a Single Dose of MMB 200 mg in Subjects With Moderate Hepatic Impairment and Matched Healthy Subjects (MMB PK Analysis Set)

PK Parameter	Mean[a] (%CV)		% Geometric Least-Squares Mean Ratio (90% CI)
	Moderate Hepatic Impairment (N=10)	Normal Hepatic Function (N=10)	
AUC_{inf} (h·ng/mL)	6268.9 (56.2)	5958.2 (57.0)	108.02 (71.00, 164.35)
AUC_{last} (h·ng/mL)	5799.3 (47.9)	5823.1 (55.4)	104.50 (70.24, 155.46)
C_{max} (ng/mL)	482.4 (46.1)	623.4 (42.7)	79.34 (52.00, 121.04)
CL/F (L/h)	40.0 (46.6)	44.9 (56.2)	—
V_z/F (L)	422.2 (52.9)	418.5 (41.6)	—
T_{max} (h)[b]	4.00 (3.00, 6.00)	3.50 (3.00, 4.00)	—
$t_{1/2}$ (h)[b]	7.38 (4.84, 8.57)	6.77 (5.82, 9.30)	—

a Means presented are unadjusted
b Median (Q1, Q3)

Table 19: MMB PK Parameters Following a Single Dose of MMB 200 mg in Subjects With Severe Hepatic Impairment and Matched Healthy Subjects (MMB PK Analysis Set)

PK Parameter	Mean[a] (%CV)		% Geometric Least-Squares Mean Ratio (90% CI)
	Severe Hepatic Impairment (N=10)	Normal Hepatic Function (N=10)	
AUC_{inf} (h*ng/mL)	9807.1 (53.9)	5346.3 (67.2)	197.11 (128.87, 301.48)
AUC_{last} (h*ng/mL)	8997.4 (47.3)	5203.0 (65.8)	189.04 (125.90, 283.84)
C_{max} (ng/mL)	547.6 (36.7)	528.5 (51.5)	112.63 (75.10, 168.92)
CL/F (L/h)	24.8 (40.2)	52.0 (50.9)	—
V_z/F (L)	318.5 (51.7)	511.9 (52.3)	—
T_{max} (h)[b]	4.00 (4.00, 4.00)	4.00 (2.00, 4.00)	—
$t_{1/2}$ (h)[b]	8.90 (5.50, 14.06)	7.45 (5.20, 9.61)	—

a Means presented are unadjusted
b Median (Q1, Q3)

MMB AUC was comparable, whereas Cmax was decreased by 21% between patients with moderate hepatic impairment (Child-Pugh B) and patients with normal hepatic function. MMB Cmax was increased by 13% and AUC was increased by 97% in patients with severe hepatic impairment (Child-Pugh C) compared with patients with normal hepatic function.
There is a decrease in M21 exposure (by 48% in AUCinf and 76% in Cmax) in subjects with severe hepatic impairment. Concerning GS-642112, the increases in plasma exposures in subjects with

moderate and severe hepatic impairment are not expected to impact MMB activity, as GS-642112 is an inactive metabolite.

The effect of race/ethnicity on the PK and safety of MMB (200 mg MMB, single dose) was evaluated in study GS-US-352-0108 and in the POPPK modelling:

Table *20*: PK parameters for MMB following a single oral dose of MMB 200 mg under fasted conditions

Parameters	Japanese[a] (N = 14)	Caucasian[a] (N = 14)	% Geometric Least Squares Mean Ratio[b] (90% CI)
C_{max} (ng/mL) Mean (%CV)	1006.0 (29.3)	729.4 (35.9)	144.11 (108.53, 191.37)
T_{max} (h) Median (Q1, Q3)	3.00 (1.50, 3.00)	3.00 (2.00, 3.00)	—
$t_{1/2}$ (h) Median (Q1, Q3)	4.25 (3.87, 6.13)	6.76 (5.86, 9.65)	—
$AUC_{0\text{-}last}$ (ng•h/mL) Mean (%CV)	8023.9 (43.5)	5652.6 (57.5)	155.10 (105.51, 228.01)
AUC_{inf} (ng•h/mL) Mean (%CV)	8074.4 (44.0)	5788.4 (58.0)	152.79 (103.59, 225.36)

ANOVA = analysis of variance; CV = coefficient of variation; Q1 = first quartile; Q3 = third quartile

a Means presented are unadjusted means

b Percentage geometric least squares mean ratio used means from ANOVA model with ethnicity as a fixed effect

A comparison of the pharmacokinetic data revealed that exposure (AUCinf) was approximately 53% higher in Japanese subjects compared to Caucasian subjects in this study GS US 352 0108. Despite the trend for this slight increase in mean exposures in Japanese subjects, there was a considerable overlap in momelotinib exposures (Cmax and AUC) between the two populations and the differences in exposure between Japanese and Caucasian subjects are not considered to be clinically relevant based on the overall safety profile of momelotinib and lack of exposure-safety relationship for momelotinib in subjects with myelofibrosis.

Of note, the evaluation of the covariate "race" in the popPK analysis is considered exploratory in nature, as supportive evidence to the dedicated clinical pharmacology study.

A summary of older subjects with myelofibrosis enrolled in the momelotinib three phase 3 studies (controlled) and in GS-US-352-1672 as the one uncontrolled supportive study is provided in the table below:

	Age 65-74 (Older subjects number / total number)	Age 75-84 (Older subjects number / total number)	Age 85+ (Older subjects number / total number)
Controlled Studies			
MOMENTUM	94/195 (48.2%)	57/195 (29.2%)	4/195 (2.1%)
SIMPLIFY-1	176/432 (40.7%)	69/432 (16.0%)	2/432 (<1%)
SIMPLIFY-2	73/156 (46.8%)	27/156 (17.3%)	1/156 (<1%)
Non-controlled Studies			
GS-US-352-1672	19/41 (46.3%)	9/41 (22.0%)	2/41 (4.9%)

The safety and efficacy of Omjjara in children and adolescents less than 18 years of age have not been established.

Pharmacokinetic interaction studies

The PK interaction potential of momelotinib and its major metabolite M21 has been evaluated in a number *in vitro* studies and in two *in vivo* DDI studies.

Momelotinib as victim of drug interactions

In vitro metabolism data indicate that CYP1A2, CYP2C8, CYP2C9, CYP2C19 and CYP3A4 are involved in the metabolism of MMB and formation of M21. Aldehyde oxydase is also involved in the formation of M21 following metabolism by CYP enzymes.

In vitro, MMB and M21 were identified as substrates for P-gp, BCRP and OATP1B1/1B3, but not for OCT1.

The effect of multiple dose ritonavir (100 mg daily for 7 days) as strong inhibitor of CYP3A4, P-gp, and BCRP on the PK of multiple dose of momelotinib (100 mg daily for safety issues) has been evaluated (study GS-US-352-1151, cohort 1). A mild inhibitory effect has been observed on momelotinib Cmax (23% increase, 90% CI: 96.4%, 157.7%). Momelotinib AUCtau was increased by 13.5% and the associated 90% CI of the GLSM ratio remained within the protocol-defined no-effect boundary of 70% to 143%. No marked increase in exposure of the metabolite M21 has been observed: 29.8% increase in Cmax (90% CI: 109.8%, 153.5%) and 24% increase in AUCtau (90% CI: 110.1%, 139.62%).

The effect of rifampicin 600 mg single-dose and multiple doses (9 days) on the PK of a single dose of momelotinib 200 mg (recommended daily dose) has also been investigated (study GS-US-352-1151, cohort 3). The single dose of rifampicin was tested to determine the impact of OATP inhibition, while the multiple dose evaluated the impact of a strong CYP3A4 induction on the PK of momelotinib. Rifampicin also induced CYP2C8, CYP2C9 and CYP2C19 isoenzymes and transporters such as P-gP and BCRP, also involved in the metabolism and the transport of momelotinib and the transport of its major metabolite M21. A slight to moderate inhibitory effect of OATP1B1 and OATP1B3 on the PK of momelotinib has been shown (increase in Cmax by 40.4% (90%CI:97.16; 202.87) and AUCinf by 57.1% (90%CI: 122.01; 202.34). When the induction effect is only considered, a 29.4% decrease (90%CI:52.06;95.68) in Cmax and 46.1% decrease (90%CI:44.43;65.50) in AUCinf as well as an increase in major metabolite M21 (31.1% increase in Cmax; 90%CI 98.5, 174.5) were observed. Additionally, a 14.6% decrease in AUCinf of M21 has been shown (90%CI 71.39, 102.1). When the total effect of rifampicin multiple doses is considered, a slight decrease in AUCinf (GMR [90% CI]: 84.75% [71.01, 101.16]), and no impact in Cmax (GMR [90% CI]: 99.08% [82.16, 119.50], included in the default no-effect boundary of 80 to 125%) were observed.

The effect of the gastric pH reducing agent omeprazole 20 mg was evaluated on single-dose 200 mg PK of momelotinib under fasting conditions (Study GS-US-352-0102 – part D). A mild decrease in momelotinib exposure (decrease ~36% (90%CI: 55.12; 75.41) and ~33% (90%CI: 61.19; 72.60) in Cmax and AUCinf, respectively; similar effect on M21 exposure) has been observed.

Momelotinib as perpetrator of drug interactions

The following cut-offs are used for momelotinib for evaluation of interaction potential *in vivo*:

Table 21*:* Cut-offs are used for momelotinib for evaluation of interaction potential *in vivo* 22

	Formula	Momelotinib	M21
Intestinal concentration	0.1 x dose/250 ml	193 µM	
Portal vein concentration	25 x f_u x ((C_{max} + (F_a x F_g x k_a x dose/Q_H))	69.7 µM	
Portal vein concentration adjusted with Blood/plasma ratio	25 x ($f_{u/Rb}$) x (($C_{max,\ plasma}$xRb) + (F_a x F_g x k_a x dose/Q_H))	98.3 µM	
Maximal systemic concentration	50 x $C_{max,unbound,ss}$	5.2 µM	4.55 µM

Molecular weight momelotinib base = 414.47 g/mol; M21 = 428.4 g/mol; M21 = 376.4 g/mol; momelotinib base dose = 200 mg (482.5 µmole); momelotinib $C_{max,ss,\ plasma,\ total}$ = 479.3 ng/mL = 1.16 µM (arithmetic mean, clinical Study SIMPLIFY-1 GS-US-352-0101, 200 mg tablets) ; momelotinib $C_{max,ss,plasma,unbound}$= 0.104 µM; momelotinib $f_{u,\ plasma}$ = 0.09 (studies GS-US-352-1152 and GS-US-352-1153); F_a*F_g = 1 (worst-case scenario), ka = 0.1 min^{-1} (worst case scenario); Q_H = 97 L/h = 1.617 l/min; blood/plasma ratio = 0.7 (mass-balance study GS-US-352-1149); $F_{u,blood}$ = $F_{u,plasma}$/Rb = 0.13; M21 arithmetic mean $C_{max,ss}$ = 486,9 ng/mL = 1.14 µM (clinical study SIMPLIFY-2 GS-US-352-1214, 200 mg tablet QD dosing); M21 $C_{max,ss,plasma,unbound}$ = 0.091 µM; M21 $f_{u,\ plasma}$ = 0.08 (studies GS-US-352-1152 and GS-US-352-1153)

The concentration cut-off of 50 x Cmax,ss,plasma,unbound for the metabolite is calculated = **4.56 µM**. The arithmetic mean Cmax,ss of 486 ng/mL (= 1.14 µM; molecular mass = 428.4 g/mol; M21 fu = 0.08) has been observed for M21 in the clinical SIMPLIFY-2 after 2 weeks administration of once daily 200 mg tablet.

The *in vitro* results for momelotinib and M21 as perpetrators are shown in the tables below.

Table 22: Summary of *in vitro* results for DDI potential of momelotinib and M21 with enzymes (CYPs and UGTs)

Enzyme	**Inducer *in vitro***		**IC50 (µM)[a]**		**TDI parameters : K_i (µM); K_{inact} (min^{-1})**	
	MMB	**M21**	**MMB**	**M21**	**MMB**	**M21**
CYP1A2	Yes	Yes	28.7	> 25		
CYP2B6	Yes	?	9.6	> 25		
CYP2C8	N.D	N.D	>25	> 25		
CYP2C9	N.D	N.D	>30	> 25		
CYP2C19	N.D	N.D	>30	> 25		
CYP2D6	N.D	N.D	>30	> 25		
CYP3A4	?	?	>30	> 25		
UGT1A1	N.D	N.D	0.9	15.9	N.D	N.D
UGT1A3	N.D	N.D	>25	>25	N.D	N.D
UGT1A4	N.D	N.D	>25	>25	N.D	N.D
UGT1A6	N.D	N.D	>25	>25	N.D	N.D
UGT1A9	N.D	N.D	4.2	>25	N.D	N.D
UGT2B7	N.D	N.D	>25	>25	N.D	N.D

MMB = momelotinib; M21 = major metabolite
Empty box: no; N.D: not determined
[a] Assuming Ki = IC50/2

Table 23: Summary of *in vitro* results for DDI potential of momelotinib and M21 with transporters

Transporter inhibition *in vitro*	Momelotinib	M21
OAT1	< 5 % inhibition at 15 µM	< 5 % inhibition at 10 µM
OAT3	5 % inhibition at 15 µM	< 5 % inhibition at 10 µM
OCT1	16 % inhibition at 15 µM	21 % inhibition at 10 µM
OCT2	< 5 % inhibition at 15 µM	15 % inhibition at 10 µM
OATP1B1	6 % inhibition at 15 µM	IC50 = 8.4 µM
OATP1B3	< 5 % inhibition at 15 µM	IC50 = 8.5 µM
BCRP	IC50 = 2.9 µM	6 % inhibition at 10 µM
P-gp	12 % inhibition at 15 µM	< 5 % inhibition at 10 µM
MATE1	34 % inhibition at 15 µM	IC 50 = 2.4 µM
MATE2-K	n.d.	n.d.
BSEP	< 5 % inhibition at 15 µM	19 % inhibition at 10 µM

N.d. : not determined.
[#]IC50 was converted to K_i based on K_i = IC50/2, that is K_i was substituted by worst case assumption.

In vitro evaluations indicated that momelotinib and M21 have no potential to significantly inhibit CYP1A2, CYP2C8, CYP2C9, CYP2C19 and CYP2D6 at clinically relevant concentrations. A direct inhibition by momelotinib of CYP2B6 cannot be ruled out. With a calculated R-value of 1.023, the risk has been correctly addressed by the applicant and the SmPC has been updated to mention that the specific NTI CYP2B6 substrates should be co-administered with caution.

Momelotinib is an inhibitor of UGT1A1 and UGT1A9 at clinically relevant concentrations. Momelotinib and its major circulating metabolite are not inhibitors of the other isoforms (UGT1A3/4/6 and 2B7) at clinically relevant concentrations. The lack of effect on other UGT isoenzymes has been added to section 5.2.

Clear signs of concentration dependent induction are observed for CYP1A2 for momelotinib and M21 and CYP2B6 for momelotinib. No *in vitro* induction signal has been shown for CYP2B6 for M21 and for CYP3A4 for both momelotinib and M21.

The effect of multiple doses of momelotinib 200 mg (8 days) on CYP3A enzyme activity using the probe substrate MDZ (potential momelotinib induction of CYP3A4) in healthy volunteers has shown a mild induction on the PK of midazolam with a 8 % (90% CI: 78.6; 107.1 %) decrease in Cmax and a 16% (90% CI: 73.4; 96.3%) decrease in AUC0-t. Whilst it is possible this potential inductive effect is offset by gut-level CYP3A4 inhibition by momelotinib, this inhibition potential seems to be minimal as corroborated by the observed decrease in midazolam's AUC when co-administrated with momelotinib and no changes in midazolam's half-life (5.33h for midazolam + momelotinib vs 5.82h for midazolam).

In vitro data for momelotinib or its major metabolite M21 suggest a clinically relevant inhibitory potential for BCRP, OATP1B1, OATP1B3 and MATE1. No or only minor inhibition has been observed *in vitro* for BSEP, OAT1, OAT3 and OCT2 at clinically relevant concentrations. It cannot be ruled out that momelotinib is a clinically relevant inhibitor of P-gP in the intestine. Caution is advised when administering momelotinib with P-gp substrates with a narrow therapeutic index.

The effect of multiple doses of momelotinib 200 mg (5 days) on BCRP using the probe substrate rosuvastatin single dose (also OATP1B1/1B3 substrate) has shown a moderate inhibitor effect:

rosuvastatin Cmax was increased by 223% (90% CI: 264.4; 394.3%) and rosuvastatin AUC0-last was increased by 180 % (90% CI: 234,5%; 334,2%).

No *in vivo* study has been performed with oral contraceptives.

2.6.2.2. Pharmacodynamics

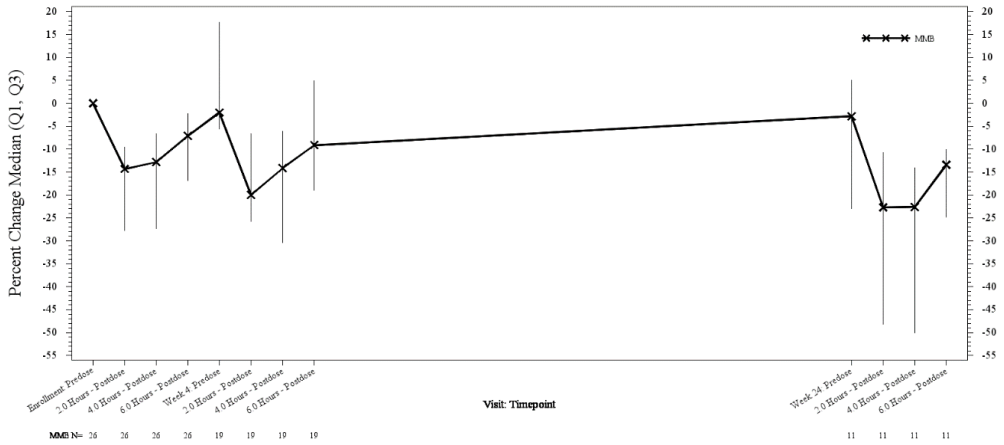
Mechanism of action

MMB is an orally bioavailable, small molecule inhibitor of the Janus kinases (JAK) JAK1 and JAK2 and the activin A receptor type 1 (ACVR1)/activin receptor like kinase 2 (ALK2). It interferes with the JAK STAT (signal transducers and activators of transcription) signaling pathways, which are dysregulated in MF pathogenesis thus contributing to clinical manifestations of the disease. MMB also inhibits the ACVR1 SMAD (mothers against decapentaplegic) signaling pathway resulting in reduced hepcidin expression in the liver, thereby increasing iron availability for erythropoiesis. This confers an additional effect on anaemia and impacts the need for red blood cell (RBC) transfusions.

Primary and Secondary pharmacology

A translational single arm, open label Phase 2 study (GS-US-352-1672) was performed in MF patients with 200 mg tablet formulation to investigate the effects in transfusion-dependent patients with primary and secondary myelofibrosis and the proposed mechanism of action: the inhibition of the JAK STAT and the inhibition ACVR1 SMAD pathways. The inhibition of the latter was assumed to result in decreased production of hepcidin, improved iron availability and erythropoiesis. Patients received MMB for up to 24 weeks in the study.

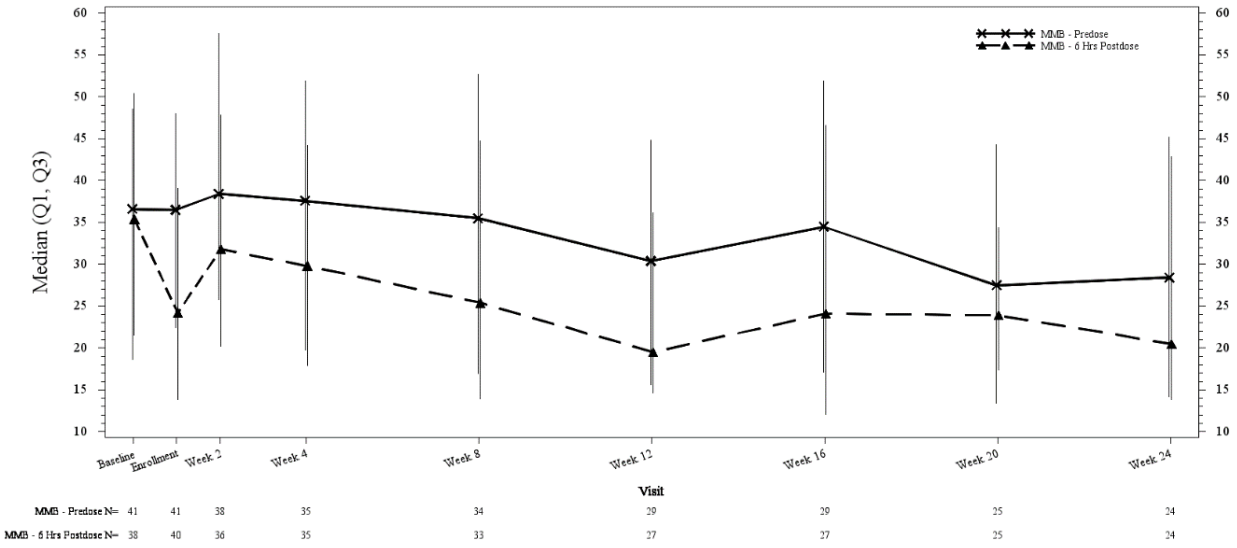
Inhibition of JAK1/JAK2 was assessed by analysis of the PD biomarker: change in phospho STAT3 (pSTAT3) in interleukin (IL) 6 stimulated CD3+ CD4+ T cell. Samples for analysis of pSTAT3 were collected predose and at 2, 4, and 6 hours postdose at enrollment (first dose) and weeks 4 and 24. MMB treatment reduced pSTAT3 in IL 6 stimulated T cells at 2 hours postdose at both first dose and steady state, consistent with potent inhibition of the JAK STAT pathway. Data were reported as the percentage of T cells positive for pSTAT3. At 2 hours after the first dose, pSTAT3 decreased by a median of 14.3%. At Weeks 4 and 24, predose (trough) pSTAT3 was 2.0% and 2.8% lower, respectively, compared with Day 1 predose. At Weeks 4 and 24, median percentage inhibition of pSTAT3 at 2 hours postdose was 20.0% and 22.7%, respectively, compared with Day 1 predose. Maximal inhibition of pSTAT3 was reached 2 hours after each dose and inhibition persisted for ≥ 6 hours.



Source: CSR GS US 352 1672, Figure 15.12.9 Note: Percentage pSTAT3 was reported as the percentage of T cells positive for pSTAT3.

Figure 7: GS-US-352-1672: Median (Q1, Q3) Percentage Change from Baseline in pSTAT3 by Visit (Biomarker Analysis Set)

In the same study, blood samples for analysis of hepcidin, a marker of iron metabolism, were collected. As hepcidin blood concentration varies diurnally, and in order to determine a baseline for each subject, serum was obtained at the baseline visit (no MMB administered) in the morning and then 6 hours later to allow for baseline correction per time of day. After treatment (enrollment, weeks 2, 4, 8, 12, 16, 20, and 24), serum hepcidin samples were collected at predose in the morning and 6 hours postdose.



Source: CSR GS US 352 1672, Figure 15.12.5.1 MMB, momelotinib; Q1, Q3, first quartile, third quartile.

Figure 8: GS-US-352-1672: Median (Q1, Q3) Hepcidin (nM) Levels by Visit (Biomarker Analysis Set)

At every time point, median blood hepcidin decreased 6 hours after dosing with MMB and exhibited a downward trend over time, consistent with the decreased hepcidin production with MMB. These data suggest that MMB inhibits hepcidin production, consistent with inhibition of ACVR1. Increased circulating hepcidin resulting from systemic inflammation in MF is associated with reduced iron availability for erythropoiesis. Among all subjects, daily inhibition of hepcidin did not lead to an increase from baseline in serum iron at week 24.

Increased circulating hepcidin is associated with reduced iron availability for erythropoiesis. Among all subjects, daily inhibition of hepcidin did not lead to an increase from baseline in serum iron at Week 24, but a transient median increase in serum iron of 39.8% was observed in transfusion-independent responders at Week 4. Transferrin, hemoglobin, reticulocytes, and hematocrit also increased at Week 2 in transfusion-independent responders. After the peak at Week 4, serum iron decreased consistent with restoration of iron homeostasis, and hemoglobin and hematocrit increased through Week 24. Platelet counts also increased.

Further, by Week 24, 34.1% of subjects were transfusion independent for ≥12 weeks at any time on study, 39.0% of subjects had no RBC transfusion for at least 8 weeks at any time. At Week 24, 12.2% of subjects had a ≥ 35% reduction in spleen volume, and 15.8% of subjects had a ≥ 50% reduction from baseline to Week 24 in TSS based on the modified MPN-SAF TSS.

The results of this study are consistent with an inhibition of the JAK-STAT pathway and show hepcidin decrease associated with improving iron metabolism and erythropoiesis consistent with inhibition of

ACVR1/ALK2, providing a mechanistic explanation for the reduction in transfusion dependency in TD patients with MF treated with MMB.

These clinical data are consistent with those observed in nonclinical studies where MMB, administered orally for three days at 5, 10 and 25 mg/kg, led to a dose dependent reduction of pSTAT3 and pSMAD1/5/8 levels in the liver as well as a reduction in circulating hepcidin in an anaemia of inflammation rat model (Asshoff, 2017).

Effect on corrected QT interval

GS-US-352-1150 study (Thorough QT) was Phase 1, Partially-Blinded, Randomized, Placebo- and Positive-Controlled Study to Evaluate the Effect of Momelotinib on the QT/QTc Interval in Healthy Subjects. It was designed to evaluate the effect of MMB at therapeutic (200 mg, 1 × 200 mg tablet) and supratherapeutic (800 mg, 4 × 200 mg tablets) exposures on the change from baseline in corrected QT interval (QTc) in 48 healthy adult subjects.

The PK of MMB, the relationship between the concentration of MMB and QT/QTc intervals, and the effect of MMB on other ECG parameters were explored along with the safety and tolerability of MMB. Each period consisted of single tablet dose (on days 1, 11, 21, and 31) with one of the following treatments: therapeutic dose of MMB at 200 mg, supratherapeutic dose of MMB at 800 mg, placebo control, and moxifloxacin positive control (not blinded). Intensive sampling for MMB PK assessments was performed on days 1, 11, 21, and 31 (at predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours postdose). On treatment days, time matched digital 12 lead ECGs were collected in triplicate at various time points over a 24 hour period. In addition, a single ECG was collected at approximately 2 hours postdose for safety monitoring. All ECG acquisitions were completed before blood sample collections. Forty eight healthy adult subjects were enrolled and completed the study.

No subject had a QTcF interval change from predose baseline > 30 or > 60 msec at any time point during any treatment (including MMB 200 and 800 mg, placebo, and moxifloxacin 400 mg). No treatment emergent absolute QTcF intervals > 480 or > 500 msec were observed for any subject following any treatment. Three subjects had treatment emergent absolute QTcF intervals > 450 msec following moxifloxacin treatment.

Concentration QTc relationship.

A linear mixed effect model was used to quantify the relationship between plasma concentrations of MMB and M21 and time matched, baseline adjusted, placebo corrected QT corrected by Fridericia method (ΔΔQTcF) with sex as a fixed effect and subject as a random effect. Although the effect of MMB concentration on ΔΔQTcF was statistically significant (p = 0.037), no clinically relevant relationship between MMB plasma concentration and ΔΔQTcF was concluded due to the small negative slope (0.002) in the plot of ΔΔQTcF versus MMB plasma concentration. A linear mixed effect model showed no relevant relationships between M21 plasma concentration and ΔΔQTcF.

A linear mixed effect model was used to quantify the relationship between plasma concentrations of MMB and M21 and ΔΔQTcF (time matched, baseline adjusted, placebo corrected QTcF), with sex as a fixed effect and subject as a random effect.

Although the effect of MMB concentration was statistically significant (p = 0.037), the small, negative slope (0.002) suggested that there were no clinically relevant relationships between MMB plasma concentrations and ΔΔQTcF interval. For M21, the linear mixed effect model showed that there were no relevant relationships between M21 plasma concentration and ΔΔQTcF interval.

Exposure-response analyses

E-R analyses were conducted following the completion of the population PK analyses with an updated model.

With the data from all 3 Phase 3 studies, E-R analyses were conducted by using population PK model estimates of daily average individual exposures and considering dose modifications. The E-R analyses were conducted to investigate the relationship of MMB exposures versus efficacy endpoints at Week 24 (e.g., TSS percent change from baseline, TSS responders, SVR, splenic volume responder, anemia/transfusions) and safety endpoints (e.g., grade ≥ 3 adverse events, early discontinuation, new onset grade ≥3 anemia, new onset grade ≥3 thrombocytopenia, incidence of diarrhea, incidence of peripheral neuropathy, incidence of indirect bilirubin 2 fold increase).

The E-R analyses were presented using the exposure metrics derived from the updated PopPK model. These analyses, while considering limitations and exploratory nature of the model in patients, suggest that (i) there is a statistically significant E-R relationship for the TI response at Week 24 with higher MMB exposure associated with higher odds of being TI at Week 24 in JAKi exposed patients, but there does not appear to be such a relationship in JAKi naïve patients; (ii) there is no statistically significant E-R relationship for Grade ≥3 anemia and MMB exposure using an unadjusted analysis. However, a trend of higher MMB exposure associated with a decrease in the odds of Grade ≥3 anemia is observed, after adjusting for RBC count at baseline; (iii) there is a statistically significant E-R relationship for spleen-related endpoints with greater splenic volume reduction at Week 24 and a higher probability of SVR ≥35% at higher MMB exposures, regardless of adjusting for different patient-specific or disease-related covariates; (iv) there is a flat E-R relationship for safety endpoints (Grade ≥3 AEs, early discontinuation, Grade ≥3 thrombocytopenia, any Grade diarrhea) except a trend was observed for a higher incidence of any Grade peripheral neuropathy at higher MMB exposure.

2.6.3. Discussion on clinical pharmacology

Absorption

MMB is a low-solubility drug and has pH-dependent solubility. MMB showed moderate to high *in vitro* permeability. No absolute bioavailability study has been conducted. Based on mass balance data and assuming all metabolites are formed after absorption, absorption would be >85%. MMB is classified as a BCS class 2 compound.

In general, the design of the relative BA and food effect study is acceptable.

The 200 mg MMB form II tablet was shown to be bioequivalent to the 300 mg form I capsule in terms of AUC, and was just outside the 80-125% boundary for Cmax. This is acceptable since strict bioequivalence is not required between phase I/II and phase III formulations. Given that the commercial formulation is identical to the phase III formulation (i.e 200 mg form II tablet), no additional bioequivalence studies are needed.

The effect of food on MMB form II tablet was investigated with a low-fat and high-fat meal. Given the modest changes observed with food intake in this study and the administration of MMB to patients in all Phase 3 studies irrespective of food intake, the SmPC wording that MMB can be taken with or without food is accepted.

Distribution

Some differences in protein binding results were observed between studies using different assay methodologies. However, these differences do not impact the calculation of the pharmacologic activity index significantly.

Blood/plasma ratio from the mass balance study is consistent with the *in vitro* data.

Elimination

In the mass balance study, 69.3% of the dose was recovered in feces and 27.5% in urine. More than 85% of the radioactive dose was excreted as metabolites, while parent drug accounted only for 12.6% and 0.6% of the dose in feces and urine, respectively. Metabolism is thus the major elimination pathway, whereas urinary excretion and active secretion of parent drug in bile or intestine are minor elimination pathways. MMB was shown to be a substrate of P-gp and BCRP *in vitro*. MMB was not investigated as a substrate of renal transporters, which is acceptable given the very limited urinary excretion.

MMB is metabolized via multiple metabolism pathways, primarily mediated by CYP enzymes. Based on the proposed metabolism scheme, the formation of M21 with sequential metabolism to M8, M28 or potentially M5 and/or M14, is a major pathway contributing to more than 25% of drug elimination. In vitro experiments indicated that CYP3A4, CYP1A2, CYP2C8, CYP2C9 and CYP2C19 are involved in the metabolism of MMB and the formation of M21. Polymorphic CYPs (CYP2C9 and CYP2C19) play however a minor role in MMB metabolism and hence it is unlikely that clinical consequences will arise from CYP polymorphism. Following metabolism by CYP enzymes, aldehyde oxidase was shown to be involved in M21 formation. Interaction studies with a CYP3A4 inhibitor and inducer were conducted (see DDI).

Since it is unclear if the major faecal metabolite M14 (21.4% of dose in faeces, 1.8% in urine) is a secondary metabolite formed by oxidation of M19 or via hydrolysis of M8/M21 (or both), the pathway to M19 could theoretically also contribute to ≥ 25% of drug elimination. However, given that MMB metabolism *in vitro* (hepatocytes and HLM) was greatly reduced by a general CYP inhibitor, and that M19 is a minor circulating metabolite formed by amide hydrolysis of MMB, the pathway to M19 seems not to be a major elimination pathway.

Overall, the elimination of MMB is considered sufficiently characterized. For the pharmacologically active metabolite M21, CYP3A4 seems to be involved in its clearance based on *in vivo* studies conducted with ritonavir and rifampicin. Since M21 has approximately 34% activity of MMB against JAK1/2 and 40% versus ACVR1, no further identification of potential enzymes involved is required.

In plasma, M21 was the only major metabolite contributing to > 10% of total radioactivity and > 25% of parent exposure and its interaction potential has been investigated (see interactions). The PK of M21 has been characterised in studies in healthy volunteers as well as in MF patients. M21 consistently showed higher systemic exposure than MMB.

Dose proportionality and time dependency

MMB and M21 exposure increased less than dose proportional with increasing single dose for doses above 200 mg. No clinical studies evaluated dose proportionality at steady state for the MMB tablet form II. This is acceptable considering that MMB should be taken as a single 200 mg tablet once daily in line with SmPC recommendations.

In line with the short half-life of MMB and M21 and the once daily administration, no significant accumulation seems to occur based on comparison of trough concentrations from week 2 up to week 24. No direct comparison of PK parameters (AUC, Cmax) after single and multiple administrations of 200 mg MMB (tablet) in MF patients is available. Indirect comparison with PK parameters after a single MMB administration in healthy volunteers (200 mg tablet) or in MF patients (300 mg capsule) suggests the absence of significant accumulation.

Pharmacokinetics in target population

Based on the pooling of PK parameters from different clinical studies, it can be concluded that exposures (Cmax and AUC) of MMB in healthy volunteers and subjects with MF were similar.

Population PK analysis

The approach taken by the applicant for model evaluation is overall state of the art.

It was asked to the applicant to submit the results of the new model (previously referred as sensitivity #1) with improved predictive performances. In its D120 response, the applicant presented the complete results for the sensitivity analysis #1 model for both parent (MMB) and metabolite (M21) (question 14). The updated model was used for subsequent E-R analysis and the results were reflected in the conclusions.

Otherwise, the applicant acknowledged that they didn't have enough data for a formal covariate analysis for most of the covariates. However, it was considered that there was sufficient data to assess covariates effects for age, sex and body weight as part of the PopPK analysis performed using data (combination of sparse and intense PK sampling) from 5 myelofibrosis studies (CCL09101, YM387-II-02, SIMPLIFY-1, SIMPLIFY-2, MOMENTUM) that was adequate to support the conclusion that these covariates did not have a significant or clinically relevant effect on momelotinib PK exposure parameters. The applicant acknowledged that there was limited frequency for covariates for race and concomitant medication. To further support the covariate assessment on PK exposure, the applicant performed an additional analysis to assess the influence of intrinsic factors (i.e., age, sex, bodyweight, and race) on momelotinib exposure (AUCinf and Cmax based on noncompartmental PK based on intense PK sampling) using data from six clinical pharmacology studies in which healthy adult subjects received a single dose of 200 mg of momelotinib in fasted state. A total of 150 individuals were included in this analysis. The totality of evidence (clinical PK and PopPK) supports the conclusions that age, gender, race (White, Black, Asian) and weight do not have a clinically relevant effect on the PK of momelotinib.

Modelling and simulation results are not robust enough to support a statement of covariate (bodyweight, age, gender and race) effects on the PK of momelotinib.
Additional analyses results using data from six clinical pharmacology studies in scatterplots were provided and the applicant clarified on which metrics exactly the covariate effects are precluded.

Gender and race (White vs Asian) do not have a clinically relevant effect on the pharmacokinetics of momelotinib based on exposure (AUC) data in healthy subjects. Exploratory results of population pharmacokinetics analysis in patients did not show any effects of age, weight, or gender on momelotinib pharmacokinetics, as reflected in the section 5.2 of the SmPC.

Special populations

Overall, the pharmacokinetics in special populations are well described.

The applicant was asked to further discuss the adequacy of the single dose study design to appropriately characterise the PK of momelotinib in subjects with renal impairment (given the non-linear PK) and whether conclusions on dosing recommendations can be drawn from single-dose data. Based on the justification provided by the applicant, it was considered that the single dose design employed in study GS-US-352-1152 was appropriate to characterize and compare exposures in renally impaired subjects.

As hepatic elimination is a major route of excretion for momelotinib, hepatic impairment may result in increased plasma momelotinib concentrations. In this context, the applicant provided the results of a dedicated study of momelotinib and its main metabolites in patients with moderate and severe hepatic impairment.

The applicant considered the reduced exposure of the pharmacologically active metabolite, M21, to guide the dose adjustment recommendation. The overall 37% (based on geometric mean ratio) increase of AUC for the combined exposure justifies the recommended dose reduction of 25% of the starting dose from 200mg to 150mg once daily to account for the increase in plasma exposures of momelotinib and the decrease in plasma exposures of M21 in subjects with severe hepatic impairment.

Given that momelotinib exhibits high extent of plasma protein binding (>90%), the unbound concentrations of the drug and active metabolites should have been analysed in renal and hepatic impaired patients, in addition to total concentrations. The percentage of free fractions of momelotinib and M21 is presented at 4h and 24h in all subjects in renal impairment study GS-US-352-1152 and in hepatic impairment study GS-US-352-1153. Given the similarities in free fractions between impaired and non-impaired populations both in the renal and hepatic impairment studies, the conclusions using total exposure are judged acceptable.

Apparent differences in exposure between Japanese and Caucasian subjects (53% increase) are not considered to be clinically relevant based on the overall safety profile of momelotinib and lack of exposure-safety relationship for momelotinib in subjects with myelofibrosis. This is further corroborated by no differences in exposure-response relationships observed for all efficacy measures (in terms of both Spleen Volume Reduction (SVR) and Total Symptom Score (TSS) endpoints) between Japanese, Asian and non-Asian subjects with MF in the Phase 3 studies.

Based on the results obtained, dose adjustment is not considered necessary for patients with different racial or ethnic backgrounds.

Based on POP PK analysis, dose modifications are not considered necessary for patients based on age, body weight and gender.

Pharmacokinetic interaction studies

Momelotinib as victim of drug interactions

In vitro, MMB and M21 were not a substrate of the OCT1 receptor.

CYP3A4 showed the highest contribution to the metabolism of momelotinib and the formation of M21. Furthermore, MMB as well as M21 were shown to be substrates of Pgp and BCRP *in vitro*. While a mild inhibitory effect on momelotinib PK has been observed with ritonavir administrated concomitantly as strong inhibitor of CYP3A4, P-gP and BCRP, the applicant has considered that the ritonavir effect is not clinically relevant.

Ritonavir (a strong CYP3A4 inhibitor) increased momelotinib Cmax by 23.3% and AUC by 13.5%. Tmax and t1/2 of momelotinib remained unchanged. These changes are not considered clinically relevant and a dose adjustment is not warranted when Omjjara is co-administered with a CYP3A4 inhibitor. However,
the argumentation provided by the applicant on PgP and BCRP inhibition is not followed as the applicant did not provide any supporting data on the clinical impact of the co-regulation he is referring to. The absence of characterization of the effect of strong P-gp and BCRP inhibitors should be described in the SmPC and appropriate recommendation should be provided (*pending issue*).

An *in vitro* signal has been observed for OATP1B1 and OATP1B3 for MMB and M21 as substrate. A slight to moderate increase in momelotinib exposure has been observed with rifampicin single-dose in healthy volunteers.

The applicant agreed to revise the text in section 4.5 relating to inhibitors of OATP1B1/1B and to mention that coadministration with a single dose of rifampicin (inhibitor of OATP1B1/1B3) moderately

increased momelotinib exposure (Cmax by 40.4% and AUCinf by 57.1%). In addition, it is stated that caution and monitoring for adverse reactions is advised in case of concomitant use with inhibitors of OATP1B1/1B3.

When the impact of the strong CYP3A inducer rifampicin on the PK of momelotinib is considered solely, a moderate induction effect has been observed. Consequently, the applicant has recommended additional monitoring in case of concomitant use of strong CYP3A4 inducer or the use of an alternative drug to the strong CYP3A4 inducer.

The applicant clarified text to provide comparison of single-dose rifampicin + momelotinib and multiple dose rifampicin + momelotinib in the SmPC. The applicant considers that reduction in momelotinib exposure due to induction by multiple dose rifampicin would not lead to a clinically significant reduction in efficacy.

Coadministration of strong CYP3A4 inducers may lead to decreased momelotinib exposure and consequently a risk for reduced efficacy. Additional monitoring is recommended with concomitant use of momelotinib and strong CYP3A4 inducers or an alternative medicinal product to the strong CYP3A4 inducer should be considered.

Coadministration of omeprazole, a representative PPI, slightly decreased momelotinib exposure. The applicant does not consider the changes clinically relevant.

Even if not optimal and even if 40 mg has had the greatest potential for interaction, it is agreed that the 20mg dose allows an adequate characterisation of the effect of omeprazole dosing with momelotinib.

The DDI risk as victim and perpetrator through aldehyde oxidase has been sufficiently discussed.

The results of the *in vitro* phenotyping study (AD-352-2021) indicated that momelotinib (MMB) metabolism was through multiple enzymes including CYP3A (fm ~0.36), CYP2C8, CYP2C19 and CYP2C9 (fm ~0.15 - 0.2 each) and CYP1A2 (fm ~0.1). Aldehyde oxidase (AO) was involved in M21 (active metabolite) formation in the sequential step after the primary CYP pathway. Since AO is a high-capacity enzyme and based on the profiles of known AO substrates, clinically significant DDIs with M21 (due to the clinical inhibition of AO) are unlikely to occur [Dalvie, 2019; Zaleplon and Ziprasidon Labels].

Momelotinib as perpetrator of drug interactions

In accordance with the EMA Guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2**), only the potential perpetrator profile of the parent drug and the major metabolite M21 (AUC both larger than one fourth of the AUC of parent drug and larger than 10% of the drug-related exposure) is discussed below.

First of all, regarding the experimental conditions of the *in vitro* perpetrator studies, a number of uncertainties were identified during the first round. Especially, was not clear whether stability and non-specific binding of momelotinib and M21 have been adequately handled in all *in vitro* systems used. Further justifications were awaited to support that the actual unbound concentrations of momelotinib and M21 in the *in vitro* system are representative of the nominal concentrations.

Non-specific binding to human liver microsomes were conducted for both MMB and M21 in an *in vitro* study AD-352-2031. Therefore, the *in vitro* inhibitory potency of MMB and M21 towards CYP450 and UGT enzymes in human liver microsomes were corrected for free fraction for the DDI risk assessment. The applicant acknowledges the gaps in the *in vitro* study design (i.e., the media concentrations of MMB and M21 were not measured in the *in vitro* systems using cellular assays for transporter inhibition or CYP hepatocyte induction) which could impact the *in vitro* DDI risk assessment for MMB and M21.

However, a clinical DDI study with rosuvastatin and single dose rifampin was conducted to address the *in vivo* BCRP and OATP1B1/1B3 inhibition DDI, respectively (GS-US-352-1151). In addition, any potential *in vivo* DDI risk via P-gp inhibition by MMB or M21 at the gut level was already recognized and is reflected in updated SmPC wording following the worst-case scenario analysis (refer to Response of Q98). Also worth noting is that MMB and M21 did not inhibit OAT1/3 and OCT2 (<5% inhibition) at the highest assay concentrations (OPT-2012-066, OPT-2012-086, OPT-2012-126, AD3522019, AD3522030). Therefore, additional non-specific binding would not make a significant impact to the overall outcome of *in vitro* DDI risk assessment.

For CYP and UGT inhibition studies using human liver microsomes, the incubations were done up to 60 min. In vitro metabolic stability in human hepatic microsomes indicated that MMB concentrations were relatively stable for 60 minute incubations. Less than 20% parent turn-over was detected in NADPH-dependent metabolism samples, while no measurable non-NADPH dependent degradation of MMB was detected over the 60 min incubation (CDCO-Cytopia_07_025, CDCO-Cytopia_08_004). In addition, all the assays were designed so that conditions were linear with respect to time and protein concentration while substrates were present at concentrations lower than their respective Km values. Therefore, the performance of the *in vitro* perpetrator DDI studies is judged acceptable.

CYP enzymes and UGT

In vitro inhibition of all mandatory CYP enzymes has been studied for both momelotinib and the major metabolite M21.

Based *on vitro* results, the risk of a clinically relevant direct inhibition of CYP2B6 by momelotinib cannot be ruled out (IC50/2 < 5.2 µM) but at clinically relevant concentrations neither momelotinib nor the major circulating metabolite M21 represent a risk of inhibition of CYP1A2, 2C8, 2C9, 2C19 and 2D6 enzymes. With a calculated R-value of 1.023, the risk by CYP2Bhas been correctly addressed by the applicant and the SmPC has been updated to mention that the specific NTI CYP2B6 substrates should be co-administered with caution.

In addition, UGT inhibition has been studied. Momelotinib is an inhibitor of UGT1A1 and UGT1A9 at clinically relevant concentrations, but the clinical relevance is unknown. The applicant agrees to add in section 5.2. that momelotinib is an inhibitor of UGT1A1 and UGT1A9 at clinically relevant concentrations but that the clinical relevance is unknown and that momelotinib and its major circulating metabolite are not inhibitors of the other isoforms (UGT1A3/4/6 and 2B7) at clinically relevant concentrations.

The use of two UGT substrates and the positive controls has been justified. Both sulindac sulfone and naloxone were used as UGT1A3 and UGT2B7 substrates in various literature references [Brunell, 2011; Gall, 1999]. In addition, the validation for these substrates and positive controls were also conducted and established at the test facility.

Because cellular stress has been observed for all 3 donors for both momelotinib and M21, is cannot be ruled out that the *in vitro* induction results are masked by the cell toxicity. Rising levels of mRNA to more than 100% increase (2-fold) with rising momelotinib concentrations were observed up to 1 µM for CYP1A2 and 2B6 for momelotinib in at least one donor and then began to drop at 3 µM and after. The same observation was done for M21 up to 3 µM (and then a drop at 10 µM) in one donor for CYP1A2. As a consequence a potential induction by momelotinib and M21 of CYP1A2 and CYP2B6 at clinically relevant drug concentrations cannot be ruled out. The applicant recognizes the limitation of the *in vitro* hepatocyte induction assay due to cellular stress observed at higher concentrations tested, which hindered generating *in vitro* enzyme induction kinetic parameters for DDI risk assessment. Dose dependent weak CYP1A2 mRNA induction was indicated *in vitro* (60N-1687) for MMB at clinically relevant concentration in 2 donors tested, but with < 20% response of the positive control, 50 µM omeprazole. Only a small CYP2B6 mRNA increase (<3-fold) was observed in 1 of 3 donors tested (60N-

1687), suggesting very weak induction potential by MMB. For M21, there were no notable dose dependent increase on CYP1A2 and CYP2B6 mRNA levels at clinically relevant concentrations tested *in vitro*. Although only very weak induction for CYP1A2 and CYP2B6 was observed *in vitro*, a clinically relevant DDI cannot be ruled out completely. The SmPC section 4.5 wording for CYP450 substrates has been updated accordingly, stating that narrow therapeutic index or sensitive substrate drugs of CYP1A2 (e.g., theophylline, tizanidine) or CYP2B6 (e.g., cyclophosphamide) should be co-administered with caution.

Regarding a potential CYP3A4 induction, no fold-change result of CYP3A4 mRNA was ≥ 2-fold for both momelotinib and M21 but the results were dropping progressively in all 3 donors across rising momelotinib and M21 concentrations, while cytotoxicity has been observed for both momelotinib and M21. In addition, the concentrations of momelotinib used for CYP3A4 are too low to exclude an *in vivo* DDI in the enterocytes. Therefore, a potentially clinically relevant *in vivo* induction of CYP3A4 cannot be ruled out based on these *in vitro* results.

However, an *in vivo* DDI study has been carried out investigating the effect of multiple doses of MMB on midazolam, a sensitive CYP3A4 substrate. A mild induction effect has been observed.

Study GS-US-352-1151 Cohort 4 assessed the potential effect of momelotinib to alter midazolam exposure via induction of CYP3A4. In this study, momelotinib was dosed at the therapeutic clinical dose of 200mg QD for 7 days prior to the assessment of midazolam + momelotinib.

Despite the predefined no-effect boundaries in the study, the applicant considers that study GS-US-352-1151 demonstrates a very weak (if any) induction of CYP3A4 by momelotinib as assessed via interaction with the sensitive CYP3A4 substrate midazolam. Whilst it is possible this potential inductive effect is offset by gut-level CYP3A4 inhibition by momelotinib, this inhibition potential seems to be minimal as corroborated by the observed decrease in midazolam's AUC when co-administrated with momelotinib and no changes in midazolam's half-life (5.33h for midazolam + momelotinib vs 5.82h for midazolam). The overall net effect on midazolam's exposure remains minimal and supports guidance for coadministration of momelotinib with sensitive CYP3A4 substrates.

Based on the total evidence provided by the applicant and even if the design of the study is not optimal to cover a maximal induction, the midazolam study informs sufficiently on the potential of CYP3A induction which is judged minimal. No change in midazolam's half-life is observed.

The proposed indication may include women of childbearing potential. A clinically relevant induction of CYP1A2, CYP2B6 and CYP3A cannot be ruled out based on *in vitro* results. Furthermore, there may still be mechanisms of induction which presently are unknown.

Without an *in vivo* dedicated DDI study studying the impact of momelotinib on oral contraceptives, a risk of induction of other non-CYP3A enzymes cannot be completely excluded. The effectiveness of concomitant administration of oral contraceptives may be reduced and given that embryo-foetal toxicity has been shown with momelotinib in studies in animals, female patients of child-bearing potential receiving momelotinib must use highly effective contraceptive methods during treatment. In this context, the applicant agreed to update sections 4.4, 4.6, and 5.2 to reflect that women using oral hormonal contraceptives should add an additional barrier method during OMJJARA treatment and for at least one week after the last dose.

Transporters

The effect of momelotinib and M21 on all mandatory transporters has been investigated. In addition, the potential inhibition on optional transporters OCT1, MATE1 and BSEP has been investigated for both momelotinib and M21.

Positive inhibitory signals for momelotinib or its major metabolite M21 have been found *in vitro* at clinically relevant concentrations for BCRP, OATP1B1, OATP1B3 and MATE1.

For the effect of momelotinib on OATP1B1/1B3, the applicant acknowledged the gaps in the *in vitro* assay such as the upper concentration was only up to 15 µM and the preincubation step was not performed in OATP1B inhibition experiments to better investigate the *in vitro* inhibitory potency of MMB. Given that MMB has low solubility, it is unlikely to achieve the targeted concentrations *in vitro* to cover the calculated clinically relevant hepatic exposure, therefore further *in vitro* investigations will not cover clinically relevant concentrations. Further, it was noted that M21 was an *in vitro* inhibitor for OATP1B1 and 1B3, but the static DDI model predicted no clinically relevant risk based on regulatory DDI guidance.

A clinical DDI study with rosuvastatin (BCRP substrate, OATP1B1, OATP1B3 substrate) was conducted to assess the DDI potential of BCRP inhibition and OATP1B1/1B3 inhibition in human subjects (GS-US-352-1151). Overall, the rosuvastatin Cmax was increased 3.2-fold and AUCinf was increased 2.7-fold upon co-administration of MMB, but T1/2 remained unchanged, indicating that the rosuvastatin DDI was caused by BCRP inhibition by MMB at the gut level and unlikely through inhibition of OATP1B1 and 1B3 in liver. Based on the DDI study with rosuvastatin, the applicant accepted to add appropriate statement in Section 4.5 of the SmPC saying that momelotinib is an inhibitor of breast cancer resistance protein (BCRP) *in vitro*. Upon CHMP's request, the statement has been extended to the other BCRP substrates.

Regarding MATE1, no *in vivo* studies have been conducted using MATE1 substrates. In vitro, the MATE1 inhibition assay determined an IC50 of 2.4 µM for M21 and further static analysis indicated potential clinically relevant DDI with R value of 1.93 calculated using EMA DDI guidance. Upon EMA's request, the SmPC is adequately updated to use caution when co-administrating sensitive MATE1 substrates (e.g., metformin).

For OCT1, the applicant acknowledged the upper concentration of 15 µM in the *in vitro* assay is not sufficient to cover the calculated hepatic inlet concentration. Due to the solubility limitation of MMB (<3µg/mL at pH 7, m2.7.1), it is unlikely to achieve the targeted clinically relevant concentration therefore, an additional *in vitro* study will not cover clinically relevant concentrations. Therefore, the applicant updated the SmPC Section 4.5 to use caution when co-administrating sensitive OCT1 substrates (e.g., metformin).

No or only minor inhibition has been observed *in vitro* for BSEP, OAT1, OAT3 and OCT2 at clinically relevant concentrations. The negative *in vitro* signals have been added in the section 5.2 of the SmPC.

The potential inhibitory effect on MATE2 has not been evaluated. However, due to the solubility limitations of MMB and M21, an *in vitro* assay will not likely provide an adequate assessment. Therefore, the applicant revised the SmPC for caution with coadministration with metformin and other sensitive MATE1 and MATE2 substrates.

Pharmacodynamics

MMB treatment reduced pSTAT3 and hepcidin after dosing is in line with the proposed mechanism of action. An acute and sustained reduction of circulating hepcidin was observed for the duration of the 24 week study, associated with increased iron levels and haemoglobin, following administration of momelotinib to patients with myelofibrosis.

Study GS US 352 1150 (QT) was designed to evaluate the effect of MMB at therapeutic (200 mg, 1 x 200 mg MMB tablet) and supratherapeutic (800 mg, 4 × 200 mg MMB tablets) exposures on the change from baseline in QTc interval in a single dose crossover design. As the result of GS-US-352-1150 study, no subject had a QTcF interval change from predose baseline > 30 or > 60 msec at any

time point during any treatment (including MMB 200 and 800 mg, placebo, and moxifloxacin 400 mg). No treatment emergent absolute QTcF intervals > 480 or > 500 msec were observed for any subject following any treatment. The results of the TQT study were negative as defined by ICH E14 guidance.

One of the exploratory objectives of MOMENTUM trial was to explore potential correlates with response including but not limited to mutational analysis. As regards potential predictive biomarkers, some exploratory analyses were conducted using samples from SIMPLIFY-1 and -2 studies, while such analyses are still ongoing for MOMENTUM trial. Therefore, the results for baseline ferritin levels potentially differentially enriched for the week 24 TI response for momelotinib compared to the control arms are not yet available for the latter.

Data currently available on the inflammatory cytokine responses to momelotinib treatment are limited and inconclusive, and further data are awaited, e.g., from the SIMPLIFY-1 study.

E-R analyses

There were no clinically relevant relationships between time matched, baseline adjusted, placebo corrected QTcF and plasma concentrations of MMB or its metabolites based on a linear mixed effect model that was used to quantify the relationship between plasma concentrations of MMB and M21 and ΔΔQTcF (time matched, baseline adjusted, placebo corrected QTcF), with sex as a fixed effect and subject as a random effect.

With the data from all 3 Phase 3 studies, E-R analyses were conducted by using population PK model estimates of daily average individual exposures and considering dose modifications. The E-R analyses were conducted to investigate the relationship of MMB exposures versus efficacy endpoints at Week 24 (e.g., TSS percent change from baseline, TSS responders, SVR, splenic volume responder, anemia/transfusions) and safety endpoints (e.g., grade ≥ 3 adverse events, early discontinuation, new onset grade ≥3 anemia, new onset grade ≥3 thrombocytopenia, incidence of diarrhea, incidence of peripheral neuropathy, incidence of indirect bilirubin 2 fold increase).

The E-R analyses were presented using the exposure metrics derived from the updated PopPK model. These analyses, while considering limitations and exploratory nature of the model in patients, suggest that (i) there is a statistically significant E-R relationship for the TI response at Week 24 with higher MMB exposure associated with higher odds of being TI at Week 24 in JAKi exposed patients, but there does not appear to be such a relationship in JAKi naïve patients; (ii) there is no statistically significant E-R relationship for Grade ≥3 anemia and MMB exposure using an unadjusted analysis. However, a trend of higher MMB exposure associated with a decrease in the odds of Grade ≥3 anemia is observed, after adjusting for RBC count at baseline; (iii) there is a statistically significant E-R relationship for spleen-related endpoints with greater splenic volume reduction at Week 24 and a higher probability of SVR ≥35% at higher MMB exposures, regardless of adjusting for different patient-specific or disease-related covariates; (iv) there is a flat E-R relationship for safety endpoints (Grade ≥3 AEs, early discontinuation, Grade ≥3 thrombocytopenia, any Grade diarrhea) except a trend was observed for a higher incidence of any Grade peripheral neuropathy at higher MMB exposure.

2.6.4. Conclusions on clinical pharmacology

In conclusion, the pharmacokinetics of momelotinib has been adequately studied.

2.6.5. Clinical efficacy

2.6.5.1. Dose response studies

Four main studies contributed to the selection of dose for pivotal studies, the first three conducted in patients in subjects with PMF or post PV/ET MF and the last one - in healthy volunteers:

- **CCL09101** – phase I/II study to safety, tolerability, dose limiting toxicities (DLTs), maximum tolerated dose (MTD), and PK of the MMB capsule Form I
- **YM387 II 02** - phase I/II study to determine the PK of capsule administered BID
- **GS US 352 0102** – phase I to assess the relative bioavailability of a tablet formulation of MMB compared with the capsule
- **GS US 352 1672** – phase II study with tablet formulation to evaluate MMB PK in transfusion dependent subjects with MF and to assess biomarkers of inhibition of JAK1/2 and ACVR1 in transfusion dependent subjects with MF treated with MMB

CCL09101 study

In the Phase 1 dose escalation phase, the MMB dose was escalated from 100 mg to 400 mg daily through 5 successive cohorts of subjects in a 3 + 3 design. Escalation to the next dose group occurred if none of the first 3 subjects experienced a dose limiting toxicity (DLT) or if ≤ 2 of 6 subjects experienced a DLT. In the 400 mg once daily (QD) cohort, 2 of 6 subjects experienced a total of 2 DLTs with no other DLTs observed at other doses. In the Phase 2 portion of the study, the 150 mg and 300 mg QD cohorts were selected for cohort expansion in addition to a 150 mg BID cohort. The recommended daily dose of the MMB capsule (Form I) was determined to be 300 mg QD.

YM387 II 02 study

The study evaluated dose levels of 200 mg BID and 250 mg BID in the dose escalation and dose confirmation phases to investigate whether additional therapeutic benefit could be achieved with higher daily doses administered in this regimen. No events met the protocol defined criteria for DLT in the dose escalation phase, though the MMB 250 mg BID dose was not well tolerated. Of the 7 subjects who initially received 250 mg BID, only one subject received this dose for over 30 days. All 6 others either had dose decreases, dose interruptions, or discontinued from the study within 30 days. Therefore, only 200 mg BID dose group was expanded in the dose-confirmation phase.

Table below presents PK parameters at steady state following once daily or BID dosing regimen from studies CCL09101 and YM387-II-02.

Table 24: Comparison Between Studies CCL09101 and YM387-II-02: PK Parameters Following QD or BID Dosing of MMB Form I Capsule at Steady State

Study	CCL09101			YM387-II-02
PK Parameter	150 mg QD (N = 17-18) [1]	300 mg QD (N = 25-27) [1]	150 mg BID (N = 13-14) [1]	200 mg BID (N = 13-21) [1]
C_{max} (ng/mL)	338.5 (59.2)	658.3 (53.8)	320.8 (94.0)	505.0 (61.3)
T_{max} (h) [2]	2.00 (1.00, 2.13)	2.00 (1.58, 2.93)	1.99 (1.50, 2.00)	2.00 (1.00, 2.08)
$t_{1/2}$ (h) [2]	4.67 (3.77, 5.53)	4.60 (2.98, 5.45)	3.02 (2.54, 4.37)	4.87 (3.70, 5.31)
AUC_{tau} (ng·h/mL) [3]	2349.9 (82.9)	4281.3 (54.7)	1744.8 (101.8)	3095.6 (56.3)

Source: CSR CCL09101; YM387-II-02 [1] Number of subjects was different for different PK parameters. [2] All data are presented as mean (CV%) except Tmax and t1/2 are presented as median (Q1, Q3). [3] AUCtau = AUC0-24 for QD; AUCtau = AUC0-12 for BID. AUCtau, area under the plasma concentration time curve over the dosing interval; BID, twice daily; Cmax, maximum plasma concentration; Q1, Q3, first quartile, third quartile; QD, once daily; t1/2, terminal elimination half life; Tmax, time to Cmax.

Table 25: Comparison Between Studies CCL09101 and YM387-II-02: Responses (mITT Population) And Discontinuation (Safety Population) by Initial Dose

Study	**CCL09101**			**YM387-II-02**
Response/Safety Category: n (%)	**150 mg QD (N=52)**	**300 mg QD (N=59)**	**150 mg BID (N=42)**	**200 mg BID (N = 53)**
Clinical Improvement	23 (44.2%)	34 (57.6%)	23 (54.8%)	31 (58.5)
Splenomegaly > 5 cm at baseline	48	52	37	44
Spleen Responders	15 (31.3%)	17 (32.7%)	12 (32.4%)	33 (75.0)
Transfusion Dependent Subjects at Baseline	24	30	15	25
Transfusion Responders	12 (50.0%)	20 (66.7%)	8 (53.3%)	9 (36.0)
Anemic Subjects at Baseline	33	42	29	35
Anemia Responders	13 (39.4%)	20 (47.6%)	9 (31.0%)	10 (28.6)
Average Daily Dose (mg) [3]	217.43	297.71 [1]	296.76	293.7 [2]
Decrease in Dose due to AE	12 (23.1%)	24 (40.0%) [1]	12 (28.6%)	26 (48.1%)
Number of Patients with at Least 1 TEAE Leading to Study Discontinuation	5 (9.6)	8 (13.3) [1]	7 (16.7)	17 (31.5)

Source: CCL09101 Tables 9-1, 9-2, 9-4, 11-1, 11-9; YM387-II-02 Tables 9-1, 9-2, 9-7, 11-1, 11-10.
Note: mITT (modified intent-to-treat) Population consisted of all enrolled subjects who received at least 1 dose of MMB and had at least 1 postbaseline IWG-MRT evaluation. [1] n = 60 [2] n = 54 [3] Median is reported

Taking both studies **CCL09101 and YM387 II 02 study** into consideration, the therapeutic activity of MMB 300 mg once daily was similar regarding spleen size reduction, transfusion and anemia response, and decreased symptoms when compared to 200 mg BID.

However, the 200 mg BID had a higher discontinuation rate, more pronounced side effects (e.g., thrombocytopenia, peripheral neuropathy), and similar average daily doses when compared to 300 mg once daily regimen. The higher daily dose given as 200 mg BID or 250 mg BID regimen led to more dose adjustment during treatment due to AEs without having more benefit. Given the similar benefit-risk across the range of exposures in the 150 mg once daily, 300 mg once daily, and 200 mg BID doses, benefit-risk data were in support of the 300 mg once daily dose which was taken forward in subsequent development studies.

Therefore, the 300 mg capsule formulation was identified as the optimal dose with a favourable benefit risk profile in the phase 1 2 dose escalation/dose confirmation studies CCL09101 and YM387 II 02 based on overall PK, safety, and therapeutic activity profiles of once daily and BID doses in subjects with MF.

GS US 352 0102

A bridging PK study was conducted to evaluate the relative bioavailability between a new tablet formulation and the capsule formulation**.** The study evaluated the relative bioavailability of several MMB doses in tablets (dihydrochloride monohydrate salt Form II; 100, 150, 200, or 300 mg) compared with the capsule formulation used in studies CCL09101 and YM387 II 02. Data from this study indicated that the 200 mg tablet (Form II) dose provided similar exposure to the 300 mg capsule dose used in earlier studies (please refer to the PK part of the report) leading to selection of the 200 mg tablet (Form II) dose for the subsequent Phase 3 program.

GS-US-352-1672 study

This translational Phase 2 study was performed in transfusion-dependent MF patients at MMB 200 mg starting dose of the tablet formulation QD for all subjects to demonstrate the mechanism of action of MMB (please refer to the PD part of the report). Biomarker, phosphorylated signal transducer and activator of transcription 3 (pSTAT3) in interleukin (IL) 6 stimulated T cells sampled from study subjects were also collected on the same schedule as PK samples. Peripheral hepcidin decreased 6 hours after dosing with MMB and exhibited a downward trend over time, consistent with the decreased hepcidin production with MMB. This study confirmed that the 200 mg once daily tablet was associated with evidence of desired pharmacology and demonstrated efficacy with an acceptable safety profile.

Overall, the safety, efficacy, and PK data from earlier Phase 1-2 studies CCL09101 and YM387-II-02, a bioequivalence Phase 1 study GS-US-352-0102, and data from the translational Phase 2 study GS-US-352-1672 justify the selection of MMB 200 mg tablet Form II once daily for pivotal studies in patients with myelofibrosis.

The dose of MMB 200 mg tablet once daily was used in all of the Phase 3 conducted in MF.

Further, the **E-R analyses** were conducted based on results from phase 3 studies MOMENTUM, SYMPLIFY-1 and SYMPLIFY-2 (please refer to the PK/PD part of the report).

2.6.5.2. Main studies

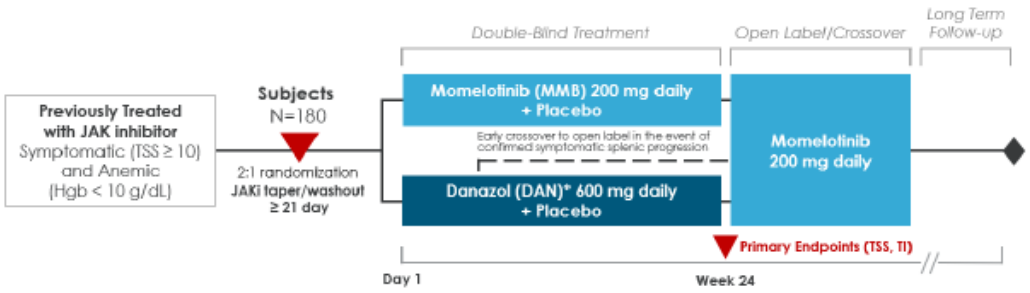
The applicant submitted 2 main studies (one in JAKi-treated patients and one in Jaki-naïve patients).

Main study for JAKi*-treated *patients: **Study SRA-MMB-301 (MOMENTUM), a Phase 3, Randomized, Double-blind Study to Evaluate the Activity of Momelotinib (MMB) versus Danazol (DAN) in Symptomatic, Anemic Subjects with Primary Myelofibrosis (PMF), Post-polycythemia Vera (PV) Myelofibrosis, or Post-essential Thrombocythemia (ET) Myelofibrosis who were Previously Treated with JAK Inhibitor Therapy**

Main study for JAKi-naive patients: **Study GU-US-352-0101 (SIMPLIFY-1), a Phase 3, Randomized, Double-blind Active-controlled Study Evaluating Momelotinib vs. Ruxolitinib in Subjects with Primary Myelofibrosis (PMF) or Post-Polycythemia Vera or Post- Essential Thrombocythemia Myelofibrosis (Post-PV/ETMF)**

Methods

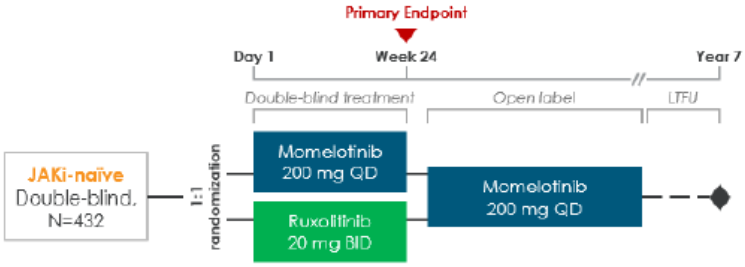
MOMENTUM is an international, randomized, double blind, active controlled, pivotal phase 3 study of the efficacy and safety of MMB versus DAN in subjects with intermediate or high risk primary MF (PMF) or post polycythemia vera or post essential thrombocythemia (post PV/ET) MF who previously received JAK inhibitor therapy and were symptomatic and anemic. The 24 week double blind, randomized treatment period was completed and open label treatment with MMB is ongoing.



Abbreviations: DAN, Danazol; Hgb, hemoglobin; JAKi, Janus kinase inhibitor; TSS, total symptom score

Figure 9: MOMENTUM trial design schema

SIMPLIFY 1 was an international, randomized, double blind, active controlled, pivotal phase 3 study of the efficacy and safety of MMB versus RUX in JAK inhibitor naïve subjects with intermediate or high risk PMF or post PV/ET MF. The primary objective was to determine the efficacy of MMB compared with RUX as measured by SRR at week 24.



Abbreviations: BID, twice daily; JAKi, Janus kinase inhibitor; LTFU, long-term follow-up; QD, once daily.

- **Study Participants**

Table 26: Key eligibility criteria in MOMENTUM and SIMPLIFY-1 studies

Inclusion Criteria	MOMENTUM	SIMPLIFY-1
Age	≥ 18 years	Same as MOMENTUM
MF diagnosis	Confirmed diagnosis of PMF per the WHO 2016 criteria, or post-PV/ET MF per the IWG-MRT criteria	Same as MOMENTUM
History of JAK inhibitor therapy	Previously treated with an **approved JAK inhibitor** • for ≥ 90 days, • or for ≥ 28 days if therapy was complicated by RBC transfusion requirement of ≥ 4 units in an 8-week period or grade 3 or 4 adverse events of thrombocytopenia, anemia, or hematoma No additional nontreatment	**No history of JAK inhibitor therapy**. MF therapy required in the opinion of the investigator. Exclusion: Eligible for allogeneic bone marrow or stem cell transplantation

Inclusion Criteria	MOMENTUM	SIMPLIFY-1
	interval required if JAK inhibitor was discontinued before screening. Ongoing JAK inhibitor taper required over at least 1 week. If low dose (eg, RUX 5 mg once daily), taper could be reduced or not required with sponsor approval. A nontreatment interval began ≥ 7 days before day BL1.	
Symptoms	Symptomatic, defined as an MFSAF TSS ≥ 10 assessed by a single MFSAF v4.0 assessment at screening before the first day of baseline assessments (day BL1)	Not specified
Anemia	Anemic, defined as any of the following: • For any subject: received a transfusion within 28 days before day BL1, with pretransfusion Hgb < 10 g/dL • For subject not receiving JAK inhibitor at screening, Hgb < 10 g/dL during the baseline period (days BL1-BL7) • For subject receiving JAK inhibitor at screening, Hgb < 10 g/dL during screening, before day BL7 Exclusion: Known clinically significant anemia due to iron, vitamin B12, or folate deficiencies, or autoimmune or hereditary hemolytic anemia, or gastrointestinal bleeding, or thalassemia	Not specified
Splenomegaly	Palpable splenomegaly ≥ 5 cm below the left costal margin or spleen volume ≥ 450 cm^3 on imaging,), assessed during Screening, at any point prior to Randomization	Palpable splenomegaly ≥ 5 cm below the left costal margin Exclusion: Prior splenectomy and splenic irradiation within 3 months prior to the first dose of study drug
Concomitant or prior treatment	Exclusion of: • Active anti-MF therapy within 1 week prior to Day BL1. Supportive care including steroids for non-MF indications may be used • Erythropoiesis	Exclusion Prior use of a JAK1 or JAK2 inhibitor Use of strong cytochrome P450 (CYP)3A4 inhibitors or strong CYP3A4 inducers or dual

Inclusion Criteria	MOMENTUM	SIMPLIFY-1
	stimulating agent (ESA) within 4 weeks prior to Randomization • Danazol within 3 months prior to Randomization • Splenic irradiation within 3 months prior to Randomization • Current treatment with simvastatin, atorvastatin, lovastatin or rosuvastatin	inhibitors of CYP3A4 and CYP2C9 within 1 week prior to the first dose of study drug Use of chemotherapy, immunomodulating therapy, biologic therapy, radiation therapy, or investigational therapy within 4 weeks of the first dose of study drug Changes to dose of iron chelator therapy within 14 days of the first dose of study drug
Prognostic risk category	High risk, intermediate-2 risk, or intermediate-1 risk MF defined by the DIPSS or DIPSS-plus	High risk or intermediate-2 risk defined by the IPSS for PMF, or intermediate-1 risk defined by the IPSS and associated with symptomatic splenomegaly, hepatomegaly, anemia (Hgb < 10 g/dL), and/or **unresponsiveness to available therapy**
ECOG	0, 1, or 2	Same as MOMENTUM
Acceptable laboratory assessments	ANC ≥ 0.75 × 10^9/L	ANC ≥ 0.75 × 10^9/L in the absence of growth factor in the prior 7 days
	Platelet count ≥ 25 × 10^9/L (without requirement for platelet transfusion)	Platelet count ≥ 50 × 10^9/L (≥ 100 × 10^9/L if AST or ALT ≥ 2 × ULN) in the absence of platelet transfusion or thrombopoietin mimetics in the prior 7 days
	Peripheral blood blast count < 10%	Same as MOMENTUM
	AST and ALT ≤ 3 × ULN (≤ 5 × ULN if liver was involved by extramedullary hematopoiesis per investigator opinion or if related to iron chelator therapy that was started within the prior 60 days)	Same as MOMENTUM
	Calculated CrCl of ≥ 30 mL/min, calculated according to Cockcroft-Gault	Calculated CrCl of ≥ 45 mL/min
	Direct bilirubin ≤ 2.0 × ULN	Same as MOMENTUM
Safety-	Active uncontrolled infection	Ongoing active

Inclusion Criteria	MOMENTUM	SIMPLIFY-1
related exclusion criteria	(subjects receiving outpatient antibacterial and/or antiviral treatments for infection that is under control or as infection prophylaxis may be included in the trial)	infection (subjects receiving outpatient antimicrobial treatment for infections that are under control may be included)
	Significant active or chronic bleeding event ≥ Grade 2 per CTCAE v5.0, within 4 weeks prior to randomization	Active or chronic bleeding within 4 weeks prior to the first dose of study drug;
	Unstable angina pectoris within 6 months prior to randomization Symptomatic congestive heart failure within 6 months prior to randomization Uncontrolled cardiac arrhythmia within 6 months prior to randomization QTcF interval > 500 msec, unless attributed to bundle branch block Current progressive thrombosis despite treatment	Symptomatic congestive heart failure; unstable angina pectoris; cardiac arrhythmia; QTc interval > 450 msec, unless attributed to bundle branch block
	Presence of peripheral neuropathy ≥ Grade 2 per CTCAE v5.0	Presence of peripheral neuropathy ≥ CTCAE Grade 2
	Unresolved non-hematologic toxicities from prior therapies that are > Grade 1 per CTCAE v5.0 Child-Pugh score ≥ 10	Unresolved non-hematologic toxicities from prior therapies that are > CTCAE Grade 1
	Known positive status for HIV Chronic active or acute viral hepatitis A, B, or C infection, or hepatitis B or C carrier (testing required for hepatitis B and C)	Known positive status for HIV Chronic active or acute viral hepatitis A, B, or C infection (testing required for hepatitis B and C), or hepatitis B or C carrier
Exclusion for other malignancy	Prior or concurrent malignancy, whose natural history or treatment has a significant potential to interfere with the safety or efficacy assessment of the investigational regimen	History of a concurrent or second malignancy with exceptions

- **Treatments**

Study SRA-MMB-301 (MOMENTUM)

- MMB starting dose was **200 mg once daily**. Blinded MMB treatment continued through week 24 of the randomized treatment period, then in open label treatment for **up to an additional 180 weeks**. After ≥ 24 weeks of open label treatment, subjects could continue long term treatment with MMB in the ongoing single arm extended access study SRA MMB 4365 (XAP).

- DAN starting total daily dose was **600 mg**, administered **in two divided doses**. DAN treated subjects continue open label treatment with DAN from week 24 through the end of week 48 or could cross over to open label MMB: 1) after completing 24 weeks of randomized treatment, 2) at the end of week 24 if treatment was discontinued early but study assessments were continued and no prohibited medication was administered (unless approved by the sponsor), or 3) any time before the end of week 24 if the protocol defined criteria were met for splenic progression. After ≥ 24 weeks of open label treatment with MMB, subjects could continue long term MMB treatment in study XAP.

Study GU-US-352-0101 (SIMPLIFY-1)

- MMB was administered at a starting dose of 200 mg once daily.
- RUX starting dose of RUX was between 5 and 20 mg twice daily (BID), inclusive, based on platelet count, creatinine clearance, and transaminase levels (aspartate aminotransferase [AST] or alanine aminotransferase [ALT]) at screening.

The duration of blinded study treatment was 24 weeks. After the double blind treatment period, all subjects remaining on therapy in the study were to continue or begin open label treatment with MMB for **up to an additional 216 weeks** to obtain data on long term treatment. The maximum participation in the treatment period for any subject was 4 years (208 weeks). Following treatment, subjects will be followed for safety and disease status for a period of 3 months (12 weeks) and for survival approximately every 6 months for 5 years (260 weeks). Treatment with RUX was not allowed during the open label period. After study termination by the sponsor, eligible subjects could continue long term treatment with MMB in study XAP.

- **Objectives**

Study SRA-MMB-301 (MOMENTUM)

Primary objectives

- To determine the efficacy of MMB versus DAN assessed by improvement in Myelofibrosis Symptom Assessment Form (MFSAF) TSS in subjects with PMF, post-PV MF, or post-ET MF who were previously treated with approved JAK inhibitor therapy
- To compare the effect of MMB versus DAN on TI status at week 24

Secondary objectives

- To compare SRR for subjects treated with MMB versus DAN
- To compare change from baseline MFSAF TSS for subjects treated with MMB versus DAN
- To compare RBC transfusion requirements in subjects treated with MMB versus DAN
- To assess the duration of MFSAF TSS response
- To assess duration of TI status at week 24
- To compare the benefit of MMB versus DAN on anaemia response and transfusion requirements, and to estimate the duration of response
- To compare the effect of MMB versus DAN on TI status at week 24
- To characterize the safety of MMB
- To compare the OS and leukemia-free survival (LFS) of subjects treated with MMB versus DAN

- To compare patient-reported fatigue and physical function for MMB versus DAN
- To compare patient-reported health status and health-related QoL for MMB versus DAN
- To assess association of MMB exposure (PK) with outcome

Study GU-US-352-0101 (SIMPLIFY-1)

Primary objectives

- To determine the efficacy of MMB compared with RUX as measured by splenic response rate at Week 24 (SRR24)

Secondary objectives

- To determine the effect of MMB compared with RUX on the improvement of total symptom score (TSS) at Week 24
- To determine the effect of MMB compared with RUX on rate of RBC transfusions through Week 24
- To determine the effect of MMB compared with RUX on rate of RBC transfusions through Week 24

To determine the effect of MMB compared with RUX on RBC TD rate at Week 24

- **Outcomes/endpoints**

Table 27: Primary and Key Secondary/Secondary Endpoints in the Hierarchical Testing for MOMENTUM and SIMPLIFY-1

MOMENTUM	SIMPLIFY-1
Primary **1st** Difference in MFSAF **TSS response rate** at wk 24 defined as the proportion of subjects who achieve a ≥ 50% reduction in TSS over the 28 days immediately prior to the end of wk 24 compared to baseline, as measured by *MFSAF v4.0 diary* **2nd TI rate at wk 24** proportion of patients with TI at the end of wk 24 TI is defined as not requiring RBC transfusion (except in the case of clinically overt bleeding) for ≥ 12 weeks, with all and Hgb levels during the ≥ 12 weeks interval of ≥ 8g/dL (except in the case of clinically overt bleeding)	Primary **SRR** (reduction in spleen volume ≥ 35% from baseline) at wk 24
Key secondary **SRR** (reduction in spleen volume ≥ 25% from baseline) at wk 24 **Change from baseline in MFSAF TSS at wk 24** **SRR** (reduction in spleen volume ≥ 35% from baseline) at wk 24 **Proportion with zero RBC units transfused during the RT period**	Secondary **TSS response rate** at wk 24 (the proportion of subjects who achieves a ≥ 50% reduction from baseline in TSS to wk 24, as measured by the *modified MPN-SAF TSS v2.0 diary)* **RBC transfusion rate** during the double-blind treatment period **TI rate at wk 24** **TD rate at wk 24**

For MOMENTUM, multiplicity between the 2 primary endpoints was adjusted by hierarchical testing. If superiority for TSS response rate at week 24 was statistically significant ($p \leqslant 0.05$) in favor of MMB, the study was to be considered positive and a superiority test performed for TI rate at week 24. If the result of the superiority test for TI rate at week 24 was not significant, a noninferiority test was to be performed; at least 80% of the DAN response rate had to be preserved for MMB to demonstrate noninferiority. For SIMPLIFY-1, SRR and TSS response rate were tested for noninferiority; at least 60% (for SRR) and 67% (for TSS) of the RUX response rates had to be preserved for MMB to demonstrate noninferiority. MFSAF, Myelofibrosis Symptom Assessment Form; RBC, red blood cell; RT, randomized treatment; SRR, splenic response rate; TD, transfusion dependence; TI, transfusion independence; TSS, total symptom score; wk, week

- **Sample size**

Study SRA-MMB-301 (MOMENTUM)

A sample size of **180 subjects** was determined based on power considerations to detect a statistically significant treatment difference in the proportion of subjects with TSS response (primary endpoint), as well as in the proportion of subjects with TI status and in Splenic Response Rate (SRR, secondary endpoint). With a sample size of 180 subjects to be randomized to MMB or DAN in a 2:1 ratio, using a 2-sided significance level of 0.05, the study has

- a 98.8% power to detect a true difference of 21% in TSS (23% with MMB versus 2% with DAN), or
- a 90% power to detect a true difference of 15% in TSS (17% with MMB versus 2% with DAN) based on the method in Fleiss et al (1980)
- a 90% power to detect a true difference of 24% in the proportion of subjects with TI status (45% versus 21%) and a true difference of 14% in SRR (15% versus 1%).

All power computations were made with East software, version 6.5 (Cytel), or SAS, Version 9.4. No formal interim analyses were performed (An interim analysis for sample size reassessment was removed at protocol amendment 2.0).

Study GU-US-352-0101 (SIMPLIFY-1)

With a sample size of **420 subjects** to be randomized to MMB or RUX in a 1:1 ratio, the study was planned to provide > 90% power for testing the noninferiority hypothesis on SRR24, assuming a SRR for MMB of 34% [lower bound of the 95% CI on the ruxolitinib effect on splenic response rate observed in ruxolitinib Study 351 Comfort I (Verstovsek et al 2012)]. The sample size of 420 subjects provides

- 90% power for testing the noninferiority hypothesis on RR-TSS24, assuming a RR-TSS24 for MMB of 38% (lower bound of the 95% CI on the ruxolitinib effect on response rate observed in ruxolitinib Study 351 Comfort I),
- at least 85% power for testing a ≥15% difference between the two treatment groups on RR-TI24 and RR-TD24, using a chi-square test.

provide ~80% power at the 2-sided 0.05 level using a negative binomial model., assuming 1) MMB improves the rate of RBC transfusion by 20% compared with placebo (ie, with an expected transfusion rate of 0.62 units/subject-month), and 2) a dispersion parameter of 2.5.

- **Randomisation and Blinding (masking)**

Study SRA-MMB-301 (MOMENTUM)

Subjects were randomized in a 2:1 ratio via the interactive response technology/system (IRT/IXRS) to receive MMB plus DAN placebo (MMB arm) or DAN plus MMB placebo (DAN arm). A non-deterministic biased-coin minimization method (Pocock, 1975; Han, 2009) was used to reduce imbalance between treatment arms for the following baseline potential prognostic factors:

- MFSAF TSS baseline score (≥ 22 versus < 22)
- Baseline palpable spleen length below the LCM (≥ 12 cm versus < 12 cm)
- Baseline RBC or whole blood units transfused in the 8-week period prior to randomization (0, 1-4, and 5+)
- Investigational site.

Allocation probabilities of 0.9 and 0.8 were used in randomizing a patient to MMB arm and DAN arm, respectively, when it is the preferred treatment arm per the imbalance score. If the imbalance scores of the two treatment arms are identical, then a weighted coin was flipped with probability of 2/3 for selecting MMB as the preferred treatment and probability of 1/3 for selecting DAN as the preferred treatment. The unbiased randomization ratio under these allocation probabilities was 2:1 (Han, 2009). The weighted sum of the marginal imbalance was used as the imbalance score to minimize marginal imbalance across the 4 factors.

A re-randomization test was conducted as a sensitivity analysis of the first primary efficacy endpoint of MFSAF TSS response rate at week 24. Ten thousand simulated trials were generated so that subjects randomized in the study were rerandomized into 2 arms under the same study randomization method, producing an empirical distribution of the CMH test statistic under the null hypothesis. Subjects were rerandomized in the same order they were originally randomized, taking into account stratification factors based on baseline TSS, spleen size, number of transfusion units, and study site. The empirical p-value (i.e. the rerandomization p-value) was the frequency, calculated as total number of times out of 10,000, that a simulated test statistic was strictly larger than the test statistic on the observed data using the original randomization allocation.

Study SRA-MMB-301 has a double-blinded randomized treatment period of 24 weeks for subjects, investigators, study site personnel, and sponsor personnel involved in the conduct of the study blinded to the identity of the treatment assignments. The DMC included at least one unblinded independent biostatistician who was involved in charter development, SAP analysis, data monitoring and analysis.

For subjects discontinuing study drug before the week 24 visit, every attempt was to be made to maintain blinding of treatment assignment and to continue all study assessments through the end of week 24. Unless required for safety reasons, treatment assignments remained blinded. Requests for unblinding were directed to the medical monitor. If immediate unblinding was required, the investigator could obtain the treatment assignment from the IRT, and the activity was logged by the system and the sponsor automatically notified.

Following completion of Week 24 assessments, subjects were given the option to receive momelotinib in the open label extended treatment period.

Subjects who completed week 24 and elected to receive momelotinib in the open-label extended treatment period remained blinded.

Subjects who elected to receive danazol in the open-label treatment period after blinded randomised period were unblinded to their treatment assignment after completing week 24. Subjects with confirmed symptomatic splenic progression before week 24 were also unblinded before receiving momelotinib in the open-label treatment period to confirm they received danazol in the randomized treatment period.

The management of blinding for this study, including protection of data and maintaining the blind to minimize the potential bias on study conduct, is described in the SRA-MMB-301 Blinding/Unblinding Plan (v3.0, 17 Jun 2021).

Study GU-US-352-0101 (SIMPLIFY-1)

Subjects were randomized via interactive web response system (IXRS) on a 1:1 basis to receive MMB QD plus RUX placebo BID (MMB arm) or RUX BID plus MMB QD placebo (RUX arm). Treatment assignment was stratified by:

- TD (yes or no); TD was defined as having received at least 4 units of RBC transfusions or had a hemoglobin level < 8 g/dL in the 8 weeks prior to randomization, excluding cases associated with clinically overt bleeding.

- Platelet count (< 100 × 10^9/L, ≥ 100 × 10^9/L and ≤ 200 × 10^9/L, or > 200 × 10^9/L).

The SIMPLIFY-1 study is a double-blind study. The blinded randomized treatment period had a duration of 24 weeks. During this period subjects, investigators, study site personnel, and sponsor personnel involved in the conduct of the study were blinded to the identity of the treatment assignments. Only a sponsor-independent statistician designated to provide statistical support for the DMC was unblinded. Double-blind treatment assignments remained blinded until all subjects had completed Week 24 and the study was unblinded for the purpose of the final efficacy analysis.

Treatment assignment was to remain blinded. Breaking the blind was allowed in the following events:

- In the event of a medical emergency to determine subject emergency medical care.

- For expedited reporting of suspected unexpected serious adverse reactions (SUSARs), the sponsor's Drug Safety and Public Health (DSPH) department was allowed to independently unblind cases.

- In the double-blind phase, subjects with symptomatic spleen growth were discontinued from blinded study drug and unblinded by the investigator.

Unblinding was recorded in the IXRS.

- **Statistical methods**

Study SRA-MMB-301 (MOMENTUM)

The primary analyses of the primary and key secondary efficacy endpoints was planned when each subject has completed the randomized treatment period, crossed over early or dropped out from the randomized treatment.

Analysis Populations:

- ITT population: all randomized subjects. Subjects were evaluated based on randomized treatment. The ITT analysis set was used as the primary analysis set for efficacy analyses.
- Safety population: all subjects in the ITT population who received ≥ 1 dose of study drug.
- Per protocol population: randomized subjects who received ≥ 1 dose of study drug and had no important protocol deviation.

Multiple comparisons / Multiplicity:

A hierarchical method was used for the analysis of both primary as well as key secondary efficacy endpoints to control the study-wide type I error at 5% (2-sided).

Table 28: Hierarchical test order of primary and key secondary endpoints

Hierarchical Testing					
Test Order	**Endpoint**	**Testing**	**Criterion for significance**	**Testing***	**Criterion for significance**
1	MFSAF TSS 24 response (primary)	Superiority	$P \leq 0.05$		
2	TI 24 status (primary)	Superiority	$P \leq 0.05$	Non-inferiority*	lower limit of 95% confidence interval on (MMB TI proportion) – 0.80*(DAN TI proportion) > 0
3	SRR 24 (based on 25% reduction criterion)	Superiority	$P \leq 0.05$		
4	MFSAF TSS 24 change from baseline	Superiority	$P \leq 0.05$		
5	SRR 24 (based on 35% reduction criterion)	Superiority	$P \leq 0.05$		
6	Rate of no transfusion at Week 24	Superiority	$P \leq 0.05$		

* If superiority is not met for TI 24 status, then the lower limit of the 95% confidence interval of the non-inferiority difference will be compared to 0.

The primary endpoint TSS response rate at week 24 (TSS24) was planned to be tested for superiority at 2-sided level 0.05 first. If superiority for TSS response rate at week 24 was statistically significant ($p \leq 0.05$) in favour of momelotinib, the study was to be considered positive and a superiority test of the second primary endpoint TI rate at week 24 was performed at 2- sided level 0.05. If the result of the superiority test for TI at week 24 was not significant, a noninferiority test was to be performed for TI rate at week 24 at 2-sided level 0.05 under pre-specified percentage of control arm treatment effect to preserve (80% of the danazol response rate).

If the second primary efficacy endpoint of TI rate at week 24 demonstrated at least statistically significant noninferiority between treatments, the first key secondary endpoint (SRR at Week 24) was evaluated for statistical significance (2-sided $p \leq 0.05$). Each next key secondary endpoint was evaluated for statistical significance only if all preceding tests in the hierarchy were statistically significant in favour of momelotinib.

Analyses of all other secondary and related endpoints were descriptive with nominal p-values.

The study meets both primary endpoints if superiority of TSS 24 is significant and at least non-inferiority of TI 24 is significant regardless of the significance of TI 24 superiority.

Methods:

- First primary endpoint MFSAF TSS 24 response (≥ 50% reduction in mean TSS over the 28 days before the end of Week 24):
    - The PRO measure used to determine the primary endpoint is the Myelofibrosis Symptom Assessment Form version 4.0 Diary (MFSAF v4.0). The MFSAF v4.0 is publicly available, maintained and licensed by the Critical Path (C-PATH) Institute on behalf of the Mayo Clinic for use in clinical trials. The questionnaire includes 7 items to assess important symptoms of MF: fatigue, night sweats, pruritus, abdominal discomfort, pain under ribs on left side of body, early satiety, and bone pain (see Table below). MFSAF v4.0 measures the severity of

these symptoms, by scoring each item on a 11-point numeric rating scale (NRS) with 0 corresponding to "absent" and 10 corresponding to "worst imaginable". The item scores were summed for a Total Symptom Score (TSS) that can range from 0 to 70, where a higher score represents more severe disease-related symptoms. The MFSAF v4.0 was completed by patients daily using the SF550 Bluebird ePRO device, distributed by eResearch Technologies (ERT), during the baseline assessment period (7 days), daily throughout the 24-week Randomized Treatment Period and further each 4 weeks (7 days during the Open-label Extended Treatment Period.

  - TSS scores obtained after receiving prohibited anti-MF therapy or steroids for the treatment of MF or who exceeded the permitted use of steroids for non-MF conditions, were considered missing. If more than one TSS was reported on a given day, the last TSS on the day was used for analysis. If no consecutive 28-day period with ≥ 20 available daily TSS was available or the last randomized treatment participation day was before day 161, the week 24 TSS was considered missing. In case of missing the week 24 TSS, subjects were considered non-responders.

  - The superiority test of MFSAF TSS response has been performed using a Cochran-Mantel-Haenzel test (CMH), stratified by: MFSAF TSS baseline score (≥ 22 versus < 22), baseline palpable spleen length below the LCM (≥ 12 cm versus < 12 cm), and baseline RBC or whole blood units transfused in the 8-week period prior to randomization (0, 1-4, and 5+), as recorded for randomization. Primary inference will be based on the asymptotic p-value based on the Wald statistic from this CMH test.

- Second primary endpoint TI 24 status:

  - Subjects receiving other active MF therapy during the randomized treatment period and subjects without TI at week 24 (including missing TI data) were classified as "Not TI" (ie, non-responder) at week 24.

  - The superiority test of Week 24 TI status has been performed using a CMH test, stratified by baseline MFSAF TSS, baseline spleen length, and baseline RBC or whole blood units transfused. Primary inference is based on the asymptotic p-value based on the Wald statistic from this CMH test.

  - If the result of the superiority test was not statistically significant, a noninferiority test was to be performed. Noninferiority was based on synthesis approach where the treatment effect of the active control is not pre-specified, but the percentage of the active control effect to be preserved is specified. As such, noninferiority was to be declared if 80% of the response rate in the DAN arm was preserved in the MMB arm. The 80% of DAN response threshold represents approximately 4 percentage points under the expected DAN response proportion of 21%. The expected response proportion for DAN of 21% is based on available clinical literature for DAN treatment in MF with consideration of the patient population to be enrolled in this study.

  - A stratum-adjusted 2-sided 95% CI was calculated for the difference between the proportion of subjects with TI in the MMB arm and 80% of the proportion of subjects with TI in the DAN arm. If the lower bound of the CI was greater than 0, MMB was to be declared noninferior to DAN.

- First and third key secondary endpoints SRR 24 based on ≥25% and ≥35% spleen volume reduction criterion, respectively:

  - Scans (MRI or CT if subject unable to have an MRI) were performed at local imaging centers and sent to a central imaging laboratory for assessment of spleen volume. When feasible, the same imaging modality was used throughout the study.

  - Scans performed ≤ 10 days after the beginning of open-label treatment could be considered valid for assessment. Subjects with scans performed > 10 days after the beginning of open-

label treatment, subjects receiving other active MF therapy during the randomized treatment period, subjects with a missing evaluation at baseline or week 24, and subjects with differing spleen scanning modalities at baseline and week 24 were set to non-responder for SRR at week 24.

- The superiority test has been performed using a CMH test, stratified by baseline MFSAF TSS, baseline spleen length, and baseline RBC or whole blood units transfused.

- Second key secondary endpoint MFSAF TSS 24 change from baseline:

  - Changes from baseline in TSS at weeks 4, 8, 12, 16, 20, and 24 were analyzed using a mixed model for repeated measurements (MMRM), i.e. missing data are handled by direct-likelihood approach under the missing at random (MAR) assumption, using all available subject-level derived scores (daily data summarized for each 4-week period). The model included terms for treatment, time point (week) as the categorical variable, and treatment-by-week interaction, as well as baseline MFSAF TSS, baseline palpable spleen length, and baseline RBC or whole blood units transfused as fixed effects. Least squares (LS) mean, SE, and 95% CI were presented by treatment at each time point. The p-value for the LS mean difference between the 2 treatments at week 24 was calculated and used as the primary inference for this endpoint.

  - Individual symptom scores, mean TSS, and their change and percent change from baseline were summarized using descriptive statistics by treatment at each evaluation time point. For calculation of mean TSS at Weeks 4, 8, 12, 16, 20, 24, if fewer than 20 daily measurements out of 28 are available, TSS will be set to missing for the time point considered.

  - The superiority test has been performed using a CMH test, stratified by baseline MFSAF TSS, baseline spleen length, and baseline RBC or whole blood units transfused.

- Fourth key secondary endpoint Rate of no transfusion at Week 24:

  - The superiority test for change in MFSAF TSS from baseline at week 24 in the momelotinib arm compared to the danazol arm, has been performed using a CMH test, stratified by baseline MFSAF TSS, baseline spleen length, and baseline RBC or whole blood units transfused.

- Overall survival (OS), Leukemia-Free Survival (LFS):

  - Subjects without a documented event were handled by censoring (on the last date known to be alive or at the date of last disease assessment for OS and LFS, respectively).

  - Summary statistics were provided by treatment with number of events, median and 95% CI, and survival probabilities at specific time points presented.

  - The survival functions were estimated by the Kaplan-Meier method. The survival curves of the 2 treatment groups was compared using a log-rank test stratified by baseline MFSAF TSS, baseline spleen length, and baseline RBC or whole blood units transfused as recorded in the IRT was used. A stratified Cox regression model was used to estimate the hazard ratio and its 95% CI.

<u>Subgroups</u>

The dual primary and all key secondary endpoints were summarized by treatment (including forest plots) in the following subgroups:

- Transfusion status (TI / TR / TD) at baseline
- Transfusion status (TI / non-TI) at baseline
- Sex (male, female)
- Age (< 65, ≥ 65 years)

- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, other)
- Baseline platelet count (< 50, ≥ 50 but ≤ 150, > 150 but ≤ 300, > 300 × 10^9 /L)
- Baseline platelet count (≤ 150, > 150 × 10^9 /L)
- Baseline platelet count (≤ 200, > 200 × 10^9 /L)
- Baseline MFSAF TSS (< 22, ≥ 22)
- Baseline median spleen volume (less than the median, greater than or equal to the median)
- RBC or whole blood units transfused in the 8-week period before randomization (0, 1-4, ≥ 5 units)
- Baseline Hgb (< 8, ≥ 8 g/dL)
- Baseline glomerular filtration rate (30-60, ≥ 60 mL/min)
- Baseline DIPSS prognostic category (low, intermediate-1, intermediate-2, high risk)
- MF diagnosis (PMF, post-PV MF, post-ET MF)
- JAK2 mutation status (positive, negative, unknown)
- Prior JAK inhibitor total daily dose received immediately before enrollment (3 groups: 0; < 20 mg twice a day of RUX or ≤ 200 mg of fedratinib; ≥ 20 mg twice a day of RUX or > 200 mg of fedratinib)
- Geographic region (Asia, Australasia, Europe, North America)
- Duration of JAK inhibitor treatment received before randomization (< 12, ≥ 12 weeks)
- Receiving ongoing JAK inhibitor at screening (yes, no)

Selected other secondary endpoints were analysed in subgroups based on TI or TD as applicable.

Sensitivity and supportive analyses:

Selected sensitivity analyses and supportive analyses of the primary efficacy endpoints, key secondary endpoints, and other secondary endpoints were to be conducted, in particular the following:

- Primary endpoint MFSAF TSS 24 response:
    - Sensitivity analysis in the population of subjects excluding those with major violations in PRO data.
    - Sensitivity analysis by constructing an exact (unstratified) CI for the treatment effect (using Pearson chi-square test) to evaluate the impact of stratification on results and more specifically the impact of empty strata on the power of the test.
    - If > 10% of subjects crossed over from DAN to MMB treatment before the end of week 24, sensitivity analysis on data collected before the treatment switch by carrying forward the MFSAF TSS value from latest time point under DAN treatment for subjects who crossed over.
    - Sensitivity analysis to assess the robustness of the results to the method of handling missing data (NRI approach in primary analysis): Observed case (OC) approach (i.e. without imputation for missing values), Last observation carried forward (LOCF) approach (i.e. carrying forward the latest non-missing MFSAF TSS value) and Multiple imputation (MI) procedure (i.e. imputing plausible values for missing scores; multiple imputation step was performed by treatment and strata used at randomization; logistic regression model was applied to the derived response status, including fixed categorical effects for baseline MFSAF TSS, baseline spleen length, and baseline RBC or whole blood units transfused

- A re-randomization test, calculating a rerandomization p-value, on the first primary efficacy endpoint of MFSAF TSS response rate at week 24, to assess the impact of the used allocation procedure.

- Primary endpoint TI 24 status:
  - A supplemental analysis of TI status was performed considering subjects who crossover from DAN to MMB before Week 24 TI status evaluation as non-responders ("Not TI") at Week 24.

- Key secondary endpoint MFSAF TSS 24 change from baseline
  - Validity of missing at random assumption: A control-based multiple imputation under a missing not at random assumption was investigated to assess the extent to which the missing at random assumption in the MMRM was robust.
  - Validity of the multivariate normality assumption was also investigated.

- OS:
  - An analysis of OS up to week 24.
  - Comparison of cumulative incidences of non-COVID-19 and COVID-19 deaths up to week 24 between treatment groups using a competing risk approach. The cumulative incidences of non-COVID-19 and COVID-19 deaths over time were estimated using a nonparametric Aalen-Johansen estimator in which subjects with competing events due to the other cause were not censored at the time of the event. The nonparametric cumulative incidence estimates between treatment arms were compared using Gray's method. The treatment effect was estimated by the Fine and Gray model for subdistribution hazards under a proportional hazard assumption.

Missing data

The following approaches were default methods for handling of missing data:

- For response binary efficacy outcomes (primary and key secondary efficacy endpoints): Missing data were handled in the primary analysis using the non-responder imputation (NRI) approach, considering subjects with a missing evaluation as a non-responder. For sensitivity purpose, alternative endpoint-specific methods were considered (multiple imputation, observed case approach, censoring).
- For time-to-event variables: Missing data were handled by censoring subjects with unobserved events.
- For continuous outcomes collected at several post-baseline timepoints, missing data will be handled through direct-likelihood approach by using a mixed model for repeated measurements (MMRM). When the data are examined via MMRM (repeated measures mixed model), the missing data are handled by ML (machine learning) approach under the missing at random (MAR) assumption. The parameter of interest is estimated such that it maximizes the overall likelihood including both subjects with missing and non-missing outcome.

For sensitivity purpose, alternative endpoint-specific methods were considered (multiple imputation, observed case approach, censoring).

Study GU-US-352-0101 (SIMPLIFY-1)

Per SAP, a final (primary) analysis was planned when all subjects had reached the Week 24 time point, at the end of the double blind phase. Optionally follow-up analyses for regulatory requirements for long-term efficacy, safety, and overall survival follow-up were also prespecified by the SAP. No formal

interim efficacy analyses were planned. The CSR (report date 30 MAR 2021) is reporting the results of a follow-up analysis with data cut-off date 01 JUL 2019. The results of the final (primary) analysis (data cut-off date of 12 SEP 2016), referred to by the CRS as the "Week 24 Interim Analysis", were reported in the Interim Week 24 CSR, dated 16 MAR 2017. An additional follow-up analysis from the open-label treatment phase (Week 48 interim analysis) had been conducted with data cut-off date of 12 SEP 2017 and was reported in the Interim 2 CSR (report date 11 APR 2018).

Analysis Populations:

- ITT population: all randomized subjects. Subjects were evaluated based on randomized treatment. The ITT analysis set was used as the primary analysis set for efficacy analyses, except for the secondary efficacy endpoint of TSS response rate at Week 24, for which the analysis was performed on subjects in the ITT Analysis Set who had a baseline TSS > 0 or who had a baseline TSS = 0 but a nonzero or missing TSS at Week 24.
- Safety population: all subjects in the ITT population who received ≥ 1 dose of study drug.
- Per protocol population: randomized subjects who received ≥ 1 dose of study drug, had a baseline TSS, was diagnosed with MF, had a baseline spleen volume measurement within 30 days prior to randomization, had exposure to study drug ≥ 80% of the planned exposure duration in the double-blind phase, ie, duration of exposure to study drug ≥ 135 days.

Multiple comparisons / Multiplicity:

A hierarchical method was used for the analysis of primary and secondary efficacy endpoints to control the study-wide type I error at 5% (2-sided). The following testing order was followed:

1) Noninferiority of MMB to RUX on splenic response rate at Week 24
2) Noninferiority of MMB to RUX on TSS response rate at Week24
3) Superiority of MMB to RUX on TI response rate at Week 24
4) Superiority of MMB to RUX on TD response rate at Week 24
5) Superiority of MMB to RUX on rate of RBC transfusion in the double-blind phase
6) Superiority of MMB to RUX on splenic response rate at Week 24
7) Superiority of MMB to RUX on TSS response rate at Week 24

If a null hypothesis was not rejected, formal sequential testing was stopped, and only nominal significance was cited for the subsequent hypotheses and considered exploratory.

Methods:

- Primary endpoint SRR 24 based on ≥35% spleen volume reduction criterion:
    - Scans (MRI or CT if subject unable to have an MRI) were performed at local imaging centers and sent to a central imaging laboratory for assessment of spleen volume. Only assessments with the same imaging modality as the baseline assessment were used for the analysis.
    - Subjects with missing baseline spleen volume or with unavailable Week 24 spleen volume due to early discontinuation from the double-blind phase or a missing scan were considered nonresponders.
    - Noninferiority was to be declared if 60% of the MMB/RUX splenic response rate was preserved, corresponding to preservation of 77% of the RUX/placebo response ratio, applying the fixed margin method. Non-inferiority of MMB will be evaluated using the CMH approach to adjust for the stratification factors. If the lower bound of the 2-sided 95% confidence interval for the difference in splenic response rates $p_a - 0.6p_c$ is greater than 0, then MMB was be declared non-inferior to ruxolitinib.
    - If non-inferiority is established, the 2-sided 95% CI for the difference in splenic response rate ($p_a - p_c$) was obtained to test the superiority of MMB vs. RUX. If the lower bound of this 2-sided 95% CI was greater than 0, MMB was be declared superior to ruxolitinib in splenic

response rate.

- Secondary endpoint modified MPN-SAF TSS 24:

  - The PRO measure used to determine the primary endpoint is the modified Myeloproliferative Neoplasm Symptom Assessment Form v2.0 (MPN-SAF). The modified MPN-SAF is an 8-item questionnaire developed to assess symptom burden and quality of life in patients with MPNs, including patients with MF (fatigue, tiredness, early satiety, abdominal discomfort, night sweats, pruritus, bone pain, pain under ribs on the left side, and inactivity). The TSS is calculated using seven items from the modified MPN-SAF TSS (inactivity item is excluded as it is not considered a symptom but rather an impact of MF). The modified MPN-SAF v2.0 measures the severity of these symptoms, by scoring each item on a 11-point numeric rating scale (NRS) with 0 corresponding to "absent" and 10 corresponding to "worst imaginable". The item scores were summed for a TSS that can range from 0 to 70. The modified MPN-SAF v2.0 was completed by patients daily on an electronic diary (eDiary) device during the baseline assessment period (7 days) and throughout the 24-week Randomized Treatment. No PRO data were collected after Week 24.

  - The primary analysis was based on subjects in the ITT Analysis Set who had a baseline TSS > 0 or who had a baseline TSS = 0 but a nonzero or missing TSS at Week 24. The daily TSS was considered missing if any individual scores were missing. If multiple records were available on the same day, the last record was used. If no consecutive 28-day period with ≥ 20 available daily TSS was available or the last randomized treatment participation day was before day 162, the week 24 TSS was considered missing. Subjects with missing Week 24 TSS but non-missing baseline TSS were considered non-responders.

  - Non-inferiority was to be declared if 67% of the response rate in the RUX arm was preserved in the MMB arm. The CMH approach was to be to adjust for the stratification factors. If the lower bound of the 2-sided 95% confidence interval for the difference in TSS $p_a - 0.67p_c$ was greater than 0, then MMB was be declared non-inferior to RUX.

  - If non-inferiority was established, the 2-sided 95% CI for the difference in TSS ($p_a - p_c$) was obtained to test the superiority of MMB vs. RUX. If the lower bound of this 2-sided 95% CI is greater than 0, MMB was be declared superior to ruxolitinib in TSS.

- Secondary endpoints RBC TI 24 and TD 24:

  - Superiority of MMB compared to RUX was tested for these endpoints using a CMH testing approach adjusted for stratification factors.

  - For the primary analysis of RBC TI response status at Week 24, subjects with a last double-blind phase participation date prior to Day 162 were considered TD (not TI).

  - Cases associated with clinically overt bleeding were excluded.

- Secondary endpoint Rate of TBV transfusion in the DB phase:

  - Calculated by dividing the total number of RBC units transfused in the double-blind phase by duration of the double-blind phase (in months)

  - Transfusions due to clinically overt bleeding will be excluded from this analysis.

  - Analysis used a negative binomial regression method with an offset parameter to account for follow-up time. To account for multiple units within a transfusion, identical recurrence times were perturbed so that they appeared non-identical.

Subgroups

The primary and secondary endpoints were summarized by treatment (including forest plots) in the following subgroups: age (< 65 years or ≥ 65 years), gender (male or female), race (white or all other races), baseline spleen volume (< median or ≥ median), baseline TSS (quartiles: < Q1, ≥ Q1

and < median, ≥ median and < Q3, ≥ Q3), baseline transfusion dependence (defined as requiring at least 4 units of transfusion or a hemoglobin < 8 g/dL in the 8 weeks prior to randomization), baseline hemoglobin (< 8 g/dL or ≥ 8 g/dL), baseline platelet count (< 100, ≥100 and ≤ 200, > 200 [x 10^9/L]), IPSS prognostic category (intermediate or high-risk), MF disease status (PMF, post-PV MF, or post-ET MF), JAK2V617F mutation (positive or negative, based on medical history), Region (Western Europe, Eastern Europe, or Asia)

Sensitivity and supportive analyses:

Selected sensitivity analyses and supportive analyses of the primary efficacy endpoint and key secondary endpoints were to be conducted, in particular the following:

- Primary endpoint SRR 24:

  - 1. Analysis based on the Per Protocol Analysis Set.

  - 2. Unstratified exact and CMH methods for both noninferiority and superiority were performed on the ITT Analysis Set without adjusting for the stratification factor.

  - 3. Last observation carried forward (LOCF): For subjects with missing spleen volume at Week 24, the last prior available spleen volume was used to impute missing spleen volume at Week 24. A missing spleen volume due to splenectomy or early discontinuation of study drug in the double-blind phase due to symptomatic spleen growth, disease progression, or death were not carried forward and were treated as nonresponders.

  - 4. The noninferiority analysis of MMB versus RUX was also performed using the fixed-margin approach (or 95% CI lower limit method) with a margin of 16% in MMB-RUX response rate difference. Based on the historical data (Verstovsek, 2012), the lower bound of the 95% CI on the difference in response rates was ~32%. Given the range of response rates, an NI margin of 16% would correspond to a ~50% preservation of the treatment effect of the ruxolitinib control (compared to placebo).

- Secondary endpoint modified MPN-SAF TSS 24:

  - In addition to the same 4 sensitivity analyses as performed for SRR 24, also the following sensitivity analyses were performed:

  - 5. ITT Analysis Set with a nonmissing baseline TSS > 0 or with a baseline TSS = 0 but a nonzero or missing TSS at Week 24, applying relaxed rule of available daily TSS in the analysis window (baseline TSS: average of ≥ 1 available daily TSS in the 7-day baseline period; baseline TSS was missing if no daily TSS was available in the 7-day baseline period)

  - 6. Week 24 TSS: average of ≥ 4 available daily TSS in the consecutive 28-day period. If no consecutive 28-day period with ≥ 4 available daily TSS was available or the last randomized treatment participation day was before day 162, the week 24 TSS was considered missing.

- Secondary endpoints RBC TI 24 and TD 24:

  Similar sensitivity analyses as the first 2 sensitivity analyses for the primary endpoint SRR 24 were also performed for RBC TI24 and TD 24 consisted of all subjects who were randomized, regardless of study drug, with study treatment assignment designated according to initial randomization.

Missing data

All available data were included in data listings and tabulations. Models for repeated measures will be valid under the 'missingness at random' (MAR) assumption, in case a general linear model (GLM) is used. In case a GEE is used, the model will be valid under 'missingness completely at random' (MCAR). If confidence intervals are to be calculated for proportions, missing data will be considered as failure, corresponding with a "Non-responder imputation" (NRI) approach. For sensitivity purpose, alternative endpoint-specific methods were considered (LOCF).

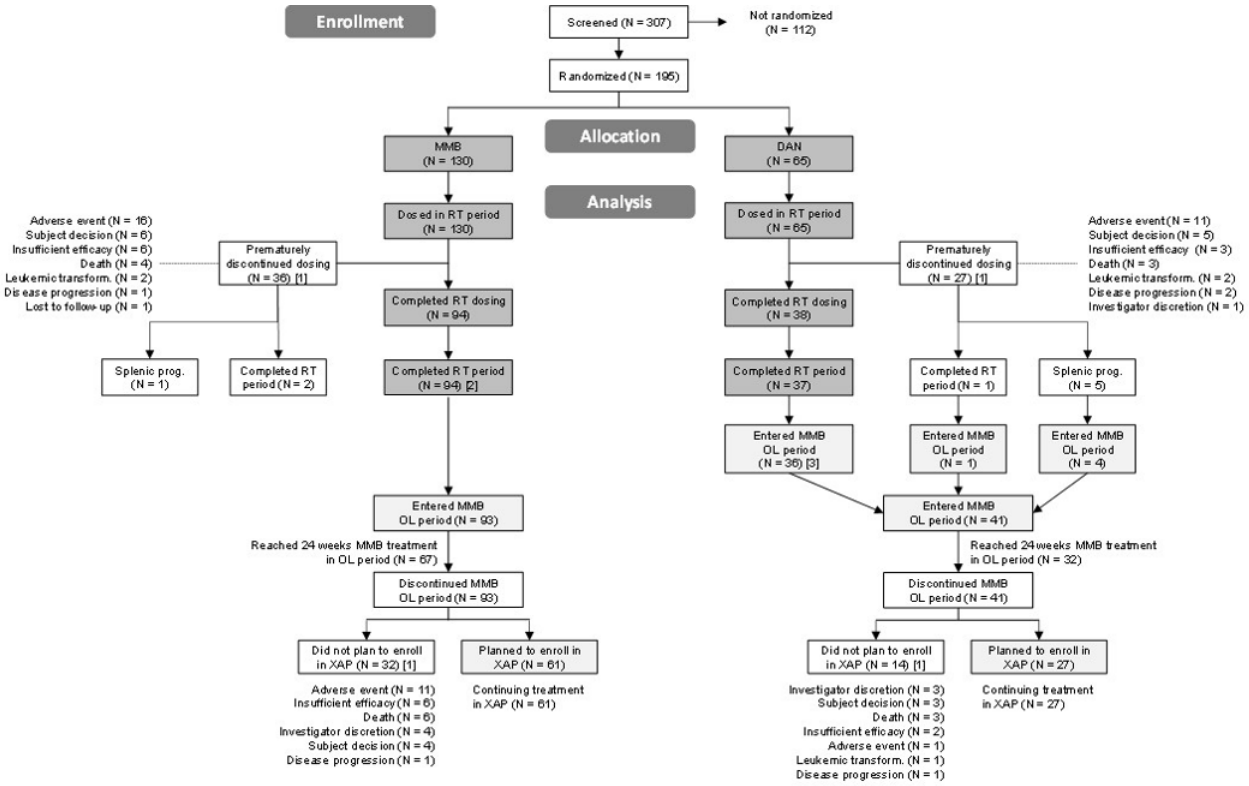
Results

- **Participant flow**

Study SRA-MMB-301 (MOMENTUM)

In MOMENTUM study, data cutoff date of primary analysis at Week 24 was **03 DEC 2021.** Updated data of Week 48 Analysis were provided with data cutoff date of **17 Jan 2023.**

195 subjects were randomized 2:1, 130 subjects to the MMB group and 65 subjects to the DAN group. 94 of the 130 subjects (72.3%) in the MMB group and 38 of the 65 subjects (58.5%) in the DAN group completed treatment in the blinded RT phase. In the OL phase, 93 of the 130 subjects (71.5%) MMB-treated subjects continued to receive MMB (MMB to MMB) and 41 of the 65 subjects (63.1%) DAN-treated subjects crossed over to MMB (DAN to MMB). No subject who completed randomized treatment with DAN chose to continue open-label treatment with DAN. Overall, most subjects in the OL phase completed Week 48 (Week 24 in OL Phase) visit (67 of 93 MMB to MMB [72.0%] subjects and 32 of 41 DAN to MMB [78.0%] subjects).



Source: Table 14.1.1.2

[1] Twelve subjects who discontinued study drug during the study planned to enroll in XAP for long-term survival follow-up only: 9 MMB (5 prematurely discon 4 discontinued OL treatment) and 3 DAN (1 RT, 2 OL treatment) (Listing 16.2.1.2).

[2] One subject had confirmed splenic progression at the end of the RT period.

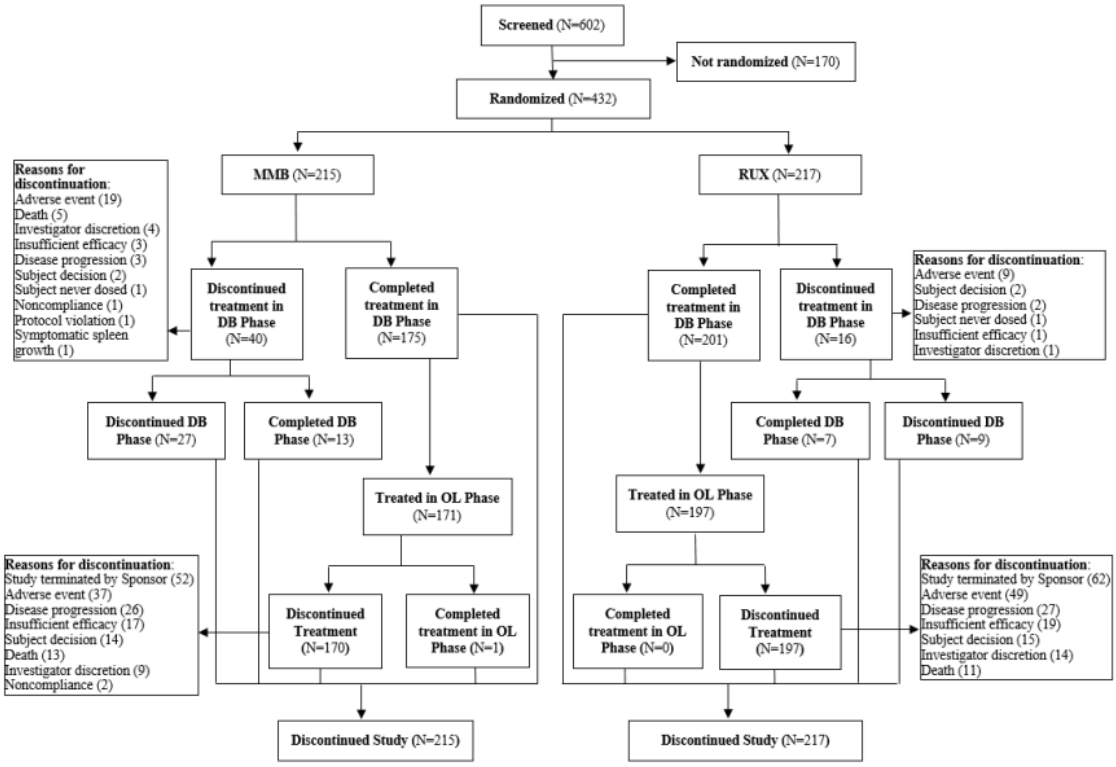
[3] One subject had confirmed splenic progression at the end of the RT period and entered the OL period.

DAN, danazol; MMB, momelotinib; OL, open-label; prog., progression; RT, randomized treatment; transform., transformation; XAP, MMB extension study SRA-M

Figure 10: Subject disposition flow chart (MOMENTUM)

Study GU-US-352-0101 (SIMPLIFY-1)

In SIMPLIFY-1 study, as of data cutoff date of **01 JUL 2019**, 432 subjects were 1:1 randomized, from which 215 subjects were assigned to the MMB group and 217 subjects to the RUX group. As 1 subject in each treatment group was randomized but not treated, a total of 214 subjects in the MMB group and 216 subjects in the RUX group received treatment. Most subjects in the MMB arm who completed randomized treatment (171/175 subjects, 79.5%) started open-label MMB treatment. In the RUX arm, most subjects who completed randomized treatment period (197/201 subjects, 90.8%) crossed-over to MMB. All but 1 subject (who crossed over from RUX arm) in the continuing MMB open-label treatment prematurely discontinued study drug during the open-label phase.



DB = double-blind; MMB = momelotinib; OL = open-label; RUX = ruxolitinib
Source: Table 15.8.1.3

Figure 11: Subject disposition flow chart (SIMPLIFY-1)

- **Recruitment**

Study SRA-MMB-301 (MOMENTUM)

The MOMENTUM study was conducted at 107 active study sites (78 Europe, 14 North America, 10 Asia, 5 Australasia). The number of subjects randomized at each study site ranged from 1 to 7.

Table 29: Key dates defining recruitment, unblinding, analyses ad follow-up (MOMENTUM)

Event	Date
First subject screened	07 Feb 2020
First subject dosed	24 Apr 2020
Last subject randomized	17 Jun 2021
Last subject last visit for double-blind randomized treatment period	03 Dec 2021
Data cutoff for ongoing data for clinical study report	03 Dec 2021
Database lock for analysis for this report	13 Jan 2022
Treatment unblinding	13 Jan 2022

Study GU-US-352-0101 (SIMPLIFY-1)

The double-blind phase of the SIMPLIFY-1 study was conducted at 131 active study sites (82 Europe, 16 North America, 22 Asia, 11 Australasia). No individual study site enrolled > 3.0% of the total subjects.

Table 30: Key dates defining recruitment, unblinding, analyses ad follow-up (SIMPLIFY-1)

Event	Date
First Subject Screened	06 December 2013
First Subject Enrolled (or Randomized)	17 January 2014
Last Subject Enrolled (or Randomized)	28 March 2016
Last Data Collection for the Primary Endpoint (Last Week 24 MRI)	08 September 2016
Last Subject Last Visit for Double-Blind Phase	12 September 2016
Data Cutoff for Interim Week 24 Interim Analysis	12 September 2016
Treatment Unblinding	21 October 2016
Data Cutoff for Interim Week 48 Interim Analysis	12 September 2017
Last Subject Last Observation for Final Report	02 May 2019
Database Finalization for Final Report	01 July 2019

- **Conduct of the studies**

Study SRA-MMB-301 (MOMENTUM)

Changes in the planned analysis

The statistical analysis plan was finalized on 30 DEC 2021 (V2.0), which is before the date of treatment unblinding for statistical analyses (13 JAN 2022). No changes to SAP were provided. The clinical SAP was finalized after the latest protocol Amendment 2.0 (18 DEC 2018).

Protocol amendments

The original protocol v1.0 (dated 27 Jun 2019) was globally amended twice.

In addition, 1 minor administrative amendment (Amendment v1.2: 28 Aug 2019; addition of a sponsor approval page) and 12 country-specific amendments were required. Subjects were first enrolled in the study under protocol amendment v1.2. The main changes and additions are listed below:

Protocol Amendment v1.1 (Global) - 16 Aug 2019:

- Clarified criteria for dose reduction due to thrombocytopenia, neutropenia, and nonhematologic or other toxicities; and subsequent dose re-escalation.
- Modified thresholds for platelet count recovery required to resume treatment based on baseline value.
- Updated procedures for managing transition from randomized treatment to open-label treatment so treatment assignment would only be unblinded when required to determine eligibility for open-label treatment with MMB or DAN.

Protocol Amendment v2.0 (Global) - 18 Dec 2020:

- Removed interim analysis for sample size reassessment from the study design.
- Modified the planned statistical analysis: moved the MMRM analysis of the MFSAF TSS secondary endpoint to the fourth position in the overall statistical testing hierarchy; revised description of the hierarchal statistical testing of secondary endpoints, updated descriptions of the secondary endpoints.
- Changed timing of first dose after randomization, JAK inhibitor nontreatment period, exclusion of active anti-MF medication, and baseline spleen volume assessment to allow flexibility for scheduling randomization and day 1.
- Inclusion criteria were modified:

  - Criterion 3: an MFSAF TSS of ≥ 10 units was required during screening prior to baseline day 1
  - Criteria 4a and 4c: clarified the definition of anemic.
  - Criterion 5b: added that subjects receiving a low dose of a JAK inhibitor could have a reduced taper period, or no taper, with sponsor approval.
  - Criterion 9: platelet count must be met without requirement for platelet transfusion.
- Exclusion criteria were modified:
  - Criterion 1b: clarified that approved JAK inhibitors were prohibited and reduced the study period and window for use.
  - Criterion 1c: reduced the study period and window for use of anti-MF therapy.
  - Criterion 1e: investigational JAK inhibitors were prohibited within 4 weeks prior to randomization.
  - Criterion 7: added thalassemia as a cause of clinically significant anemia.
- Updated criteria for adjusting or stopping doses to provide guidance that investigator clinical discretion should be used and that in the event of grade 3 or 4 toxicity, relevant laboratory tests should be closely monitored per investigator clinical discretion.
- Clarified the anticipated risks of DAN to emphasize that the provided safety information references the approved indications for DAN and should be interpreted by the investigator for guidance when assessing subjects in this study.
- Updated criteria for crossing over to open-label MMB to add sponsor approval for short-term use of restricted anti-MF medication to treat severe splenic progression, revise criteria for splenic progression, and add sponsor approval for spleen volume measurements read locally.
- Updated restricted treatment use for consistency with exclusion criterion 1 and to clearly define the beginning and end of the study period.
- Added that alternative methods, including paper forms, could be used to record PRO responses in exceptional circumstances, with sponsor approval.
- Updated adverse event and serious adverse event reporting criteria and procedures.
- Clarified requirements for hepatitis testing.
- Added that local laboratory assessments could be used to determine eligibility, with sponsor approval, if central laboratory assessments were not available prior to day 1.
- Clarified the window (± 7 days) for MFSAF assessments and PRO responses during the open-label extended treatment period.
- Added that subjects requiring antihypertensive medication should be closely monitored on the day of the first study drug dose and that medication could be administered if clinically necessary.
- Added that investigators were to advise subjects on the conservation of gametes prior to receiving study drug due to the possibility of infertility.
- Added a protocol addendum for guidance on modified study procedures that could be followed during the COVID-19 pandemic.

Protocol deviations

Important (major) protocol deviations were defined by the applicant as deviations from the protocol that could significantly affect the rights, safety, or well-being of subjects or the completeness, accuracy, and reliability of the study data. These reported for 5 subjects (2.6%) overall in the study, including 1 subject (0.8%) in the MMB group and 4 subjects (6.2%) in the DAN group. One deviation in each group involved a subject receiving a restricted medication (ESA in the MMB group and rosuvastatin in the DAN group). Two deviations in the DAN group involved accidental unblinding (described next), and 1 involved informed consent (spouse signed for subject). One accidental unblinding involved the investigator entering the treatment assignment of 1 subject who was unblinded

for safety reasons into the electronic data capture system, thereby unblinding a sponsor staff member. The other accidental unblinding involved a clinical research associate forwarding an email with unblinding information for 1 subject to the sponsor and contract research organization teams. Both unblinding events occurred after the subjects discontinued treatment. Corrective actions were taken in both cases.

Additional violations in PRO data collection:

The vendor supplying the ePRO device and software experienced a cyberattack on 20 Sep 2020, causing the vendor to proactively disconnect servers from the internet. The resulting 12-day interruption of new screening of subjects led to a notification of the temporary recruitment stop and submission of the resumption of study screening where required by local regulations. All data entered in ePRO devices by subjects during this period were successfully uploaded when the servers were reconnected to the internet. A small amount of data were lost due to errors with ePRO devices during the outage. Study site activities prevented or limited by the outage included data entry, triggering of visit-based questionnaires on the devices by sites, viewing subject data, and monitoring compliance. Thirty-three minor protocol deviations were associated with this event. In addition, at one study site in South Korea, more than 1 MFSAF questionnaire a day was completed for some subjects. An investigation of these violations in PRO data collection showed that the events were isolated to 4 of 5 subjects enrolled at this single study site.

Study GU-US-352-0101 (SIMPLIFY-1)

Protocol amendments

The original protocol (dated 26 Jun 2013) was amended 3 times during the study. In addition, 1 minor amendment (Amendment 1.1: 12 Feb2014) and 3 country-specific amendments (2 for Japan only and 1 for South Korea only) were required. Subjects were first enrolled in the study under the original study protocol. The main changes and additions are listed below:

Protocol Amendment 1 (Global) – 13 Dec 2013:

- Updated study objectives per regulatory agency guidance
- Updated inclusion criteria based on newly available nonclinical data
- Updated exclusion criteria based on regulatory agency guidance, newly available nonclinical data, and requirements for radiology review
- Clarified follow-up procedures and duration
- Clarified that the PK profile of the MMB metabolites GS-642112 and GS 644603 was to be evaluated
- Updated study assessments based on evolving data for MF and JAK inhibitors and requirements for radiology review
- Updated planned statistical analysis of secondary endpoints per regulatory agency guidance
- Updated safety endpoints to include assessment of OS per regulatory agency guidance
- Updated clinical and nonclinical background information, and the study rationale based on newly available nonclinical data, as well as newly evolving clinical data for MF and JAK inhibitors
- Updated relative bioavailability data for MMB tablets versus capsules based on the most recent Gilead Sciences (Gilead) internal data
- Updated MMB administration based on newly available internal data
- Clarified requirements for MMB dose increases during the open-label phase
- Clarified procedure and requirements for restarting study drug after dose interruption or tapering
- Updated requirements for increasing study drug dose in the event of insufficient efficacy

- Removed requirement that ECG may only be collected after subject has been supine for at least 3 minutes
- Updated table of analytes to be measured based on newly evolving data for MF and JAK inhibitors
- Updated IWG-MRT/ELN assessments to reflect June 2013 guidelines
- Updated screening requirement to not require bone marrow aspirate/biopsy if performed within 90 days prior to the first dose of study drug
- Added certain subgroup analyses from the SAP
- Updated exploratory endpoints based on newly evolving data for MF and JAK inhibitors

Amendment 1.1 (Global): 12 February 2014:

- Updated text to address the Grounds for Non-acceptance (GNA) from the European Voluntary Harmonization Procedure (VHP)
- Updated exclusion criteria to include the use of dual inhibitors of CYP3A4 and CYP2C9
- Updated dose increase instructions for insufficient efficacy of study drug
- Added information regarding metabolism of MMB by CYP3A4

Amendment 2: 18 July 2014

- Updated text to address the GNA from the European VHP. These updates were made in Amendment 1.1 and were reconciled into Amendment 2.
- Added ophthalmic examinations to assess for cataracts and visual acuity based on MMB Investigator's Brochure, version 7
- Clarified methods for managing missing data in the primary analysis
- Updated language regarding concomitant medications based on newly available drug-drug interaction data
- Clarified maximum duration of study
- Updated MMB clinical trials list as of June 2014
- Clarified duration of blinding of treatment assignments per Italian Central Ethics Committee request
- Clarified conditions for permanent discontinuation, dose interruption, and restarting of study drug
- Updated table of analytes and assessment schedule to reflect deletion of C-reactive protein (CRP), deletion of thiocyanate, and addition of ferritin
- Updated exploratory endpoints as follows:
    - Removed progression-free survival
    - Removed response rates for ANC and platelets, as well as rate of new onset of anemia
- Added rate of new RBC TD by Week 24 among those who were not TD at baseline
- Clarified the primary analysis in terms of missing data

Amendment 3: 20 July 2017

- Protocol study visits extended to allow continued treatment with MMB through Week 216.
- To align with Investigator's Brochure Edition 11, dated 14 Jul 2017.
- Updated MMB formulation to allow for contingency to use plain-faced or debossed, round or triangle-shaped tablet presentation, should the clinical drug supply be depleted or expire prior to the end of the study.

- Updated to reflect the actual exploratory endpoints analyzed and clarify definitions.

Amendment 3.1 (South Korea only): 23 October 2017

- To correct footnote sequence error in the Double-Blind and Open- Label Study Procedures Tables.

Protocol deviations

The occurrence of important protocol deviations during the double-blind phase was higher in the MMB group (20.5%, 44 subjects) than in the RUX group (14.7%, 32 subjects). The majority of important protocol deviations during the combined screening and double-blind treatment phase were GCP violations related to the consenting process (the majority due to delayed reconsenting; 9.8% in the MMB group and 5.5% in the RUX group) and missing data related to key endpoints (5.6% in the MMB group and 5.1% in the RUX group).

The occurrence of important protocol deviations in the open-label phase was comparable for the group of subjects who received MMB during the double-blind phase and remained on MMB (8.8%, 15 subjects) and those who were randomized to RUX during the double-blind phase and switched to MMB (8.1%, 16 subjects). Similar to the double-blind phase, the majority of important protocol deviations during the open-label phase were GCP violations related to the consenting process (the majority due to delayed reconsenting; 5.8% in the MMB to MMB group and 5.6% in the RUX to MMB group) and missing data related to key endpoints (1.8% and 2.5%, respectively). For the overall exposed to MMB group, 18.9% of subjects had at least 1 important protocol violation, primarily GCP violations (10.9%) and missing data related to key endpoints (6.1%).

Table 31: Important protocol deviations (Screening and double-blind phase, ITT population, SIMPLIFY-1)

Protocol Deviation, n (%)	MMB (N = 215)	RUX (N = 217)	Total (N = 432)
Number of Subjects with at Least 1 Important Protocol Deviation	44 (20.5%)	32 (14.7%)	76 (17.6%)
GCP Violation	21 (9.8%)	12 (5.5%)	33 (7.6%)
Missing Data Related to Key Endpoints	12 (5.6%)	11 (5.1%)	23 (5.3%)
Eligibility Violation	6 (2.8%)	5 (2.3%)	11 (2.5%)
Received Excluded Concomitant Medication During the Treatment Phase	3 (1.4%)	4 (1.8%)	7 (1.6%)
Wrong Treatment/Incorrect Dose	2 (0.9%)	4 (1.8%)	6 (1.4%)
Other Treatment Compliance	3 (1.4%)	0	3 (0.7%)

GCP = Good Clinical Practice; MMB = momelotinib; RUX = ruxolitinib
A description of the deviations is presented in Listing 16.2.2.2.
Source: Table 15.8.2.3

Table 32: Important protocol deviations (Open-label phase and overall exposed to MMB, ITT population, SIMPLIFY-1)

Protocol Deviation Category	Open-label Phase (Week 24 Onward)			Overall Exposed to MMB	
	Continuing (MMB to MMB) (N=171)	Switch (RUX to MMB) (N=197)	Total (N=368)	MMB in DB phase (N=215)	Total (N=412)
Subjects with at least 1 important protocol deviation	15 (8.8%)	16 (8.1%)	31 (8.4%)	62 (28.8%)	78 (18.9%)
Protocol deviation coded term					
GCP violation	10 (5.8%)	11 (5.6%)	21 (5.7%)	34 (15.8%)	45 (10.9%)
Missing data related to key endpoints	3 (1.8%)	5 (2.5%)	8 (2.2%)	20 (9.3%)	25 (6.1%)
Eligibility violation	0	0	0	6 (2.8%)	6 (1.5%)
Received excluded concomitant medication during the treatment period	1 (0.6%)	0	1 (0.3%)	4 (1.9%)	4 (1.0%)
Wrong treatment/incorrect dose	1 (0.6%)	1 (0.5%)	2 (0.5%)	3 (1.4%)	4 (1.0%)
Other treatment compliance	0	0	0	3 (1.4%)	3 (0.7%)

DB = double-blind; GCP = Good Clinical Practice; MMB = momelotinib; RUX = ruxolitinib
A description of the deviations is presented in Listing 16.2.2.2.
Source: Table 15.8.2.4

Changes in the planned analysis

The statistical analysis plan was amended several times with the last amendment 2.1 dating from 19 SEP 2014, which is before the date of treatment unblinding for statistical analyses (21 OCT 2016). The clinical SAP was finalized prior to protocol Amendment 3 (20 JUL 2017); however, changes in Amendment 3 described above did not affect the planned statistical analyses and thereby did not warrant an additional update of the clinical SAP. The following changes were made in the SAP prior to the Week 24 unblinded analysis:

- For transfusion related secondary endpoints, the sequential testing order was changed to test the rate of RBC transfusion in the DB phase after the testing of TI 24 response rate and TD 24 response rate, based on experiences in the SIMPLIFY-2 study (TI 24 and TD 24 were expected to have larger power). Testing of superiority of MMB to RUX on SRR 24 and TSS 24 was added to the sequential testing procedure.
- Some exploratory endpoints, including PFS and duration of TSS were removed.
- Definition of exploratory endpoint "Time to TI" was changed to be defined on subjects who are not TI at baseline and achieved TI at any postbaseline in the double-blind phase.
- Definition of exploratory endpoint "duration of TI" was changed to the interval from the first onset date of TI response to the earliest onset date of loss of TI response among those subjects who are not TI at baseline but achieved TI at any post baseline in the double-blind phase.
- For secondary endpoints of rate of transfusion, TD and TI, the transfusion and Hgb level used for derivation will exclude cases associated with clinically overt bleeding.

Post-hoc analyses

Supportive exploratory post hoc analyses aimed to better understand the magnitude of MMB's symptomatic benefit and the mechanistically-based anaemia benefit. A separate post-hoc statistical analysis plan was written (11 MAR 2021). The following post-hoc exploratory analyses were conducted:

- Post-hoc analyses related to splenic response: Duration of splenic response
- Post-hoc analyses related to symptom response:
  - Assessment of non-inferiority using an alternative non-inferiority margin, applying the 2-sided 95%-95% fixed-margin method to the COMFORT-I result. Based on TSS response rates at week 24 in COMFORT-I of 45.9% in the RUX group and 5.3% in the placebo group, the modified Wald response ratio of RUX/placebo was estimated as 8.2759 (95% CI: 4.2096, 16.2702). Under the 95%-95% approach, the entire treatment effect of RUX over placebo was estimated by the lower bound of the 95% CI of 4.2096. Applying the requirement of 50% of the RUX active treatment effect over placebo to be retained in the MMB group of SIMPLIFY-1 in log scale, the noninferiority margin for the MMB/RUX ratio was derived as 0.4874.
  - An assessment of change and percent change in TSS compared to baseline as described for symptomatic subjects (subjects with baseline TSS of at least 10)
  - An assessment of the difference in the adjusted treatment group means using a longitudinal mixed-effects model (Mixed-effect Model Repeated Measure [MMRM]) to estimate the treatment effect using TSS as a continuous variable
  - An examination of the individual item scores at baseline and their changes over time
  - An evaluation of combined symptom score 6 (CSS6), TSS without the inclusion of the fatigue
- Post-hoc analyses related to anemic response: transfusion independence by Week 48; duration of TI at any time; proportion of subjects receiving an RBC transfusion; zero-inflated negative binomial (ZINB) model for total RBC transfusion rate; recurrent event model for RBC transfusion; time to first, third, and fifth units of RBC transfusions; Hbg increases at Week 24 in ITT and TI subgroups.

Post hoc subgroup analyses: baseline TI, non-TI, TSS (≥ 10, Hbg (< 10 g/dL, < 12 g/dL and ≥ 12 g/dL), TSS ≥ 10 AND Hbg < 10 g/dL, platelet count (≤150, > 150 and ≤ 300, > 300 [x 10^9/L]).

- **Baseline data**

Table 33: Clinically Important Demographic and Baseline Characteristics by Study (ITT)

Characteristic, Mean (Min, Max or %)	**MOMENTUM (N = 195)**	**SIMPLIFY-2 (N = 156)**	**SIMPLIFY-1 (N = 432)**
Age, years, Mean (SD)	70.38 (7.86)	67.4 (8.00)	64.7 (10.62)
Male, n (%)	123 (63.1)	93 (59.6)	244 (56.5)
PMF/Post-PV MF/Post-ET MF (%)	63.6/19.5/16.9	60.3/19.2/20.5	56.5/22.7/20.8
Int-1/Int-2/High risk (%)	5.1/57.4/35.4	25.0/57.7/17.3	20.6/33.1/46.3
Prior JAK inhibitor exposure in weeks, range	133.96 (4, 617.6)	66.48 (3.7, 257.6)	0
Mean total symptom score, range	27.21 (4.9, 67.7)	19.2 (0, 57)	18.7 (0, 56)
Transfusion independent, n (%)	27 (13.8)	51 (32.7)	299 (69.2)
Transfusion dependent, n (%)	97 (49.7)	85 (54.5)	105 (24.3)
Transfusion requiring, n (%)	71 (36.4)	20 (12.8)	28 (6.5)
Mean Hgb g/dL, range	7.99 (3.8, 10.7)	9.4 (6, 16)	10.6 (6, 19)
Mean platelet count × 10^9/L, range	144.68 (24, 733)	155.9 (9, 777)	301.2 (50, 2865)
Hgb < 10 g/dL, n (%)	195 (100)	105 (67.3)	180 (41.7)
Platelet count ≤ 200 × 10^9/L, n (%)	150 (76.9)	118 (75.6)	170 (39.4)
Mean spleen volume cm^3, range	2341.13 (609.5, 9717.2)	2457.2 (241, 7433)	2185.1 (206, 9022)

Source: CSR SRA MMB 301 Table 14.1.3.1, Table 14.1.3.2, Table 14.1.4.4, Table 14.2.1.2, Table 14.2.1.5; CSR GS US 352 0101 Table 15.8.3.1.1, Table 15.8.3.2.1, Table 15.8.3.5; CSR GS US 352 1214 Table 15.8.3.1.1, Table

15.8.3.2.1, Table 15.8.3.5; Table 2.7.3.3.1 ET, essential thrombocythemia; Hgb, hemoglobin; Int, intermediate; JAK, Janus kinase; Min, Max, minimum, maximum; PMF, primary myelofibrosis; PV, polycythemia vera.

Table 34: Clinically Important Demographic and Baseline Characteristics in overall ITT population (MOMENTUM) and the post-hoc defined anaemic subpopulations with Hgb < 10 g/dL (SIMPLIFY-2/SIMPLIFY-1)

Characteristic, Mean (Min, Max or %)	MOMENTUM (N = 195)	SIMPLIFY-2 (N = 105)	SIMPLIFY-1 (N = 180)
Age, years, Mean (SD)	70.38 (7.86)	68.7 (7.26)	67.1 (9.11)
Male, n (%)	123 (63.1)	70 (66.7)	106 (58.9)
PMF/Post-PV MF/Post-ET MF (%)	63.6/19.5/16.9	64.8/15.2/20.0	62.8/12.8/24.4
Int-1/Int-2/High risk (%)	5.1/57.4/35.4	11.4/64.8/23.8	3.3/25.6/71.1
Prior JAK inhibitor exposure in weeks, range	133.96 (4, 617.6)	63.74 (3.7, 257.6)	0
Mean total symptom score, range	27.21 (4.9, 67.7)	18.2 (0, 56)	18.5 (0, 50)
Transfusion independent, n (%)	27 (13.8)	14 (13.3)	66 (36.7)
Transfusion dependent, n (%)	97 (49.7)	77 (73.3)	92 (51.1)
Transfusion requiring, n (%)	71 (36.4)	14 (13.3)	22 (12.2)
Mean Hgb g/dL, range	7.99 (3.8, 10.7)	8.4 (6, 10)	8.6 (6, 10)
Mean platelet count × 10^9/L, range	144.68 (24, 733)	162.6 (28, 777)	262.2 (54, 2865)
Hgb < 10 g/dL, n (%)	195 (100)	105 (100)	180 (100)
Platelet count ≤ 200 × 10^9/L, n (%)	150 (76.9)	79 (75.2)	96 (53.3)
Mean spleen volume cm^3, range	2341.13 (609.5, 9717.2)	2504.4 (392, 6740)	2140.1 (352, 9022)

Source: CSR SRA MMB 301 Table 14.1.3.1, Table 14.1.3.2, Table 14.1.4.4, Table 14.2.1.2, Table 14.2.1.5; Appendix 2 GS US 352 0101 Table 15.8.3.1.1a, Table 15.8.3.2.1a, Table 15.8.3.5a; Appendix 2 GS US 352 1214 Table 15.8.3.1.1a, Table 15.8.3.2.1a, Table 15.8.3.5a, Table 2.7.3.3.1a

Table 35: Key demographic and baseline characteristics in MOMENTUM, SIMPLIFY-1 and SIMPLIFY-2 (ITT and post-hoc defined Hgb < 10 g/dL subgroup)

	MOMENTUM		SIMPLIFY-1				SIMPLIFY-2			
			Hgb <10 g/dL Subgroup		ITT population		Hgb <10 g/dL Subgroup		ITT population	
Characteristic	MMB N = 130	DAN N = 65	MMB N = 86	RUX N = 94	MMB N = 215	RUX N = 217	MMB N = 66	BAT N = 39	MMB N = 104	BAT N = 52
Age at baseline (years)										
Median	71.00	72.00	70	68	67.0	66.0	67.0	70.0	67.0	69.5
Min, max	38.0, 86.0	54.0, 86.0	41, 85	25, 86	28, 85	25, 86	51, 92	52, 82	41, 92	52, 82
Age group, n (%)										
< 65 years	29 (22.3)	11 (16.9)	24 (27.9)	36 (38.3)	90 (41.9)	95 (43.8)	24 (36.4)	9 (23.1)	41 (39.4)	14 (26.9)
≥ 65 years	101 (77.7)	54 (83.1)	62 (72.1)	58 (61.7)	125 (58.1)	122 (56.2)	42 (63.6)	30 (76.9)	63 (60.6)	38 (73.1)
Sex at birth, n (%)										
Male	79 (60.8)	44 (67.7)	50 (58.1)	56 (59.6)	124 (57.7)	120 (55.3)	52 (78.8)	18 (46.2)	69 (66.3)	24 (46.2)
Female	51 (39.2)	21 (32.3)	36 (41.9)	38 (40.4)	91 (42.3)	97 (44.7)	14 (21.2)	21 (53.8)	35 (33.7)	28 (53.8)
Race, n (%)										
White	107 (82.3)	50 (76.9)	69 (80.2)	76 (80.9)	179 (83.3)	178 (82.0)	54 (81.8)	34 (87.2)	83 (79.8)	44 (84.6)
Black or African American	2 (1.5)	2 (3.1)	2 (2.3)	0	2 (0.9%)	2 (0.9%)	5 (7.6)	0	6 (5.8)	0
Asian	12 (9.2)	6 (9.2)	7 (8.1)	8 (8.5)	17 (7.9)	20 (9.2)	0	0	0	0
Not permitted	na	na	6 (7.0)	10 (10.6)	15 (7.0)	16 (7.4)	7 (10.6)	5 (12.8)	15 (14.4)	8 (15.4)
Other	7 (5.4)	5 (7.7)	2 (2.3)	0	2 (0.9)	1 (0.5)	na	na	na	na
Ethnicity, n (%)										
Hispanic or Latino	5 (3.8)	6 (9.2)	1 (1.2)	2 (2.1)	6 (2.8)	4 (1.8)	3 (4.5)	4 (10.3)	5 (4.8)	4 (7.7)
Not Hispanic or Latino	115 (88.5)	54 (83.1)	78 (90.7)	80 (85.1)	191 (88.8)	194 (89.4)	53 (80.3)	30 (76.9)	81 (77.9)	40 (76.9)
Not permitted	na	na	7 (8.1)	12 (12.8)	18 (8.4)	19 (8.8)	10 (15.2)	5 (12.8)	18 (17.3)	8 (15.4)
Not reported	9 (6.9)	3 (4.6)	na	na	na	na	na	na	na	na
Geographic region, n (%)										
Asia	11 (8.5)	6 (9.2)	8 (9.3)	7 (7.4)	17 (7.9)	18 (8.3)	na	na	na	na
Australasia	4 (3.1)	3 (4.6)	na	na	na	na	na	na	na	na
Europe	98 (75.4)	44 (67.7)	na	na	na	na	37 (56.1)	32 (82.1)	70 (67.3)	43 (82.7)
Eastern Europe	na	na	25 (29.1)	36 (38.3)	70 (32.6)	86 (39.6)	na	na	na	na
Western Europe [1]	na	na	53 (61.6)	51 (54.3)	128 (59.5)	113 (52.1)	na	na	na	na
North America [1]	17 (13.1)	12 (18.5)	na	na	na	na	29 (43.9)	7 (17.9)	34 (32.7)	9 (17.3)
MF disease type, n (%)										
PMF	78 (60.0)	46 (70.8)	59 (68.6)	54 (57.4)	128 (59.5)	116 (53.5)	45 (68.2)	23 (59)	64 (61.5)	30 (57.7)
Post-PV MF	27 (20.8)	11 (16.9)	11 (12.8)	12 (12.8)	48 (22.3)	50 (23.0)	8 (12.1)	8 (20.5)	18 (17.3)	12 (23.1)
Post-ET MF	25 (19.2)	8 (12.3)	16 (18.6)	28 (29.8)	39 (18.1)	51 (23.5)	13 (19.7)	8 (20.5)	22 (21.2)	10 (19.2)
Time since MF diagnosis (years), n	na	na	86	94	213	217	65	39	103	52
Mean (SD)	na	na	3.2 (3.86)	3.1 (4.41)	3.6 (4.75)	3.1 (4.45)	6.0 (6.59)	5.1 (4.75)	5.8 (6.02)	5.3 (4.56)
Median	na	na	1.7	1.6	1.6	1.5	3.2	3.9	3.7	4.0

Characteristic	MOMENTUM		SIMPLIFY-1				SIMPLIFY-2			
			Hgb <10 g/dL Subgroup		ITT population		Hgb <10 g/dL Subgroup		ITT population	
	MMB N = 130	DAN N = 65	MMB N = 86	RUX N = 94	MMB N = 215	RUX N = 217	MMB N = 66	BAT N = 39	MMB N = 104	BAT N = 52
Q1, Q3	na	na	0.6, 4.0	0.3, 2.7	0.5, 4.4	0.3, 3.0	2.2, 8.0	2.1, 6.8	2.2, 7.5	2.2, 7.2
Min, max	na	na	0.1, 22.5	0.1, 22.0	0, 28.0	0, 24.2	0.3, 33.5	0.2, 24.9	0.3, 33.5	0.2, 24.9
Prior JAK inhibitor therapy duration (weeks)										
Mean (SD)	138.52 (123.02)	124.83 (120.03)	na	na	na	na	63.98 (68.37)	63.30 (56.66)	68.90 (66.98)	61.36 (52.93)
Median	98.71	95.86	na	na	na	na	39.64	42.86	47.43	46.71
Q1, Q3	39.86, 194.14	36.00, 151.14	na	na	na	na	13.07, 86.14	10.79, 115.07	15.43, 104.43	13.43, 105.29
Min, max	4.1, 477.0	4.0, 617.6	na	na	na	na	5.9, 257.6	3.7, 175.7	5.9, 257.6	3.7, 175.7
Prior JAK inhibitor therapy duration, n (%)										
< 12 weeks	3 (2.3)	2 (3.1)	na	na	na	na	6 (9.1)	7 (17.9)	13 (12.5)	9 (17.3)
≥ 12 weeks	127 (97.7)	63 (96.9)	na	na	na	na	13 (19.7)	8 (20.5)	16 (15.4)	10 (19.2)
Ongoing JAK inhibitor at screening	58 (44.6)	32 (49.2)	na	na	na	na	47 (71.2)	24 (61.5)	75 (72.1)	33 (63.5)
Missing	na	na	na	na	na	na	50 (75.8)	29 (74.4)	77 (74.0)	39 (75.0)
Prognostic risk category, n (%)	DIPSS		IPSS				DIPSS			
Intermediate-1	7 (5.4)	3 (4.6)	2 (2.3)	4 (4.3)	46 (21.4)	43 (19.8)	5 (7.6)	7 (17.9)	23 (22.1)	16 (30.8)
Intermediate-2	72 (55.4)	40 (61.5)	26 (30.2)	20 (21.3)	76 (35.3)	67 (30.9)	44 (66.7)	24 (61.5)	62 (59.6)	28 (53.8)
High	50 (38.5)	19 (29.2)	58 (67.4)	70 (74.5)	93 (43.3)	107 (49.3)	17 (25.8)	8 (20.5)	19 (18.3)	8 (15.4)
ECOG performance status, n (%)										
0	16 (12.3)	15 (23.1)	30 (34.9)	24 (25.5)	76 (35.3)	72 (33.2)	19 (28.8)	15 (38.5)	36 (34.6)	19 (36.5)
1	83 (63.8)	34 (52.3)	48 (55.8)	56 (59.6)	122 (56.7)	120 (55.3)	44 (66.7)	18 (46.2)	61 (58.7)	26 (50.0)
2	31 (23.8)	16 (24.6)	8 (9.3)	14 (14.9)	17 (7.9)	25 (11.5)	3 (4.5)	6 (15.4)	7 (6.7)	7 (13.5)
TSS at baseline, n [2]	130	65	85	93	213	214	45	28	104	52
Mean (SD)	27.96 (13.84)	25.70 (12.79)	19.0 (13.72)	18.1 (11.90)	19.4 (13.18)	17.9 (11.47)	21.82 (9.95)	27.39 (13.34)	18.5 (12.97)	20.5 (16.03)
Median	26.43	23.57	17.6	16.3	17.4	16.4	21.14	24.29	15.6	15.9
Q1, Q3	16.71, 38.00	15.33, 36.14	6.3, 29.3	8.9, 24.9	8.4, 27.6	8.6, 25.0	13.86, 27.17	15.93, 37.00	8.7, 25.8	7.1, 29.9
Min, max	5.2, 67.7	4.9, 53.7	0, 50	0, 45	0, 53	0, 56	10.3, 53.0	10.3, 55.5	0, 57	0, 56
TSS category, n (%) [3]										
< 22	53 (40.8)	26 (40.0)	na	na	126 (59.2)	141 (65.9)	45 (68.2)	23 (59.0)	66 (63.5)	31 (59.6)
≥ 22	77 (59.2)	39 (60.0)	na	na	87 (40.8)	73 (34.1)	21 (31.8)	16 (41.0)	38 (36.5)	21 (40.4)
< 10	8 (6.2)	5 (7.7)	na	na	61 (28.6)	65 (30.4)	21 (31.8)	11 (28.2)	29 (27.9)	17 (32.7)
≥ 10	122 (93.8)	60 (92.3)	na	na	152 (71.4)	149 (69.6)	45 (68.2)	28 (71.8)	75 (72.1)	35 (67.3)

Characteristic	MOMENTUM		SIMPLIFY-1				SIMPLIFY-2			
			Hgb <10 g/dL Subgroup		ITT population		Hgb <10 g/dL Subgroup		ITT population	
	MMB N = 130	DAN N = 65	MMB N = 86	RUX N = 94	MMB N = 215	RUX N = 217	MMB N = 66	BAT N = 39	MMB N = 104	BAT N = 52
Palpable spleen length below the left costal margin, n (%) [3]										
< 12 cm	66 (50.8)	32 (49.2)	na	na	na	na	22 (33.3)	15 (38.5)	37 (35.6)	18 (34.6)
≥ 12 cm	55 (42.3)	28 (43.1)	na	na	na	na	44 (66.7)	24 (61.5)	66 (63.5)	34 (65.4)
Central lab spleen volume (cm^3), n	129	63	86	94	214	217	66	39	104	52
Mean (SD)	2367.10 (1302.27)	2287.95 (1154.83)	1981.4 (776.14)	2285.2 (1286.90)	2186.9 (1201.63)	2183.3 (1243.84)	2625.5 (1467.27)	2299.6 (1157.20)	2512.0 (1541.35)	2347.7 (1133.32)
Median	2112.02	2059.27	1788.1	1958.5	2009.6	1910.8	2576.8	2049.3	2201.9	2062.9
Q1, Q3	1445.5, 2954.8	1446.4, 2816.9	1429.9, 2532.6	1367.7, 2831.1	1347.9, 2727.9	1361.5, 2749.4	1340.9, 3541.6	1369.2, 2804.3	1327.2, 3329.2	1537.7, 2850.4
Min, max	609.5, 9717.2	627.7, 6016.1	352, 4027	686, 9022	324, 6862	206, 9022	392, 6740	458, 5299	241, 7433	458, 5299
Transfusion independent, n (%)	17 (13.1)	10 (15.4)	25 (29.1)	41 (43.6)	147 (68.4)	152 (70.0)	5 (7.6)	9 (23.1)	32 (30.8)	19 (36.5)
Transfusion dependent, n (%)	63 (48.5)	34 (52.3)	49 (57.0)	43 (45.7)	53 (24.7)	52 (24.0)	52 (78.8)	25 (64.1)	58 (55.8)	27 (51.9)
RBC units transfused ≤ 8 weeks before randomization, n (%) [3]										
0	28 (21.5)	13 (20.0)	na	na	na	na	na	na	na	na
1-4	58 (44.6)	27 (41.5)	na	na	na	na	na	na	na	na
≥ 5	44 (33.8)	25 (38.5)	na	na	na	na	na	na	na	na
RBC units transfused ≤ 8 weeks before randomization, n	na	na	86	94	215	217	66	39	104	52
Mean (SD)	na	na	2.5 (3.31)	2.2 (3.30)	1.1 (2.66)	1.1 (2.52)	4.4 (3.64)	3.8 (3.63)	3.1 (3.59)	3.1 (3.51)
Median	na	na	2.0	0	0	0	4.0	3.0	2.0	2.0
Q1, Q3	na	na	0, 4.0	0, 3.0	0, 2.0	0, 0	1.0, 8.0	1.0, 6.0	0.0, 6.0	0.0, 5.0
Min, max	na	na	0, 17	0, 13	0, 17	0, 13	0, 12	0, 15	0, 12	0, 15
Hemoglobin (g/dL), n	129	65	86	94	215	216	66	39	104	52
Mean (SD)	8.06 (1.14)	7.86 (0.83)	8.6 (0.95)	8.7 (1.00)	10.6 (2.09)	10.7 (2.37)	8.2 (0.89)	8.8 (0.75)	9.4 (1.92)	9.5 (1.59)
Median	8.00	8.00	8.6	9.0	10.5	10.3	8.1	8.7	9.0	9.2
Q1, Q3	7.50, 8.80	7.30, 8.40	7.9, 9.4	8.1, 9,6	9.1, 12.0	9.2, 11.9	7.6, 8.8	8.3, 9.5	7.9, 10.7	8.5, 10.1
Min, max	3.8, 10.7	5.7, 9.7	6, 10	6, 10	6, 16	6, 19	6, 10	7, 10	6, 16	7, 14
Hemoglobin category, n (%)										
< 8 g/dL	62 (47.7)	32 (49.2)	28 (32.6)	21 (22.3)	28 (13.0)	21 (9.7)	27 (40.9)	6 (15.4)	27 (26.0)	6 (11.5)
≥ 8 g/dL	67 (51.5)	33 (50.8)	58 (67.4)	73 (77.7)	187 (87.0)	195 (89.9)	39 (59.1)	33 (84.6)	77 (74.0)	46 (88.5)
< 10 g/dL	126 (96.9)	65 (100)	86 (100)	94 (100)	86 (40.0)	94 (43.3)	66 (100)	39 (100)	66 (63.5)	39 (75.0)
≥ 10 g/dL	3 (2.3) [4]	0	0	0	129 (60.0)	122 (56.2)	0	0	38 (36.5)	13 (25.0)

Characteristic	MOMENTUM		SIMPLIFY-1				SIMPLIFY-2			
			Hgb <10 g/dL Subgroup		ITT population		Hgb <10 g/dL Subgroup		ITT population	
	MMB N = 130	DAN N = 65	MMB N = 86	RUX N = 94	MMB N = 215	RUX N = 217	MMB N = 66	BAT N = 39	MMB N = 104	BAT N = 52
< 12 g/dL	129 (99.2)	65 (100)	86 (100)	94 (100)	159 (74.0)	164 (75.6)	66 (100)	39 (100)	na	na
≥ 12 g/dL	0	0	0	0	56 (26.0)	53 (24.4)	0	0	na	na
Platelet count ($\times 10^9$/L), n	128	64	86	94	215	217	64	39	102	52
Mean (SD)	151.68 (130.90)	130.69 (100.97)	229.3 (155.88)	292.3 (323.20)	300.9 (206.86)	301.5 (255.85)	186.4 (161.60)	123.5 (95.39)	170.8 (148.01)	126.5 (95.92)
Median	97.00	94.00	186.5	205.0	240.5	249.0	125.5	91.0	118.5	90.5
Q1, Q3	60.00, 195.50	53.50, 175.00	126.0, 290.0	135.0, 373.0	155.0, 384.0	146.0, 396.0	75.5, 273.5	64.0, 151.0	70.0, 223.0	64.0, 166.5
Min, max	24.0, 733.0	26.0, 459.0	62, 884	54, 2865	50, 1165	52, 2865	32, 777	28, 509	9, 777	27, 509
Platelet count ($\times 10^9$/L), n (%)										
< 50	18 (13.8)	13 (20.0)	na	na	na	na	6 (9.1)	5 (12.8)	9 (8.7)	7 (13.5)
≥ 50 and ≤ 150	63 (48.5)	30 (46.2)	na	na	47 (21.9)	57 (26.3)	33 (50.0)	24 (61.5)	57 (54.8)	30 (57.7)
> 150 and ≤ 300	33 (25.4)	15 (23.1)	na	na	89 (41.4)	71 (32.7)	12 (18.2)	8 (20.5)	18 (17.3)	12 (23.1)
> 300	14 (10.8)	6 (9.2)	na	na	79 (36.7)	89 (41.0)	13 (19.7)	2 (5.1)	18 (17.3)	3 (5.8)
≤ 150	81 (62.3)	43 (66.2)	na	na	47 (21.9)	57 (26.3)	39 (59.1)	29 (74.4)	66 (63.5)	37 (71.2)
> 150	47 (36.2)	21 (32.3)	na	na	168 (78.1)	160 (73.7)	25 (37.9)	10 (25.6)	36 (34.6)	15 (28.8)
< 100	66 (50.8)	34 (52.3)	13 (15.1)	13 (13.8)	18 (8.4)	23 (10.6)	25 (37.9)	20 (51.3)	42 (40.4)	27 (51.9)
≥ 100 and ≤ 200	31 (23.8)	19 (29.2)	36 (41.9)	34 (36.2)	66 (30.7)	63 (29.0)	21 (31.8)	13 (33.3)	33 (31.7)	16 (30.8)
≤ 200	97 (74.6)	53 (81.5)	na	na	84 (39.1)	86 (39.6)	na	na	na	na
> 200	31 (23.8)	11 (16.9)	37 (43.0)	47 (50.0)	131 (60.9)	131 (60.4)	18 (27.3)	6 (15.4)	27 (26.0)	9 (17.3)

[1] Western Europe includes North America for SIMPLIFY-1.

[2] TSS was assessed using MFSAF v4.0 in MOMENTUM and the modified MPN-SAF v2.0 in SIMPLIFY-1.

[3] Data were from the case report form.

[4] Baseline Hgb levels were 10.0, 10.6, and 10.7 g/dL.

Prior and concomitant MF therapies

Study SRA-MMB-301 (MOMENTUM)

JAK inhibitor therapy:

All 195 subjects received prior JAK inhibitor therapy as required by the protocol. All subjects (100%) received RUX and 9 subjects (4.6%) also received fedratinib. The mean (SD) duration of prior treatment with JAK inhibitors was 138.52 (123.02) weeks in the MMB group and 124.83 (120.03) weeks in the DAN group. The overall median duration of prior treatment with JAK inhibitors was 98.57 weeks (1.9 years).

Table 36: Summary of prior JAK inhibitor therapy (ITT population, MOMENTUM)

	MMB (N = 130)	DAN (N = 65)	Total (N = 195)
Prior JAKi therapy			
Ruxolitinib	130 (100.0%)	65 (100.0%)	195 (100.0%)
Fedratinib	7 (5.4%)	2 (3.1%)	9 (4.6%)
Duration of prior JAKi therapy (weeks)			
N	130	65	195
Mean (SD)	138.52 (123.02)	124.83 (120.03)	133.96 (121.89)
Median	98.71	95.86	98.57
Q1, Q3	39.86, 194.14	36.00, 151.14	39.57, 191.14
Min, Max	4.1, 477.0	4.0, 617.6	4.0, 617.6
Duration of prior Ruxolitinib (weeks)			
N	130	65	195
Mean (SD)	135.96 (120.94)	123.69 (117.09)	131.87 (119.51)
Median	96.14	95.86	95.86
Q1, Q3	39.86, 193.00	36.00, 151.14	39.57, 185.57
Min, Max	4.1, 477.0	4.0, 583.6	4.0, 583.6
Duration of prior Fedratinib (weeks)			
N	7	2	9
Mean (SD)	47.55 (40.16)	36.93 (4.14)	45.19 (35.13)
Median	31.71	36.93	34.00
Q1, Q3	15.86, 92.43	34.00, 39.86	22.00, 42.71
Min, Max	13.1, 115.0	34.0, 39.9	13.1, 115.0

Study GU-US-352-0101 (SIMPLIFY-1)

Patients with prior use of a JAK-inhibitor were excluded from the SIMPLIFY-1 study. From the patients enrolled in the double-blind treatment phase, 33.0% of patients in the MMB arm and 32.7% of patients in the RUX arm received prior MF therapy. In both treatment arms, hydroxycarbamide was the most frequent used prior MF therapy (around 20 – 25% of patients).

Treatment Compliance

MOMENTUM

Table 37: Treatment Compliance During 24 Weeks of Randomized Treatment and the Entire Treatment Period (Safety Population, MOMENTUM)

	Randomized Treatment		Entire Treatment Period [1]			
Parameter	MMB (N = 130)	DAN (N = 65)	MMB (N = 38)	MMB→MMB (N = 92)	DAN→MMB (N = 40)	MMB Overall (N = 170)
Dose intensity (mg/day) [2]						
n	130	65	38	92	40	170
Mean (SD)	188.84 (18.41)	576.47 (65.28)	186.51 (18.05)	187.19 (21.52)	181.28 (34.08)	185.65 (24.39)
Median	200.00	600.00	195.83	200.00	200.00	200.00
Q1, Q3	181.82, 200.00	600.00, 600.00	174.48, 200.00	180.31, 200.00	168.21, 200.00	174.71, 200.00
Min, max	128.3, 200.0	241.8, 600.0	138.7, 200.0	105.1, 200.0	50.0, 200.0	50.0, 200.0
Relative dose intensity (%) [3]						
n	130	65	38	92	40	170
Mean (SD)	94.42 (9.20)	96.08 (10.88)	93.26 (9.02)	93.59 (10.76)	90.64 (17.04)	92.82 (12.19)
Median	100.00	100.00	97.92	100.00	100.00	100.00
Q1, Q3	90.91, 100.00	100.00,100.00	87.24, 100.00	90.16, 100.00	84.11, 100.00	87.35, 100.00
Min, max	64.1, 100.0	40.3, 100.0	69.4, 100.0	52.6, 100.0	25.0, 100.0	25.0, 100.0

Source: Table 14.3.0.1, Table 14.3.0.3

[1] The MMB group includes subjects treated with MMB in the randomized treatment period who did not continue in the open-label treatment period. MMB→MMB includes subjects treated with MMB in the randomized treatment period who continued to receive MMB in the open-label treatment period. DAN→MMB includes subjects treated with DAN in the randomized treatment period who crossed over to receive MMB in the open-label treatment period.

[2] Dose intensity = actual cumulative dose / actual duration of the treatment (days).

[3] Relative dose intensity = actual dose intensity / planned dose intensity.

DAN, danazol; Min, max, Minimum, maximum; MMB, momelotinib; Q1, Q3, first quartile, third quartile.

SIMPLIFY-1

Table 38: Treatment Compliance During Double Blind Treatment Phase (Safety Population, SIMPLIFY-1)

	MMB (N=214)	RUX (N=216)
Number of Subjects who Returned at Least 1 Bottle and had calculable drug adherence	214 (100.0%)	216 (100.0%)
On-treatment Adherence Rate (%)		
N	214	216
Mean (SD)	98.5 (5.24)	97.8 (10.66)
Median	100.0	99.2
Q1, Q3	98.2, 100.6	96.9, 100.0
Min, Max	67, 111	41, 182
Subjects with on-treatment Adherence Rate by Category		
< 75%	2 (0.9%)	5 (2.3%)
>= 75% to < 90%	8 (3.7%)	8 (3.7%)
>= 90%	204 (95.3%)	203 (94.0%)

- **Numbers analysed**

Study SRA-MMB-301 (MOMENTUM)

Table 39: Analysis sets for the double-blind treatment phase (MOMENTUM)

Population	MMB (N = 130)	DAN (N = 65)	Total (N = 195)
Intent-to-treat [1]	130 (100%)	65 (100%)	195 (100%)
Safety [2]	130 (100%)	65 (100%)	195 (100%)
Per protocol [3, 4]	129 (99.2%)	61 (93.8%)	190 (97.4%)

Study GU-US-352-0101 (SIMPLIFY-1)

Table 40: Analysis sets for the double-blind treatment phase (SIMPLIFY-1)

	MMB (N=215)	RUX (N=217)
ITT Analysis Set	215 (100.0%)	217 (100.0%)
Safety Analysis Set	214 (99.5%)	216 (99.5%)
Per-Protocol Analysis Set	179 (83.3%)	203 (93.5%)
Reasons for Exclusion	36 (16.7%)	14 (6.5%)
Duration on any study drug is < 80% of planned 168 days, ie <135 days	32 (14.9%)	10 (4.6%)
Missing Baseline Total Symptom Score	2 (0.9%)	3 (1.4%)
Not treated with any study drug	1 (0.5%)	1 (0.5%)
Missing Baseline spleen volume within 30 days prior to randomization	1 (0.5%)	0

Table 41: Analysis sets for the open-blind treatment phase and overall exposure to momelotinib period (SIMPLIFY-1)

	Open-label Phase		Overall Exposed to MMB	
	Continuing (MMB to MMB) (N=171)	Switch (RUX to MMB) (N=197)	MMB in DB (N=215)	Total (N=412)
ITT Analysis Set	171 (100.0%)	197 (100.0%)	215 (100.0%)	412 (100.0%)
Safety Analysis Set	171 (100.0%)	197 (100.0%)	214 (99.5%)	411 (99.8%)
PK Analysis Set	-	82 (41.6%)	206 (95.8%)	288 (69.9%)

- **Outcomes and estimation**

Study SRA-MMB-301 (MOMENTUM)

Following initial submission of the application, the applicant identified a vendor error related to the MOMENTUM anti-myelofibrosis prohibited medication dataset which resulted in a misclassification of one patient for the endpoints of transfusion independence status at Week 24 and splenic response rate at Week 24 (subject should be considered non-responder instead of responder). Below, the analysis data cutoff date of 03 Dec 2021 was used for all efficacy analyses of the 24-week randomized treatment period (reported in the originally submitted clinical study report dated 15 Aug 2022), except for the analyses of endpoints that included TI rate and SRR at week 24, for which the database lock date of 17 Jan 2023 was used (provided in response to first LoQ), due to correction of the subjects who received a prohibited anti-MF medication. For secondary and exploratory analyses that included data collected through the end of study (including OS and LFS), the updated database lock date of 17 Jan 2023 was used.

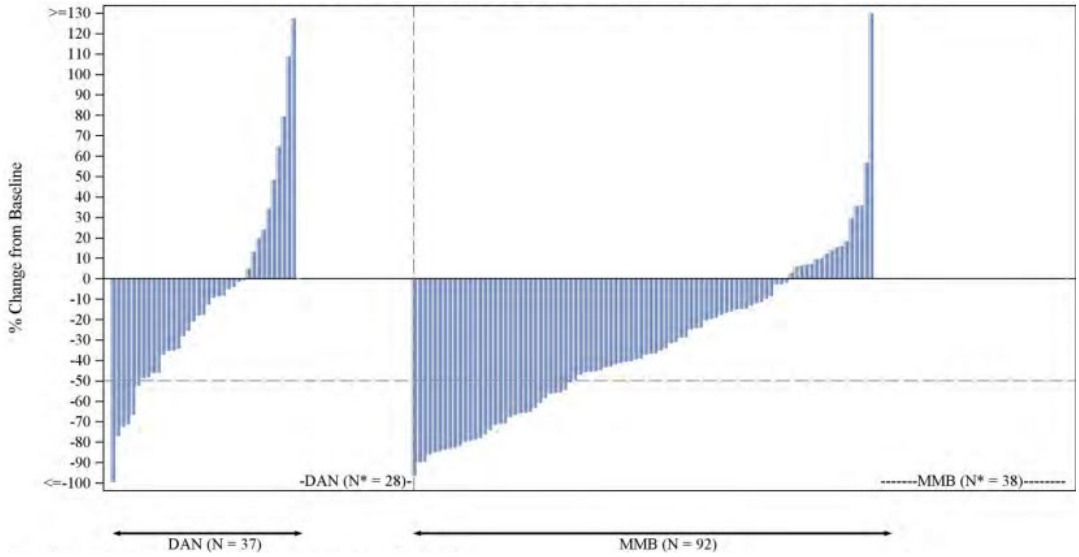
Primary Efficacy Endpoints in MOMENTUM

First primary endpoint: MFSAF TSS 24

Table 42: MFSAF TSS Response Rate at Week 24 (ITT population, MOMENTUM)

	MOMENTUM	
TSS Response Rate at Week 24	**MMB (N = 130)**	**DAN (N = 65)**
Evaluable at week 24, n	130	65
Responder, n (%)	32 (**24.6%**)	6 (**9.2%**)
Exact 95% CI [1]	17.49, 32.94	3.46, 19.02
Superiority proportion difference, % (95% CI)	**15.67** (5.54, 25.81)	
p-value	**0.0095**	
Nonresponder, n (%)	98 (75.4%)	59 (90.8%)
Last TSS date before day 161	38 (29.2%)	28 (43.1%)
Last participation date on day 161 or later but TSS at week 24 not available	0	0
Increase from baseline > 0% at week 24	17 (13.1%)	10 (15.4%)
Reduction from baseline < 50% at week 24	43 (33.1%)	21 (32.3%)

Proportion differences were analyzed using the stratified CMH method. [1] Exact binomial CI for MOMENTUM.
CMH, Cochran-Mantel-Haenszel; DAN, danazol; ITT, intent-to-treat; MMB, momelotinib; na, not applicable; RUX, ruxolitinib; TSS, total symptom score.



The number of subjects without week 24 data is represented as blank space for each treatment group. N, number of subjects with percent change in TSS at week 24 available. N*, number of subjects without a week 24 TSS. DAN, danazol; ITT, intent-to-treat; MFSAF, Myelofibrosis Symptom Assessment Form; MMB, momelotinib; TSS, total symptom score.

Figure 13: Percent Change From Baseline in MFSAF TSS at Week 24 for Each Subject (ITT Population, MOMENTUM)

	MMB→MMB		DAN→MMB	
	Week 24 Responder (N = 32)	Week 24 Nonresponder (N = 61)	Week 24 Responder (N = 6)	Week 24 Nonresponder (N = 35)
MFSAF TSS response rate at week 48				
Evaluable at week 48, n	25	43	5	25
Responders, n (%) [1]	18 (72.0%)	12 (27.9%)	5 (100%)	10 (40.0%)
Nonresponders, n (%) [2]	7 (28.0%)	31 (72.1%)	0	15 (60.0%)

Table 44: Summary of MFSAF TSS response rate at Week 48 (ITT population, MOMENTUM)

Percentages were calculated based on the number of subjects who crossed over to open-label treatment with MMB and had sufficient TSS data available for response evaluation. [1] Had a ⩾ 50% reduction from baseline mean MFSAF TSS during the 28-day period immediately before the end of week 48. [2] Completed the week 48 visit and did not meet responder criteria defined in [1].

Second primary endpoint: TI rate at Week 24

The superiority test did not demonstrate a statistically significant between-group difference (p = 0.1265). The response rate was 30.00% (95% CI: 22.28, 38.66) for the MMB group and 20.00% (95% CI: 11.10, 31.77) for the DAN group, with a treatment difference of 9.80% (95% CI: -2.03, 21.62).

A noninferiority test demonstrated statistically significant noninferiority of MMB compared with DAN, with a delta for noninferiority (defined as p[MMB] - 0.8 × p[DAN]) of 13.58% (95% CI: 1.86, 25.30).

MMB could be declared noninferior to DAN because the lower bound of the 95% CI was greater than 0. One subject in the MMB group with TI at week 24 received several transfusions for overt bleeding within 12 weeks before week 24.

The proportion of subjects with TI at baseline was low in both groups (13.1% MMB, 15.4% DAN). Overall, the proportion of subjects with TI at week 24 increased from baseline by 16.9% in the MMB group and 4.6% in the DAN group.

Table 45: TI rate at Week 24 (ITT population, MOMENTUM)

Endpoint	MMB (N = 130)	DAN (N = 65)
Second: Transfusion independence rate at week 24		
Responder, n (%)	39 (**30.0%**)	13 (**20.0%**)
Response rate (95% CI) [1]	30.00 (22.28, 38.66)	20.00 (11.10, 31.77)
Superiority test: Treatment arm difference by stratified CMH (95% CI)	9.80 (-2.03, 21.62)	
p-value [2]	0.1265	
Noninferiority test: Treatment arm difference for noninferiority (95% CI) [2, 3]	13.58 (1.86, 25.30)	
1-sided p-value	0.0116	
Nonresponder, n (%)	91 (70.0%)	52 (80.0%)
Missing week 24 evaluation	34 (26.2%)	27 (41.5%)
≥ 1 RBC or whole blood transfusion in the 12-week period	63 (48.5%)	36 (55.4%)
≥ 1 central or local Hgb laboratory level < 8 g/dL in the 12-week period	45 (34.6%)	22 (33.8%)
No more than 1 Hgb assessment in the 12-week period	5 (3.8%)	4 (6.2%)
Time between Hgb assessments ≥ 42 days in the 12-week period	13 (10.0%)	10 (15.4%)
Week 24 visit out of window (161-176 days)	2 (1.5%)	1 (1.5%)
Prohibited anti-MF medication during randomized treatment period	5 (3.8%)	1 (1.5%)

Proportion differences were analyzed using the stratified CMH method except where noted.
"(nominal)" is used to clarify a nominal p-value for a descriptive result of a hypothesis test that was included only after a hypothesis test was not rejected in a hierarchical test sequence.
[1] Exact binomial CI for MOMENTUM.
[2] For MOMENTUM, delta = p(MMB) – 0.80 × p(DAN), where p(MMB) was the proportion of subjects with TI in the MMB group and p(DAN) was the proportion of subjects with TI in the DAN group. The 95% CI was stratum adjusted.
CMH, Cochran-Mantel-Haenszel; DAN, danazol; ITT, intent-to-treat; MMB, momelotinib; na, not applicable; RUX, ruxolitinib; TI, transfusion independence.

Table 46: Summary of TI rate at Week 48 (ITT population, MOMENTUM)

	MMB→MMB		DAN→MMB	
	Week 24 Responder (N = 39)	Week 24 Nonresponder (N = 54)	Week 24 Responder (N = 13)	Week 24 Nonresponder (N = 28)
TI rate at week 48				
Evaluable at week 48, n	34	33	10	20
Responders, n (%) [1]	30 (88.2%)	8 (24.2%)	8 (80.0%)	10 (50.0%)
Nonresponders, n (%) [2]	4 (11.8%)	25 (75.8%)	2 (20.0%)	10 (50.0%)

Percentages were calculated based on the number of subjects who crossed over to open-label treatment with MMB and had sufficient transfusion and Hgb data available for response evaluation. [1] Completed the week 48 visit and had no RBC or whole blood transfusion, no Hgb level < 8 g/dL, and provided Hgb assessments during the 12 weeks immediately before the week 48 visit. [2] Completed the week 48 visit and did not meet the TI criteria defined in [1].

Secondary Efficacy Endpoints in MOMENTUM

First and third key secondary endpoint: SRR at Week 24 based on ≥ 25% and ≥ 35% reduction in spleen volume from baseline, respectively

The first and third key secondary efficacy endpoints were met as demonstrated by statistically significant superiority of MMB over DAN.

Table 47: SRR at Week 24, ≥25% reduction in spleen volume (ITT population, MOMENTUM)

Endpoint	MMB (N = 130)	DAN (N = 65)
Key Secondary		
First: SRR at week 24 based on ≥ 25% reduction in spleen volume		
Responder, n (%)	51 (**39.2%**)	4 (**6.2%**)
Response rate (95% CI) [1]	39.23 (30.79, 48.18)	6.15 (1.70, 15.01)
Treatment arm difference by stratified CMH (95% CI)	**33.05** (22.59, 43.51)	
p-value	**< 0.0001**	
Nonresponder, n (%)	79 (60.8%)	61 (93.8%)
Missing baseline evaluation	0	0
Missing week 24 evaluation	38 (29.2%)	28 (43.1%)
Scan taken > 10 days after start of open-label treatment	2 (1.5%)	0
Different modalities of spleen scan at baseline and week 24	2 (1.5%)	0
< 25% reduction or increased spleen volume	36 (27.7%)	33 (50.8%)
Prohibited anti-MF medication during randomized treatment period	5 (3.8%)	1 (1.5%)

All p-values were 2-sided. [1]Exact binomial CI.

Table 48: SRR at Week 24, ≥35% reduction in spleen volume (ITT population, MOMENTUM)

Endpoint	MMB (N = 130)	DAN (N = 65)
Key Secondary		
Third: SRR at week 24 based on ≥ 35% reduction in spleen volume		
Responder, n (%)	29 (**22.3%**)	2 (**3.1%**)
Response rate (95% CI) [1]	22.31 (15.48, 30.44)	3.08 (0.37, 10.68)
Treatment arm difference by stratified CMH (95% CI)	**18.18** (9.77, 26.59)	
p-value	**0.0011**	
Nonresponder, n (%)	101 (77.7%)	63 (96.9%)
Missing baseline evaluation	0	0
Missing week 24 evaluation	38 (29.2%)	28 (43.1%)
Scan taken > 10 days after start of open-label treatment	2 (1.5%)	0
Different modalities of spleen scan at baseline and week 24	2 (1.5%)	0
< 35% reduction or increased spleen volume	59 (45.4%)	35 (53.8%)
Prohibited anti-MF medication during randomized treatment period	5 (3.8%)	1 (1.5%)

All p-values were 2-sided. [1] Exact binomial CI

Table 49: Summary of SRR (≥25% and ≥35% reduction from baseline spleen volume at Week 48 (ITT population, MOMENTUM)

SRR (≥ 25% Reduction From Baseline Spleen Volume) at Week 48	MMB→MMB		DAN→MMB	
	Week 24 25% Responder (N = 51)	Week 24 25% Nonresponder (N = 42)	Week 24 25% Responder (N = 4)	Week 24 25% Nonresponder (N = 37)
Evaluable at week 48, n	43	24	3	27
Responder, n (%)	35 (81.4%)	8 (33.3%)	3 (100%)	8 (29.6%)
Nonresponder, n (%)	8 (18.6%)	16 (66.7%)	0	19 (70.4%)
SRR (≥ 35% Reduction From Baseline Spleen Volume) at Week 48	**MMB→MMB**		**DAN→MMB**	
	Week 24 35% Responder (N = 29)	Week 24 35% Nonresponder (N = 64)	Week 24 35% Responder (N = 2)	Week 24 35% Nonresponder (N = 39)
Evaluable at week 48, n	24	43	2	28
Responder, n (%)	19 (79.2%)	10 (23.3%)	1 (50.0%)	3 (10.7%)
Nonresponder, n (%)	5 (20.8%)	33 (76.7%)	1 (50.0%)	25 (89.3%)

SRR at week 48 was assessed in subjects who crossed over to open-label treatment with MMB and had a week 48 spleen scan. The imaging modality was required to match at baseline and week 48. 25% responder at week 24 was defined as a subject with ≥ 25% reduction from baseline spleen volume at week 24. 35% responder at week 48 was defined as a subject with ≥ 35% reduction from baseline spleen volume at week 24.

Second key secondary endpoint: Change in MFSAF Total Symptom Score From Baseline at Week 24

The second key secondary endpoint was met, as demonstrated by statistically significant superiority of MMB over DAN in change from baseline in MFSAF TSS at week 24.

Table 50: Change in MFSAF TSS from baseline at Week 24 (ITT population, MOMENTUM)

TSS Change From Baseline at Week 24	MOMENTUM ITT MMB (N = 130)	MOMENTUM ITT DAN (N = 65)
Baseline		
Mean (SD)	27.96 (13.84)	25.70 (12.79)
LS mean (SE)	na	na
Week 24		
LS mean (SE)	**-9.36** (1.08)	**-3.13** (1.62)
LS mean difference (SE)	**-6.22** (1.92)	
95% CI	-10.0, -2.43	
p-value [1]	**0.0014**	

The MMRM model was adjusted for baseline MFSAF TSS (< 22 vs ≥ 22), baseline palpable spleen length below the left costal margin (< 12 cm vs ≥ 12 cm), and baseline RBC or whole blood units transfused in the 8-week period before randomization (0, 1-4, ≥ 5 units) [1] p-value for the LS mean difference between 2 groups from the MMRM

Fourth key secondary endpoint: Rate of no transfusion at Week 24

This endpoint was met, as demonstrated by statistically significant superiority of MMB over DAN.

Table 51: Rate of no transfusion at Week 24 (ITT population, MOMENTUM)

Endpoint	MMB (N = 130)	DAN (N = 65)
Key Secondary		
Fourth: Rate of no transfusion at week 24		
Responder, n (%)	46 (**35.4%**)	11 (**16.9%**)
Response rate (95% CI) [1]	35.38 (27.20, 44.25)	16.92 (8.76, 28.27)
Treatment arm difference by stratified CMH (95% CI)	**17.20** (7.99, 26.40)	
p-value	**0.0012**	
Nonresponder, n (%)	84 (64.4%)	54 (83.1%)

All p-values were 2-sided, [1] Exact binomial CI.

Other secondary endpoints

- Proportion of subjects with ≤ 4 RBC or whole blood units transfused during the 24-week RT Period was 55.4% for MMB and 44.6% for DAN, with a proportion difference by stratified CMH method of 10.62% (95% CI: -2.40, 23.64), p = 0.1133.
- Cumulative Transfusion Risk at Week 24: the overall mean number of units transfused during the RT period was estimated from a ZINB model as 7.24 units (95% CI: 5.49, 8.98) for the MMB group and 13.99 units (95% CI: 9.99, 17.99) for the DAN group, with a treatment difference of -6.75 units (95% CI: -11.11, -2.39), p = 0.0024. The estimated mean cumulative transfusion risk at week 24 from a proportional hazards recurrent events model was lower for MMB compared with DAN (6.55 vs 10.86). The hazard ratio for an RBC unit transfused for MMB compared with DAN was 0.556 (95% CI: 0.397, 0.778), p = 0.0006.

Study GU-US-352-0101 (SIMPLIFY-1)

Primary Efficacy Endpoints

SRR at Week 24 based on ≥ 35% reduction in spleen volume from baseline

Table 52: SRR at Week 24, ≥ 35% reduction in spleen volume (ITT, SIMPLIFY-1)

Endpoint	MMB (N = 215)	RUX (N = 217)
Primary		
SRR at week 24 based on ≥ 35% reduction in spleen volume		
Responder, n (%)	57 (**26.5%**)	64 (**29.5%**)
Exact 95% CI (95% CI) [1]	20.74, 32.94	23.51, 36.04
Noninferiority proportion difference - stratified CMH method, % (95% CI)	**9** (2, 16)	
p-value	**0.014**	
Nonresponder, n (%)	158 (73.5%)	153 (70.5%)
Missing baseline evaluation	1 (0.5%)	0
Missing week 24 evaluation	31 (14.4%)	13 (6.0%)
Last participation date < Day 141 in double-blind phase	24 (11.2%)	7 (3.2%)
< 35% reduction or increased spleen volume	127 (59.1%)	140 (64.5%)
> 0% spleen volume increase at Week 24	26 (12.1%)	28 (12.9%)

All p-values were 2-sided. [1] Exact binomial CI.

Secondary Efficacy Endpoints in SIMPLIFY-1

1. MPN-SAF TSS response rate at Week 24

In the SIMPLIFY-1 study, the first secondary endpoint of noninferiority of MMB to RUX in TSS response rate at week 24 was not met and formal sequential testing was stopped.

Table 53: MPN-SAF TSS Response Rate at Week 24 (ITT population, SIMPLIFY-1)

	SIMPLIFY-1	
TSS Response Rate at Week 24	**MMB (N = 215)**	**RUX (N = 217)**
Evaluable at week 24, n	211	211
Responder, n (%)	60 (28.4%)	89 (42.2%)
Exact 95% CI [1]	22.45, 35.03	35.43, 49.15
Noninferiority proportion difference, % (95% CI)	0 (-8, 8) [2]	
p-value	0.98	
Nonresponder, n (%)	151 (71.6%)	122 (57.8%)
Last TSS date before day 162 [2]	31 (14.7%)	12 (5.7%)
Last participation date on day 162 or later but TSS at week 24 not available [3]	5 (2.4%)	9 (4.3%)
Increase from baseline > 0% at week 24	47 (22.3%)	32 (15.2%)
Reduction from baseline < 50% at week 24	114 (54.0%)	101 (47.9%)

SIMPLIFY-1 evaluable subjects included subjects with baseline TSS > 0 and subjects with baseline TSS of 0 but nonzero or missing TSS at week 24. Proportion differences were analyzed using the stratified CMH method. [1] Exact binomial CI for MOMENTUM and based on Clopper-Pearson method without stratification for SIMPLIFY-1. [2] Delta = p(MMB) – 0.67 × p(RUX), where p(MMB) was the proportion with TSS response in the MMB group and p(RUX) was the proportion with TSS response in the RUX group. [3] Day 162 for SIMPLIFY-1.

2. TI response rate at Week 24

In the SIMPLIFY-1 trial, given the null hypotheses for the previous secondary endpoint was not rejected, formal sequential testing was stopped and this endpoint was not formally tested for superiority. Only nominal significance was cited and considered exploratory.

Table 54: TI rate at Week 24 (ITT population, SIMPLIFY-1)

	SIMPLIFY-1	
TI Rate at Week 24	**MMB (N = 215)**	**RUX (N = 217)**
Responder, n (%)	143 (66.5%)	107 (49.3%)
Exact 95% CI [1]	59.78, 72.79	42.48, 56.16
Proportion difference - Stratified CMH method (95% CI)	18 (9, 26)	
p-value	< 0.001 (nominal)	
Nonresponder, n (%)	72 (33.5%)	110 (50.7%)
Transfusion (except bleeding) in the last 12 weeks	32 (14.9%)	87 (40.1%)
Any hemoglobin assessment < 8 g/dL in the last 12 weeks	27 (12.6%)	68 (31.3%)
Last participation date prior to Day 162 in DB phase	32 (14.9%)	12 (5.5%)
Other	17 (7.9%)	34 (15.7%)

The TI rate at week 24 was higher for MMB compared with RUX (66.5% vs 49.3%), p < 0.001. The proportion of subjects with TI at baseline was high in both groups (68.4% MMB, 70.0% RUX). Overall,

the proportion of subjects with TI at week 24 decreased from baseline by 1.9% in the MMB group and by 20.7% in the RUX group.

3. TD rate at Week 24

Table 55: TD rate at Week 24 (ITT population, SIMPLIFY-1)

TD Rate at Week 24	SIMPLIFY-1	
	MMB (N = 215)	RUX (N = 217)
TD at week 24, n (%)	65 (30.2%)	87 (40.1%)
Exact 95% CI [1]	24.17, 36.85	33.52, 46.94
Proportion difference, % (95% CI)	-10 (-19, -2)	
p-value	0.019	

A smaller proportion of subjects in the MMB group were TD at Week 24 (30.2%, 65 subjects) compared with the RUX group (40.1%, 87 subjects). The proportion difference was -10% (nominal p-value: 0.019)

4. Rate of RBC transfusion in the double-blind phase

In SIMPLIFY-1 trial, the median RBC transfusion rate was lower for MMB (0 units/month; range, 0.0-9.1) compared with RUX (0.4 units/month; range, 0.0-8.2), with a transfusion rate ratio of 0.28 (95% CI: 0.19, 0.43), nominal p < 0.001, per the negative binomial model adjusted for strata.

- **Ancillary analyses**

Subgroup analysis in subgroups by anaemia severity for SIMPLIFY-1 and SIMPLIFY-2, including post-hoc defined subgroup with Hgb < 10 g/dL

SIMPLIFY-1 study

Table 56: SRR at Week 24, ≥ 35% reduction in spleen volume (ITT population and Hgb < 10 g/dL subgroup, SIMPLIFY-1)

	Hemoglobin <10 g/dL Subgroup		Overall ITT Population	
SRR at Week 24	MMB (N = 86)	RUX (N = 95)	MMB (N = 215)	RUX (N = 217)
Responder, n (%)	27 (31.4)	31 (32.6)	57 (26.5)	64 (29.5)
Exact 95% CI [1]	21.81, 42.30	23.36, 43.02	20.74, 32.94	23.51, 36.04
Superiority proportion difference, % (95% CI)	0 (-13, 14)		-3 (-12, 5)	
p-value	na		0.45	
Noninferiority proportion difference, % (95% CI)	13 (2, 25)		9 (2, 16)	
p-value	na		0.014	

SIMPLIFY-2 study

Table 57: SRR at Week 24, ≥ 35% reduction in spleen volume (ITT population and anemia subgroups, SIMPLIFY-2)

Endpoint	ITT Population		Hgb < 10 g/dL		Hgb ≥ 10 and < 12 g/dL	
	MMB (N = 104)	BAT (N = 52)	MMB (N = 66)	BAT (N = 39)	MMB (N = 27)	BAT (N = 7)
Primary efficacy endpoint						
SRR (reduction in spleen volume ≥ 35% from baseline) at week 24						
Responder, n (%)	7 (6.7%)	3 (5.8%)	6 (9.1%)	2 (5.1%)	1 (3.7%)	0
Exact 95% CI [1]	2.75, 13.38	1.21, 15.95	3.41, 18.74	0.63, 17.32	0.09, 18.97	0.00, 40.96
Superiority proportion difference, % (95% CI) [2]	1 (-9, 10)		4 (-16, 23)		4 (-38, 44)	
p-value	0.90					

1. Secondary endpoint of MPN-SAF TSS response rate at Week 24

SIMPLIFY-1 study

Table 58: MPN-SAF TSS Response Rate and Change from baseline at Week 24 (ITT population and Hgb < 10 g/dL subgroup, SIMPLIFY-1)

	Hgb <10 g/dL Subgroup		ITT Population	
	MMB (N = 86)	RUX (N = 95)	MMB (N = 215)	RUX (N = 217)
TSS Response Rate at Week 24				
Evaluable at week 24, n	84	94	211	211
Responder, n (%)	**21 (25.0)**	**34 (36.2)**	**60 (28.4)**	**89 (42.2)**
Exact 95% CI [1]	16.19, 35.64	26.51, 46.73	22.45, 35.03	35.43, 49.15
Superiority proportion difference, % (95% CI)	-12 (-26, 2)		-14 (-23, -5)	
p-value	na		0.9985 [2]	
Noninferiority proportion difference, % (95% CI)	0 (-12, 12) [3]		0 (-8, 8) [3]	
p-value	na		0.98	
Non-responders	63 (75.0)	60 (63.8)	151 (71.6)	122 (57.8)
Last TSS date before day 162	16 (19.0)	8 (8.5)	31 (14.7)	12 (5.7)
Last participation date on day 162 or later but TSS at week 24 not available	3 (3.6)	6 (6.4)	5 (2.4)	9 (4.3)
Increase from baseline > 0% at week 24	17 (20.2)	13 (13.8)	47 (22.3)	32 (15.2)
Reduction from baseline < 50% at week 24	43 (51.2)	46 (48.9)	114 (54.0)	101 (47.9)
TSS Change From Baseline at Week 24 [4]				
Baseline				
n	85	94	213	214
Mean (SD)	19.0 (13.72)	18.1 (11.84)	19.4 (13.18)	17.9 (11.47)
Week 24				
LS mean (SE)	-5.06 (0.94)	-6.68 (0.82)	-5.87 (0.93)	-7.11 (0.91)
LS mean difference (SE)	1.62 (1.25)		1.24 (0.83)	
95% CI	-0.85, 4.09		-0.40, 2.88	
p-value	na		0.1380	

SIMPLIFY-2 study

Table 59: MPN-SAF TSS Response Rate at Week 24 (ITT population and anemia subgroups, SIMPLIFY-2)

TSS Response Rate at Week 24	ITT Population		Hgb < 10 g/dL		Hgb ≥ 10 and < 12 g/dL	
	MMB (N = 104)	BAT (N = 52)	MMB (N = 66)	BAT (N = 39)	MMB (N = 27)	BAT (N = 7)
Evaluable at week 24, n	103	51	65	38	27	7
Responder, n (%)	27 (26.2%)	3 (5.9%)	21 (32.3%)	1 (2.6%)	5 (18.5%)	1 (14.3%)
Exact 95% CI [1]	18.04, 35.80	1.23, 16.24	21.23, 45.05	0.07, 13.81	6.30, 38.08	0.36, 57.87
Proportion difference, % (95% CI) [2]	20 (9, 32)		30 (10, 48)		4 (-38, 44)	
p-value	< 0.001					
Nonresponder, n (%)	76 (73.8%)	48 (94.1%)	44 (67.7%)	37 (97.4%)		
Last TSS date before day 162	28 (27.2%)	10 (19.6%)	18 (27.7%)	7 (18.4%)		
Last participation date on day 162 or later but TSS at week 24 not available	3 (2.9%)	3 (5.9%)	1 (1.5%)	3 (7.9%)		
Increase from baseline > 0% at week 24	25 (24.3%)	23 (45.1%)	15 (23.1%)	17 (44.7%)		
Reduction from baseline < 50% at week 24	45 (43.7%)	34 (66.7%)	25 (38.5%)	26 (68.4%)		

2. Secondary endpoint of transfusion independence (TI) rate and transfusion dependence rate (TD) rate at Week 24

SIMPLIFY-1 study

Table 60: TI rate and TD rate at Week 24 (ITT population and Hgb < 10 g/dL subgroup, SIMPLIFY-1)

	Hemoglobin <10 g/dL Subgroup		Overall ITT Population SIMPLIFY-1	
	MMB (N = 86)	RUX (N = 95)	MMB (N = 215)	RUX (N = 217)
TI Rate at Week 24				
Responder, n (%)	**40 (46.5)**	**26 (27.4)**	**143 (66.5)**	**107 (49.3)**
Exact 95% CI [1]	35.68, 57.59	18.72, 37.48	59.78, 72.79	42.48, 56.16
Superiority proportion difference, % (95% CI)	22.00 (9.0, 36.0)		18 (9, 26)	
p-value	na		< 0.001 (nominal)	
TD Rate at Week 24				
Responder, n (%)	**41 (47.7)**	**58 (61.1)**	**65 (30.2)**	**87 (40.1)**
Exact 95% CI [1]	36.79, 58.73	50.50, 70.89	24.17, 36.85	33.52, 46.94
Superiority proportion difference, % 95% (CI), stratified CMH method	-16 (-30, -2)		-10 (-19, -2)	
p-value	na		0.019 (nominal)	

SIMPLIFY-2 study

Table 61: TI rate at Week 24 (ITT population and anemia subgroups, SIMPLIFY-2)

Endpoint	ITT Population		Hgb < 10 g/dL		Hgb ≥ 10 and < 12 g/dL	
	MMB (N = 104)	BAT (N = 52)	MMB (N = 66)	BAT (N = 39)	MMB (N = 27)	BAT (N = 7)
Transfusion independence rate at week 24						
Responder, n (%)	45 (43.3%)	11 (21.2%)	22 (33.3%)	5 (12.8%)	16 (59.3%)	2 (28.6%)
Exact 95% CI [1]	33.59, 53.35	11.06, 34.70	22.20, 46.01	4.30, 27.43	38.80, 77.61	3.67, 70.96
Proportion difference, % (95% CI) [2]	20 (9, 32)		21 (1, 39)		31 (-12, 71)	
p-value	0.001					

Table 62: TD rate at Week 24 (ITT population and anemia subgroups, SIMPLIFY-2)

Endpoint	ITT Population		Hgb < 10 g/dL		Hgb ≥ 10 and < 12 g/dL	
	MMB (N = 104)	BAT (N = 52)	MMB (N = 66)	BAT (N = 39)	MMB (N = 27)	BAT (N = 7)
Transfusion dependence rate at week 24						
Dependent, n (%)	52 (50.0%)	33 (63.5%)	39 (59.1%)	28 (71.8%)	9 (33.3%)	4 (57.1%)
Exact 95% CI [1]	40.03, 59.97	48.96, 76.38	46.29, 71.05	55.13, 85.00	16.52, 53.96	18.41, 90.10
Proportion difference (95% CI) [2]	-13 (-29, 3)		-13 (-32, 7)		-24 (-61, 17)	
p-value	0.10					

The proportion of subjects with Hgb responses (ie, increases of ≥ 1, ≥ 1.5, or ≥ 2 g/dL from baseline)

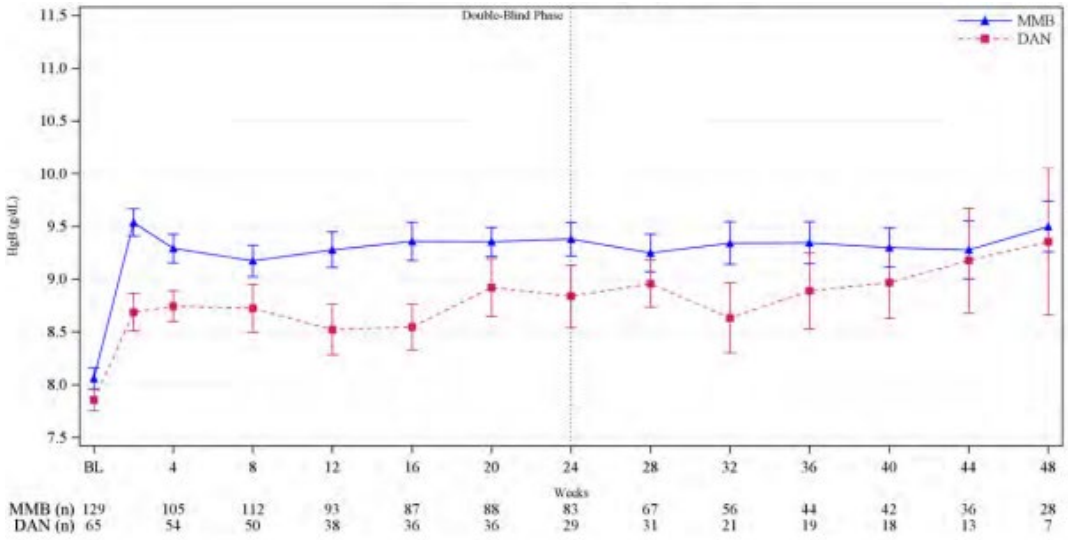
MOMENTUM

Table 63: Rates of Hemoglobin Response Defined as ≥ 1, ≥ 1.5, or ≥ 2 g/dL Increases From Baseline During the 24-Week Randomized Treatment Period (ITT population, MOMENTUM)

Hgb Response Rate	MOMENTUM	
	MMB	DAN
Entire 24-week RT period		
ITT population, N	130	65
Increase of ≥ 1 g/dL	69 (53.1%)	22 (33.8%)
Exact 95% CI [1]	44.13, 61.88	22.57, 46.65
Proportion difference, % (95% CI)	**19.00** (4.68, 33.32)	
p-value	0.0124	
Increase of ≥ 1.5 g/dL	52 (40.0%)	15 (23.1%)
Exact 95% CI [1]	31.51, 48.95	13.53, 35.19
Proportion difference, % (95% CI)	**15.68** (2.47, 28.90)	
p-value	0.0282	
Increase of ≥ 2 g/dL	38 (29.2%)	13 (20.0%)
Exact 95% CI [1]	21.59, 37.85	11.10, 31.77
Proportion difference, % (95% CI)	**6.97** (-5.41, 19.35)	
p-value	0.2844	

Hgb Response Rate	MOMENTUM	
	MMB	DAN
Last 12 weeks of RT period		
ITT population, N	130	65
Increase of ≥ 1 g/dL	50 (38.5%)	17 (26.2%)
Increase of ≥ 1.5 g/dL	38 (29.2%)	12 (18.5%)
Increase of ≥ 2 g/dL	28 (21.5%)	8 (12.3%)

Hemoglobin values within 4 weeks post-transfusion were excluded. Proportion differences were analyzed using the stratified CMH method. [1]Exact binomial CI for MOMENTUM.



Subjects treated with DAN during the 24-week randomized treatment period crossed over to MMB for open-label treatment.

Figure 14: Mean (±SE) Hemoglobin Levels Over Time (ITT Population, MOMENTUM)

SIMPLIFY-2

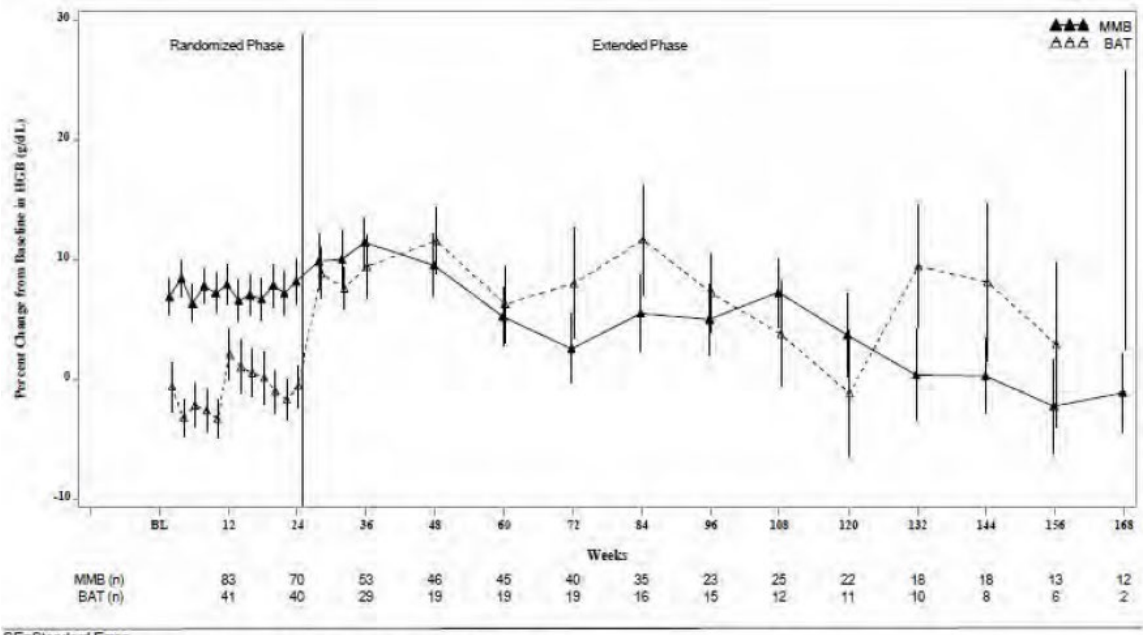
Table 64: Hemoglobin Increases at Week 24 (ITT Population, SIMPLIFY-2)

	Intent-to-Treat Analysis Set	
	MMB (N = 104)	BAT (N = 52)
Increase of ≥ 0.5 g/dL at Week 24 excluding 4 week post-transfusion		
Including missing response, n	104	52
Yes	49 (47.1%)	13 (25.0%)
No	26 (25.0%)	27 (51.9%)
Missing	29 (27.9%)	12 (23.1%)
Excluding Missing Response, n	75	40
Yes	49 (63.3%)	13 (32.5%)
No	26 (34.7%)	27 (67.5%)
Increase of ≥ 1 g/dL at Week 24 excluding 4 week post-transfusion		
Including missing response, n	104	52
Yes	36 (34.6%)	10 (19.2%)
No	39 (37.5%)	30 (57.7%)
Missing	29 (27.9%)	12 (23.1%)
Excluding missing response, n	75	40
Yes	36 (48.0%)	10 (25.0%)
No	39 (52.0%)	30 (75.0%)
Increase of ≥ 1.5 g/dL at Week 24 excluding 4 week post-transfusion		
Including missing response, n	104	52
Yes	27 (26.0%)	4 (7.7%)
No	48 (46.2%)	36 (69.2%)
Missing	29 (27.9%)	12 (23.1%)
Excluding missing response, n	75	40
Yes	27 (36.0%)	4 (10.0%)
No	48 (64.0%)	36 (90.0%)
Increase of ≥ 2 g/dL at Week 24 excluding 4 week post-transfusion		
Including missing response, n	104	52
Yes	17 (16.3%)	0
No	58 (55.8%)	40 (76.9%)
Missing	29 (27.9%)	12 (23.1%)
Excluding missing response, n	75	40
Yes	17 (22.7%)	0
No	58 (77.3%)	40 (100%)

Haemoglobin increase: at least 1 increase versus baseline, in the 12 weeks before Week 24 excluding all hemoglobin values 4 weeks post-transfusion Abbreviations: BAT = best available therapy; MMB = momelotinib; RT = Randomized

Haemoglobin increases at Week 24 versus baseline was a post hoc exploratory analysis in which haemoglobin increases were categorized into ⩾ 0.5, ⩾ 1, ⩾ 1.5, and ⩾ 2 g/dL. Haemoglobin values within 4 weeks post-transfusion were removed to avoid confounding transfusion-induced increases in haemoglobin.

Mean percent changes in haemoglobin over time are depicted for both treatment phases in Figure below.

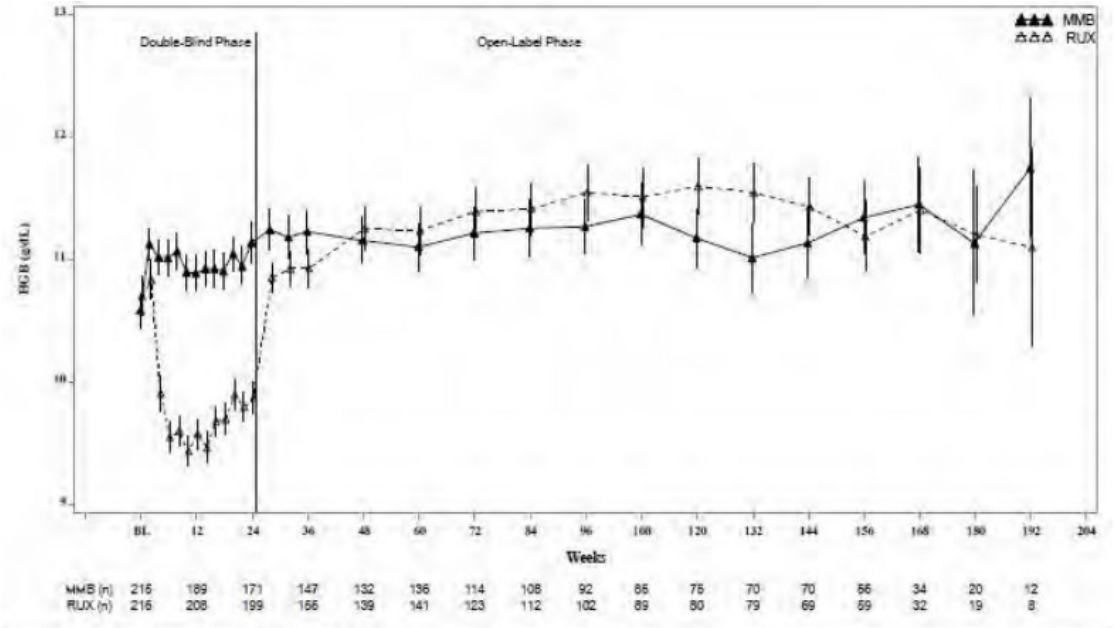


SE=Standard Error;
For efficacy analyses of Hgb, assessments from both central and local labs are included.
Source: Table 15.12.6.14.1, 15.12.6.14.2, Listing 16.2.8.1.1

Data Extracted: CRF data: 25JUN2019
Source: ...\version3\prog\g-adhoc-line-comb.sas v9.4 Output file: adhoc-g-se-hgb-db-ol.out 17JUL2020:00:54

Figure 15: Mean (± SE) Plot of Hemoglobin, Change and Percent Change from Baseline Over Time in the RT and ET Phases (Intent-to-Treat Analysis Set, SIMPLIFY-2)

SIMPLIFY-1



Source: Table 15.12.6.14.1, 15.12.6.14.2, Listing 16.2.8.1.1

Data Extracted: CRF data: 01JUL2019
Source: ...\version3\prog\g-adhoc-line-comb.sas v9.4 Output file: adhoc-g-se-hgb-db-ol.out 21SEP2020:12:19

Figure 16: Mean (±SE) Hemoglobin Levels Over Time (ITT Population, SIMPLIFY-1)

At baseline, the mean (median) hemoglobin level was 10.6 g/dL (10.5 g/dL) in the MMB group and 10.7 g/dL (10.3 g/dL) in the RUX group. MMB induced a rapid increase in Hgb levels that was maintained over time. In the RUX group, mean hemoglobin level decreased, reaching a nadir at week 8 – 12, after which mean hemoglobin level showed a recovering trend, however did not completely recover by Week 24. Beyond week 24, with the majority of patients crossed over to MMB treatment, hemoglobin levels reached and exceeded the mean baseline level.

The proportion of subjects with Hgb responses (ie, increases of ≥ 1, ≥ 1.5, or ≥ 2 g/dL from baseline) (exploratory and post-hoc analysis)

Table 65: Rates of Hemoglobin Response Defined as ≥0.5, ≥ 1, ≥ 1.5, or ≥ 2 g/dL Increases From Baseline During the 24-Week Randomized Treatment Period (ITT population and TI population, SIMPLIFY-1)

	SIMPLIFY-1	
Hgb Response Rate	**MMB**	**RUX**
Last 12 weeks of RT period		
ITT population, N	215	217
Missing	34 (15.8%)	14 (6.5%)
Increase of ≥ 0.5 g/dL	111 (51.6%)	45 (20.7%)
Increase of ≥ 1 g/dL	80 (37.2%)	36 (16.6%)
Increase of ≥ 1.5 g/dL	51 (23.7%)	25 (11.5%)
Increase of ≥ 2 g/dL	36 (16.7%)	13 (6.0%)
TI at baseline, n	147	152
Missing	20 (13.6%)	6 (3.9%)
Increase of ≥ 0.5 g/dL	74 (50.3%)	24 (15.8%)
Increase of ≥ 1 g/dL	49 (33.3%)	18 (11.8%)
Increase of ≥ 1.5 g/dL	29 (19.7%)	12 (7.9%)
Increase of ≥ 2 g/dL	18 (12.2%)	3 (2.0%)

Hemoglobin values within 4 weeks post-transfusion were excluded.
Proportion differences were analyzed using the stratified CMH method.

The proportion of subjects with increased Hgb from baseline during the 12 weeks before week 24 was consistently higher in each incremental category in the MMB group versus the RUX group for the ITT population and the subgroup of subjects with TI at baseline.

- Proportion of TI at Week 24 in subjects with baseline TD (subgroup analysis):

  Around a quarter of subjects [24.7% MMB (n = 53), 24.0% RUX (n = 52)] were TD at baseline (requiring ≥ 4 RBC or whole blood transfusion units or a hemoglobin < 8 g/dL in the 8 weeks before randomization, excluding cases associated with clinically overt bleeding). A greater proportion of subjects with baseline TD in the MMB group converted to TI at week 24 compared with the RUX group: 30.2% (n = 16) vs 17.3% (n = 9). The treatment difference was 13% (95% CI: -3, 30).

- Proportion of patients with zero RBC transfusions during the randomized treatment period (post-hoc analysis): a greater proportion of the MMB group had zero transfusions through week 24 compared with RUX (73% vs 46%)

- Proportion of patients with ≤4 RBC transfusions during the randomized treatment period (post-hoc analysis): the proportion of subject with 4 or fewer units transfused up to Week 24 were 83% (MMB) and 62% (RUX).

In the Hgb <10 g/dL subgroup, the Hgb levels were consistently higher in the MMB group compared to the RUX group throughout the entire randomized treatment period. Treatment with MMB resulted in a >0.5 g/dL increase in mean Hgb levels by Week 2 that remained stable and above baseline levels over the 24-week treatment period. In the RUX Hgb <10 g/dL subgroup in SIMPLIFY-1, there was a modest increase in Hgb levels by Week 2 (<0.5 g/dL). Following this, Hgb levels decreased to a new nadir around Week 4 that remained stable with a characteristic recovery that returned Hgb to baseline levels by Week 24. Recall however that 61.1% of the RUX group were transfusion dependent by week 24. The RUX effect on Hgb levels in the Hgb <10 g/dL subgroup were not consistent with the overall ITT population, in which Hgb levels remained below baseline, possibly due to the confounding factor of transfusions and/or RUX dose adjustments.

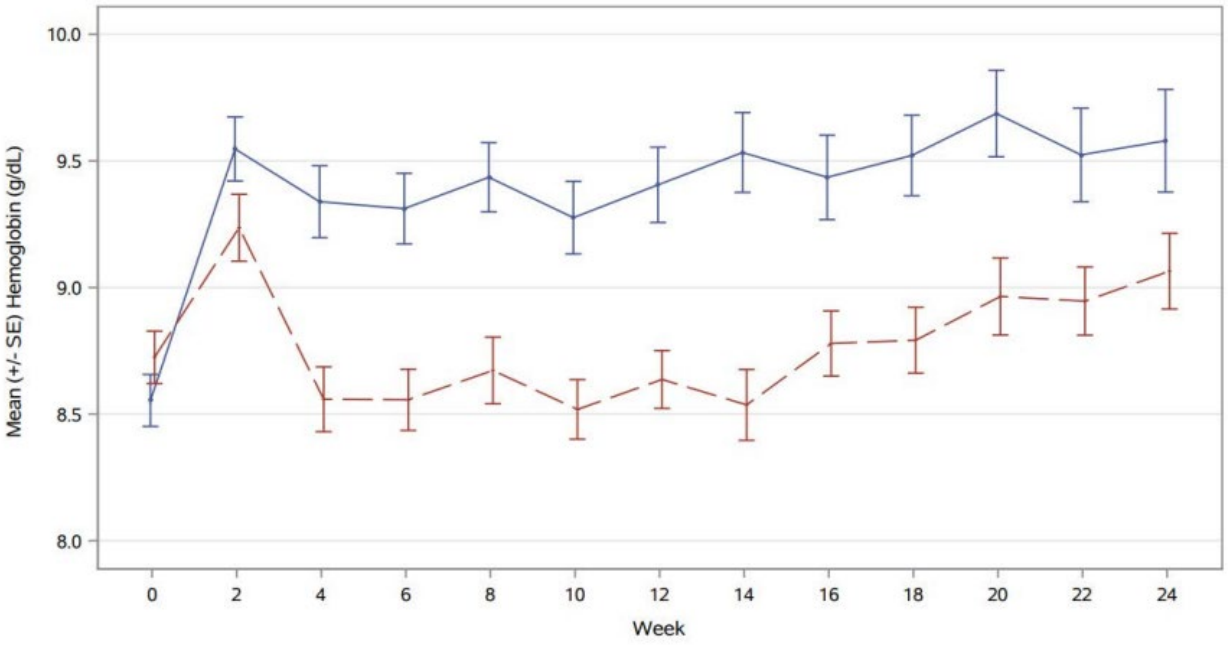


Figure 17: Mean (±SE) Hemoglobin Levels Over Time during the double-blind phase (Hgb < 10 g/dL subpopulation, SIMPLIFY-1)

Post-hoc subgroup analysis in function of baseline hemoglobin < 10 g/dL, ≥ 10 g/dL and < 12 g/dL, < 12 g/dL, ≥ 12 g/dL; TSS ≥ 10; TSS ≥ 10 AND hemoglobin < 10 g/dL; platelet count ≤ 150,> 150 and ≤ 300, > 300 x 10^9/L

Table 66: Post-hoc subgroup analyses of SRR, MPN-SAF TSS and TI rate at Week 24 (ITT-population, SIMPLIFY-1)

Subgroup	SIMPLIFY-1	
	MMB (N = 215)	RUX (N = 217)
SRR at Week 24		
Overall splenic responders	57 (26.5%)	64 (29.5%)
BL Hgb category		
< 10 g/dL	27/86 (31.4%)	31/95 (32.6%)
≥ 10 and < 12 g/dL	19/73 (26.0%)	17/69 (24.6%)
< 12 g/dL	46/159 (28.9%)	48/164 (29.3%)
≥ 12 g/dL	11/56 (19.6%)	16/53 (30.2%)
BL TSS Category		
TSS ≥ 10	38/152 (25.0%)	43/149 (28.9%)
TSS ≥ 10 AND hemoglobin < 10 g/dL	17/59 (28.8%)	22/65 (33.8%)
BL transfusion status		
TI	41/147 (27.9%)	46/152 (30.3%)
Non-TI	16/68 (23.5%)	18/65 (27.7%)
TD	12/53 (22.6%)	15/52 (28.8%)
BL platelet count (× 10^9/L)		
≥ 50 and ≤ 150	11/47 (23.4%)	2/57 (3.5%)
> 150 and ≤ 300	31/89 (34.8%)	23/71 (32.4%)
> 300	15/79 (19.0%)	39/89 (43.8%)
TSS Response Rate at Week 24		
Overall evaluable TSS responders	60/211 (28.4%)	89/211 (42.2%)
BL Hgb category		
< 10 g/dL	21/84 (25.0%)	34/94 (36.2%)
≥ 10 and < 12 g/dL	25/71 (35.2%)	29/64 (45.3%)
< 12 g/dL	46/155 (29.7%)	63/158 (39.9%)
≥ 12 g/dL	14/56 (25.0%)	26/53 (49.1%)
BL TSS Category		
TSS ≥ 10	50/152 (32.9%)	64/149 (43.0%)
TSS ≥ 10 AND hemoglobin < 10 g/dL	15/59 (25.4%)	21/65 (32.3%)
BL transfusion status		
TI	45/146 (30.8%)	66/148 (44.6%)
Non-TI	15/65 (23.1%)	23/63 (36.5%)
TD	12/51 (23.5%)	20/50 (40.0%)
BL platelet count (× 10^9/L)		
≥ 50 and ≤ 150	13/45 (28.9%)	19/57 (33.3%)
> 150 and ≤ 300	29/88 (33.0%)	29/69 (42.0%)
> 300	18/78 (23.1%)	41/85 (48.2%)
TI Rate at Week 24		
Overall TI responders	143 (66.5%)	107 (49.3%)
BL Hgb category		
< 10 g/dL	40/86 (46.5%)	26/95 (27.4%)
≥ 10 and < 12 g/dL	59/73 (80.8%)	35/69 (50.7%)
< 12 g/dL	99/159 (62.3%)	61/164 (37.2%)
≥ 12 g/dL	44/56 (78.6%)	46/53 (86.8%)
BL TSS Category		
TSS ≥ 10	100/152 (65.8%)	76/149 (51.0%)
TSS ≥ 10 AND hemoglobin < 10 g/dL	25/59 (42.4%)	18/65 (27.7%)
BL transfusion status		
TI	119/147 (81.0%)	94/152 (61.8%)
Non-TI	24/68 (35.3%)	13/65 (20.0%)
TD	16/53 (30.2%)	9/52 (17.3%)
BL platelet count (× 10^9/L)		
≥ 50 and ≤ 150	29/47 (61.7%)	24/57 (42.1%)
> 150 and ≤ 300	64/89 (71.9%)	38/71 (53.5%)
> 300	50/79 (63.3%)	45/89 (50.6%)

Analyses of changes in individual symptom item scores from baseline at Week 24

- **MOMENTUM study**: analysis of change in MFSAF individual symptom item scores from baseline at Week 24:

Table 67: Treatment Differences in Change in MFSAF Individual Item Scores From Baseline at Week 24 (ITT population, MOMENTUM)

MFSAF Individual Item Score	LS Mean Difference (95% CI) [1]	p-value [2]
Disease-related fatigue	-0.71 (-1.42, 0.00)	0.0513
Night sweats	-1.27 (-2.00, -0.53)	0.0009
Itching	-0.31 (-1.14, 0.51)	0.4546
Abdominal discomfort	-1.11 (-1.91, -0.31)	0.0068
Rib pain	-0.80 (-1.54, -0.05)	0.0363
Fullness	-0.78 (-1.58, 0.01)	0.0530
Bone pain	-1.19 (-1.92, -0.46)	0.0016

[1] Based on MMRM adjusted for baseline MFSAF TSS (< 22 vs ≥ 22), baseline palpable spleen length below the left costal margin (< 12 cm vs ≥ 12 cm), and baseline RBC or whole blood units transfused in the 8-week period before randomization (0, 1-4, ≥ 5 units). [2] p-value for the least squares mean difference between the 2 arms from the MMRM.

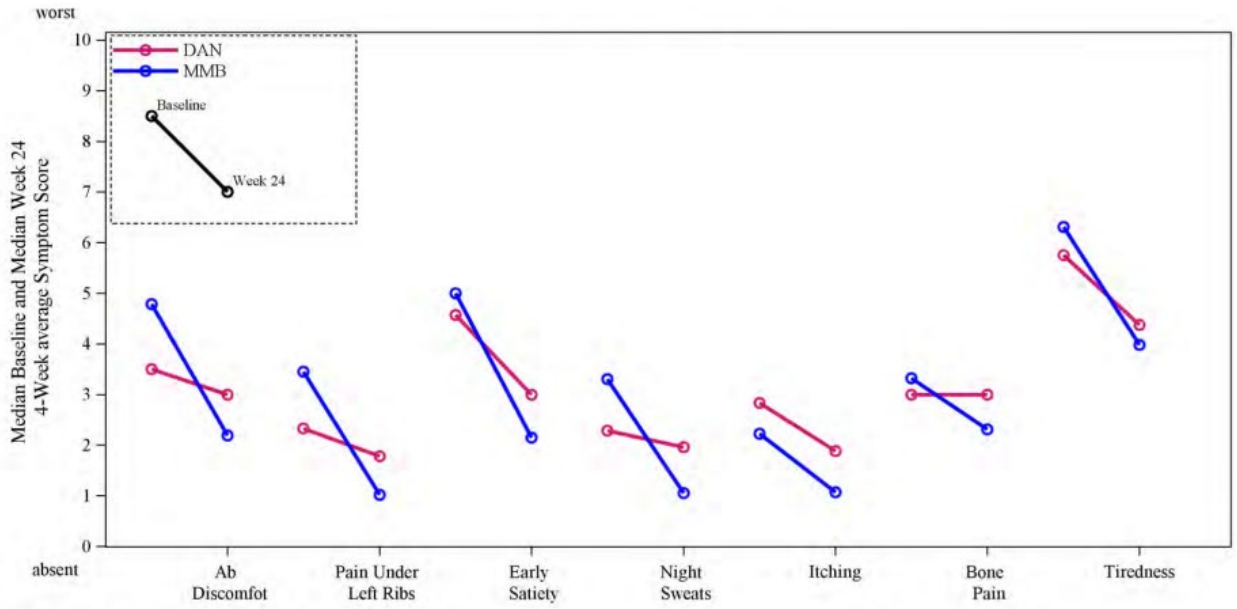


Figure 18: Median Individual MFSAF Symptom Scores at Baseline and Week 24 (ITT Population, MOMENTUM)

Reductions (improvements) in MFSAF individual item scores from baseline at week 24 were greater in the MMB than in the DAN group based on the MMRM analysis, with the greatest treatment differences noted in night sweats, abdominal discomfort, bone pain, and rib pain, favouring MMB ($p < 0.05$).

Table 68: Change From Baseline at Week 24 in Disease-Related Fatigue, Cancer-Related Fatigue, and Subject-Reported Physical Function (ITT population, MOMENTUM)

Change From Baseline at Week 24	MMB (N = 130)	DAN (N = 65)
Disease-Related Fatigue by MFSAF		
Baseline MFSAF fatigue item score, mean (SD)	6.20 (2.14)	5.77 (2.08)
Change from baseline at week 24		
Least squares mean (SE) [1]	-1.53 (0.20)	-0.82 (0.31)
Least squares mean difference (SE) [1]	-0.71 (0.36)	
95% CI [1]	-1.42, 0.00	
p-value [2]	0.0513	
Cancer-related fatigue by EORTC QLQ-C30		
Baseline EORTC QLQ-C30 fatigue item score, mean (SD)	63.82 (24.07)	55.38 (24.81)
Change from baseline at week 24		
Least squares mean (SE) [1]	-14.34 (2.35)	-3.52 (3.65)
Least squares mean difference (SE) [1]	-10.82 (4.21)	
95% CI [1]	-19.15, -2.48	
p-value [2]	0.0113	
Subject-reported physical function by PROMIS		
Baseline PROMIS physical function score, mean (SD)	32.49 (9.55)	34.38 (10.45)
Change from baseline at week 24		
Least squares mean (SE) [1]	1.19 (0.77)	-0.11 (1.21)
Least squares mean difference (SE) [1]	1.31 (1.42)	
95% CI [1]	-1.49, 4.11	
p-value [2]	0.3570	

[1] Based on MMRM adjusted for baseline MFSAF TSS (< 22 vs ≥ 22), baseline palpable spleen length below the left costal margin (< 12 cm vs ≥ 12 cm), and baseline RBC or whole blood units transfused in the 8-week period before randomization (0, 1-4, ≥ 5 units). [2] p-value for the least squares mean difference between the 2 groups from the MMRM

- **SIMPLIFY-1 study**: analysis of change in MFSAF individual symptom item scores from baseline at Week 24 from the modified MPN SAF TSS v2.0 (post-hoc analysis):

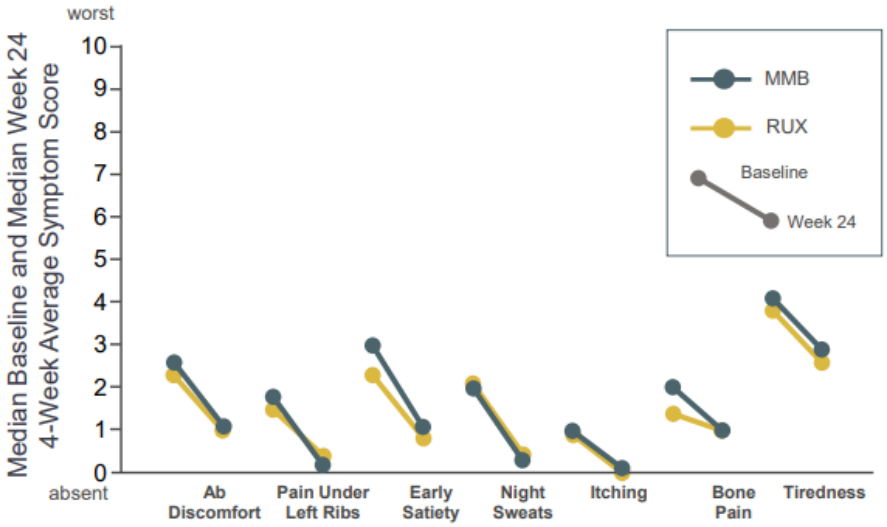


Figure 19: Median Individual MPN-SAF Symptom Scores at Baseline and Week 24 (ITT Population, SIMPLIFY-1)

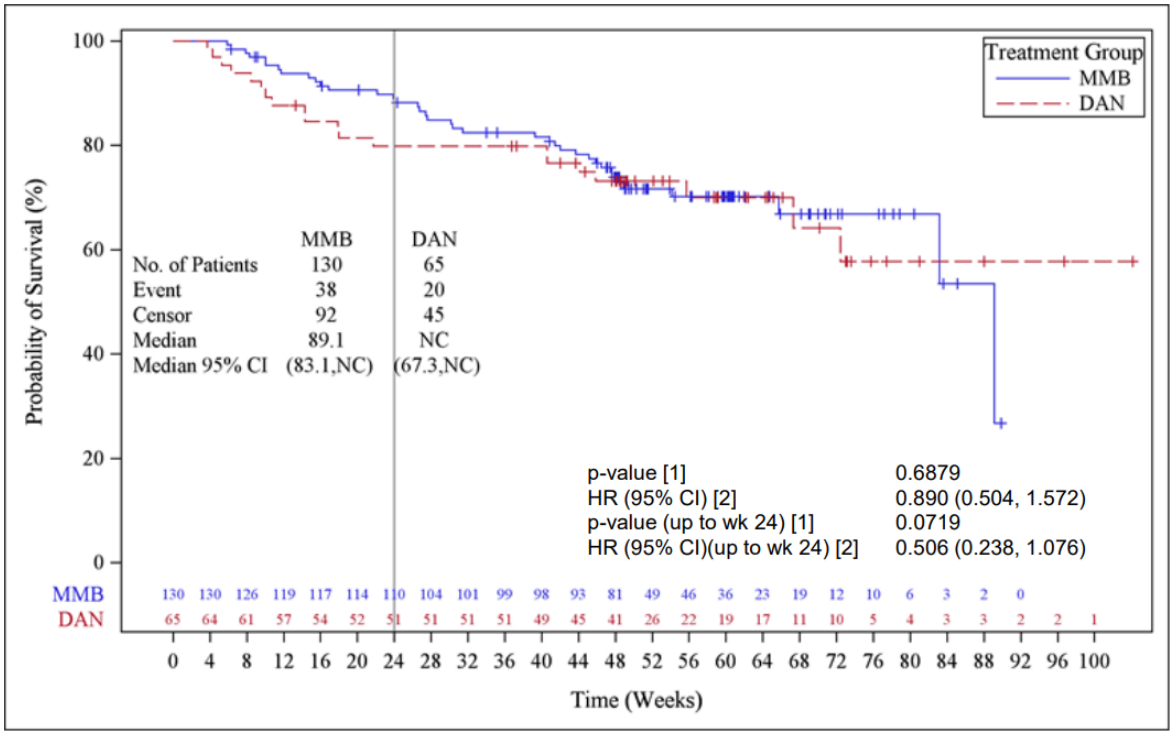
Overall survival

In MOMENTUM trial, OS was a prespecified secondary endpoint. As of database lock date of 17 Jan 2023, during the entire study period (randomized and open-label treatment period), a total of 58 events (deaths) occurred in 38 subjects (29.2%) from the former randomized MMB group and 20 subjects (30.8%) from the former DAN group.

Table 69: Overall survival (ITT population, MOMENTUM)

	MOMENTUM (ITT Population)	
Overall Survival	**MMB (N = 130)**	**DAN (N = 65)**
Median follow-up [1]	393.00 days (1.1 y)	377.00 days (1.0 y)
Event (death), n (%)	38 (29.2%)	20 (30.8%)
Censored, n (%)	92 (70.8%)	45 (69.2%)
Kaplan-Meier estimate overall		
Median (95% CI)	624.0 (582.0 [1.6 y, NC)	NC (471.0 days [1.3 y], NC)
Min, max	41, 629+ days (0.11, 1.7 y)	26, 729+ days (0.07, 2.0 y)
Hazard ratio (95% CI) [2]	**0.890 (0.504, 1.572)**	
p-value [3]	0.6879	
Overall survival up to week 24		
Hazard ratio (95% CI) [3]	0.506 (0.238, 1.076)	
p-value [3]	0.0719	

[1] By reverse Kaplan-Meier method for MOMENTUM. Based on the safety population for SIMPLIFY-1.
[2] From a stratified Cox proportional hazards model. [3] From a stratified log-rank test.



Vertical line at week 24 indicates when ongoing subjects received MMB as open-label treatment.+ indicates a censored observation. [1] From a stratified log-rank test. [2] Hazard ratio (MMB vs DAN) was from a stratified Cox proportional hazards model with a single factor of treatment group and baseline MFSAF total symptom score (< 22 vs ≥ 22), baseline palpable spleen length below the left costal margin (< 12 vs ≥ 12 cm), and baseline red blood cell or whole blood units transfused in the 8-week period before randomization (0, 1-4, ≥ 5 units) as strata

Figure 20: Kaplan-Meier Plot of Overall Survival (ITT Population, MOMENTUM)

In SIMPLIFY-2 trial, Overall Survival was a prespecified exploratory endpoint.

Table 70: Overall Survival for the Combined RT and ET Phases (Safety Analysis Set, SIMPLIFY-2)

	Week 24 Interim Analysis		Week 48 Interim Analysis		Final Analysis	
	MMB (N = 104)	**BAT (N = 52)**	**MMB (N = 104)**	**BAT (N = 52)**	**MMB (N = 104)**	**BAT (N = 52)**
Subjects with events						
Death, n (%)	**14 (13.5%)**	**11 (21.2%)**	**34 (32.7%)**	**19 (36.5%)**	**46 (44.2%)**	**23 (44.2%)**
Subjects died in the RT Phase	6 (42.9%)	5 (45.5%)	6 (17.6%)	5 (26.3%)	6 (13.0%)	5 (21.7%)
Subjects died in ET Phase	5 (35.7%)	2 (18.2%)	11 (32.4%)	4 (21.1%)	14 (30.4%)	4 (17.4%)
Subjects died in follow-up	3 (21.4%)	4 (36.4%)	17 (50.0%)	10 (52.6%)	26 (56.5%)	14 (60.9%)
Subjects censored, n (%)	90 (86.5%)	41 (78.8%)	70 (67.3%)	33 (63.5%)	58 (55.8%)	29 (55.8%)
Kaplan-Meier estimate of overall survival (months)						
25-percentile (95% CI)	NR (11.47, NR)	15.77 (5.91, 16.39)	18.69 (11.47, 23.82)	12.19 (5.91, 21.29)	18.69 (11.47, 23.82)	12.19 (5.91, 22.34)
Median (95% CI)	NR	15.77 (15.77, 16.39)	27.70 (24.28, NR)	NR (20.27, NR)	34.33 (27.33, NR)	37.52 (21.29, NR)
75-percentile (95% CI)	NR	16.39 (15.77, 16.39)	NR	NR	NR	NR
Min, Max	0.30, 24.15	0.43, 16.39	0.30, 37.65	0.43, 29.01	0.30, 50.40	0.43, 44.32
Stratified log-rank test p-value	**0.24**		**0.47**		**0.86**	
Stratified Hazard Ratio (95% CI)	0.62 (0.28, 1.38)		0.81 (0.45, 1.44)		0.96 (0.58, 1.59)	

Death in RT Phase is death occurring on or after the first RT dose up to the earliest of the last RT dose + 30 days, or the first ET dose -1 day. Death in the ET Phase is death occurring on or after the first ET dose up to the last ET MBB dose + 30 days. Death in the Follow-up Phase is death occurring after 30 days of the last dose in RT or ET Phases, whichever was latest. Overall survival (months) = (date of death or censoring – date of first dose in the RT Phase + 1) / 30.4375.

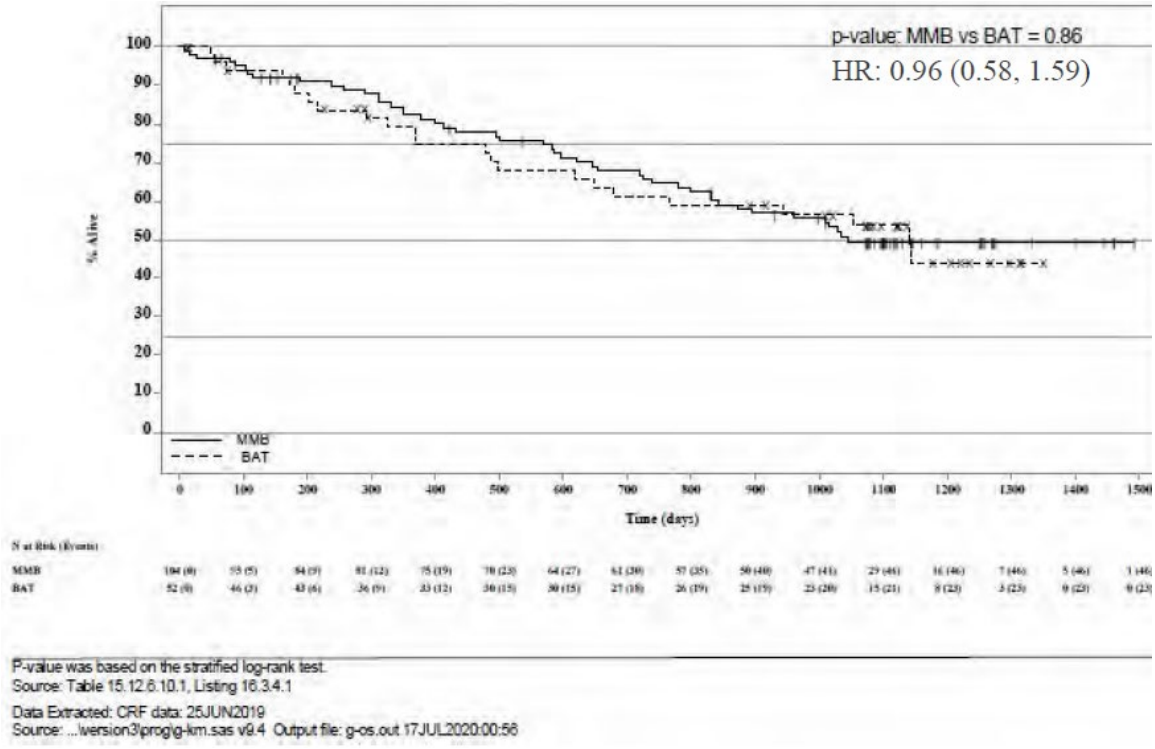


Figure 21: Kaplan-Meier Plot of Overall Survival (Safety Analysis Set, SIMPLIFY-2)

In SIMPLIFY 1 trial, overall survival analysis (exploratory endpoint) is based on safety population (1 subject in each treatment group was randomized but not treated, and therefore included in ITT analysis set but not in Safety analysis set). OS data presented below are derived from follow-up data from XAP as of the data cutoff date of 03 Dec 2021.

During the entire period, a total of 140 events (deaths) occurred in 67 subjects (31.3%) from the former randomized MMB group and 73 subjects (33.8%) from the former RUX group as of the data cutoff date of 03 Dec 2021. The hazard ratio was estimated as 1.03 (95% CI: 0.74, 1.44; log-rank test p = 0.8646). The median Kaplan-Meier estimate of OS was not reached in either group. As less than 7 subjects were followed when the median was estimated for the RUX group, the result should be interpreted with caution. The 1-, 2-, and 3-year survival rates in the MMB group were approximately 93%, 82% and 71%.

Table 71: Overall survival (Safety Analysis Set, SIMPLIFY-1, DCO of 03 Dec 2021)

	Week 24 Analysis (data cut-off date of 12 Sep 2016)		**Follow-up data from XAP as of the data cutoff date of 03 Dec 2021**	
Overall Survival	**MMB (N = 214)**	**RUX (N = 216)**	**MMB (N = 214)**	**RUX (N = 216)**
Median follow-up [1]			3.43 y	3.47 y
Event (death), n (%)	14 (6.5%)	19 (8.8%)	67 (31.3%)	73 (33.8%)
Censored, n (%)	200 (93.5%)	197 (91.2%)	147 (68.7%)	143 (66.2%)
Kaplan-Meier estimate overall				
Median (95% CI)	NR	NR	NR (4.73 y, NR)	NR (4.94 y, NR)
Min, max	0.72, 29.63 mo	0.36, 29.83 mo	0.06, 7.53 y	0.03, 7.35 y
Hazard ratio (95% CI) [2]	0.80 (0.40, 1.59)		1.03 (0.74, 1.44)	
p-value [3]	0.52		0.8646	

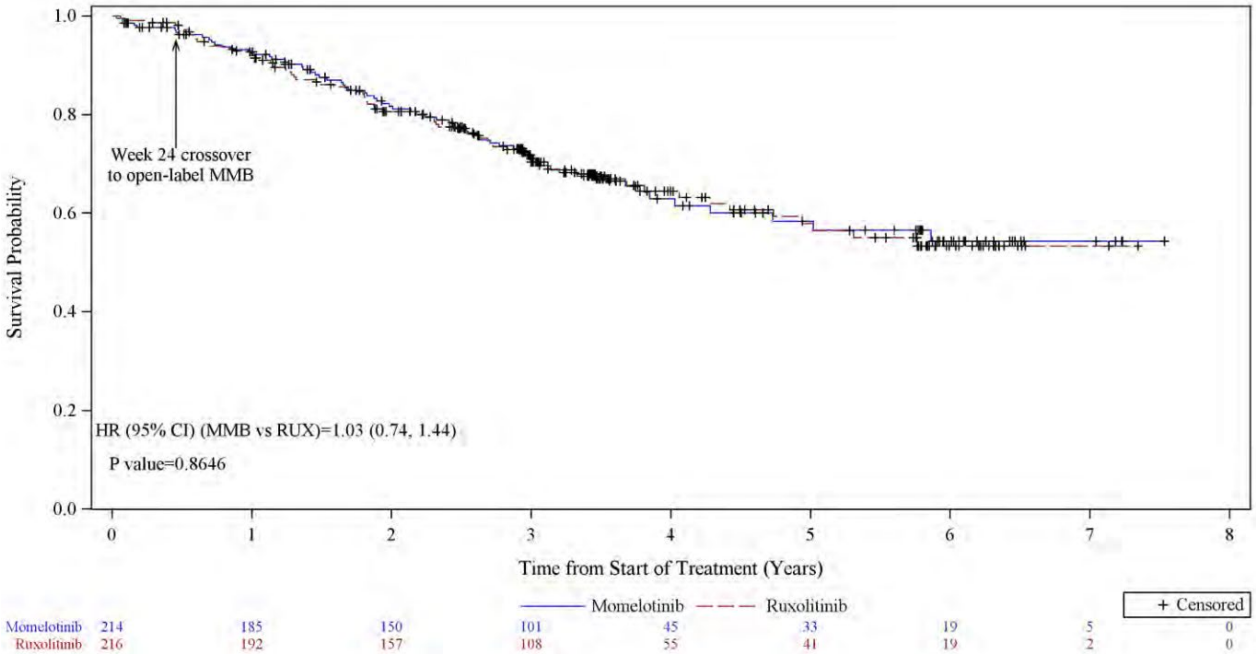


Figure 22: Kaplan-Meier Plot of Overall Survival (Safety Analysis Set, SIMPLIFY-1, data cut-off date of 03 Dec 2021)

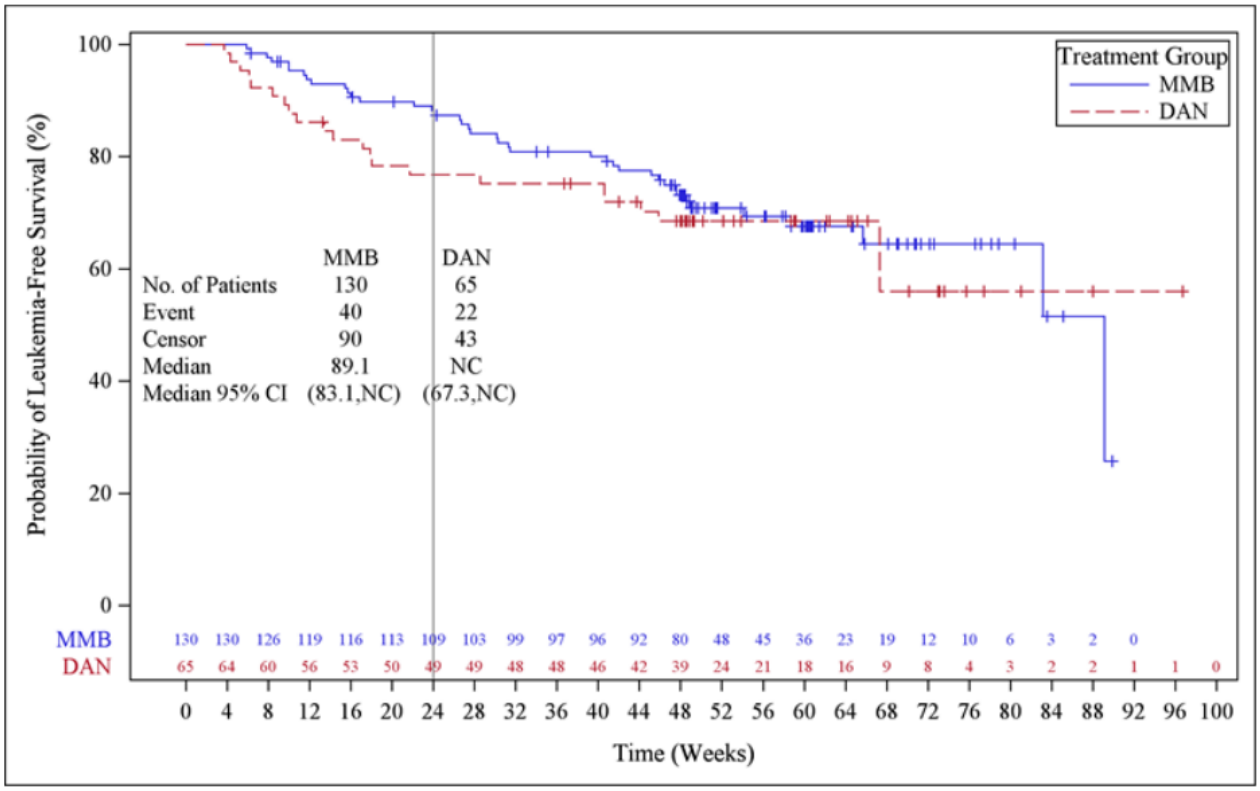
Leukemia-free survival (LFS)

In MOMENTUM trial, LFS was as OS a secondary endpoints not included in the prespecified hierarchical testing. Provided data are as of database lock date of 17 Jan 2023.

Table 72: Leukemia-free survival (ITT population, MOMENTUM)

	MOMENTUM (ITT Population)	
Leukemia-Free Survival	**MMB (N = 130)**	**DAN (N = 65)**
Median follow-up [1]	361.00 days (1.0 y)	372.00 days (1.0 y)
Event, n (%)	40 (30.8%)	22 (33.8%)
Leukemic transformation	5 (3.8%)	5 (7.7%)
Death	35 (26.9%)	17 (26.2%)
Censored, n (%)	90 (69.2%)	43 (66.2%)
Kaplan-Meier estimate		
Median (95% CI)	624.0 (582.0 [1.7 y], NC)	NC (471.0 [1.3 y], NC)
Min, max	41, 629+ days (1.3 mo, 1.7 y)	26, 677+ days (0.9 mo, 1.9 y)
Hazard ratio (95% CI) [2]	0.804 (0.466, 1.386)	
p-value [3]	0.4320	

[1] By reverse Kaplan-Meier method for MOMENTUM. Based on the safety population for SIMPLIFY-1.
[2] From a stratified Cox proportional hazards model.
[3] From a stratified log-rank test.



Vertical line at week 24 indicates when ongoing subjects received MMB as open-label treatment.+ indicates a censored observation.

Figure 23: Kaplan-Meier Plot of Leukemia-Free Survival (ITT Population, MOMENTUM)

In SIMPLIFY-2 trial, LFS was a prespecified exploratory endpoint.

Table 73: Analysis of Leukemia-free Survival for the Combined RT and ET Phases (Safety Analysis Set,SIMPLIFY-2)

	Interim Week 24 Analysis		Interim 2 Analysis		Final Analysis	
	MMB (N = 104)	BAT (N = 52)	MMB (N = 104)	BAT (N = 52)	MMB (N = 104)	BAT (N = 52)
Subjects with events	**15 (14.4%)**	**12 (23.1%)**	**36 (34.6%)**	**20 (38.5%)**	**48 (46.2%)**	**24 (46.2%)**
Leukemic transformation, n (%)	4 (3.8%)	1 (1.9%)	7 (6.7%)	1 (1.9%)	7 (6.7%)	1 (1.9%)
Death	11 (10.6%)	11 (21.2%)	29 (27.9%)	19 (36.5%)	41 (39.4%)	23 (44.2%)
Subjects censored	89 (85.6%)	40 (76.9%)	68 (65.4%)	32 (61.5%)	56 (53.8%)	28 (53.8%)
Kaplan-Meier estimate of leukemia-free survival (months)						
25-percentile (95% CI)	NR (11.50, NR)	15.77 (5.68, 16.39)	16.26 (10.94, 21.29)	12.12 (5.68, 21.29)	16.43 (10.94, 21.29)	12.19 (5.68, 21.29)
Median (95% CI)	NR	15.77 (15.77, 16.39)	27.73 (24.28, NR)	25.13 (20.27, NR)	33.97 (27.33, NR)	37.52 (20.27, NR)
75-percentile (95% CI)	NR	16.39 (15.77, 16.39)	NR	NR	NR	NR
Min, Max	0.23, 24.21	0.43, 16.39	0.23, 37.72	0.43, 29.01	0.23, 50.40	0.43, 44.32
Stratified log-rank test p-value	0.19		0.52		0.85	
Stratified hazard ratio (95% CI)	0.60 (0.28, 1.29)		0.83 (0.47, 1.46)		0.95 (0.58, 1.57)	

Abbreviations: BAT = best available therapy; ET = extended treatment; MMB = momelotinib; NR = not reached; RT = randomized treatment Leukemia-free survival (months) = (date of leukemic transformation, death or censoring – date of randomization+ 1) / 30.4375.

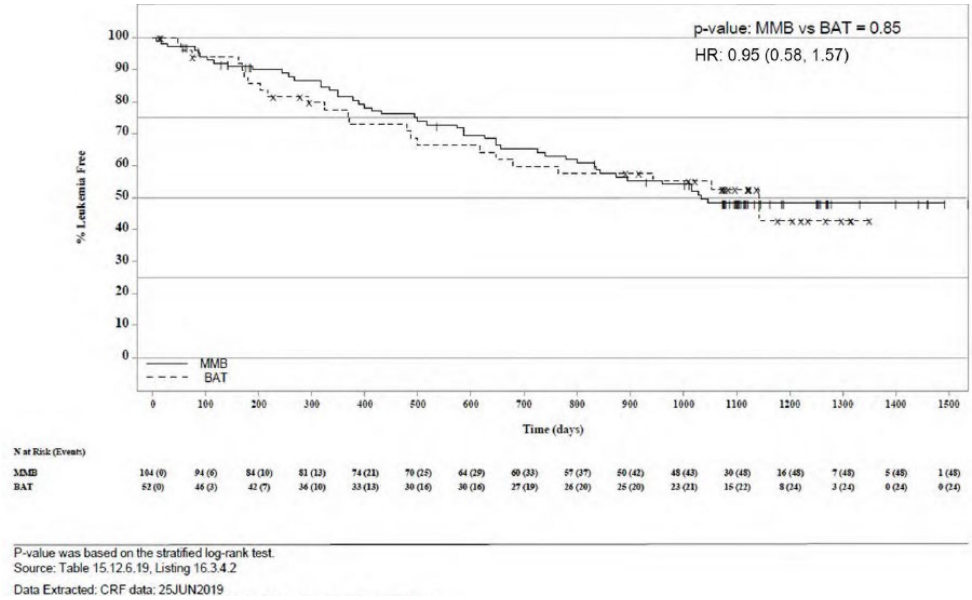


Figure 24: Kaplan-Meier Plot of Leukemia-Free Survival (Safety population, SIMPLIFY-2)

In the SIMPLIFY-1 trial, in the MMB group, 67 subjects (31.2%) had events, including 12 subjects (5.6%) with leukemic transformation and 55 subjects (25.6%) who died. In the RUX group, 68 subjects (31.3%) had events, including 9 subjects (4.1%) with leukemic transformation and 59 subjects (27.2%) who died. The median Kaplan-Meier estimate of LFS was not reached for the MMB group and was 53.06 months for the RUX group in the final analysis. The hazard ratio was 1.07 (95% CI: 0.76, 1.50), p = 0.70.

Table 74: Leukemia-free survival (ITT population, SIMPLIFY-1)

	Week 24 Analysis (data cut-off date of 12 Sep 2016)		Final analysis (data cut-off date 01 Jul 2019)	
Leukemia-Free Survival	**MMB (N = 215)**	**RUX (N = 217)**	**MMB (N = 215)**	**RUX (N = 217)**
Median follow-up [1]			35.4 mo	35.2 mo
Event, n (%)	15 (7.0%)	20 (9.2%)	67 (31.2%)	68 (31.3%)
Leukemic transformation	1 (0.5%)	2 (0.9%)	12 (5.6%)	9 (4.1%)
Death	14 (6.5%)	18 (8.3%)	55 (25.6%)	59 (27.2%)
Censored, n (%)	200 (93.0%)	197 (90.8%)	148 (68.8%)	149 (68.7%)
Kaplan-Meier estimate				
Median (95% CI)	NR	NR	NR (44.09, NR)	53.06 mo (48.72, NR)
Min, max			0.03, 59.30 mo	0.36, 56.34 mo
Hazard ratio (95% CI) [2]	0.81 (0.42, 1.59)		1.07 (0.76, 1.50)	
p-value [3]	0.54		0.70	

[1] By reverse Kaplan-Meier method for MOMENTUM. Based on the safety population for SIMPLIFY-1.
[2] From a stratified Cox proportional hazards model.
[3] From a stratified log-rank test.

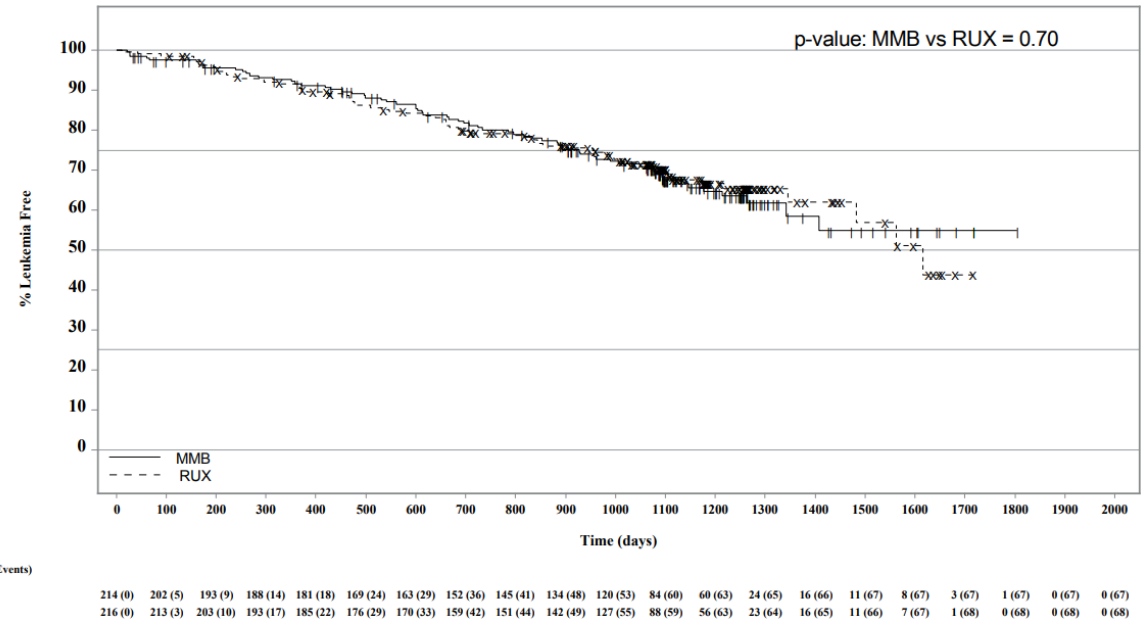


Figure 25: Kaplan-Meier Plot of Leukemia-Free Survival (ITT Population, SIMPLIFY-1, data cut-of date 01 Jul 2019)

Missing data sensitivity analyses

[Note: worst-case analyses: imputing non-response for MMB subjects and response for control arm subjects; modified worst-case analysis: subjects in the MMB arm with missing data due to reasons other than disease progression were analyzed as non-responders, control arm subjects with missing data due to reasons other than insufficient efficacy or disease progression, the more favorable treatment arm was used to impute missing data for the control arm (MMB arm for MOMENTUM and SIMPLIFY-2 for all 3 endpoints and TI rate in SIMPLIFY-1; RUX arm for TSS response and SRR in SIMPLIFY-1)]

MOMENTUM [Discontinuation during RT due to reasons indicating insufficient efficacy or disease progression: MMB: 11/130 (8.5%), DAN: 11/65 (16.9%)]

- **MFSAF TSS response rate at W24 [**Missing data at W24: MMB: 39/130 (30%), DAN: 28/65 (43.1%); Primary analysis: 24.6% (95% CI: 17.5%, 32.9%) vs 9.2% (95% CI: 3.5%, 19.0%), superiority proportion difference: **15.7**% (95% CI : 5.5%, 25.8%), p-value : **0.0095]**
  - Complete case analysis under MCAR : 35.2% (95% CI: 25.4%, 45.9%) vs 16.2% (95% CI: 6.2%, 32.0%), superiority proportion difference: **20.7**% (95% CI : 6.0%, 35.5%), p-value : **0.0210**
  - Multiple imputation under MAR : 31.1% (95% CI: 22.7%, 39.4%) vs 13.4% (95% CI: 4.0%, 22.9%), superiority proportion difference: **17.5**% (95% CI : 4.8%, 30.2%), p-value : **0.0071**
  - Observed case analysis: 35.2% (95% CI: 25.4%, 45.9%) vs 16.2% (95% CI: 6.2%, 32.0%), superiority proportion difference: **20.7**% (95% CI : 6.0%, 35.5%), p-value : **0.0210**
  - Last observation carried forward analysis: 29.2% (95% CI: 21.6%, 37.9%) vs 10.8% (95% CI: 4.4%, 20.9%), superiority proportion difference: **18.3**% (95% CI : 7.6%, 29.1%), p-value : **0.0043**
  - Modified worst-case analysis : 24.6% (95% CI: 17.5%, 32.9%) vs 15.4% (95% CI: 5.4%, 25.4%), superiority proportion difference: **9.2**% (95% CI : -3.2%, 21.7%), p-value : **0.1460**
  - Worst-case analysis : 24.6% (95% CI: 17.5%, 32.9%) vs 52.3% (95% CI: 39.5%, 64.9%), superiority proportion difference: **-27.7**% (95% CI : -42.2, -13.3%), p-value : **0.9999**
  - Tipping point analysis: An average shift of at least 13 points in the patients with missing TSS on Week 24 compared to those with non-missing TSS (on a scale of 70 points) would be needed to change statistical significance.
- **SRR at W24 [**Missing data at W24: MMB: 43/130 (33.1%), DAN: 28/65 (43.1%); Primary analysis: 22.3% (95% CI: 15.5%, 30.4%) vs 3.1% (95% CI: 0.4%, 10.7%), superiority proportion difference: **18.2**% (95% CI : 9.8%, 26.6%), p-value : **0.0011]**
  - Complete case analysis under MCAR : 33.3% (95% CI: 23.6%, 44.3%) vs 5.4% (95% CI: 0.7%, 18.2%), superiority proportion difference: **26.8**% (95% CI : 13.6%, 39.9%), p-value : **0.0022**
  - Multiple imputation under MAR : 31.2% (95% CI: 21.9%, 40.5%) vs 6.5% (95% CI: 0%, 13.9%), superiority proportion difference: **24.0**% (95% CI : 12.1%, 35.8%), p-value : **0.0001**
  - Modified worst-case analysis : 22.3% (95% CI: 15.5%, 30.4%) vs 11.1% (95% CI: 1.9%, 20.4%), superiority proportion difference: **10.3**% (95% CI : -1.4, 22.1%), p-value : **0.0854**

- Worst-case analysis : 22.3% (95% CI: 15.5%, 30.4%) vs 46.2% (95% CI: 33.7%, 59.0%), superiority proportion difference: **-25.3**% (95% CI : -39.8, -0.8%), p-value : **0.9997**
- Tipping point analysis: No tipping point could be identified to change the statistical significance

- **TI rate at W2 [**Missing data at W24: MMB: 34/130 (26.2%), DAN: 27/65 (41.5%); primary analysis: 30.0% (95% CI: 22.3%, 38.7%) vs 20.0% (95% CI: 11.1%, 31.8%), non-inferiority proportion difference: **13.6**% (95% CI : 1.9%, 25.3%), p-value : **0.0116]**
  - Complete case analysis under MCAR : 36.1% (95% CI: 27.1%, 45.9%) vs 26.0% (95% CI: 14.6%, 40.3%), non-inferiority proportion difference: **16.2**% (95% CI : 2.5%, 29.9%), p-value : **0.0101**
  - Multiple imputation under MAR : 35.0% (95% CI: 26.3%, 43.8%) vs 22.8% (95% CI: 12.0%, 33.7%), non-inferiority proportion difference: **16.8**% (95% CI : 4.1%, 29.4%), p-value : **0.0048**
  - Modified worst-case analysis : 30.0% (95% CI: 22.3%, 38.7%) vs 24.7% (95% CI: 13.4%, 36.0%), non-inferiority proportion difference: **10.1**% (95% CI : -2.3%, 22.6%), p-value : **0.0551**
  - Worst-case analysis : 30.0% (95% CI: 22.3%, 38.7%) vs 43.1% (95% CI: 30.8%, 56.0%), non-inferiority proportion difference: **-4.6**% (95% CI : -17.2%, 8.0%), p-value : **0.7642**
  - Tipping point analysis: Reversing the result of NI from statistical significance to non-significance would require the odds of being a TI responder at week 24 in the 22 MMB subjects with missing data to be ~0.09 times the odds of being a TI responder at week 24 in the subjects with complete data. In other words, the MMB response rate in the missing subjects would need to be more than 10 times lower than that for subjects in the MMB arm with non-missing week 24 TI status (ie, response rate reduced from the observed 35% response rate in the completers to approximately 5%) to reverse the statistical significance in the non-inferiority test.

SIMPLIFY-2 [33.7% vs 21.2% of subjects in the MMB arm and the BAT arm (88% of subjects received ruxolitinib as best available therapy, mostly lower dose) discontinued randomized treatment early, respectively. However, there are confounders (discontinuation data of BAT were inconsistently collected and reported because changes in therapy or no therapy were permissible options for the BAT arm, open-label study, variable treatment comparator) making this difference not clinically meaningful; Discontinuation during RT due to reasons indicating insufficient efficacy or disease progression: MMB: 8/104 (7.7%), BAT: 2/52 (3.8%)]

- **MFSAF TSS response rate at W24** [Primary analysis: 26.2% (95% CI: 18.0%, 35.8%) vs 5.9% (95% CI: 1.2%, 16.2%), superiority proportion difference: **20**% (95% CI : 9%, 32%), p-value : **< 0.001**]
  - Last observation carried forward analysis: 27.2% (95% CI: 18.9%, 36.8%) vs 7.8% (95% CI: 2.2%, 18.9%), superiority proportion difference: **19%** (95% CI : 8%, 31%), p-value : **0.002**
  - Modified worst-case analysis : 26.2% (95% CI: 18.0%, 35.8%) vs 11.1% (95% CI: 1.7%, 20.4%), superiority proportion difference: **14.8%** (95% CI : 1.4, 28.2%), p-value : **0.03**

- Other less conservative sensitivity analyses were not performed as the statistical significance was held despite the imbalance in missing data between the MMB and BAT arms

- **SRR at W24** [Primary analysis: 6.7% (95% CI: 2.8%, 13.4%) vs 5.8% (95% CI: 1.2%, 16.0%), superiority proportion difference: **1**% (95% CI : -9%, 10%), p-value : **0.90**]
  - Last observation carried forward analysis: 6.7% (95% CI: 2.8%, 13.4%) vs 5.8% (95% CI: 1.2%, 16.0%), superiority proportion difference: **1**% (95% CI : -9%, 10%), p-value : **0.90**
  - Worst-case analysis: 6.7% (95% CI: 2.8%, 13.4%) vs 30.8% (95% CI: 18.7%, 45.1%), superiority proportion difference: **-24.4**% (95% CI : -38.6%, -10.2%), p-value : **0.9996**
  - Additional missing data analysis for SRR (≥35% reduction from baseline spleen volume) was not performed due to the lack of statistical significance and a small number of responders in the original analysis.
- **TI rate at W24** [Missing data at W24: MMB: 21 (20.2%), BAT: 9 (17.3%) who discontinued early from the randomized treatment period (for reasons other than lack of efficacy, disease progression, leukemic transformation, or adverse event of MF) without a documented RBC transfusion or Hgb < 8 g/dL during the terminal 12 weeks prior to week 24 and were therefore considered missing for TI status at week 24; Primary analysis: 43.3% (95% CI: 33.6%, 53.3%) vs 21.2% (95% CI: 11.2%, 34.7%), superiority proportion difference: **22.9**% (95% CI : 9.1%, 36.6%), p-value : **0.001**]
  - Modified worst-case analysis : 43.3% (95% CI: 33.6%, 53.3%) vs 28.7% (95% CI: 15.8%, 41.5%), superiority proportion difference: **15.3**% (95% CI : 0.1%, 30.5%), p-value : **0.0487**
  - Worst-case analysis : 43.3% (95% CI: 33.6%, 53.3%) vs 42.3% (95% CI: 28.7%, 56.8%), superiority proportion difference: **1.6**% (95% CI : -14.7%, 17.8%), p-value : **0.8499**
  - Other less conservative sensitivity analyses were not performed as the statistical significance was held in the modified worst-case sensitivity analysis despite the imbalance in missing data between the MMB and BAT arms

SIMPLIFY-1 [Discontinuation during RT due to reasons indicating insufficient efficacy or disease progression: MMB: 9/215 (4.2%), RUX: 4/217 (1.8%)]

- **MFSAF TSS response rate at W24** [Missing data at W24: MMB: 36/211 (17.1%), RUX: 21/211 (10.0%); Primary analysis: 28.4% (95% CI: 22.5%, 35.0%) vs 42.2% (95% CI: 35.4%, 49.1%), non-inferiority proportion difference: **0%** (95% CI : -8%, 8%), p-value : **0.98**]
  - Complete case analysis under MCAR : 34.3% (95% CI: 27.3%, 41.8%) vs 46.8% (95% CI: 39.6%, 54.2%), non-inferiority proportion difference: **3.0**% (95% CI : -5.6%, 11.6%), p-value **: 0.2501**
  - Multiple imputation under MAR : 33.0% (95% CI: 26.4%, 39.6%) vs 44.2% (95% CI: 37.4%, 51.0%), non-inferiority proportion difference: **3.3**% (95% CI : -4.8%, 11.4%), p-value : **0.2135**
  - Modified worst-case analysis : not performed due to the lack of statistical significance in the original analysis
  - Worst-case analysis : 28.4% (95% CI: 22.5%, 35.0%) vs 52.1% (95% CI: 45.2%, 59.0%), non-inferiority proportion difference: **-6.5**% (95% CI : -14.2%, 1.2%), p-value : **0.9505**

- Tipping point analysis: In order to claim statistical significance for the non-inferiority test, the week 24 TSS scores of the missing MMB subjects had to be at least 8.0 points lower than those of the MMB subjects with data.
- Best-case analysis: 43.1% vs 42.2%, non-inferiority proportion difference: **15**% (95% CI : 7%, 23%), p-value : **< 0.001**

- **SRR at W24** [Missing data at W24: MMB: 31/215 (14.4%), RUX: 13/217 (6.0%); Primary analysis: 26.5% (95% CI: 20.7%, 32.9%) vs 29.5% (95% CI: 23.5%, 36.0%), non-inferiority proportion difference: **9**% (95% CI : 2%, 16%), p-value : **0.014**]
  - Complete case analysis under MCAR : 31.0% (95% CI: 24.4%, 38.2%) vs 31.4% (95% CI: 25.1%, 38.2%), non-inferiority proportion difference: **12.1**% (95% CI : 4.4%, 19.8%), p-value : **0.0010**
  - Multiple imputation under MAR : 30.0% (95% CI: 23.6%, 36.4%) vs 31.1% (95% CI: 24.9%, 37.4%), non-inferiority proportion difference: **11.2**% (95% CI : 3.8%, 18.6%), p-value : **0.0015**
  - Modified worst-case analysis : 26.5% (95% CI: 20.7%, 32.9%) vs 31.1% (95% CI: 24.8%, 37.4%), non-inferiority proportion difference: **7.7**% (95% CI : 0.7, 14.8%), p-value : **0.0153**
  - Worst-case analysis : 26.5% (95% CI: 20.7%, 32.9%) vs 35.5% (95% CI: 29.1%, 42.2%), non-inferiority proportion difference: **5.1**% (95% CI : -1.9%, 12.2%), p-value **: 0.0769**
  - Tipping point analysis: No tipping point could be identified to change the statistical significance
- **TI rate at W24** [Missing data at W24: MMB: 32/215 (14.9%), RUX: 12/217 (5.5%); Primary analysis: 66.5% (95% CI: 59.8%, 72.8%) vs 49.3% (95% CI: 42.5%, 56.2%), superiority proportion difference: **18**% (95% CI : 9%, 26%), p-value : **< 0.0001**]
  - Modified worst-case analysis : Not performed because statistical significance was demonstrated in the more rigorous worst-case analysis.
  - Worst-case analysis : 66.5% (95% CI: 59.8%, 72.8%) vs 55.3% (95% CI: 48.4%, 62.0%), superiority proportion difference: **11.6**% (95% CI : 3.0%, 20.2%), p-value : **0.0042**

Subgroup analyses in function of baseline demographics and disease characteristics

Study SRA-MMB-301 (MOMENTUM)

Subgroup analysis in function of baseline demographics and disease characteristics

First primary endpoint: MFSAF TSS 24

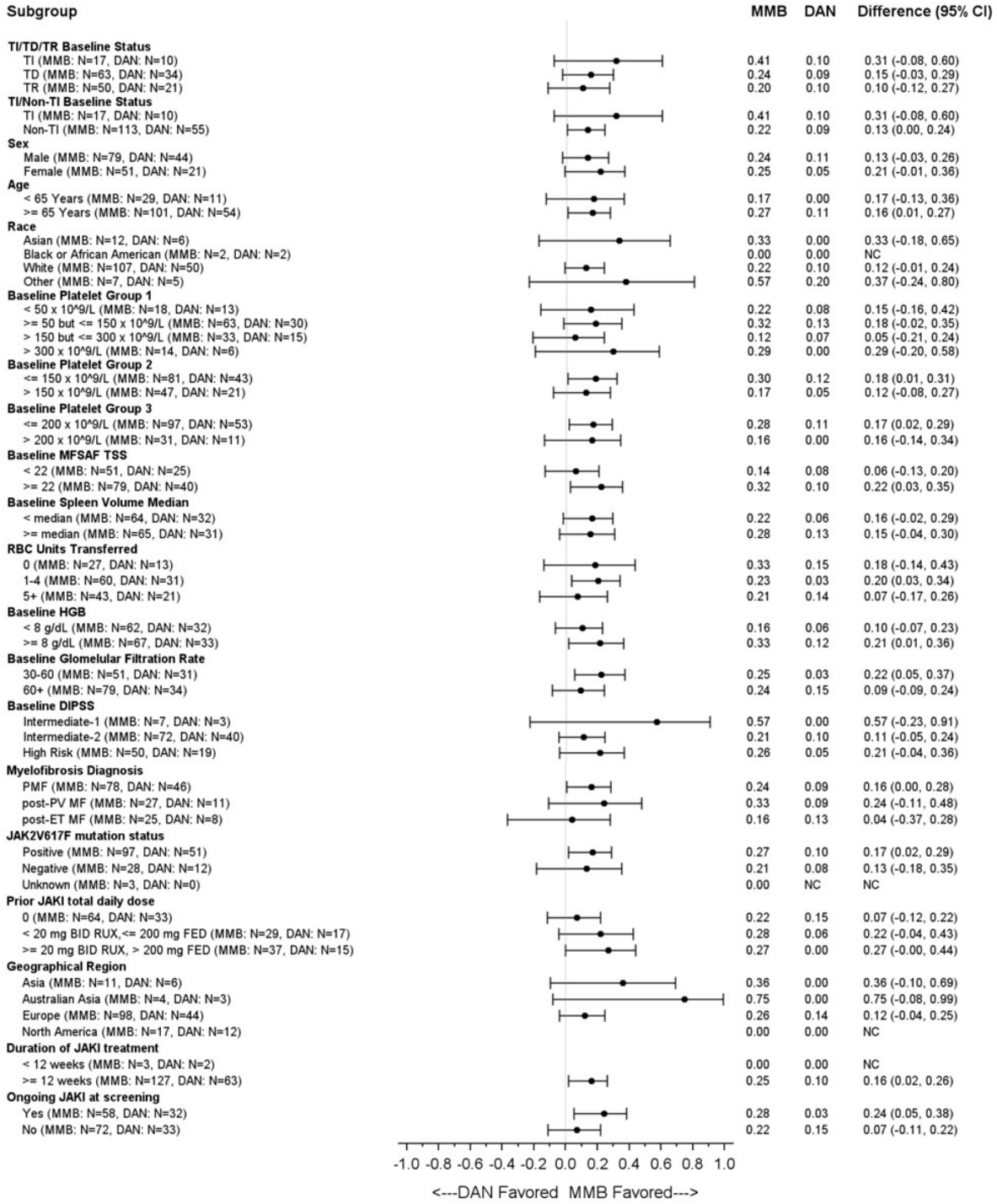


Figure 26: Forest plot of MFSAF TSS response rate at Week 24 by subgroup (ITT Population, MOMENTUM)

Second primary endpoint: TI rate at Week 24

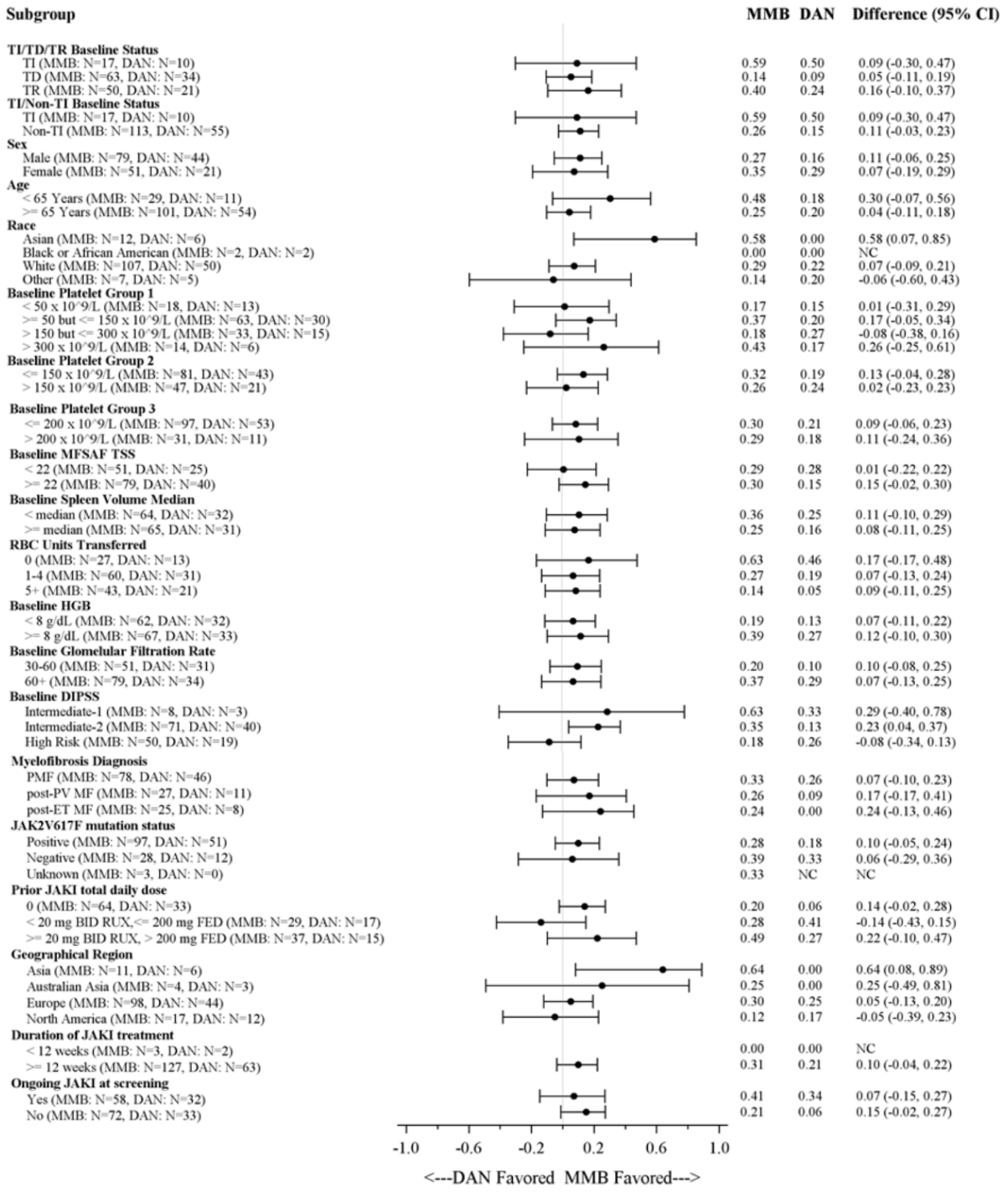


Figure 27: Forest plot of superiority difference of TI rate at Week 24 by subgroup (ITT Population, MOMENTUM)

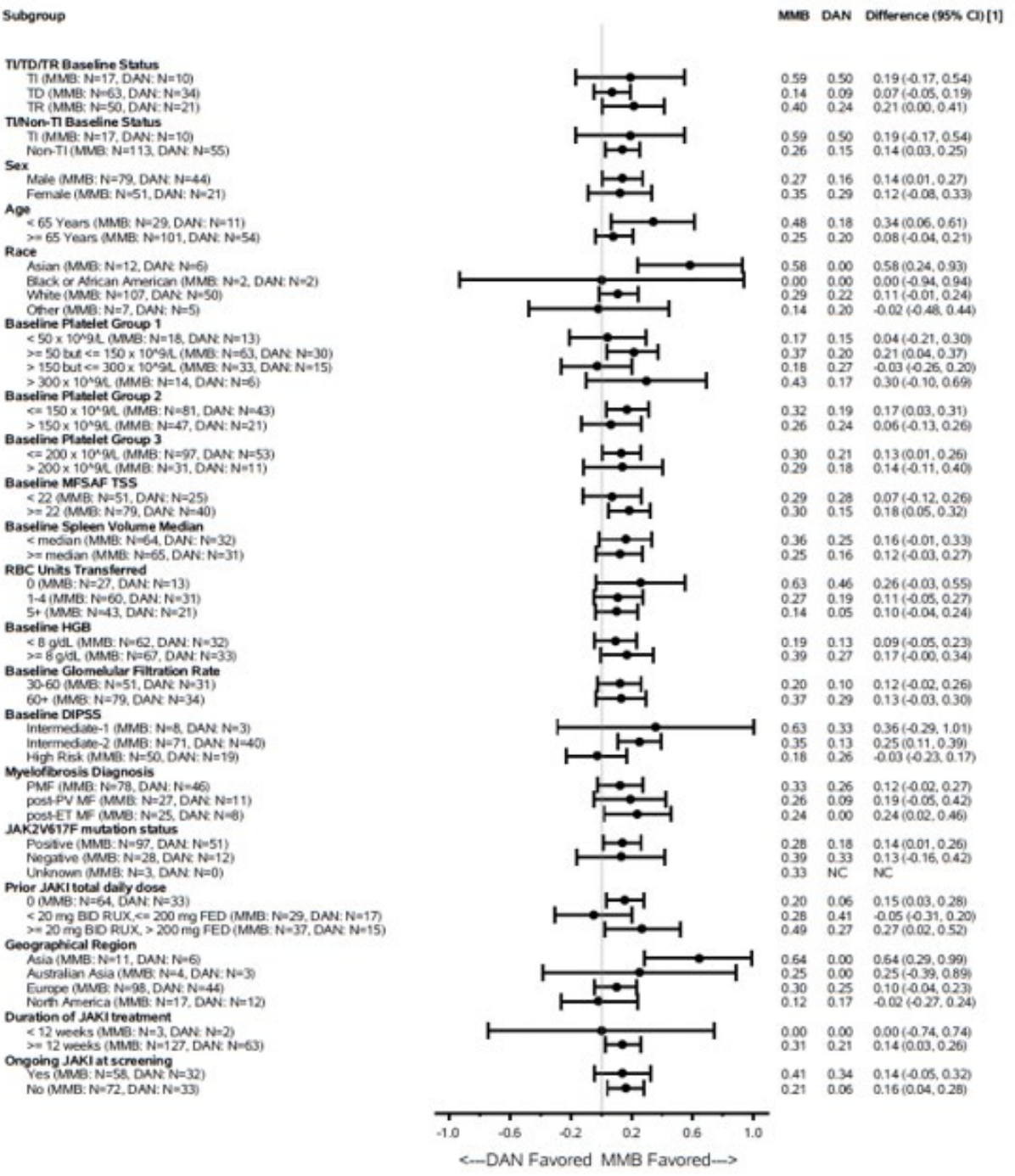


Figure 28: Forest plot of non-inferiority difference of TI rate at Week 24 by subgroup (ITT Population, MOMENTUM)

Study GU-US-352-0101 (SIMPLIFY-1)

Pre-specified subgroup analysis for baseline demographics and disease characteristics

Primary endpoint: SRR at Week 24 based on ≥ 35% reduction in spleen volume from baseline

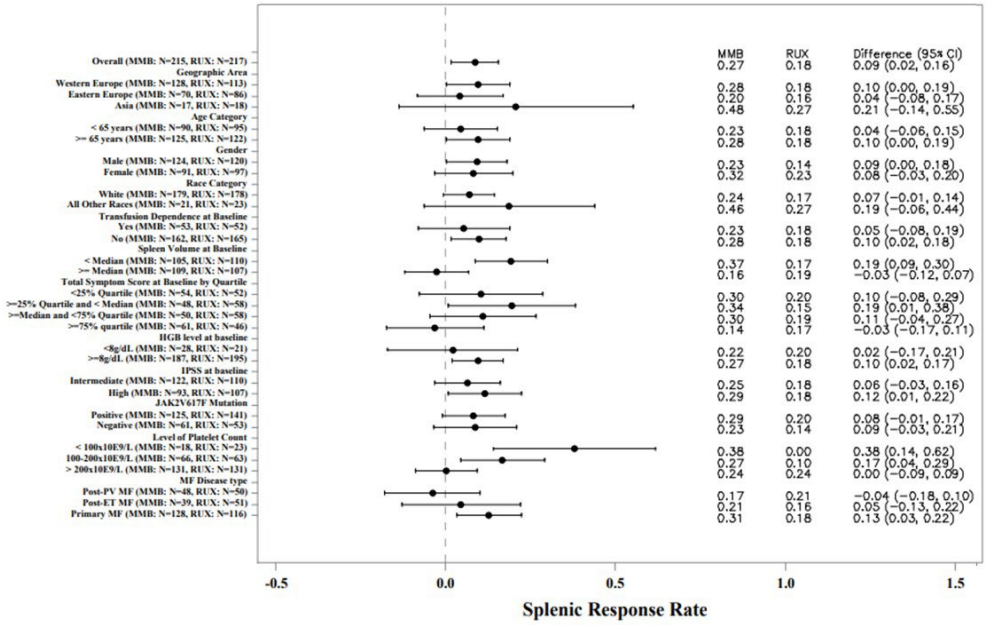


Figure 29: Forest plot of Splenic Response Rate Based on ≥ 35% Reduction in Spleen Volume From Baseline at Week 24 by subgroup (ITT Population, Noninferiority, SIMPLIFY-1)

Secondary endpoint: MNP-SAF TSS at Week 24

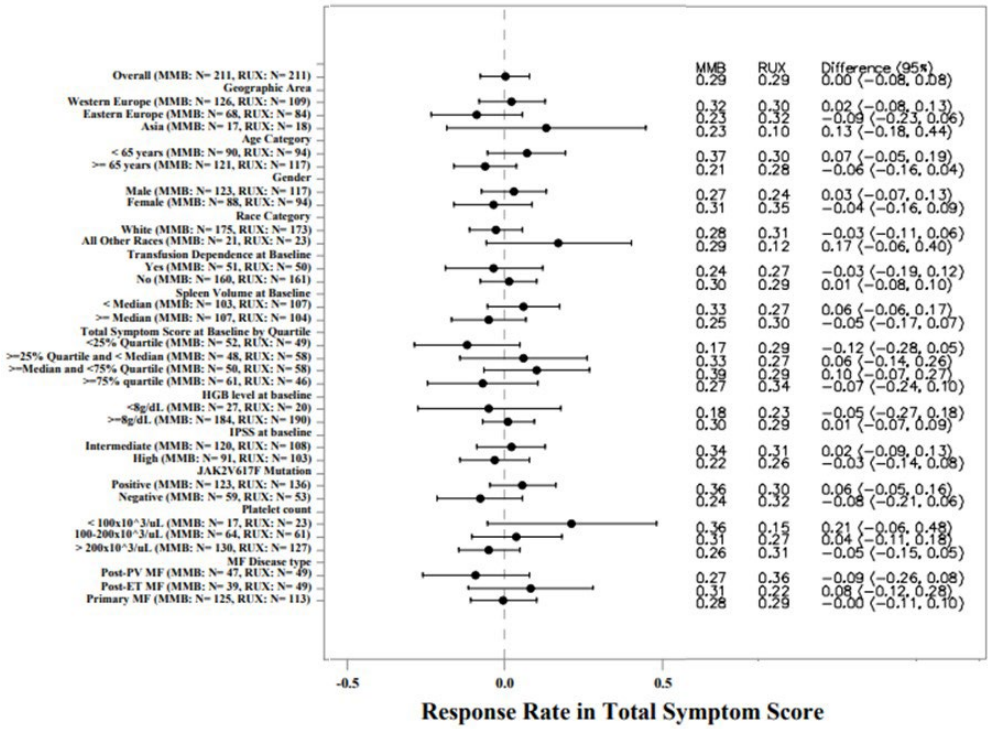


Figure 30: Forest plot of MPN-SAF TSS response rate at Week 24 by subgroup (ITT Population, noninferiority, SIMPLIFY-1)

Post-hoc analysis using an alternative non-inferiority margin for the secondary endpoint MPN-SAF TSS at Week 24 in SIMPLIFY-1

An alternative noninferiority margin of 0.4874 was derived in a post hoc analysis using the standard 95%-95% fixed-margin method. The lower bounds of the 95% CIs for the MMB/RUX response ratios using the 7-item TSS in the ITT population, 6-item TSS in the ITT population, and 7-item TSS in symptomatic subjects with baseline TSS ≥ 10 all ruled out 0.4874.

Table 75: Post-hoc analyses of MPN-SAF TSS Response Rate at Week 24 using the 95%-95% Fixed-Margin Method (ITT-population, SIMPLIFY-1)

Analysis Population / Method	MMB		RUX		Response Ratio (MMB/RUX)		
	N	TSS RR	N	TSS RR	Ratio	95% CI LB	95% CI UB
ITT / 7-item TSS [1]	211	28.4%	211	42.2%	0.6760	0.5187	0.8809
ITT / 6-item TSS [2]	211	36.0%	211	48.8%	0.7391	0.5897	0.9264
Symptomatic [3] / 7-item TSS	152	32.9%	149	43.0%	0.7675	0.5737	1.0269

Modified Wald response ratio and 95% CI are presented. Noninferiority was demonstrated if the lower bound of the 95% CI for the response ratio (MMB/RUX) ruled out 0.4874 (or equivalently, 95% CI LB of p[MMB] – 0.4874 × p[RUX] > 0).

[1] Original analysis.

[2] Based on the 6-item TSS used in COMFORT-I that excluded the fatigue/tiredness item.

[3] Symptomatic defined as baseline TSS ≥ 10.

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 80: Summary of efficacy for trial SRA-MMB-301 (MOMENTUM)

Title: A Randomized, Double Blind, Phase 3 Study to Evaluate the Activity of Momelotinib (MMB) Versus Danazol (DAN) in Symptomatic, Anemic Subjects With Primary Myelofibrosis (PMF), Post Polycythemia Vera (PV) Myelofibrosis, or Post Essential Thrombocythemia (ET) Myelofibrosis Who Were Previously Treated With JAK Inhibitor Therapy		
Study identifier	Protocol Identifier: SRA-MMB-301 EudraCT Number: 2019 000583 18 ClinicalTrials.gov: NCT04173494	
Design	Phase 3, international, randomized (2:1), double blind, active controlled study comparing the efficacy and safety of MMB versus DAN in symptomatic, anemic subjects with myelofibrosis (MF) who previously received JAK inhibitor therapy.	
	Duration of main phase:	24 Weeks (randomized, double-blind period from Day 1 to Week 24)
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	24 weeks (open-label period from Week 24 to Week 48)

Hypothesis	First primary endpoint of Total Symptom Score response rate at Week 24 was tested for superiority of MMB versus DAN. If achieved, second primary endpoint of Transfusion Independence response rate at Week 24 was tested for non-inferiority and superiority of MMB versus DAN.		
Treatments groups	Momelotinib (MMB)+Danazol (DAN)-matched placebo		130 subjects were randomly assigned to MMB 200 mg tablets administered orally once daily (QD) plus DAN-matched placebo capsule administered orally twice daily (BID) for 24 weeks in the randomized double-blind period. MMB treatment could continue in the open-label period.
	Danazol (DAN)+ Momelotinib (MMB)-matched placebo		65 subjects were randomly assigned to DAN 300 mg capsules administered orally BID plus MMB-matched placebo tablets administered orally QD for 24 weeks in the randomized double-blind period. Crossover to MMB treatment was permitted in the open-label period.
Endpoints and definitions	First primary endpoint	Total Symptom Score (TSS) Response Rate at Week 24	Defined as the proportion of subjects with a ≥ 50% reduction in mean Myelofibrosis Symptom Assessment Form(MFSAF)version 4.0 TSS assessed daily over the 28 days immediately before the end of week 24 compared with baseline obtained over 7 days prior to randomization.
	Second primary endpoint	Transfusion Independence (TI) Rate at Week 24	Defined as the proportion of subjects with TI in the terminal 12 weeks of the 24 week randomized treatment period. TI is defined as zero red blood cell transfusion (except in the case of clinically overt bleeding) and no hemoglobin value <8 g/dL for ≥ 12 weeks immediately before the week 24 visit.
	First key secondary endpoint	Splenic Response Rate (SRR) at Week 24 [≥25% reduction in spleen volume]	Defined as the proportion of subjects who had splenic response based on ≥ 25% reduction in spleen volume from baseline.
	Second key secondary endpoint	Absolute change in MFSAF TSS from baseline at Week 24	Defined as the absolute change from baseline in least squares mean MFSAF TSS over the 28 days immediately before the end of week 24.
	Third key secondary endpoint	SRR at Week 24 [≥35% reduction in spleen volume]	Defined as the proportion of subjects who had splenic response based on ≥ 35% reduction in spleen volume from baseline.
Database lock	03 December 2021		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	**Intent to treat population**: defined as all patients who were randomized. The 24 week timepoint for the primary analysis is defined from Day 1 to Week 24.		
Descriptive statistics and estimate variability	Treatment group	MMB + DAN matched placebo	DAN + MMB matched placebo
	Number of subject	130	65
	TSS response rate Percentage (%)	24.62	9.23
	95% confidence interval (CI)	17.49, 32.94	3.46, 19.02
	TI rate, Percentage (%)	30.00	20.00
	95% CI	22.28, 38.66	11.10, 31.77
	SRR [≥25% reduction in spleen volume] Percentage (%)	39.23	6.15
	95% CI	30.79, 48.18	1.70, 15.01
	Absolute change in MFSAF TSS from baseline at Week 24 Least squares mean estimated from mixed model for repeated measures (MMRM)	-9.36	-3.13
	Standard Error (SE)	1.08	1.62
	SRR [≥35% reduction in spleen volume] Percentage (%)	22.31	3.08
	95% CI	15.48, 30.44	0.37, 10.68
	Rate of no transfusion at Week 24 (%)	35.38	16.92
	95% CI	27.20, 44.25	8.76, 28.27
Effect estimate per comparison	First Primary endpoint: **TSS response rate**	Comparison groups	MMB/placebo versus DAN/placebo
		Difference for superiority by stratified Cochran Mantel Haenszel (CMH) test	15.67
		95% CI	5.54, 25.81
		P-value (2-sided) CMH test	0.0095

	Second primary endpoint: **TI rate**	Comparison groups	MMB/placebo versus DAN/placebo
		Difference for noninferiority (refer to NOTES)	13.58
		95% CI	1.86, 25.30
		P-value (1-sided) CMH test	0.0116
		Difference for superiority by stratified CMH test	9.80
		95% CI	-2.03, 21.62
		P-value (refer to NOTES)	0.1265
	First key secondary endpoint**: SRR [≥25% reduction in spleen volume]**	Comparison groups	MMB/placebo versus DAN/placebo
		Difference by stratified CMH test	33.05
		95% CI	22.59, 43.51
		P-value (2-sided) CMH test	< 0.0001
	Second key secondary endpoint: **Absolute change in MFSAF TSS from baseline at Week 24**	Comparison groups	MMB/placebo versus DAN/placebo
		Difference (SE)	-6.22 (1.92)
		95% CI	-10.0, -2.43
		P-value (2 sided) CMH test	0.0014
	Third key secondary endpoint**: SRR [≥35% reduction in spleen volume]**	Comparison groups	MMB/placebo versus DAN/placebo
		Difference by stratified CMH test	18.18
		95% CI	9.77, 26.59
		P-value (2-sided) CMH test	0.0011
	Fourth key secondary endpoint**: Rate pf no transfusion at Week 24**	Comparison groups	MMB/placebo versus DAN/placebo
		Difference by stratified CMH test	17.20
		95% CI	7.99, 26.40
		P-value (2-sided) CMH test	0.0012

Notes	**Week 24 TI rate non-inferiority hypothesis testing**: a stratum adjusted 2 sided 95% CI based on Koch et al was calculated for the difference between the proportion of subjects with TI in the MMB group and 80% of the proportion of subjects with TI in the DAN group. If the lower bound of the CI was greater than 0, MMB was to be declared noninferior to DAN **Summary of Subject Disposition during the 24 Week Period:** 94 subjects (72.3%) in the MMB group and 38 subjects (58.5%) in the DAN group completed randomized treatment. For subjects who discontinued randomized treatment early, adverse event was the most common reason overall in both groups (16 subjects, 12.3% MMB; 11 subjects, 16.9% DAN) followed by subject decision (6, 4.6% MMB; 5, 7.7% DAN).

Table 76: Summary of efficacy for trial GS-US-352-0101 (SIMPLIFY-1)

Title: A Phase 3, Randomized, Double-blind Active-controlled Study Evaluating Momelotinib versus Ruxolitinib in Subjects with Primary Myelofibrosis (PMF) or Post-polycythemia Vera or Post-essential Thrombocythemia Myelofibrosis (Post-PV/ET MF)		
Study identifier	Protocol Identifier: SRA-MMB-301 EudraCT Number: 2013-002707-33 ClinicalTrials.gov: NCT01969838	
Design	Phase 3, international, randomized (1:1), double blind, active controlled study comparing MMB versus RUX in JAK inhibitor naïve subjects with intermediate or high risk PMF or post PV/ET MF	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	24 Weeks (randomized, double-blind period, from Day 1 to Week 24) not applicable up to 5 Years (open-label period, from Week 24 to Year 5)
Hypothesis	The primary endpoint of Splenic Response Rate at Week 24 was tested for non-inferiority of MMB versus RUX. If achieved, the key secondary endpoints would be tested in a hierarchical fashion to control for the overall type I error rate of 0.05. The first key secondary endpoint of Total Symptom Score was tested for non-inferiority.	
Treatments groups	Momelotinib (MMB) + Ruxolitinib (RUX)-matched placebo	215 subjects were randomly assigned to MMB 200 mg tablets administered orally once daily (QD) plus RUX-matched placebo tablets administered orally twice daily (BID) for 24 weeks in the randomized double-blind period. MMB treatment could continue in the open-label period.
	Ruxolitinib (RUX) + Momelotinib (MMB)-matched placebo	217 subjects were randomly assigned to RUX tablets (5 to 20 mg dosage depending on platelet counts) administered orally BID plus MMB-matched placebo tablets administered orally QD for 24 weeks in the randomized double-blind period. Crossover to MMB treatment was permitted in the open-label period. RUX treatment in the open-label period was not allowed.

Endpoints and definitions	Primary endpoint	SRR at Week 24	Defined as the proportion of subjects who had splenic response based on ≥ 35% reduction in spleen volume from baseline.
	First key secondary endpoint	Total Symptom Score (TSS) Response Rate at Week 24	Defined as the proportion of subjects with a ≥ 50% reduction in mean Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) version 2.0 TSS assessed daily over the 28 days immediately before the end of week 24 compared with baseline.
	Second key secondary endpoint	Transfusion Independence (TI) Rate at Week 24	Defined as the proportion of subjects with TI in the terminal 12 weeks of the 24 week randomized treatment period. TI is defined as zero red blood cell transfusion (except in the case of clinically overt bleeding) and no hemoglobin value <8 g/dL for ≥ 12 weeks immediately before the week 24 visit.
	Key exploratory endpoint	Absolute change in TSS from baseline at Week 24	Defined as the absolute change from baseline in least squares mean modified MPN-SAF TSS over the 28 days immediately before the end of week 24.
Database lock	12 September 2016		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	**Intent to treat population**: defined as all patients who were randomized. The 24 week timepoint for the primary analysis is defined from Day 1 to Week 24.		

Descriptive statistics and estimate variability	Treatment group	MMB + RUX matched placebo	RUX + MMB matched placebo
	Number of subject	215	217
	SRR [≥35% reduction in spleen volume] Percentage (%)	26.5	29.5
	95% confidence interval (CI)	20.74, 32.94	23.51, 36.04
	TSS response rate Percentage (%)	28.4	42.2
	95% CI	22.45, 35.03	35.43, 49.15
	TI rate Percentage (%)	66.5	49.3
	95% CI	59.78, 72.79	42.48, 56.16

	Absolute change in MPN-SAF TSS from baseline at Week 24 Least squares mean estimated from mixed model for repeated measures (MMRM)	-5.87	-7.11
	Standard Error (SE)	0.93	0.91
Effect estimate per comparison	Primary endpoint: **SRR [≥35% reduction in spleen volume]**	Comparison groups	MMB/placebo versus RUX/placebo
		Difference for non-inferiority by stratified Cochran Mantel Haenszel (CMH) test	9
		95% CI	2, 16
		P-value CMH test	0.014
	First key secondary endpoint: **TSS response rate**	*Comparison groups*	MMB/placebo versus RUX/placebo
		Difference for non-inferiority by stratified CMH test (Refer to NOTES)	0
		95% CI	-8, 8
		P-value CMH test	0.98
	Second key secondary endpoint: **TI rate**	*Comparison groups*	MMB/placebo versus RUX/placebo
		Difference for superiority by stratified CMH test	18
		95% CI	9, 26
		P-value CMH test	<0.001 (nominal)
	Key exploratory endpoint: **Absolute change in MPN-SAF TSS from baseline at Week 24**	Comparison groups	MMB/placebo versus RUX/placebo
		Difference (SE)	1.24 (0.83)
		95% CI	-0.40, 2.88
		P-value CMH test	0.1380 (nominal)

Notes	**TSS Non-inferiority hypothesis testing**: the noninferiority proportion difference calculated as p(MMB) – 0.67 × p(RUX); noninferiority was to be declared if the difference ruled out 0. **Summary of Subject Disposition during the 24 Week Period:** 1 subject in each treatment group was randomized but not treated. Thus, a total of 214 subjects in the MMB group and 216 subjects in the RUX group received treatment. Overall, 175 subjects (81.4%) in the MMB group and 201 subjects (92.6%) in the RUX group completed 24 weeks of double-blind study treatment. A total of 40 subjects (18.6%) in the MMB group and 16 subjects (7.4%) in the RUX group prematurely discontinued study drug, with AEs being the most common reason for discontinuing study treatment in both groups (8.8% MMB; 4.1% RUX). **P-value**: Nominal is used to indicate nominal p values for descriptive results of hypothesis tests that were included only after a hypothesis test was not rejected in a hierarchical test sequence, or when compared with p values for hypothesis tests that were included in the overall type I error rate control. The summary table captures the key efficacy endpoints; not all secondary endpoints are presented.		
Analysis description	**Hemoglobin <12 g/dL Subgroup Population:** defined as patients with baseline hemoglobin value of <12 g/dL who were randomized. The 24 week timepoint for the secondary analysis is defined from Day 1 to Week 24. This subgroup was not prespecified.		
Descriptive statistics and estimate variability	Treatment group	MMB + RUX matched placebo	RUX + MMB matched placebo
	Number of subject	159	164
	SRR [≥35% reduction in spleen volume] Percentage (%)	28.9	29.3
	95% confidence interval (CI)	22.02, 36.64	22.43, 36.87
	TSS response rate Percentage (%)	29.7	39.9
	95% CI	22.62, 37.53	32.18, 47.96
	TI rate Percentage (%)	62.3	37.2
	95% CI	54.24, 69.82	29.79, 45.08
Effect estimate per comparison	Primary endpoint: **SRR [≥35% reduction in spleen volume]**	Comparison groups	MMB/placebo versus RUX/placebo
		Difference for non-inferiority by stratified Cochran Mantel Haenszel (CMH) test	11
		95% CI	3, 20
		P-value CMH test	0.007 (nominal)
	First key secondary endpoint: **TSS response**	*Comparison groups*	MMB/placebo versus RUX/placebo

	rate	Difference for non-inferiority by stratified CMH test	3
		95% CI	-6, 12
		P-value CMH test	0.5 (nominal)
	Second key secondary endpoint: **TI rate**	*Comparison groups*	MMB/placebo versus RUX/placebo
		Difference for superiority by stratified CMH test	26
		95% CI	16, 36
		P-value CMH test	<0.01 (nominal)
Notes	**P-value**: Nominal is used to indicate nominal p values for descriptive results of hypothesis tests that were included only after a hypothesis test was not rejected in a hierarchical test sequence, or when compared with p values for hypothesis tests that were included in the overall type I error rate control.		

2.6.5.3. Clinical studies in special populations

No individual efficacy studies in specific populations were conducted. In all three controlled trials, as well as in the supportive studies, a majority of patients was ≥ 65 years (80% in MOMENTUM, 57% in SIMPLIFY-1 and 65% in SIMPLIFY-2, respectively).

	Age 65-74 (Older subjects number / total number)	Age 75-84 (Older subjects number / total number)	Age 85+ (Older subjects number / total number)
Controlled Trials			
MOMENTUM	94/195 (48.2%)	57/195 (29.2%)	4/195 (2.1%)
SIMPLIFY-1	176/432 (40.7%)	69/432 (16.0%)	2/432 (<1%)
SIMPLIFY-2	73/156 (46.8%)	27/156 (17.3%)	1/156 (<1%)
Non-controlled Trials			
GS-US-352-1672	19/41 (46.3%)	9/41 (22.0%)	2/41 (4.9%)

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Table 77: Overall summary of primary, key secondary and other selected secondary efficacy endpoints for MOMENTUM (ITT population) with corresponding SIMPLIFY-1 results (ITT population and anemia subgroup with baseline Hgb < 10 g/dL)

	MOMENTUM		SIMPLIFY-1 [1]			
	ITT Population		ITT Population		Baseline Hgb < 10 g/dL	
MOMENTUM Endpoint	**MMB (N = 130)**	**DAN (N = 65)**	**MMB (N = 215)**	**RUX (N = 217)**	**MMB (N = 86)**	**RUX (N = 95)**

MOMENTUM Endpoint	MOMENTUM		SIMPLIFY-1 [1]			
	ITT Population		ITT Population		Baseline Hgb < 10 g/dL	
	MMB (N = 130)	DAN (N = 65)	MMB (N = 215)	RUX (N = 217)	MMB (N = 86)	RUX (N = 95)
Primary efficacy endpoints						
MFSAF TSS response rate at week 24 [2]						
Evaluable at week 24, n	130	65	211	211	84	94
Responder, n (%)	32 (24.6%)	6 (9.2%)	60 (28.4%)	89 (42.2%)	21 (25.0%)	34 (36.2%)
Exact 95% CI [3]	17.49, 32.94	3.46, 19.02	22.45, 35.03	35.43, 49.15	16.19, 35.64	26.51, 46.73
Superiority proportion difference, % (95% CI)	15.67 (5.54, 25.81)		-14 (-23, -5)		-12 (-26, 2)	
p-value	0.0095		0.9985 [4]		0.089 (nominal)	
Noninferiority proportion difference, % (95% CI)	na		0 (-8, 8) [5]		-0 (-12, 12)	
p-value	na		0.98		1.00 (nominal)	
TI rate at week 24						
Responder, n (%)	39 (30.0%)	13 (20.0%)	143 (66.5%)	107 (49.3%)	40 (46.5%)	26 (27.4%)
Exact 95% CI [3]	22.28, 38.66	11.10, 31.77	59.78, 72.79	42.48, 56.16	35.68, 57.59	18.72, 37.48
Superiority proportion difference, % (95% CI)	9.80 (-2.03, 21.62)		18 (9, 26)		22 (9, 36)	
p-value	0.1265		< 0.001 (nominal)		0.001 (nominal)	
Noninferiority proportion difference, % (95% CI)	13.58 (1.86, 25.30) [6]		na		na	
1-sided p-value	0.0064		na		na	
Key secondary efficacy endpoints						
SRR (reduction in spleen volume ≥ 25% from baseline) at week 24						
Responder, n (%)	51 (39.2%)	4 (6.2%)				
Exact 95% CI [3]	30.79, 48.18	1.70, 15.01				
Superiority proportion difference, % (95% CI)	33.05 (22.59, 43.51)					
p-value	< 0.0001					
Change from baseline in MFSAF TSS at week 24 [2]						
Evaluable at week 24, n	92	37	177	193		
Mean (SD)	-11.52 (12.86)	-3.93 (11.94)	-6.18 (9.985)	-7.26 (8.533)		
Least squares mean (SE) [7]	-9.36 (1.08)	-3.13 (1.62)	-5.87 (0.93)	-7.11 (0.91)		
Least squares mean difference (SE) [7]	-6.22 (1.92)		1.24 (0.83)			

MOMENTUM Endpoint	MOMENTUM		SIMPLIFY-1 [1]			
	ITT Population		ITT Population		Baseline Hgb < 10 g/dL	
	MMB (N = 130)	DAN (N = 65)	MMB (N = 215)	RUX (N = 217)	MMB (N = 86)	RUX (N = 95)
95% CI [7]	-10.0, -2.43		-0.40, 2.88			
p-value [8]	0.0014		0.1380 (nominal)			
SRR (reduction in spleen volume ≥ 35% from baseline) at week 24						
Responder, n (%)	29 (22.3%)	2 (3.1%)	57 (26.5%)	64 (29.5%)	27 (31.4%)	31 (32.6%)
Exact 95% CI [3]	15.48, 30.44	0.37, 10.68	20.74, 32.94	23.51, 36.04	21.81, 42.30	23.36, 43.02
Superiority proportion difference, % (95% CI)	18.18 (9.77, 26.59)		-3 (-12, 5)		0 (-13, 14)	
p-value	0.0011		0.45		0.94 (nominal)	
Noninferiority proportion difference, % (95% CI)	na		9 (2, 16) [9]		13 (2, 25)	
p-value	na		0.014		0.026 (nominal)	
Proportion of subjects with zero RBC units transfused during the RT period						
Responder, n (%)	46 (35.4%)	11 (16.9%)	73%	46%		
Exact 95% CI [3]	27.20, 44.25	8.76, 28.27	66, 78	39, 52		
Superiority proportion difference (95% CI)	17.20 (7.99, 26.40)		na			
p-value	0.0012		na			
Selected other secondary endpoints						
TD rate at week 24						
Dependent, n (%)	20 (15.4%)	16 (24.6%)	65 (30.2%)	87 (40.1%)	41 (47.7%)	58 (61.1%)
Exact 95% CI [3]	9.66, 22.76	14.77, 36.87	24.17, 36.85	33.52, 46.94	36.79, 58.73	50.50, 70.89
Proportion difference (95% CI)	-8.26 (-20.18, 3.66)		-10 (-19, -2)		-16 (-30, -2)	
p-value	0.1602		0.019 (nominal)		0.028 (nominal)	
Overall survival, n [10]	130	65	214	216		
Median follow-up [11]	275.00 days (0.75 y)	295.00 days (0.81 y)	3.43 y	3.47 y		
Death, n (%)	25 (19.2%)	16 (24.6%)	67 (31.3%)	73 (33.8%)		
Censored, n (%)	105 (80.8%)	49 (75.4%)	147 (68.7%)	143 (66.2%)		
Kaplan-Meier estimate overall						
Median (95% CI)	NC (NC, NC)	NC (390.00 days [1.1 y], NC)	NR (4.73 y, NR)	NR (4.94 y, NR)		
Range	41, 476+ days (0.11, 1.3 y)	26, 523+ days (0.07, 1.4 y)	0.06, 7.53 y	0.03, 7.35 y		
Hazard ratio (95% CI) [12]	0.734 (0.382, 1.409)		1.03 (0.74, 1.44)			
p-value [13]	0.3510		0.8646			

MOMENTUM Endpoint	MOMENTUM		SIMPLIFY-1 [1]			
	ITT Population		ITT Population		Baseline Hgb < 10 g/dL	
	MMB (N = 130)	DAN (N = 65)	MMB (N = 215)	RUX (N = 217)	MMB (N = 86)	RUX (N = 95)
Leukemia-free survival, n [10]	130	65	215	217		
Median follow-up [11]	281.00 days (9.2 mo)	275.00 days (9.0 mo)	35.4 mo	35.2 mo		
Event, n (%)	27 (20.8%)	18 (27.7%)	67 (31.2%)	68 (31.3%)		
Leukemic transformation	3 (2.3%)	4 (6.2%)	12 (5.6%)	9 (4.1%)		
Death	24 (18.5%)	14 (21.5%)	55 (25.6%)	59 (27.2%)		
Censored, n (%)	103 (79.2%)	47 (72.3%)	148 (68.8%)	149 (68.7%)		
Kaplan-Meier estimate						
Median	NC (NC, NC)	NC (NC, NC)	NR (44.09, NR)	53.06 mo (48.72, NR)		
Range	41, 476+ days (1.3, 15.6 mo)	26, 509+ days (0.9, 16.7 mo)	0.03, 59.30 mo	0.36, 56.34 mo		
Hazard ratio (95% CI) [12]	0.650 (0.351, 1.206)		1.07 (0.76, 1.50)			
p-value [13]	0.1696		0.70			

Proportion differences were analyzed using the stratified CMH method except where noted. All p values were 2 sided unless otherwise specified. "(nominal)" is used to indicate nominal p values for descriptive results of hypothesis tests that were included only after a hypothesis test was not rejected in a hierarchical test sequence, or when compared with p values for hypothesis tests that were included in the overall type I error rate control. + indicates a censored observation in MOMENTUM.

[1] Results are included for comparison with MOMENTUM and are not shown in the planned hierarchical testing order for SIMPLIFY 1.

[2] MPN SAF TSS for SIMPLIFY 1.

[3] Exact binomial CI for MOMENTUM and based on Clopper Pearson method without stratification for SIMPLIFY 1. [4] One sided p value for superiority of MMB computed from the original 2 sided nondirectional p value of 0.003 as follows: superiority p value = 1 – (0.003/2) = 0.9985.

[5] Delta = p(MMB) – 0.67 × p(RUX), where p(MMB) was the proportion with TSS response in the MMB group and p(RUX) was the proportion with TSS response in the RUX group.

[6] Delta = p(MMB) – 0.80 × p(DAN), where p(MMB) was the proportion with TI in the MMB group and p(DAN) was the proportion with TI in the DAN group. The 95% CI was stratum adjusted and based on Koch et al (Chapter 13 in Berry, 1989).

[7] MOMENTUM: Based on MMRM adjusted for baseline MFSAF TSS (< 22 vs ≥ 22), baseline palpable spleen length below the left costal margin (< 12 cm vs ≥ 12 cm), and baseline RBC or whole blood units transfused in the 8-week period before randomization (0, 1-4, ≥ 5 units). SIMPLIFY 1: Based on MMRM that included treatment, time, treatment × time, age, race, and baseline TSS.

[8] p value for the least squares mean difference between the 2 groups from the MMRM.

[9] Delta = p(MMB) – 0.60 × p(RUX), where p(MMB) was the SRR in the MMB group and p(RUX) was the SRR in the RUX group.

[10] Overall survival: Based on the ITT population for MOMENTUM and the safety population for SIMPLIFY 1. SIMPLIFY 1 includes follow up data from XAP as of the data cutoff date of 03 Dec 2021. Leukemia free survival: Based on the ITT population for both studies.

[11] By reverse Kaplan Meier method for MOMENTUM and based on the safety population for SIMPLIFY 1.

[12] From a stratified Cox proportional hazards model.

[13] Nominal p value from a stratified log rank test.

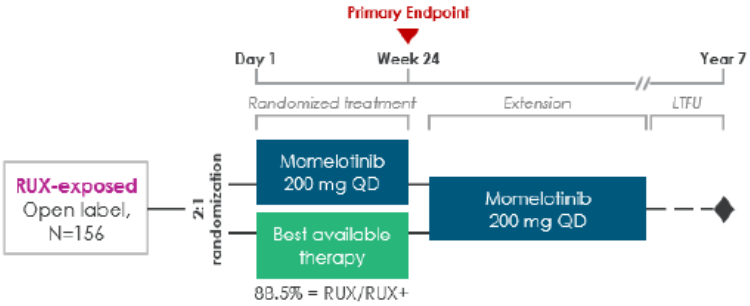
CMH, Cochran Mantel Haenszel; DAN, danazol; ITT, intent to treat; MFSAF, Myelofibrosis Symptom Assessment Form; Min, max, minimum, maximum; MMB, momelotinib; MMRM, mixed model for repeated measures; mo, months; MPN SAF, Myeloproliferative Neoplasm Symptom Assessment Form; na, not applicable; NC, not computable; NR, not reached; Q1, Q3, first quartile, third quartile; RBC, red blood cell; RT, randomized treatment; RUX, ruxolitinib; SRR, splenic response rate; TD, transfusion dependence; TI, transfusion independence; TSS, total symptom score; XAP, Study SRA MMB 4365; y, years

2.6.5.6. Supportive studies

Main supportive study for JAKi-treated patients: **Study GS-US-352-1214 (SIMPLIFY-2), a Phase 3, Randomized Study To Evaluate the Efficacy of Momelotinib Versus Best Available**

Therapy in Anemic or Thrombocytopenic Subjects with Primary Myelofibrosis, Post-polycythemia Vera Myelofibrosis, or Post-essential Thrombocythemia Myelofibrosis who were Treated with Ruxolitinib.

SIMPLIFY-2 was an international, randomized, open-label, phase 3 study of the efficacy and safety of MMB versus BAT in subjects with PMF or post-PV/ET MF whose prior treatment with RUX was associated with anemia and/or thrombocytopenia. The primary objective was to determine the efficacy of MMB compared with BAT as measured by SRR at Week 24.



Abbreviations: LTFU, long-term follow-up; QD, once daily; RUX, ruxolitinib.

MMB was administered at a starting dose of 200 mg once daily. After completion of the randomized treatment phase, subjects will be eligible to receive MMB for the duration of the study during the extended treatment phase (**up to 168 weeks**). until the termination of the study. The maximum participation in the treatment period for any subject was 192 weeks. BAT (best available therapy) was administered at the discretion of investigator.

The primary objective was to determine the efficacy of MMB versus BAT in anemic or thrombocytopenic subjects with PMF or Post-PV/ET MF who are treated with ruxolitinib as measured by SRR24

Secondary objectives included:

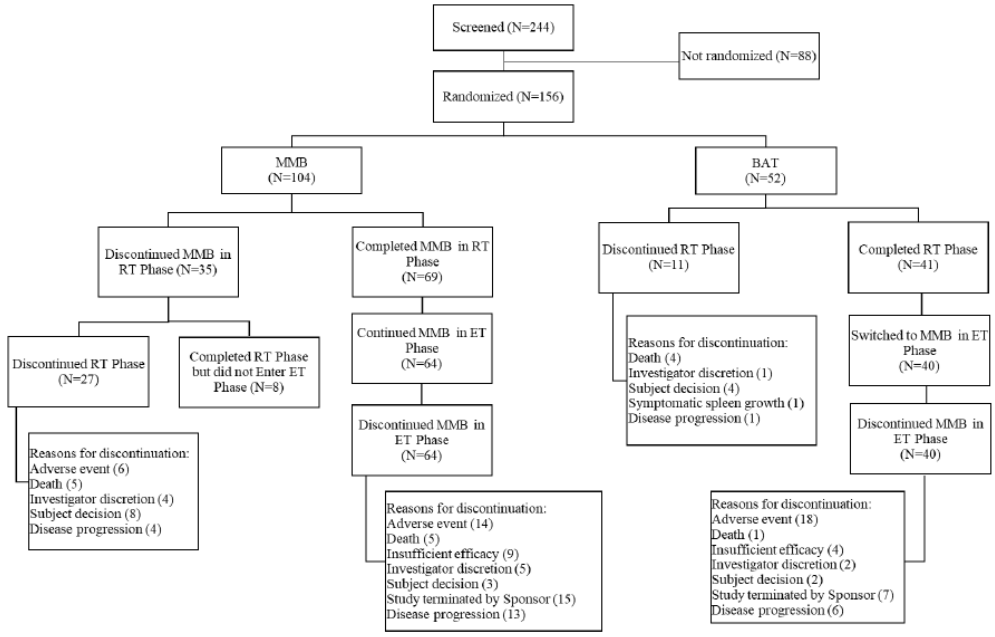
- To determine the effect of MMB compared with BAT on the improvement of TSS at Week 24
- To determine the effect of MMB compared with BAT on rate of RBC transfusions through Week 24
- To determine the effect of MMB compared with BAT on RBC TI rate at Week 24
- To determine the effect of MMB compared with RUX on RBC TD rate at Week 24

A sample size of **150 subjects** (2:1 randomization to MMB or BAT) was planned to provide > 95% power to test the primary hypothesis that MMB was superior to BAT in SRR at week 24 at the assumed SRR of 20% for MMB and 1% for BAT. Sample size assumptions were based on data from the small subset of subjects previously treated with RUX in the MMB phase 2 studies CCL09101 and YM387-II-02, and from historic data from the non-Janus kinase (JAK) inhibitor-containing BAT arm of COMFORT-II, a phase 3 study of RUX versus BAT in JAK inhibitor-naïve subjects with MF that supported the initial approval of RUX for MF (Harrison, 2012). All statistical tests were 2-sided and performed at the 5% significance level unless otherwise specified.

In SIMPLIFY-2 study, data cutoff for Week 24 Interim Analysis was **28 July 2016** and data cutoff for Week 48 Interim Analysis was **12 September 2017**.

156 subjects were randomized 2:1 to either MMB (104 subjects) or BAT (52 subjects) treatment in the RT phase. 69 of the 104 subjects (66.3%) in the MMB group and 41 of the 52 subjects (78.8%) in the BAT group completed treatment in the RT phase. In the ET phase, 64 of the 104 (61.5%) MMB-treated subjects continued to receive MMB (MMB to MMB) and 40 of the 52 (76.9%) BAT-treated subjects

switched to MMB (BAT to MMB). Overall, most subjects in the ET phase completed Week 48 (Week 24 in ET Phase) visits or later (49 of 64 MMB to MMB [76.6%] subjects and 20 of 40 BAT to MMB [50.0%] subjects).



Abbreviations: BAT = best available therapy; ET = Extended Treatment; ITT = intent-to-treat; MMB = momelotinib; RT = Randomized Treatment
Source: Table 15.8.1.3, Listing 16.2.1.3, and Listing 16.2.1.4

Figure 31: Subject disposition flow chart (SIMPLIFY-2)

Based on the available data for subjects who entered the RT phase, 95.2% in the MMB group and 94.2% in the BAT group reported the use of any prior MF therapy. Similarly, in the ET phase, 95.3% of MMB to MMB and 100.0% of BAT to MMB subjects reported the use of prior therapy. Per inclusion criterion 4, all subjects must have been treated with ruxolitinib for at least 28 days and met treatment requirements outlined in the protocol. Five subjects did not meet this criterion. Data on initiation and duration of ruxolitinib were missing for 22 subjects (13 who were randomized to the MMB arm and 9 who were randomized to the BAT arm). Other than ruxolitinib, the most frequently reported (⩾ 10% of total subjects in each phase) prior MF therapy was hydroxyurea (24.4% and 19.2%, respectively).

Primary Efficacy Endpoint: SRR at Week 24 based on ≥ 35% reduction in spleen volume from baseline

Table 78: Analysis of Splenic Response Rate at Week 24 (Randomized Treatment Phase, Intent-to-Treat Analysis Set, SIMPLIFY-2)

	MMB (N = 104)	BAT (N = 52)
Responder, n (%)	**7 (6.7%)**	**3 (5.8%)**
95% exact CI	0.0275, 0.1338	0.0121, 0.1595
Proportion difference - stratified CMH method (95% CI)	0.01 (-0.09, 0.10)	
p-value	0.90	
Proportion difference - unstratified CMH method (95% CI)	0.01 (-0.07, 0.09)	
p-value	0.82	
Proportion difference - unstratified exact method (95% CI)	0.01 (-0.16, 0.18)	
p-value	1.00	
Non-responder, n (%)	**97 (93.3%)**	**49 (94.2%)**
Baseline spleen volume not available	0	0
Spleen volume at Week 24 not available	34 (32.7%)	13 (25.0%)
Last participation date < Day 141 in RT phase	23 (22.1%)	10 (19.2%)
< 35% spleen volume reduction at Week 24	63 (60.6%)	36 (69.2%)
> 0% spleen volume increase at Week 24	34 (32.7%)	19 (36.5%)

Abbreviations: BAT = best available therapy; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = intent-totreat; MMB = momelotinib; RT = Randomized Treatment 95% Exact CI is based on Clopper-Pearson method without stratification

Secondary Efficacy Endpoint: MPN-SAF TSS response rate at Week 24

Table 79: Analysis of Response Rate in Total Symptom Score at Week 24 (Randomized Treatment Phase, Intent-to-Treat Analysis Set, SIMPLIFY-2)

	MMB (N = 104)	BAT (N = 52)
Total Symptom Score status at baseline		
Missing	0	0
TSS = 0	1 (1.0%)	3 (5.8%)
TSS > 0	103 (99.0%)	49 (94.2%)
TSS Response Rate at Week 24		
Subjects evaluable at Week 24	103	51
TSS = 0 at baseline and TSS > 0 or missing at Week 24	0	2 (3.9%)
Responder, n (%)	**27 (26.2%)**	**3 (5.9%)**
95% exact CI	0.1804, 0.3580	0.0123, 0.1624
Proportion difference - stratified CMH method (95% CI)	0.20 (0.09, 0.32)	
P-value	< 0.001	
Non-responder	**76 (73.8%)**	**48 (94.1%)**
Last participation date < Day 162 in RT phase	28 (27.2%)	10 (19.6%)
Last participation date ≥ Day 162 and TSS at Week 24 not available	3 (2.9%)	3 (5.9%)
< 50% reduction from baseline at Week 24	45 (43.7%)	34 (66.7%)
> 0% increase from baseline at Week 24	25 (24.3%)	23 (45.1%)

Abbreviations: BAT = best available therapy; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; DB =double-blind; ITT = intent-to-treat; MMB = momelotinib; RT = Randomized Treatment; TSS = Total Symptom Score a 95% Exact CI is based on Clopper-Pearson method without stratification TSS rate analysis at one visit only included evaluable subjects (ie, those with TSS > 0 at baseline or with TSS = 0 at baseline but with TSS > 0 or missing at that visit).

Secondary Efficacy Endpoint: TI response rate at Week 24

The difference was nominally significant in the SIMPLIFY-2 trial

Table 80: Analysis of RBC Transfusion Independence Response Rate at Week 24 (Randomized Treatment Phase, Intent-to-Treat Analysis Set, SIMPLIFY-2)

	MMB (N = 104)	BAT (N = 52)
Responder, n (%)	**45 (43.3%)**	**11 (21.2%)**
95% exact CI	0.3359, 0.5335	0.1106, 0.3470
Proportion difference - Stratified CMH method (95% CI)	0.23 (0.09, 0.37)	
P-value	0.001	
Non-responder, n (%)	**59 (56.7%)**	**41 (78.8%)**
Transfusion (except bleeding) in the last 12 weeks	30 (28.8%)	28 (53.8%)
Any hemoglobin assessment < 8 g/dL in the last 12 weeks	23 (22.1%)	20 (38.5%)
Last participation date prior to Day 162 in RT phase	28 (26.9%)	10 (19.2%)
Other	11 (10.6%)	4 (7.7%)

Abbreviations: BAT = best available therapy; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT =intent-to-treat; MMB = momelotinib; RBC = red blood cell; RT = Randomized Treatment Note: 95% Exact CI is based on Clopper-Pearson method without stratification.

Main supportive study for JAKi-treatment naïve patients: **Study GU-US-352-1672**

GS-US-352-1672 was a phase 2, open-label, single-arm, multicenter, translational biology study of the effect of MMB on TI and relevant disease-specific biomarkers related to iron metabolism and inflammation in transfusion-dependent subjects with PMF or post-PV/ET MF. The primary objective was to determine the TI response rate in transfusion-dependent subjects with MF treated with MMB. Other secondary endpoints included no RBC transfusions for ≥ 8 weeks anytime by week 24, SRR at week 24 and TSS response rate at week 24.

The study enrolled 41 subjects aged ≥ 18 years with PMF or post-PV/ET MF of high-risk, intermediate-2 risk, or intermediate-1 risk and TD at baseline. Most subjects (87.8%) were JAK inhibitor naïve at baseline.

Outcomes and estimations

- TI response rate by week 24: Fourteen of 41 subjects (**34.1%**; 90% CI: 22.0, 48.1) reached TI by week 24. Of the 14 subjects with a TI response by week 24, 11 had baseline Hgb ≥ 8 g/dL and 3 had baseline Hgb <8 g/dL. Non-responders included 5 subjects (12.2%) who discontinued the study before day 84 (ie, 12 weeks before week 24).
- Proportion of patients with no RBC transfusions for ≥ 8 weeks anytime by week 24: By week 24, 16 subjects (39.0%; 90% CI: 26.2, 53.1) had no RBC transfusion for ≥ 8 weeks at any time.
- SRR at week 24: Five of 41 subjects (**12.2%**; 90% CI: 4.9, 23.9) had a ≥ 35% reduction from baseline in spleen volume at week 24. Spleen volume at week 24 was not available for 15 subjects (36.6%).

- TSS response rate at week 24: Six of 38 evaluable subjects (**15.8%**; 90% CI: 7.1, 28.8) had a ≥ 50% reduction from baseline in TSS at week 24. TSS at week 24 was not available for 17 evaluable subjects (44.7%).
- Hgb levels: MMB induced an increase in Hgb that was maintained over time. In the overall biomarker analysis set, mean Hgb levels were 8.0 g/dL at baseline, 8.8 g/dL at week 2, and 8.9 g/dL at week 24.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

Study design

The applicant has submitted the results of three phase 3 randomised controlled studies and one single-arm trial to support the indications:

- in patients that have been treated with ruxolitinib:
  - MOMENTUM with 24 weeks randomized, double-blind treatment period and open-label extended treatment phase (up to 180 weeks) with momelotinib treatment in both arms. Danazol-treated subjects who did not cross-over to momelotinib at Week 24 had the option to continue danazol as open-label treatment through week 48.
  - SIMPLIFY-2 with 24 weeks randomised open-label treatment period and open-label extended treatment phase (up to 168 weeks) with momelotinib treatment in both arms.
- in JAK inhibitor naïve patients:
  - SIMPLIFY-1 with 24 weeks randomized, double-blind period and up to 5 years open-label, with momelotinib monotherapy after 24 weeks in both arms
  - GU-US-352-1672 open-label, single-arm trial with momelotinib monotherapy.

Patients have been randomised at 2:1 or 1:1 ratio to momelotinib or controls in

- MOMENTUM trial (195 patients: 130 to momelotinib arm and 65 to danazol arm),
- SIMPLIFY-2 trial (156 patients: 104 to momelotinib arm and 52 to best available therapy arm)
- SIMPLIFY-1 trial (432 patients: 215 to momelotinib arm and 217 to ruxolitinib arm)

or treated in a single-arm GU-US-352-1672 trial (41 patients).

The efficacy assessment of momelotinib in patients with moderate to severe anaemia (Hgb < 10 g/dL, as per eligibility criteria) in patients previously treated with ruxolitinib is mainly based on the results of the MOMENTUM trial. In the JAK inhibitor naïve setting, the efficacy of momelotinib in patients with moderate to severe anaemia is mainly based on post-hoc analysis in the subgroup of patients with Hgb <10 g/dL.

Starting dose justification and adjustments

The dose of momelotinib tablet was 200 mg once daily in all trials, supported by the results of early dose-finding studies with capsule to tablet formulation. For the E-R analyses please refer to PK/PD part.

Treatment was to be interrupted or reduced due to thrombocytopenia, neutropenia, or other toxicities at investigator discretion. Doses were reduced by sequential decrements (150 mg, 100 mg and 50

mg). Patients had to permanently discontinue treatment in case of leukemic transformation, pregnancy or disease progression.

Concurrent active anti-MF therapy while on study drug was prohibited, except in the control arm of the SIMPLIFY-2 trial. Patients in the control arm were also allowed to cross-over before the end of the 24 week randomization phase in case of confirmed splenic progression (defined differently across studies).

Patients received MMB treatment as long as they benefitted and tolerated MMB. Most common reasons for MMB discontinuation during the RT and OL phases included adverse events, insufficient efficacy, disease progression and subject decision. However, many patients remained on treatment long term as evidenced by the long-term extension safety study (XAP study), with most subjects maintaining their Week 24 responses and with induction of new responses in week 24 non-responders, waiving the need for guidance on treatment duration into the SmPC.

Targeted patient population as per eligibility criteria

All phase 3 trials only included adults who were required to have confirmed diagnosis of PMF in accordance with the World Health Organization (WHO) criteria, or Post-PV/ET MF in accordance with the IWG-MRT criteria. In addition, prognostic scoring systems were considered for eligibility, with haemoglobin < 10 g/dL being an important variable contributing to the risk category in IPSS (1 point), DIPSS (2 points) and DIPSS plus (1 point) models for primary MF. The latter model also includes transfusion needs as a variable (1 point).

In MOMENTUM trial eligible subjects were required to have received prior treatment with an approved JAK inhibitor for ≥90 days or less if complicated with hematologic toxicity. A wash-out period of at least 2 weeks was required since previous JAK inhibitor therapy. Eligible patients also had baseline splenomegaly (defined as palpable spleen at ≥ 5 cm below the LCM or with volume ≥ 450 cm^3), were symptomatic (defined as MFSAF TSS ≥ 10 and applied to overcome intra-patient variability in TSS over time) and had at least moderate anaemia (defined as Hgb < 10 g/dL) at screening (within 6 weeks before randomization). Only patients with high, intermediate-2 or intermediate-1 risk (defined by DIPSS or DIPSS-Plus) were eligible. This study also allowed enrolment of patients with severe thrombocytopenia (defined as platelet counts ≤ 50 x 10^9/L, however not lower than 25 x 10^9/L).

In supportive SIMPLIFY-2 trial, a similar population as in the MOMENTUM study were included, i.e. patients who received current or prior treatment with ruxolitinib that was complicated with hematologic toxicity. Similarly, patients were required to have baseline splenomegaly (defined as palpable spleen at ≥ 5 cm below the LCM) and had high or intermediate-2 risk (defined by DIPSS). Also intermediate-1 risk patients were eligible, provided it was associated with symptomatic splenomegaly and/or hepatomegaly.

In contrast to the MOMENTUM study patients enrolled in the SIMPLIFY-2 study were not required to respect a wash-out of prior JAK inhibitor therapy. In addition, study eligibility was not restricted to patients with at least moderate anaemia, although the likelihood of inclusion of anaemic patients was higher due to selection by risk. In addition, patients in the SIMPLIFY-2 study were not required to be symptomatic.

In SIMPLIFY-1 trial, only patients with no prior treatment with a JAK inhibitor were eligible. Patients were required to have high-risk or intermediate-2 risk MF (defined by IPSS), or to have intermediate-1 risk (IPSS) associated with symptomatic splenomegaly, hepatomegaly, anaemia (Hgb < 10.0 g/dL), and/or unresponsive to available therapy.

Similar as for the SIMPLIFY-2 study, the SIMPLIFY-1 study was not designed to study the effect of momelotinib in anaemia, with inclusion of mildly anaemic (Hgb ≥ 10 g/dL and < 12 g/dL) as well as non-anaemic patients in the overall eligible study population. Patients were also not required to be symptomatic.

In the early single-arm GU-US-352-1672 study, patients with high-risk or intermediate-2 risk (per DIPSS) or intermediate-1 risk per DIPSS with symptomatic splenomegaly and/or hepatomegaly,

transfusion dependent at baseline (defined as ≥ 4 U RBC transfusion in the 8 weeks prior to the first dose of MMB) were eligible. There was no requirement with regard to prior JAK-inhibitor therapy.

Comparators

In the MOMENTUM trial in JAKi exposed patients (first patient enrolled in April 2020), the efficacy and safety of momelotinib was compared to danazol. Although there is no standard-of-care in patients previously treated with a JAK inhibitor, during scientific advice the use of a single orally administered comparator was supported as it allows a double-blinded study design, needed to mitigate bias in the primary endpoint of TSS response rate. The choice of the gonadoreline antagonist danazol was supported given the focus of the momelotinib development on the effect on anaemia. Danazol is recommended by clinical guidelines for the management of MF-associated anaemia, mainly based on case series of 50 consecutive patients with MF and anaemia (Cervantes, 2015). The dose of danazol used in the MOMENTUM study (total daily starting dose of 600 mg with reduction to 400 mg or less from Week 48 to the minimum necessary dose to maintain response) was consistent with the dose used in the publication by Cervantes et al. (2015) and recommended in clinical guidelines.

However, up to today danazol is not approved in the EU for management of MF-associated anaemia. In 2021 fedratinib has received approval in the EU for treatment of disease-related splenomegaly or symptoms in MF patients including those patients who previously received treatment with ruxolitinib. Nevertheless, it can be taken into consideration that the MOMENTUM trial was designed and initiated before fedratinib was approved and available in the EU.

While danazol was accepted as a relevant comparator for a superiority claim (as a co-primary endpoint), the absence of well-controlled data supporting danazol as active comparator (e.g. versus placebo or other therapies used for anaemia management in patients with MF) is hampering the interpretation of the non-inferiority testing for TI rate at Week 24 this study. The clinical relevance of the selected non-inferiority margin is therefore also considered uncertain. Post-hoc baseline-matched indirect comparison (MAIC) analyses are suggestive for a benefit in TI rate of DAN versus placebo [odds ratio for TI during 6 months: 5.47 (95% CI: 1.88, 15.91); placebo data retrieved from a phase 3 randomized study comparing pomalidomide and placebo in transfusion dependent MF patients, Tefferi 2017], of DAN versus BAT [odds ratio for TI rate at Week 24: 2.387 (95% CI: 0.643, 8.859)] and of MMB versus placebo [odds ratio for TI during 6 months: 6.80 (95% CI: 3.00, 15.40)], however, limitations intrinsic to indirect comparisons, accentuated by the relatively small effective sample size after weighting in the DAN arm of the MAIC analysis compared to placebo (DAN 23.4 versus placebo 77), should be taken into consideration.

In supportive SIMPLIFY-2 trial in ruxolitinib-treated patients (first subject enrolled in July 2014) the efficacy and safety of momelotinib was compared to best available therapy (BAT) as per investigator's discretion in accordance with standard of care, given there were no approved therapies in EU for patients with MF who were previously treated with ruxolitinib at the time of study initiation. In addition, sequential or concurrent administration of more than one BAT was allowed, and BAT could change anytime during the study except at screening. Hence, the study was designed as an open-label study. Although any agent(s) approved for the treatment of MF or considered standard of care were allowed including no active therapy, the vast majority of patients in the BAT arm was treated with ruxolitinib (88.5%) and only a minority (12.5%) of these received the recommended dose of ruxolitinib 20 mg twice daily (dosage range of 5 -20 mg was allowed). Other main administered treatments were hydroxyurea (23.1%) and prednisone/prednisolone (11.5%). Only 2 subjects (3.8%) received no therapy.

In SIMPLIFY-1 trial in JAKi naïve patients (first subject enrolled January 2014), the choice of ruxolitinib as active comparator was considered acceptable, as it is current standard of care in the early treatment setting. The starting dose of ruxolitinib and dose modification guidelines used in the study are largely in agreement with the Jakavi (ruxolitinib) SmPC.

In the early single-arm GU-US-352-1672 translational trial in JAKi naïve patients there was no active comparator.

Choice of endpoints

Reduction of spleen volume (assessed by splenic response rate) and improvement of disease-related symptoms (assessed by total symptom score response rate) has been assessed as primary or key secondary endpoints. Both objectives are related to each other (i.e. reduction of spleen volume is associated with improvement of symptoms). Symptom improvement is considered a clinically relevant treatment benefit, as symptom burden significantly contributes to the reduced health-related quality of life observed in myelofibrosis patients.

In addition, although the SIMPLIFY-1 and SIMPLIFY-2 studies were not designed to investigate the effect of momelotinib on anaemia-related outcomes as primary endpoints, the effect of MMB on transfusion requirements was also assessed in all studies. Transfusion dependency is known to impact prognosis and is considered of relevance for the momelotinib development focused in its later stage on the relieving disease-related and treatment-related anaemia. The currently approved JAK inhibitors do not address optimally disease-related cytopenias and often induce those (including anaemia).

In the phase 3 studies, a hierarchical testing approach was used for the analysis of primary and key secondary efficacy endpoints, which is considered adequate to control the study-wise type I error at 5%, also in case of more than one primary endpoint without being composite primary endpoints (cfr. MOMENTUM)

The MOMENTUM trial includes 2 primary endpoints, i.e. the assessment of improvement of symptoms, by evaluating the MFSAF total symptom score (TSS) response rate at week 24, and assessment of anaemia-related outcomes, by evaluating the transfusion independency (TI) response at week 24. Both primary endpoints were however not designed as co-primary endpoints, as recommended during scientific advice, meaning that TSS must be positive along with transfusion independence (EMA/CHMP/SAWP/128654/2019; EMA/CHMP/SAWP/497222/2019). The study met both primary endpoints if superiority of TSS 24 was significant and at least non-inferiority of TI 24 was significant.

The first primary endpoint is the MFSAF v4.0 TSS response rate at week 24, defined as the proportion of patients with 50% reduction in mean TSS (calculated as the sum of the daily scores of the 7 items of the MFSAF v4.0) over the 28 days immediately prior to the end of Week 24 compared to baseline. The Myelofibrosis Symptom Assessment Form version 4.0 Diary (MFSAF v4.0) includes 7 items considered to be important symptoms of MF: fatigue, night sweats, pruritus, abdominal discomfort, pain under ribs on left side of body, early satiety, and bone pain. An appropriate anchor-based meaningful change threshold (MCT) analysis has been conducted to justify the 50% MCT.

The second primary endpoint was Transfusion Independency (TI) rate at Week 24, defined as the proportion of subjects with TI status (i.e. not requiring RBC or whole blood transfusion for ≥ 12 weeks, with all Hgb levels during the ≥ 12-week interval of ≥ 8 g/dL) at the end of Week 24. TI rate at Week 24 was first tested for superiority, if the superiority test for TI at week 24 was not significant, a non-inferiority test was to be performed. Switching of objective is considered an appropriate approach in case of uncertain magnitude of advantage without adjustment for multiplicity, however the clinical relevance of non-inferiority in transfusion dependency rate is uncertain, considering the lack of an acceptable active comparator.

The splenic response rate (SRR) at week 24, defined as a reduction in spleen volume of ≥ 35% from baseline as measured by MRI or CT scan, was included as key secondary endpoint (third one). This criterion is in line with the IWG-MRT criteria. SRR was tested for superiority.

In SIMPLIFY-2 trial, the primary endpoint was SRR at week 24, similarly defined as the proportion of subjects with a reduction in spleen volume ≥ 35% from baseline, which was tested for superiority. TSS response rate at week 24 was the first secondary endpoint, also tested for superiority.

Although similarly defined as in the MOMENTUM study (≥ 50% reduction in TSS), assessment of TSS in this study was based on a different PRO measure, i.e. the modified MPN-SAF v2.0 TSS. TSS was based on 7 of the 8 items (excluding inactivity), which are the same items as for the MFSAF v4.0 TSS.

TI rate at week 24 was also included as secondary endpoint (third one). It was defined as the proportion of subjects with TI in the terminal 12 before the Week 24 visit, with TI defined slightly different compared the MOMENTUM study, i.e. not requiring RBC transfusions and no central or local laboratory haemoglobin (Hgb) level < 8 g/dL. TI rate at Week was also tested for superiority.

In the SIMPLIFY-1 trial, the endpoints were similar as in the SIMPLIFY-2 study with SRR at Week 24 being the primary endpoint. The testing strategy was however different with first non-inferiority testing for SRR and TSS response rate at Week 24, which was acceptable given the uncertainty on the magnitude of advantage of momelotinib compared to ruxolitinib for these endpoints. The selected non-inferiority margins seemed however to be arbitrarily chosen, without clinical judgement on the importance of loss of efficacy of MMB compared to the reference of RUX that is associated with these non-inferiority margins [0.60 in MMB/RUX response ratio scale for primary analysis of SRR (corresponding to preservation of 77% of the RUX/placebo response ratio) and 0.16 in MMB-RUX response difference scale for exploratory analysis (corresponding to preservation of around 50% of the treatment effect of the ruxolitinib control compared to placebo); 0.67 in MMB/RUX response ratio for primary analysis TSS response ratio]. However we note that these values correspond to the lower bound of the 95% confidence intervals of the MMB/RUX response ratio or MMB-RUX response difference, and that the chance of the true difference being worse than that suggested by this bound is generally considered acceptably small.

In an early single-arm GU-US-352-1672 trial, the primary objective was to determine the TI response rate in transfusion-dependent subjects with MF treated with MMB.

Duration of trials

Week 24 data presented for the MOMENTUM study are derived from the primary analysis with data cut-off date of **03 Dec 2021**, which is also the date when the last subject reached the Week 24 time point (first subject screened: 07 Feb 2020). Week 48 analysis data presented have a cutoff date of **17 Jan 2023.**

With the exception of data for OS, the data presented for the SIMPLIFY-2 study are those as of data cut-off data of **25 Apr 2019**, at the moment of last subject last visit, after a follow-up of around 5 years (first subject screened: 19 Jun 2014). The data presented for OS are those derived from follow-up data from an MMB extension study (XAP) as of the data cutoff date of 03 Dec 2021.

The data presented for the SIMPLIFY-1 study are derived from a follow-up analysis (around 5 years of follow-up) with data cut-off date **01 Jul 2019** (first subject screened: 06 Dec 2013). OS data were also derived as of the data cutoff date of 03 Dec 2021 (XAP). Note that the final (primary) analysis, when subjects had reached the Week 24 time point, was conducted at the data cut-off point of 12 Sep 2016, for which the corresponding CSR has been submitted.

Data presented for the single-arm GU-US-352-1672 trial are those as of data cut-off date of **31 Oct 2017** (first subject screened: 29 Jan 2016)

Adequacy of methods, conduct, analyses and reporting of results

The three phase 3 studies of MMB enrolled patients in Europe, North America, Asia, and Australia/ Australasia, with the majority (approximately 70%) enrolled in Europe (72,8%, 69,5%, 72,4% in MOMENTUM, SIMPLIFY-1 and SIMPLIFY-2, respectively). The supportive phase 2 study GS-US-352-1672 enrolled patients in North America only.

In the MOMENTUM trial, following initial submission of the application, the applicant identified a vendor technical error related to the MOMENTUM anti-myelofibrosis prohibited medication dataset. Subjects which received a prohibited active anti-MF therapy during the randomized treatment period were not flagged in that prohibited anti-MF dataset owing to a dataset filter. After removal of the dataset filter, 6 subjects (5 in the MMB arm and 1 in the DAN arm) were identified as receiving prohibited active anti-MF therapy during the randomized treatment period, which should have been reported as non-responders in the primary analysis of the response-based primary and key secondary endpoints. However, 5 of the 6 subjects were already reported as non-responders in the original analysis of each

of the affected endpoints, thus requiring no corrections to their responder status. As a result, only one patient had been misclassified for the endpoints of transfusion independence status at Week 24 and splenic response rate at Week 24 (subject should be considered non-responder instead of responder). In this report, only the final corrected data are presented. The correction of data is considered not to have affected data interpretation as the affected primary efficacy endpoint (TI rate at Week 24) and 2 key secondary efficacy endpoints [SRR (reduction in spleen volume of ≥ 25% and ≥ 35%) at Week 24] tested in the prespecified hierarchical order shown were still met (non-inferiority for TI rate at Week 24 and superiority for SRR at Week 24).

In MOMENTUM and SIMPLIFY-1 studies, the SAP was finalized while the study was ongoing (SIMPLIFY-1) or even after the last subject last visit (MOMENTUM), however before the date of treatment unblinding for statistical analyses. Though, due to unblinding for safety reasons or because of confirmed splenic progression and eligibility for early cross-over, a total of 22 subjects in the MOMENTUM study and 26 subjects in the SIMPLIFY-1 study were unblinded before Week 24. However, no changes on the content of the SAP were made on the basis of blinded or unblinded data review, reassuring that the studies integrity.

The MOMENTUM study protocol was globally amended twice with the first subjects only enrolled after the first global protocol amendment. With protocol amendment v2.0, important changes were however introduced in the criteria for early crossing over from DAN to open-label MMB, i.e. revision of criteria for splenic progression and allowing in exceptional circumstances, such as severe splenic progression, the short-term use of restricted anti-MF medication. However, the number of subjects with confirmed splenic progression during the randomized treatment period was low (2 MMB, 6 DAN), with most of them meeting the definition of confirmed splenic progression under both protocol v1.0 and v2.0. In addition, out of the 6 DAN subjects with confirmed splenic progression, no subject received prohibited anti-MF therapy during the randomized treatment period. Therefore, the changes introduced from protocol version v1.0 to v2.0 had only limited impact on the interpretation of the results.

The rate of major protocol deviations in both treatment groups are within acceptable ranges (n = 1 MMB, n = 4 DAN) and are not considered to affect data interpretation. It was further noticed that 13 subjects were included with baseline MFSAF TSS score < 10, which is not in accordance to the inclusion criteria, and which have a potential to influence interpretation of study data. However, given these deviations were balanced between both treatment groups and given their relevance for the claimed indication, this issue is not further pursued. Additional minor violations in PRO data collection were due to a cyberattack which resulted in a small amount of data loss, however the protocol included appropriate missing data strategies for PRO-based endpoints. With regard to the protocol violations related to manipulation of the time zones of completed PRO questionnaires (n = 4), a sensitivity analysis for the MFSAF TSS response rate at Week 24, excluding the affected PRO data, was conducted which is considered acceptable. Although pre-specified per SAP, no further per-protocol sensitivity analyses were conducted, which is considered acceptable given the low rate of important protocol deviations which are not expected to affect data interpretation.

With regard to treatment compliance, the proportion of patients in the MMB and DAN group who managed to take at least 90% of their intended doses was lower in the MMB arm (76.2%) compared to the DAN arm (89.2%) in the randomized treatment phase, likely reflecting the difference in rate of dose modifications (dose reductions or interruptions) due to AEs, which was higher in the MMB arm compared to the DAN arm (34% and 29%, respectively), which was not accounted for in the planned intended cumulative dose, the denominator of the relative dose intensity. This increased rate of dose modifications due to AEs in the MMB arm is however associated with a lower discontinuation rate due to AEs compared to the DAN arm (17.7% and 23.1%, respectively), reflecting that with MMB AEs could be better managed compared to DAN.

In the SIMPLIFY-1 trial the original protocol was amended 3 times during the study, with first subjects enrolled in the study under the original study protocol. As of protocol amendment 1, in- and exclusion criteria were amended to increase of minimal required ANC level and CrCl, and decrease the QTc interval above which patients were excluded. The proportion of subjects screened under the original

protocol and who did not meet the revised eligibility in protocol amendment 1 however was low relative to the overall ITT population and balanced between study treatment arms (2 patients in each arm), with limited impact on the interpretation of the results.

The rate of major protocol deviations in both treatment groups in the double-blind phase of this study was higher compared to the MOMENTUM study and was imbalanced (n = 44 MMB, n = 32 RUX), however the imbalance was mainly driven by an imbalance in GCP violations, not considered to have an important impact interpretation of study data. Other protocol violations were related to missing data of key endpoints. Similar missing data strategies as for MOMENTUM were also applied in the SIMPLIFY-1 study. With regard to violations in eligibility, these were mainly related to the non-exclusion of subjects with active infection of carrier of hepatitis or with non-eligible lab values, not considered to have an important impact on data interpretation. In addition, two subjects, one in each treatment group, were randomized but not treated because of withdrawn consent. These 2 subjects were considered as non-responders in the analyses of primary and key secondary endpoints.

Sensitivity analysis for the per-protocol analysis set, excluding patients with major protocol deviations, were conducted.

Treatment compliance during the double-blind phase was high with 95% and 94% of patients in the MMB and RUX group, respectively, who managed to take at least 90% of their intended doses, and this proportion was still above 80% in the open-label phase.

Given the substantial proportion of missing data (MOMENTUM and SIMPLIFY-2) and the imbalances between treatment arms (MOMENTUM and SIMPLIFY-1), as per guideline on missing data in confirmatory trials (EMA/CPWP/EWP/1776/99 Rev.1, 2010), post-hoc sensitivity analyses using various missing data handling methods, including complete case (CC) analysis [discarding missing data; under missing completely at random (MCAR) assumption], multiple imputation (MI) analysis [under the missing at random (MAR) assumption] and tipping point analyses [exploring the impact of Missing not at random (MNAR) data] have been conducted for all main endpoints of all 3 randomized studies. In addition, exploratory worst-case analyses (imputing non-response for MMB subjects and response for control arm subjects) and modified worst-case analyses have been conducted. These modified worst-case analyses used a conservative imputation mechanism but also accounts for the reasons for discontinuation. Patients in the MMB arm with missing data due to reasons other than disease progression were analyzed as non-responders; for control arm subjects with missing data due to reasons other than insufficient efficacy or disease progression, the more favorable treatment arm was used to impute missing data for the control arm (MMB arm for MOMENTUM and SIMPLIFY-2 for all 3 endpoints and TI rate in SIMPLIFY-1; RUX arm for TSS response and SRR in SIMPLIFY-1)

Statistical analyses

Statistical testing strategy was overall adequate in all three phase 3 studies. Adjustment for multiplicity by applying a hierarchical testing strategy has been considered appropriate. The primary analyses were done on the ITT population, which is a standard approach. For SIMPLIFY-1 and SIMPLIFY-2, post-hoc analyses in the subgroup of patients with moderate or severe anaemia (Hgb <10 g/dL) were conducted.

Missing data in the primary and key secondary response-based endpoints were considered non-responders, which is one of approaches usually applied. For the key secondary endpoint changes from baseline of mean TSS in the MOMENTUM study, missing data in the primary analysis were handled using a mixed model for repeated measurements (MMRM), under the missing at random assumption (MAR). A more conservative sensitivity analysis based on the controlled multiple imputation method, which departures from an MAR (missing at random) assumption but with applying potential missing data mechanism of missing not at random (MNAR), has also been conducted.

Patients concomitantly receiving prohibited active anti-MF therapy were considered non-responders in the primary analysis of the MOMENTUM study, as they might confound the MMB and/or RUX treatment effect. No such approach however was applied for the SIMPLIFY-1 study. Seven subjects in the

SIMPLIFY-1 study (MMB 3, RUX 4) were identified as receiving prohibited active anti-MF therapy according to the MOMENTUM protocol at any time during the randomized treatment period. However, 4 of these 7 SIMPLIFY-1 subjects were non-responders. Given this low number of only 3 patients in whom effects were potentially confounded by concurrent anti-MF therapy relative to the overall ITT population, the impact on the interpretation of the results is considered limited.

The used sample size calculation method in the MOMENTUM study is considered not cautious, in particular due to uninformed underestimation of the DAN effect estimates for TSS response rate and SRR (justified by the applicant due to the lack of any published literature), resulting in an observed proportion difference for TSS response rate that is lower than assumed (15% vs 21%, respectively), still superiority of MMB compared to DAN was met. Furthermore, also the assumed true TI rate for MMB (45%, based on SIMPLIFY-2 results) is an underestimation of the observed Week 24 TI rate (30%), likely due to a larger number of anaemic patients with a higher transfusion burden at baseline relative to SIMPLIFY-2, resulting in a lower than assumed proportion difference (10% vs 24%, respectively) with MMB considered non-inferior compared to DAN (superiority not met). Although the applicant considers the observed proportion difference in TI response rate of 10% as clinically meaningful, this difference was not pre-specified for the study design which was not powered to account for this assumption.

Efficacy data and additional analyses

In general, the interpretation of the response-based primary and key secondary endpoint results of the phase 3 studies MOMENTUM, SIMPLIFY-2 and SIMPLIFY-1 is hampered due to the proportion of missing values at Week 24, which is substantial in particular for the MOMENTUM and SIMPLIFY-2 studies and which is not balanced between the MMB arm and control arm in particular for the MOMENTUM and SIMPLIFY-1 studies. However, in addition to the primary analyses, in which all patients with missing data at Week 24 were considered non-responders, post-hoc sensitivity analyses using various missing data handling methods have been conducted. The results of these sensitivity analyses were overall consistent with the primary analyses. In order to overturn statistical significance, the conducted tipping point analyses identified tipping points which are considered rather implausible (for TSS response and TI rate in MOMENTUM) or could not identify a tipping point (for SRR in MOMENTUM and SIMPLIFY-1). No tipping point analyses were conducted for TSS response rate and TI rate in SIMPLIFY-2 and for TI rate in SIMPLIFY-1 as for these endpoints even the conservative modified worst-case sensitivity analysis (TSS response rate and TI rate in SIMPLIFY-2) and/or the worst-case sensitivity analyses (TI rate in SIMPLIFY-1) showed (nominal) superiority of MMB compared to control, elevating the need to conduct less conservative sensitivity analyses.

With regard to the missed primary endpoint of SRR in SIMPLIFY-2, the applicant did not conduct sensitivity analyses due to the lack of statistical significance and a small number of responders in the original analysis.

In general, the results from conducted sensitivity analyses indicate that neither the information loss nor the methods used to handle missing data had a substantial impact on the study conclusions and therefore reassure on the reliability and the validity of the primary analysis results.

Baseline characteristics, patient population (ITT and by anaemia severity)

- Treated with ruxolitinib

In the MOMENTUM trial patients with an advanced disease and unfavourable prognosis were enrolled. Given that a vast majority of patients had intermediate-2 or high-risk disease according to DIPSS (94.9%), median survival is expected to be only a few years or less. A majority of patients was ≥ 65 years of age (79.5%) and was diagnosed with PMF (64%).

As per study eligibility criteria, all patients were symptomatic, had an enlarged spleen and had at least moderate baseline anaemia (Hgb < 10 g/dL). Around half of patients were suffering from severe

anaemia (Hgb < 8 g/dL; 48%) with minima up to 3.8 g/dL. Therefore, some patients would have been very vulnerable to further haemoglobin decrease under treatment. Only a minority of patient was transfusion independent at baseline (13.8%) and around half of patients (49.7%) were considered transfusion dependent, which is also known as an unfavourable risk factor and impacting quality of life of MF patients. Patients that were not meeting the definitions of TI or TD were considered transfusion requiring (but not fully dependent on transfusions). Further also note that a majority of patients had baseline thrombocytopenia (platelet counts ≤ 150 x 10^9/L) and 15.9% of patients had baseline severe thrombocytopenia (platelet counts ≤ 50 x 10^9/L but > 25 x 10^9/L). Based on the above characteristics and the study eligibility criteria, the majority of the MOMENTUM study population is representative for patients considered intolerant to previous JAK inhibitor therapy due to hematological complications.

Overall, the demographics and baseline disease history and characteristics are well balanced between both treatment arms.

Only a low number of patients with intermediate-1 DIPSS risk were included (n = 7 MMB, DAN = 3. More patients with intermediate-1 DIPSS risk are however included in the SIMPLIFY-2 study.

All patients were previously treated with ruxolitinib, only a minority of patients additionally received prior fedratinib [5.4% MMB (n = 7) vs 3.1% DAN (n = 2)], reflecting that ruxolitinib is currently standard of care in the early treatment setting. The small number of subjects in this subgroup of patients who received prior fedratinib do not allow to make definite conclusions on the comparison with the overall ITT group.

In the SIMPLIFY-2 trial patients seem to have a less advanced disease status as compared to patients in the MOMENTUM study with a smaller proportion of patients with intermediate-2 or high risk disease (75%), a lower median TSS (16) with 29.5% of patients with TSS < 10, a higher median baseline Hgb (9.0 g/dL, range 6 – 16), a higher proportion of patients with baseline TI status (32.7%) and 64.7% of patients ≥ 65 years of age. The proportion of patients with baseline TD status was similar as compared to the MOMENTUM study (54.5%). Compared to the MOMENTUM study, the SIMPLIFY-2 study included more patients with intermediate-1 DIPSS risk [MMB: n = 23 (22%), BAT: n = 16 (31%)], however the proportion of intermediate-1 patients in the anaemia subgroups is smaller, with only 12 intermediate-1 risk patients in the post-hoc defined subgroup of patients with Hgb < 10 g/dL [MMB: 5 (7.5%), BAT: 7 (17.9%)].

As per study eligibility criteria, the SIMPLIFY-2 study population is representative for patients considered intolerant to previous ruxolitinib due to hematological complications. A majority of patients suffered from at least moderate baseline anaemia (Hgb < 10 g/dL; 67.3%) which is the corresponding Hgb threshold used in the MOMENTUM study to select baseline moderate to severe anaemic patients. A smaller fraction of patients compared to MOMENTUM suffered from severe anaemia (Hgb < 8 g/dL; 21.2%).

Although a number of treatment options were allowed, the vast majority of patients in the BAT arm were treated with ruxolitinib (88%), with only a minority of them (12.5%) having received the recommended dose of 20 mg twice daily.

Overall, the demographics and baseline disease history and characteristics are well balanced between both treatment arms with the exception of sex at birth.

Overall, the demographic and disease characteristics of the post-hoc defined subpopulation with at least moderate anaemia (Hgb < 10 g/dL) were consistent with the overall ITT population. As expected, the notable differences in the key baseline demographic and disease characteristic between the hemoglobin subgroups and the ITT population are related to transfusion requirements (proportion of patients transfusion independent at baseline in Hgb < 10 g/dL subgroup versus ITT:13.3% versus

32.7%) and mean hemoglobin values (in Hgb < 10 g/dL subgroup: mean Hgb 8.4 versus ITT: 9.4 g/dL).

Despite a number of imbalances between both treatment arms in this subgroup (not unexpected given the lack of randomization in this particular subgroup), key baseline characteristics in both treatment arms for this subgroup were representative for a population requiring JAKi therapy (TSS ≥10: MMB: 68%, BAT: 72%; Median spleen volume: MMB: 2577 cm^3, BAT: 2049 cm^3; Transfusion dependency: MMB: 79%, BAT: 64%).

- JAKi naive

In the SIMPLIFY-1 trial, patients in general have less advanced disease compared to patients included in the MOMENTUM and to a lesser extent compared to the SIMPLIFY-2 study, mainly driven by differences in study eligibility criteria (JAK-inhibitor naïve patients versus JAK-inhibitor treated patients, no restriction to patients with at least moderate anaemia [Hgb < 10 g/dL], eligibility of asymptomatic patients [TSS < 10]).

Compared to the MOMENTUM study, the SIMPLIFY-1 study included a lower proportion of patients ≥65 years (57%), lower proportion of patients with intermediate-2 and high risk disease (79%; however per IPSS), patients had a lower median TSS (17) with 30% of patients with TSS < 10, a higher median baseline Hgb (10.4 g/dL, range 6 - 19), a majority of patients was baseline TI (69%) and only a minority was TD at baseline (24%). In addition, a small proportion of patients had moderate baseline thrombocytopenia (platelet counts ≤ 100 x 10^9/L; 10%); patients suffering from severe thrombocytopenia (platelet counts ≤ 50 x 10^9/L) were not eligible. The SIMPLIFY-1 study also included intermediate-1 IPSS risk patients (20.6%), however the proportion of intermediate-1 patients in the anaemia subgroups is smaller (13.7%), with only 5 intermediate-1 risk patients in the post-hoc defined subgroup of patients with Hgb < 10 g/dL.

Overall, the demographics and baseline disease history and characteristics are well balanced between both treatment arms, however slightly more subjects had severe anemia (Hgb <8 g/dL: 13.0% versus 9.7%) in the MMB group at baseline.

Only a minority of patients suffered from at least moderate baseline anaemia (Hgb < 10 g/dL; 41.7%). A small fraction of patients suffered from severe anaemia (Hgb < 8 g/dL; 11.3%). The baseline haemoglobin was not a stratification factor. With the exception of baseline transfusion requirements and hemoglobin values, clinically important demographic and baseline characteristics were consistent in the post-hoc defined subgroup of patients with at least moderate anaemia (Hgb < 10 g/dL) compared with the ITT population, such as proportion of patients with TSS ≥10, median spleen volume and mean platelet count. As expected, patients with at least moderate anaemia had a lower mean Hb value (8.6 g/dL versus 10.6 g/dL) and had higher transfusion requirements at baseline (proportion of patients transfusion independent at baseline: 36.7% versus 69.2%) compared to the ITT population.

Between the MMB and RUX arms within the post-hoc defined subgroup of patients with Hgb < 10 g/dL, the overall demographic and disease characteristics were consistent, however small differences in key demographic and disease characteristics in the < 10 g/dL subgroup may predict to favor the RUX arm as the MMB arm represent a slightly older population with more severe anemia (23.6% versus 22.1%) and transfusion dependence (57.0% versus 45.3%). Also, there were more subjects in the RUX arm with platelet counts > 200 x 10^9/L (MMB: 43.0%, RUX: 50.5%) and per the prescribing information, these subjects likely received the optimal RUX starting dose of 20 mg BID. Other differences did not appear to be substantial.

Single-arm GU-US-352-1672 trial

The study enrolled 41 subjects aged ≥ 18 years with PMF or post-PV/ET MF of high-risk, intermediate-2 risk, or intermediate-1 risk and TD at baseline. Most subjects (87.8%) were JAK inhibitor naïve at baseline.

Endpoints of symptoms response

- Treated with ruxolitinib

The MOMENTUM trial met its first primary efficacy endpoint, demonstrating statistically significant superior MFSAF TSS response rate at Week 24 for MMB over DAN [24.62% (95% CI: 17.49, 32.94) versus 9.23% (95% CI: 3.46, 19.02); p = 0.0095]. With the limits intrinsic to indirect comparison, a TSS response rate at Week 24 of 24.6% might be considered clinically meaningful, as a similar response rate was observed with in ruxolitinib-pretreated patients who received treatment with fedratinib 400 mg QD in the JAKARTA-2 study (using different modified 6-item MFSAF v2.0 measure).

This primary endpoint was supported by the key secondary endpoint of change from baseline MFSAF TSS at Week 24 which demonstrated a statistically significant superior difference in LS mean change, as observed in the MMRM analysis [-9.36 (1.08) versus -3.13 (1.62); p = 0.0014]. Over time, the LS mean changes from baseline in TSS was consistently larger in the MMB group compared to the DAN group. This difference in LS mean change was consistent across all individual symptoms.

Updated follow-up data of TSS response rate at Week 48 showed that in evaluable patients MMB led to durable TSS responses, with 72% of the MMB→MMB group and 100.0% of the DAN→MMB group maintaining their TSS response at week 48, and that MMB was also able to induce new responses in week 24 TSS non-responders (28% of the MMB→MMB group and 40.0% of the DAN→MMB group). Median duration of TSS response was not reached in both treatment groups.

In the supportive SIMPLIFY-2 study, despite lack of a washout period, despite the differences in the used PRO instruments and despite the uncertainty in this endpoint due to the open-label design of this study, the Week 24 modified MPN-SAF v2.0 TSS response rate observed in the SIMPLIFY-2 study supports the effect of MMB on symptom response observed in the MOMENTUM study, with a similar TSS response rate at Week 24 of 26.2% (95% CI: 18.04, 35.80), which was numerically higher compared to the BAT control arm [5.9% (95% CI: 1.23, 16.24); p < 0.001]. However, this numerical improvement in TSS is only of nominal significance due to missed statistical significance in the primary endpoint. In addition, note that in the BAT group the vast majority of patients (88%) received ruxolitinib, but only a minority of them (12%) received the full recommended dose of 20 mg BID. This suboptimal ruxolitinib dosing in the BAT group might also have contributed or might explain the numerical improvement in TSS response rate with MMB compared to BAT. (ITT analysis)

Also in the corresponding post-hoc defined subgroup of patients with at least moderate anaemia (Hgb < 10 g/dL) in the SIMPLIFY-2 study, TSS response rate at Week 24 in the MMB group (32.3%) was consistent higher compared to the corresponding subgroup in the BAT group (2.6%) (post-hoc subgroup analysis).

In addition, the SIMPLIFY-2 study also provided supportive evidence for the intermediate-1 subgroup for which only scarce data were available in the MOMENTUM study, showing a consistent meaningful benefit of MMB compared to BAT, with a response rate in the MMB arm in this subgroup (26.1%) that was consistent with the MMB arm of ITT population (26.2%) (post-hoc subgroup analysis).

However, reliability of PRO data in this study is compromised taking into account the open-label design. Bias in favour of the MMB group can therefore not be excluded. As TSS data were not collected after Week 24, duration of TSS response at Week 24 was not evaluable.

In **conclusion**, the benefit of MMB in JAKi treated patients for the treatment of disease-related symptoms is considered justified, mainly based on the results of the pivotal MOMENTUM trial in the JAK inhibitor pre-treated patient population with haemoglobin <10 g/dL per protocol eligibility.

- JAKi naïve

The SIMPLIFY-1 trial failed to demonstrate non-inferiority of MMB over RUX in the secondary endpoint of modified MPN-SAF v2.0 TSS response rate at Week 24 with a numerical higher TSS response rate in the ruxolitinib control group [28.4% (95% CI: 22.45, 35.03) versus 42.2% (95% CI: 35.43, 49.15); p = 0.98]. The mean change in TSS from baseline at Week 24 by MMRM analysis (exploratory post-hoc analysis) showed a non-significant difference in favour of RUX (LS mean change from baseline -5.87 for MMB versus -7.11 for RUX; p = 0.1380). (ITT analysis)

Also in the post-hoc defined subgroup of subjects with at least moderate anemia (25.0% MMB, 36.2% RUX), the proportion differences were consistent with the ITT population. Though, lower TSS response rate was observed in the RUX arm for the subgroup compared to ITT, resulting in numerically smaller differential treatment effects. Consistent with the ITT, the mean within-subject improvements in each treatment arm in the Hgb < 10 g/dL subgroup were however rather similar [MMB arm: -5.06 points vs RUX arm: -6.68; LS mean difference: 1.62 ((95% CI: -0.85, 4.09) (post-hoc subgroup analysis)

Also in the subgroup of intermediate-1 patients, including those with anaemia, results are generally consistent with the ITT (post-hoc subgroup analysis).

Failure to show non-inferiority of MMB compared to RUX in TSS response rate raises concerns on the robustness of analysis and on the clinically relevant magnitude of the observed MMB effect. The cause for not meeting non-inferiority was likely multifactorial, including a higher rate of early discontinuation of patients in the MMB group favouring the RUX control arm, inclusion of subjects with baseline TSS range between 0 - 10 in which there is a high intra-patient variability in TSS over time, and the not rigorously selected noninferiority margin.

The imbalance in early discontinuation was due to more subjects with low-grade adverse events leading to discontinuation of MMB, while such patients in the RUX group underwent dose reductions or temporary dose interruptions. In the primary analysis, these patients were considered non-responders, while they actually may have benefitted MMB treatment in terms of TSS up to their early discontinuation. As such, the primary analysis is expected to be a rather conservative estimate of the MMB effect on TSS response rate. However, missing data sensitivity analyses (complete case analysis, multiple imputation) consistently did not reach statistical significance of the non-inferiority treatment difference.

A best-case sensitivity analysis imputing response for the subjects who discontinued before Day 162 in the MMB group and non-response for those in the RUX group was however able to claim statistical significance for non-inferiority of MMB compared to RUX in TSS response rate. In addition, the tipping point analysis showed that in order to claim statistical significance, a theoretical average shift of at least 8 points lower in patients with missing TSS response data at W24 compared to those with complete data would be required. Although both sensitivity analysis are considered rather implausible, they suggest that the imbalance in early discontinuation may have contributed to the unmet TSS response rate results in SIMPLIFY-1, as they favoured the RUX study control arm.

As TSS data were not collected after Week 24, duration of TSS response at Week 24 was not evaluable.

Despite the numerically lower TSS response rate for MMB compared to RUX, a clinically meaningful magnitude of effect is however suggested given the consistency in magnitude of the MMB TSS response within the overall ITT populations and within the Hgb < 10 g/dL subpopulations with the 2 other phase 3 studies with MMB in JAKi treated patients (MOMENTUM: 24.6%; SIMPLIFY-2: ITT:

26.2%, Hgb < 10 g/dL: 32.3%). Also the LS mean change from baseline TSS at week 24 for MMB was also similar between symptomatic subjects (defined as baseline TSS ≥10) in both SIMPLIFY-1 and MOMENTUM subjects (-8.12 vs -9.36). This provides grounds for extrapolation of the MMB benefit on symptom control in the JAKi treated patient population to the JAKi naïve patient population.

In addition, with the limits intrinsic to cross-trial comparisons, consistent low TSS response rates with placebo or non-JAK inhibitor containing controls in phase 3 studies have been observed, including with other JAK inhibitors [COMFORT-1 (placebo): 5.3%; JAKARTA-1 (placebo): 7%; PERSIST-1 (BAT): 6.5%; MOMENTUM (DAN): 9.2%; SIMPLIFY-2 (BAT): ITT: 5.9%; Hgb < 10 g/dL: 2.6%].

On the other hand, TSS response rate for the ITT reported for MMB in SIMPLIFY-1, MOMENTUM and SIMPLIFY-2 are consistently lower compared to those reported for RUX in SIMPLIFY-1 (42%) and COMFORT-1 (46%) and compared to those reported for the two fedratinib groups in the JAKARTA-1 study (36% and 34%).

Further support for a clinically meaningful magnitude of effect of MMB on disease-related symptoms includes the similar mean within-subject improvements in each treatment arm in both the ITT and Hgb < 10 g/dL subgroup [LS mean difference in Hgb < 10 g/dL subgroup of 1.62 (95% CI: -0.85, 4.09) on a 70-point scale] and the similar improvements in individual symptom items with MMB and RUX (analysis only conducted for ITT).

With regard to the single-arm GU-US-352-1672 trial, data on TSS response rate at Week 24 were not reliable given the high rate of missing data of TSS at Week 24.

In conclusion, considering the consistency in magnitude of the MMB symptom response within the overall ITT populations and in the Hgb < 10 g/dL subpopulation across MMB phase 3 trials as well as the consistent low TSS response rates reported with placebo or non-JAK inhibitor containing controls in phase 3 studies with other JAK inhibitors in the JAKi naïve setting, and taking into account the potential contribution of the imbalance in early discontinuation in favouring the RUX control arm in the SIMPLIFY-1 study, the magnitude of the MMB effect on symptom improvement can be considered clinically meaningful, particularly in the subgroup of JAKi naïve patients suffering with moderate or severe anaemia, although the observed effect is lower when compared to approved JAK inhibitors.

Endpoints of splenic response

- Treated with ruxolitinib

In the MOMENTUM trial, the key secondary endpoint of SRR at Week 24, based on ≥ 35% reduction (as well as on ≥ 25% reduction) in spleen volume from baseline, was met demonstrating statistically significant superior SRR at Week 24 for MMB over DAN [22.31% (95%CI: 15.48, 30.44) versus 3.08% (95% CI: 0.37, 10.68); p < 0.0001]. With the limits intrinsic to indirect comparison, a SRR at Week 24 of 22.31% might be considered clinically meaningful, as a similar response rate of 22.7% was observed in ruxolitinib-pretreated patients who received treatment with fedratinib 400 mg QD in the JAKARTA-2 study.

Updated follow-up data of TI at Week 48 showed that in evaluable patients MMB led to durable splenic responses, with 76% of the MMB→MMB group and 50% of the DAN→MMB group maintaining their splenic response at week 48, and that MMB was also able to induce new splenic responses in week 24 non-responders (24% of the MMB→MMB group and 11% of the DAN→MMB group).

The SIMPLIFY-2 trial failed to demonstrate superiority of MMB over BAT in the primary endpoint of SRR at week 24 [6.7% (95%CI: 2.75, 13.38) versus 5.8% (95% CI: 1.21, 15.95); p = 0.90], and did not support the findings in JAKi treated patients in the MOMENTUM study. However, this is possibly due to confounding because, in contrast to MOMENTUM which required a wash-out period of at least 2 weeks,

no wash-out period after previous anti-MF therapy was required. As a result, in the SIMPLIFY-2 study, the majority of patients in both treatment arms (MMB: 74%, BAT: 75%) maintained the effect of ongoing JAKi therapy (however mostly low dose) while switched to MMB without washout period. This potentially confounding effect is supported by subgroup analysis of the SIMPLIFY-2 study in function of washout period and by clinical data available from the extended open-label treatment periods of the SIMPLIFY studies, which allowed immediate cross-over from RUX to MMB without washout period. (ITT analysis)

Similarly, also in the corresponding subgroup of patients with Hgb < 10 g/dL a low SRR at Week 24 was observed in the MMB group (9.1%), only slightly higher as compared to that observed in the BAT group (5.1%) (post-hoc subgroup analysis).

Also in the intermediate-1 risk subgroup, SRR was low in both treatment arms (post-hoc subgroup analysis).

In **conclusion**, the effect of MMB in the JAKi treated population for the treatment of disease-related splenomegaly is considered demonstrated, based on the results of the pivotal MOMENTUM trial in the JAK inhibitor pre-treated patient population with haemoglobin <10 g/dL per protocol eligibility.

- JAKi naive

In the SIMPLIFY-1 trial, the primary endpoint of non-inferiority of MMB over RUX in SRR at week 24 was met [26.5% (95%CI: 20.74, 32.94) versus 29.5% (95% CI: 23.51, 36.04); p = 0.014], though no clinical judgement for the selected non-inferiority margin has been provided. (ITT analysis)

Also in the post-hoc defined subgroup of subjects with at least moderate anemia (31.4% MMB, 32.6% RUX), p = 0.007), nominal p-values for non-inferiority proportion difference were statistically significant, consistent with the ITT population (post-hoc subgroup analysis).

Also in the subgroup of intermediate-1 patients, including those with anaemia, a consistent benefit of MMB over RUX has been observed compared to the ITT (post-hoc subgroup analysis).

Duration of splenic response at any time was a prespecified exploratory endpoint. Splenic responses seemed to be durable with a median duration of splenic response of 35.9 months in the MMB group and of 19.1 months in the RUX group, however a large majority of patients were censored. A smaller proportion of patients in the MMB group compared to the RUX group reported loss of response (33.3% versus 51.8%, respectively). (ITT analysis)

With the limits intrinsic to cross-trial comparison, SRR at Week 24 for the MMB group of the SIMPLIFY-1 study is consistent to that of the MMB group in the MOMENTUM study (31.4% for Hgb < 10 g/dL subgroup in SIMPLIFY-1, 22.3% in MOMENTUM).

Results of subgroup analysis by baseline platelet count (analysis in ITT population) suggested a differentiated benefit of MMB compared with RUX in thrombocytopenic patients (with baseline platelet counts < 150 × 10^9/L) with better results for SRR: 11/47 (23.4%) vs 2/57 (3.5%); TI rate: 29/47 (61.7%) vs 24/57 (42.1%) and similar TSS response rate pattern 13/45 (28.9%) vs 19/57 (33.3%). The attenuation of RUX treatment effects, in particular of TSS and SRR, based on baseline platelet counts compared with the overall ITT results was not observed with MMB. A comparison of demographics/characteristics of this subgroup with those of the ITT population suggest that the low platelet group reflects a population with more advanced disease relative to the ITT. While baseline TSS was consistent in this subgroup compared to ITT in both treatment groups, the median spleen volume in the RUX arm of the low platelet subgroup is larger than the spleen volume in the RUX arm of the overall ITT population (2240.1 vs 1910.8 cm^3, respectively), while the median spleen volume in the MMB arm of the low platelet subgroup is smaller than that in the overall ITT population (1734.0 vs 2009.6 cm^3, respectively). The impact of the lower spleen volume in the RUX arm compared with the

MMB arm in the low platelet subgroup may have contributed to the differential treatment effects in this subgroup; however, the lower ruxolitinib dose in this population is also considered a substantial contributing factor. (prespecified subgroup analysis)

Given the high rate of missing data of splenic volume at Week 24, the data on SRR at Week 24 for the single-arm GU-US-352-1672 trial were not reliable for evaluation of consistency with SIMPLIFY-1.

In **conclusion**, although no clinical judgement for the selected non-inferiority margins has been provided, both the primary (based on 0.60 non-inferiority margin in MMB/RUX response ratio scale) as well as the exploratory sensitivity analysis (based on 0.16 non-inferiority margin in MMB-RUX response difference scale) consistently showed non-inferiority of MMB compared to RUX. In addition, the point estimates, representing the best estimate of the true difference, although not positive, it is close to zero for the MMB-RUX response rate difference (-0.03) or close to 1 for the MMB/RUX response ratio (0.9), thus tending towards equally efficacious treatments. Taking this into account and considering the consistently very low splenic response rates observed with placebo (≤ 1%) in trials with other JAK inhibitors in the JAKi naïve setting as well as the inability to identify a tipping point to overturn the statistical significance of the non-inferiority treatment difference in the tipping point analysis, the magnitude of benefit of MMB on disease-related splenomegaly in JAKi naïve patients with moderate or severe anaemia can be considered clinically meaningful.

Anaemia-related endpoints

- Treated with ruxolitinib

In the MOMENTUM trial, TI rate at Week 24 was the second primary endpoint. Although no superiority could be demonstrated, this primary endpoint was met as MMB was considered statistically significantly non-inferior compared to DAN [30.0% (95% CI: 22.28, 38.66) versus 20.0% (95% CI: 11.10, 31.77), respectively; p = 0.0116]. Note that at baseline the proportion of patients with TI status was similar (13.1% MMB, 15.4% DAN).

In the subgroup of patients with baseline TD status (prespecified subgroup analysis), which consisted around half of patients (48.5% MMB, 52.3% DAN), a greater proportion of subjects in the MMB group converted to TI at week 24 compared with the DAN group (14.3% vs 8.8%).

Updated follow-up data of TI at Week 48 showed that in evaluable patients MMB led to durable TI responses, with 88.2% of the MMB→MMB group and 80.0% of the DAN→MMB group maintaining their TI response at week 48, and that MMB was also able to induce new responses in week 24 TI non-responders (24.2% of the MMB→MMB group and 50.0% of the DAN→MMB group). Median duration of TI response was not reached in both treatment groups.

Inference of efficacy in the MOMENTUM study for anaemia-related endpoints is however complicated as the treatment effect of DAN over placebo on TI rate has not previously been demonstrated and thus DAN cannot be considered an active comparator suitable for non-inferiority analyses. In addition, the observed treatment difference in TI rate (10%) is lower than expected (24%) and thus there is uncertainty on the clinical relevance of this treatment difference.

Evidence from other (key) secondary endpoints, analysing the effect on the transfusion requirements and on hemoglobin levels, is however supporting at least a protective effect of MMB on anemia:

- With regard to transfusion requirements, a statistically significant higher proportion of patients in the MMB group received no transfusion units (35.4% versus 16.9%) or ≤ 4 RBC units during treatment and up to Week 24, compared to the DAN group (55.4% versus 44.6%). A reduced need to RBC transfusions was also reflected by a lower cumulative transfusion risk at week 24 for MMB (HR = 0.556 for MMB versus DAN) and the longer median time to first RBC unit transfused

during randomized treatment phase (HR = 0.504 for MMB vs DAN). At Week 24, a smaller proportion of patients in the MMB group was considered TD compared to the DAN group (15.4% vs 24.6%).

- With regard to the effect on hemoglobin, during the entire 24 week treatment period, treatment with MMB led to higher proportions of patients with ≥ 1 (53.1% versus 33.8%), ≥ 1.5 (40.0% versus 23.1%), or ≥ 2 g/dL (29.2% versus 20.0%) increases of hemoglobin levels from baseline.
- Post-hoc analyses on transfusion intensity and on anaemia response rates (per IWG-MRT/ELN) were consistent in favouring MMB over DAN.
- A post-hoc Bayesian dynamic borrowing analysis was utilized to calculate the posterior probability of MMB to be superior to DAN in W24 TI rate, which was 93%. With augmenting the MMB arm of the MOMENTUM study with data from the Hgb < 10 g/dL subgroup from the SIMPLIFY-2 study this probability increased to 96%, which supports the assumption that it is likely that superiority may have been achieved with increased sample size.

The SIMPLIFY-2 trial provided supportive data with regard to the effect of MMB on transfusion requirements. For the secondary endpoint of TI rate at Week 24, treatment with MMB resulted in a numerical higher TI rate at Week 24 compared to treatment with BAT [(43.3% (95% CI: 33.59, 53.35) versus 21.2% (95% CI: 11.06, 34.70); nominal p = 0.001), despite a lower proportion of subjects with baseline TI status in the MMB group (30.8% vs 36.5%). However, this numerical improvement in TI rate is only of nominal significance due to missed statistical significance in the primary endpoint. The higher TI rate at Week 24 observed in the MMB group of the SIMPLIFY-2 study compared to the MMB group of the MOMENTUM study is likely due to the higher proportion of patients with baseline TI status in the SIMPLIFY-2 study (30.8% versus 13.1%). (ITT analysis)

In the corresponding subgroup of patients with Hgb < 10 g/dL in the SIMPLIFY-2 study, the TI rate at week 24 obtained with MMB was consistently higher compared to the corresponding subgroup in the BAT group (33.3% versus 12.8%) and corresponded better to the one observed with MMB in the MOMENTUM study (post-hoc subgroup analysis).

Post-hoc subgroup analyses in intermediate-1 patients indicated a consistent treatment benefit of MMB compared to BAT, however with higher response rates in both treatment arms as compared to the ITT population, explained by the lower transfusion requirements or dependency in this lower risk subgroup. (post-hoc subgroup analysis)

Other secondary endpoints further supported the beneficial effect of MMB on transfusion requirements, i.e. TI rate at Week 24 in subjects with baseline TD (32.8% MMB versus 3.7% BAT), TD rate at Week 24 (50.0% versus 63.5%) and RBC transfusion rate during the RT period (0.5 versus 1.2). (ITT analysis)

In **conclusion**, the totality of evidence in the MOMENTUM study, suggesting a trend towards superiority for MMB over DAN, is supporting that MMB does have at least a protective effect on anaemia and associated RBC transfusion requirements in JAKi treated patients with haemoglobin <10 g/dL per protocol eligibility. However due to the overall non-confirmatory nature of data, anaemia treatment effect is not demonstrated. As a result, the initially claimed indication was changed.

- JAKi naive

For the secondary endpoint of TI rate at Week 24 in the SIMPLIFY-1 trial, treatment with MMB resulted in higher TI rate at Week 24 compared to treatment with RUX [66.5% (95% CI: 59.78, 72.79) vs 49.3% (95% CI: 42.48, 56.16); nominal p < 0.001]. Note that at baseline a similar proportion of patients had TI status (68.4% MMB, 70.0% RUX). However, this numerical improvement in transfusion

burden are only of nominal significance due to missed statistical significance in the previous endpoint in the hierarchical testing. Results should thus rather be seen as exploratory. (ITT analysis)

In the subgroup of patients with baseline TD status, which consisted only a minority of patients (24.7% MMB, 24.0% RUX), a greater proportion of subjects in the MMB group converted to TI at week 24 compared with the RUX group (30.2 versus 17.3%) (post-hoc exploratory analysis).

In the post-hoc defined subgroup of subjects with at least moderate anemia a slightly larger treatment difference in favor of MMB in TI rate at week 24 has been observed compared to ITT (MMB 46.5 versus RUX 27.4; superiority % diff: 22), despite fewer subjects in MMB arm that are TI (29% vs 44%), more subjects that are TD (57% vs 46%) and more subjects that have severe anaemia (32% vs 22%). Compared to baseline, the TI rate at Week 24 increased from baseline and the TD rate at Week 24 decreased from baseline, while converse effects were observed in the RUX group with Hgb < 10 g/dL. (post-hoc exploratory analysis).

Also in the subgroup of intermediate-1 patients, including those with anaemia, a consistent benefit of MMB over RUX have been observed compared to the ITT (post-hoc subgroup analysis).

The observed effect however was measured at the time of a nadir in haematology values during RUX treatment after which recovery is known to occur, raising concerns on the clinical relevance of the MMB benefit compared to RUX and on whether the advantage of MMB compared to RUX would be maintained beyond week 24. Due to the option of cross-over, no data are available on the persistence of the transfusion independency effect of momelotinib compared to ruxolitinib after Week 24. Data on transfusion intensity up to Week 36 with ruxolitinib are however available in the COMFORT-1 study which showed a similar transfusion intensity profile for RUX in the first 24 weeks which peaked at week 8 before declining by week 24, after which it remained relatively stable up to week 36 (no further data provided). In the course of these 36 weeks, the RUX transfusion intensity also remained consistently higher as compared to placebo. In addition, with the limits of cross-trial comparisons, MMB transfusion intensity in SIMPLIFY-1 was persistently lower compared to placebo in COMFORT-1, both for the MMB arm in the RT period as well for patients treated with MMB in both treatment arms of the open-label phase beyond week 24, indirectly supporting the maintenance of MMB's advantage over RUX in reducing transfusion needs and anemia-related benefits. However, the limitations related to such indirect comparisons should be considered.

Further note that simultaneous dose reductions of RUX observed after week 8 in the SIMPLIFY-1 study were most likely responsible for the partial recovery in Hgb levels and transfusion intensity as observed with RUX after week 8, which however in turn negatively affects prognosis.

Evidence from other secondary and exploratory endpoints, analysing the effect on the transfusion requirements and on hemoglobin levels, is supporting the beneficial effect of MMB on anemia compared to RUX (ITT analysis):

- With regard to transfusion requirements a greater proportion of patients in the MMB group compared to the RUX group had zero transfusions (73% vs 46%) or ≤4 RBC transfusions during the RT period (83% vs 62%). A reduced need to RBC transfusions was also reflected by a lower cumulative transfusion risk at week 24 for MMB (HR = 0.522 for MMB versus RUX), a lower median RBC transfusion rate (0 units/month vs 0.4 units/month) and by a smaller proportion of patients in the MMB group at Week 24 that was considered TD (30.2% vs 40.1%).
- With regard to the effect on hemoglobin, during the last 12 weeks of the 24 week treatment period, treatment with MMB led to higher proportions of patients with ≥ 1 (37.2% vs 16.6%), ≥ 1.5 (23.7% v 11.5%), or ≥ 2 g/dL (16.7% vs 6.0%) increases of hemoglobin levels from baseline. While in the RUX group, mean Hgb level decreased during the first 12 weeks, MMB induced a rapid

increase in mean Hgb levels that was maintained over time. A consistent increase in mean Hgb level was observed after cross-over from RUX to MMB treatment.

In addition, the improvements in transfusion requirements and hemoglobin levels with MMB compared to RUX in the Hgb < 10 g/dL subgroup were consistent compared to the overall ITT population, despite the higher transfusion needs and the lower hemoglobin levels in this particular subgroup compared to the overall ITT population (post-hoc subgroup analysis).

Duration of TI response at any time was analysed in a post-hoc exploratory analysis. TI responses seem to be durable in both treatment groups with median duration of TI not reached after a median follow-up of 35 months in both treatment arms. Most patients maintaining their response up to treatment discontinuation. The high rate of cross-over however confounds any comparison of data obtained after Week 24. (ITT analysis)

Single-arm GU-US-352-1672 trial, which included a patient population which is not diluted by subjects who cannot improve (only patients with TD at baseline were included), supported the beneficial effect of MMB on reducing the need for RBC transfusion in JAK-inhibitor naïve patients, with 34.1% of patients who were considered TI at Week 24.

In **conclusion**, the results with MMB on anaemia-related outcomes are consistent and indicate a clinically meaningful magnitude of effect, though due to absence of hierarchical multiplicity control in the anaemia related endpoints (including TI rate at W24) of the SIMPLIFY-1 study, these data can only support for the time being an at least protective effect of MMB on anaemia and do not demonstrate the effect on anemia treatment. As a result, the initially claimed indication was changed.

Overall survival and leukemia-free survival

- Overall survival (OS):
  - Treated with ruxolitinib

In the MOMENTUM study, after a median follow-up of 1.1 years for the MMB group and 1.0 years for the DAN group (including those who crossed-over to MMB), K-M estimated median OS was 1.7 y in the MMB arm and not reached the DAN arm [HR: 0.890 (95% CI: 0.504, 1.572); p = 0.69]. A sensitivity analysis of OS up to Week 24 did not demonstrate a statistical significant difference, though there was a numerical trend in favour of MMB (HR = 0.506, log-rank test p = 0.0719).

In the SIMPLIFY-2 study, after a median follow-up of 3.07 years for the MMB group and 3.22 years for the BAT group (including those who crossed-over to MMB), K-M estimated median OS was 2.86 years (95% CI: 2.28, NR) in the former randomized MMB group and 3.13 years (95% CI: 1.77, NR) in the former BAT group [HR: 1.00 (95% CI: 0.60, 1.65); p = 0.99]. (ITT analysis)

  - JAKi naive

In the SIMPLIFY-1 study, after a median follow-up of 3.43 years for the MMB group and 3.47 years for the RUX group (including those who crossed-over to MMB), K-M estimated median OS was not reached in both treatment arms [HR: 1.03 (95% CI: 0.74, 1.44); p = 0.86]. (ITT analysis)

- Leukemia-free survival (LFS):
  - Treated with JAKi

In the MOMENTUM study, after a median follow-up of 1.0 years for both treatment groups (including those who crossed-over from DAN to MMB), K-M estimated median LFS was 1.7 y in the MMB arm and not reached in the DAN arm [HR: 0.81 (95% CI: 0.47, 1.39); p = 0.43].

In the SIMPLIFY-2 study, after a median follow-up of 2.35 years for the MMB group and 2.27 years for the BAT group (including those who crossed-over to MMB), K-M estimated median LFS was 2.83 years in the former randomized MMB group and 3.13 years in the former BAT group [HR: 0.95 (95% CI: 0.58, 1.57); p = 0.85]. (ITT analysis)

- JAKi naive

In the SIMPLIFY-1 study, after a median follow-up of 2.95 years for the MMB group and 2.93 years for the RUX group (including those who crossed-over to MMB), K-M estimated median LFS was not reached in the former randomized MMB group and 4.42 years in the former RUX group [HR: 1.07 (95% CI: 0.76, 1.50); p = 0.70]. (ITT analysis)

In **conclusion**, for all phase 3 studies, no definite conclusion of the effect of MMB on OS and LFS versus their respective comparator however can be drawn, as the comparisons with their respective control groups were heavily confounded by the high rate of cross-over from the control groups to the MMB group after Week 24 assessments (63.5% of patients randomized to DAN in MOMENTUM, 91.6% of patients randomized to RUX in SIMPLIFY-1, 38.5% of patients randomized to BAT in SIMPLIFY-2). In addition, the studies were not powered to assess superiority in survival analyses. In the MOMENTUM study, K-M curves started to diverge early for both OS and LFS to a maximum difference at the 24 week timepoint, which is the time points after which cross-over was allowed, however this was not confirmed in other studies. Supportive evidence based on retrospective analysis of long-term survival data in JAK-inhibitor naïve patients who participated in phase 1/2 clinical studies was provided. With the limits intrinsic to such retrospective analysis, these data suggested longer median OS for MMB compared to RUX.

Sensitivity analyses adjusting for the impact of cross-over (Rank Preserving Structural Failure Time, 3 approaches) further suggested an underlying trend of the survival improvement for MMB over control. The phase 3 studies further consistently suggested that transfusion independence at week 24 was associated with improved OS in both treatment groups (Mesa et al., 2022; Verstovsek et al., 2022).

Long term effects

Only limited data are available across the phase 3 studies on the further course of the disease in terms of symptom response, spleen response or transfusion requirements on the potential for efficacy withdrawal effects in patients who permanently discontinued MMB treatment before and after the Week 24 endpoint. Patients were only followed for survival and leukemic transformation (see above).

Although across the three phase 3 studies subsequent JAK inhibitor therapy (i.e., ruxolitinib, fedratinib) or hydroxyurea therapy may have been reported after permanent discontinuation of study drug, including MMB, efficacy outcomes on these therapies were not collected.

2.6.7. Conclusions on the clinical efficacy

In the **JAKi treated setting**, the benefit of MMB for the treatment of disease-related splenomegaly and symptoms can be considered clinically meaningful, based on the results of the pivotal MOMENTUM trial in the JAK inhibitor pre-treated patient population with haemoglobin <10 g/dL per protocol eligibility. In addition, the totality of evidence on anaemia-related outcomes supports at least a protective effect of MMB on anaemia and associated RBC transfusion requirements in JAKi treated patients where both disease-related and treatment-related anaemia are of significant burden. However, due to the overall non-confirmatory nature of data, a claim of anaemia treatment is not justified. Furthermore, the benefit MMB in patients previously treated with fedratinib cannot be

determined given the scarce data with MMB in fedratinib pretreated patients and given the potential differences in cross-resistance mechanisms between fedratinib and ruxolitinib.

In the **JAKi naïve setting**, based on the totality of data, MMB is considered to provide benefits: the effect on disease-related splenomegaly is considered clinically meaningful and the magnitude of effect on disease-related symptoms is consistent across momelotinib trials and consistent higher as compared with placebo or non-JAK inhibitor containing controls in phase 3 studies with other JAK inhibitors, although lower when compared to approved JAK inhibitors. In addition, patients with manifestation of at least moderate anaemia may also derive benefit at longer term, due to potentially reduced RBC transfusion requirements of particular relevance in this subgroup.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

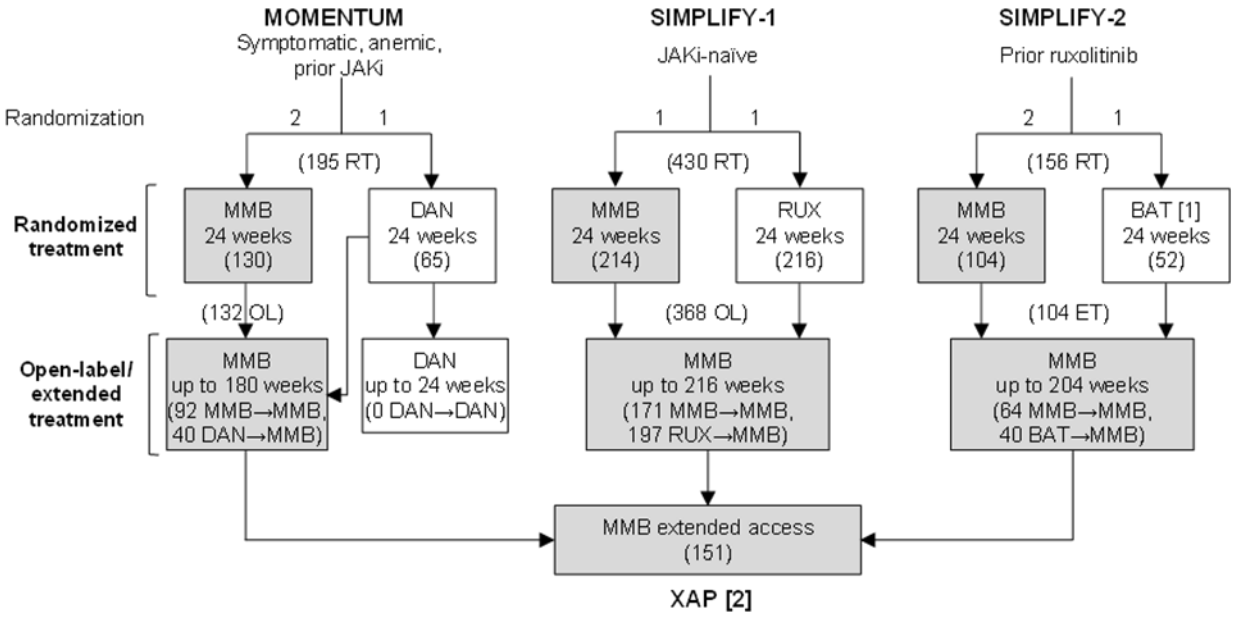
The safety profile of MMB in patients with PMF or post polycythaemia vera and post essential thrombocythemia (post PV/ET) MF is derived from the following 4 clinical studies involving 725 adults who received at least 1 dose of MMB study drug with a total follow up time of 1260.93 person years:

- One ongoing phase 3 randomized controlled study, MOMENTUM (RT complete; data cutoff 03 Dec 2021 for ongoing open label treatment with MMB)
- Two completed phase 3 randomized controlled studies, SIMPLIFY 1 and SIMPLIFY 2
- One ongoing uncontrolled long term extension safety study, XAP (subjects from phase 3 studies only, data cutoff 03 Dec 2021)

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 MMB, 262 subjects treated with RUX, and 65 subjects treated with DAN. The open label data include all 604 subjects who received open label, extended, and/or extended access treatment with MMB including the phase 3 subjects who crossed over to MMB treatment after RUX, BAT, and DAN and those who were subsequently treated in the long term extension safety study XAP. The pooled group of MMB overall includes all 725 subjects treated with MMB from the phase 3 studies, including RT and the additional open label data.

Figure 32: Momelotinib Phase 3 Studies Schematic



Numbers in parentheses are for treated subjects.
[1] BAT included ruxolitinib (88.5% of subjects). BAT for 2 subjects randomized to BAT was no therapy.
[2] Also enrolled subjects from phase 2 study GS US 352 1154, which included subjects from prior phase 1 2 studies.
BAT, best available therapy; DAN, danazol; ET, extended treatment; JAKi, Janus kinase inhibitor; MMB, momelotinib; OL, open label; RT, randomized treatment; RUX, ruxolitinib; XAP, extended access protocol.

A total of 725 phase 3 subjects were treated with MMB overall, including 448 during RT and 604 during open label treatment; 176 (24.3%) overall were ongoing as of the data cutoff date. During RT, 262 subjects were treated with RUX and 65 were treated with DAN. Of the 604 subjects treated with open label MMB, 327 subjects received MMB during RT and continued MMB treatment (MMB→MMB), and 277 subjects crossed over to MMB after RT with a comparator (40 DAN→MMB, 197 RUX→MMB, 40 BAT→MMB).

Most subjects completed the RT period (75.4% MMB, 90.5% RUX, 58.5% DAN). The most common reasons for study drug discontinuation were adverse event (10.7% MMB, 3.4% RUX, 16.9% DAN) and subject decision (3.3% MMB, 1.9% RUX, 7.7% DAN).

Most subjects treated during RT received open label treatment with MMB (73.0% MMB, 88.9% RUX, 61.5% DAN), including early crossovers (0.8% RUX, 7.7% DAN). No subject in MOMENTUM elected to receive open label treatment with DAN. Of subjects treated during RT, 11.6% MMB and 33.8% DAN were continuing open label treatment with MMB in MOMENTUM as of the data cutoff date. The most common reason for study drug discontinuation during open label treatment was study terminated by sponsor (15.0% MMB, 26.3% RUX, 0 DAN) as planned for SIMPLIFY 1 and SIMPLIFY 2 after ongoing subjects transitioned to study XAP, followed by adverse event (13.2% MMB, 24.4% RUX, 1.5% DAN), disease progression (8.7% MMB, 12.6% RUX, 0 DAN), and insufficient efficacy (6.0% MMB, 8.4% RUX, 1.5% DAN).

Subjects from all 3 studies transitioned to study XAP for extended treatment with MMB. Approximately one fifth of subjects treated during RT received extended access MMB treatment in XAP (18.1% MMB, 23.3% RUX, 13.8% DAN) and a subset were continuing as of the cutoff date (13.4% MMB, 13.4% RUX, 10.8% DAN). Disease progression was the most common reason for study drug discontinuation during XAP (1.6% MMB, 4.6% RUX, 0 DAN).

Overall, adverse event was the most reason for study drug discontinuation in every RT group (24.6% MMB, 29.4% RUX, 20.0% DAN) and during MMB open label treatment (22.4%) and overall (25.2%). Disease progression was the next most common reason during RT (12.3% MMB, 17.9% RUX, 0 DAN) and during MMB open label treatment (15.1%) and overall (13.8%).

Table 81: Integrated Subject Disposition by Study Period and Treatment (Safety Population)

	Randomized			Open-Label	Overall
	MMB (N = 448)	RUX (N = 262)	DAN (N = 65)	MMB (N = 604)	MMB (N = 725)
Duration of exposure (weeks) [1]					
n	448	262	65	604	725
Mean (SD)	20.7 (6.68)	22.7 (4.50)	17.3 (7.99)	90.5 (99.22)	88.1 (97.19)
Median (Q1, Q3)	23.9 (22.1, 24.0)	24.0 (23.7, 24.1)	23.7 (10.1, 24.0)	47.9 (16.9, 130.4)	49.0 (20.1, 119.3)
Minimum, maximum	0.3, 26.7	1.3, 26.9	0.7, 26.9	0.1, 369.4	0.3, 393.1
Duration of exposure (months) [1]					
n	448	262	65	604	725
Mean (SD)	4.8 (1.54)	5.2 (1.03)	4.0 (1.84)	20.8 (22.82)	20.3 (22.35)
Median (Q1, Q3)	5.5 (5.1, 5.5)	5.5 (5.5, 5.6)	5.5 (2.3, 5.5)	11.0 (3.9, 30.0)	11.3 (4.6, 27.4)
Minimum, maximum	0.1, 6.1	0.3, 6.2	0.2, 6.2	0.0, 85.0	0.1, 90.4
Duration of exposure, n (%)					
Any duration (> 0 weeks)	448 (100%)	262 (100%)	65 (100%)	604 (100%)	725 (100%)
≥ 4 weeks	425 (94.9%)	257 (98.1%)	63 (96.9%)	565 (93.5%)	684 (94.3%)
≥ 8 weeks	402 (89.7%)	253 (96.6%)	52 (80.0%)	515 (85.3%)	637 (87.9%)
≥ 12 weeks	385 (85.9%)	246 (93.9%)	45 (69.2%)	486 (80.5%)	602 (83.0%)
≥ 24 weeks	207 (46.2%)	148 (56.5%)	22 (33.8%)	406 (67.2%)	513 (70.8%)
≥ 48 weeks	0	0	0	302 (50.0%)	367 (50.6%)
≥ 96 weeks	0	0	0	193 (32.0%)	213 (29.4%)
≥ 36 months	0	0	0	122 (20.2%)	134 (18.5%)
≥ 48 months	0	0	0	98 (16.2%)	103 (14.2%)
≥ 60 months	0	0	0	84 (13.9%)	88 (12.1%)
Average daily dose (mg) [2]					
n	448	259	65	604	725
Mean (SD)	187.5 (26.02)	26.6 (11.24)	576.5 (65.28)	176.1 (45.43)	179.2 (34.80)
Median (Q1, Q3)	200.0 (185.9, 200.0)	28.8 (17.2, 37.9)	600.0 (600.0, 600.0)	194.3 (161.0, 200.0)	194.6 (168.8, 200.0)
Minimum, maximum	0, 229	5, 48	242, 600	0, 775	0, 494

	Randomized			Open-Label	Overall
	MMB (N = 448)	RUX (N = 262)	DAN (N = 65)	MMB (N = 604)	MMB (N = 725)
Relative dose intensity (%) [3]					
n	448	259	65	604	725
Mean (SD)	93.8 (13.01)	66.6 (28.10)	96.1 (10.88)	88.0 (22.71)	89.6 (17.40)
Median (Q1, Q3)	100.0 (92.9, 100.0)	71.9 (42.9, 94.7)	100.0 (100.0, 100.0)	97.2 (80.5, 100.0)	97.3 (84.4, 100.0)
Minimum, maximum	0, 114	13, 121	40, 100	0, 387	0, 247
Subjects with study drug modification, n (%)	173 (38.6%)	130 (60.2%) [4]	35 (53.8%)	264 (43.7%)	396 (54.6%)
Reason for study drug modification					
Adverse event	73 (16.3%)	79 (36.6%)	0	147 (24.3%)	207 (28.6%)
Serious adverse event	12 (2.7%)	0	11 (16.9%)	6 (1.0%)	17 (2.3%)
Per protocol	35 (7.8%)	62 (28.7%)	0	50 (8.3%)	81 (11.2%)
(All others in Table 2.7.4.2.1)					

[1] Duration of exposure to study drug was calculated as the number of weeks or months between the date of the last dose of study drug minus the date of the first dose of study drug plus 1.
[2] Average daily dose was calculated as the sum of the daily dose divided by the duration of exposure.
[3] Percentage relative dose intensity was calculated as the average daily dose divided by D (mg) times 100%, where D is MMB 200 mg, RUX 40 mg, or DAN 600 mg.
[4] Summarized only for the 216 subjects in SIMPLIFY-1 who received RUX because dose modification information was not consistently collected and reported in SIMPLIFY-2.
DAN, danazol; MMB, momelotinib; Q1, Q3, first quartile, third quartile; RUX, ruxolitinib.

2.6.8.2. Adverse events

Overall Summary of Adverse Events

Table 82: Integrated Overall Summary of Adverse Events by Study Period and Treatment (Safety Population)

Adverse Event Category	Randomized Treatment			Open-Label	Overall
	MMB (N = 448)	RUX (N = 262)	DAN (N = 65)	MMB (N = 604)	MMB (N = 725)
Any adverse event, n (%)	420 (93.8%)	248 (94.7%)	62 (95.4%)	547 (90.6%)	696 (96.0%)
Related	290 (64.7%)	161 (61.5%)	29 (44.6%)	328 (54.3%)	497 (68.6%)
Grade ≥ 3	207 (46.2%)	113 (43.1%)	42 (64.6%)	357 (59.1%)	484 (66.8%)
Related	109 (24.3%)	70 (26.7%)	16 (24.6%)	146 (24.2%)	230 (31.7%)
Grade 3 or 4	194 (43.3%)	113 (43.1%)	41 (63.1%)	342 (56.6%)	460 (63.4%)
Related	107 (23.9%)	70 (26.7%)	16 (24.6%)	145 (24.0%)	227 (31.3%)
Serious	131 (29.2%)	48 (18.3%)	26 (40.0%)	257 (42.5%)	347 (47.9%)
Related	38 (8.5%)	15 (5.7%)	5 (7.7%)	59 (9.8%)	93 (12.8%)
Fatal	29 (6.5%)	9 (3.4%)	11 (16.9%)	73 (12.1%)	102 (14.1%)
Leading to study drug modification	100 (22.3%)	87 (33.2%)	19 (29.2%)	185 (30.6%)	262 (36.1%)
Leading to study drug discontinuation	72 (16.1%)	13 (5.0%)	15 (23.1%)	157 (26.0%)	229 (31.6%)
Grade ≥ 3	56 (12.5%)	13 (5.0%)	11 (16.9%)	120 (19.9%)	176 (24.3%)

Shading indicates adverse events ≥ 5 percentage points higher than 1 or more other treatment group during RT.
DAN, danazol; MMB, momelotinib; RT, randomized treatment; RUX, ruxolitinib.

Common Adverse Events

Table 83: Integrated Commonly Reported Adverse Events in ⩾ 5% of Subjects in Any Group by Preferred Term by Study Period and Treatment (Safety Population)

	Randomized Treatment			Open-Label	Overall
Preferred Term	MMB (N = 448)	RUX (N = 262)	DAN (N = 65)	MMB (N = 604)	MMB (N = 725)
Any adverse event, n (%)	420 (93.8%)	248 (94.7%)	62 (95.4%)	547 (90.6%)	696 (96.0%)
Diarrhoea	102 (22.8%)	50 (19.1%)	6 (9.2%)	120 (19.9%)	194 (26.8%)
Thrombocytopenia	87 (19.4%)	69 (26.3%)	7 (10.8%)	106 (17.5%)	170 (23.4%)
Anaemia	62 (13.8%)	90 (34.4%)	10 (15.4%)	125 (20.7%)	167 (23.0%)
Nausea	75 (16.7%)	13 (5.0%)	6 (9.2%)	81 (13.4%)	141 (19.4%)
Fatigue	55 (12.3%)	36 (13.7%)	7 (10.8%)	77 (12.7%)	127 (17.5%)
Cough	45 (10.0%)	23 (8.8%)	2 (3.1%)	88 (14.6%)	126 (17.4%)
Dizziness	58 (12.9%)	27 (10.3%)	1 (1.5%)	62 (10.3%)	112 (15.4%)
Abdominal pain	48 (10.7%)	32 (12.2%)	5 (7.7%)	57 (9.4%)	102 (14.1%)
Pyrexia	41 (9.2%)	21 (8.0%)	5 (7.7%)	71 (11.8%)	102 (14.1%)
Headache	60 (13.4%)	46 (17.6%)	1 (1.5%)	50 (8.3%)	101 (13.9%)
Asthenia	49 (10.9%)	25 (9.5%)	6 (9.2%)	57 (9.4%)	96 (13.2%)
Pruritus	40 (8.9%)	17 (6.5%)	7 (10.8%)	60 (9.9%)	90 (12.4%)
Dyspnoea	42 (9.4%)	24 (9.2%)	9 (13.8%)	52 (8.6%)	89 (12.3%)
Peripheral sensory neuropathy	31 (6.9%)	12 (4.6%)	1 (1.5%)	62 (10.3%)	89 (12.3%)
Urinary tract infection	27 (6.0%)	15 (5.7%)	3 (4.6%)	70 (11.6%)	88 (12.1%)
Pneumonia	16 (3.6%)	6 (2.3%)	6 (9.2%)	68 (11.3%)	83 (11.4%)
Constipation	43 (9.6%)	17 (6.5%)	5 (7.7%)	41 (6.8%)	81 (11.2%)
Oedema peripheral	31 (6.9%)	18 (6.9%)	9 (13.8%)	50 (8.3%)	75 (10.3%)
Arthralgia	34 (7.6%)	17 (6.5%)	2 (3.1%)	45 (7.5%)	73 (10.1%)
Upper respiratory tract infection	22 (4.9%)	17 (6.5%)	1 (1.5%)	53 (8.8%)	73 (10.1%)
Decreased appetite	27 (6.0%)	15 (5.7%)	6 (9.2%)	45 (7.5%)	69 (9.5%)
Vomiting	36 (8.0%)	8 (3.1%)	0	36 (6.0%)	66 (9.1%)
Pain in extremity	24 (5.4%)	23 (8.8%)	1 (1.5%)	42 (7.0%)	65 (9.0%)
Hypertension	24 (5.4%)	22 (8.4%)	6 (9.2%)	44 (7.3%)	64 (8.8%)
Back pain	21 (4.7%)	14 (5.3%)	3 (4.6%)	48 (7.9%)	64 (8.8%)

	Randomized Treatment			Open-Label	Overall
Preferred Term	MMB (N = 448)	RUX (N = 262)	DAN (N = 65)	MMB (N = 604)	MMB (N = 725)
Hyperuricaemia	25 (5.6%)	9 (3.4%)	4 (6.2%)	41 (6.8%)	62 (8.6%)
Weight decreased	30 (6.7%)	4 (1.5%)	4 (6.2%)	35 (5.8%)	60 (8.3%)
Night sweats	20 (4.5%)	13 (5.0%)	3 (4.6%)	43 (7.1%)	60 (8.3%)
Blood creatinine increased	26 (5.8%)	2 (0.8%)	10 (15.4%)	35 (5.8%)	54 (7.4%)
Paraesthesia	31 (6.9%)	8 (3.1%)	1 (1.5%)	25 (4.1%)	51 (7.0%)
Hypotension	27 (6.0%)	3 (1.1%)	2 (3.1%)	26 (4.3%)	50 (6.9%)
Epistaxis	24 (5.4%)	19 (7.3%)	4 (6.2%)	27 (4.5%)	49 (6.8%)
Contusion	26 (5.8%)	12 (4.6%)	0	19 (3.1%)	44 (6.1%)
Rash	14 (3.1%)	6 (2.3%)	4 (6.2%)	31 (5.1%)	44 (6.1%)
Bronchitis	11 (2.5%)	7 (2.7%)	0	35 (5.8%)	44 (6.1%)
Hyperkalaemia	21 (4.7%)	6 (2.3%)	6 (9.2%)	26 (4.3%)	43 (5.9%)
Fall	15 (3.3%)	5 (1.9%)	4 (6.2%)	29 (4.8%)	43 (5.9%)
Acute kidney injury	12 (2.7%)	1 (0.4%)	8 (12.3%)	32 (5.3%)	43 (5.9%)
Abdominal pain upper	21 (4.7%)	12 (4.6%)	5 (7.7%)	24 (4.0%)	42 (5.8%)
Alanine aminotransferase increased	21 (4.7%)	11 (4.2%)	5 (7.7%)	22 (3.6%)	42 (5.8%)
Neutropenia	23 (5.1%)	15 (5.7%)	2 (3.1%)	26 (4.3%)	41 (5.7%)
Nasopharyngitis	13 (2.9%)	18 (6.9%)	2 (3.1%)	29 (4.8%)	40 (5.5%)
Insomnia	10 (2.2%)	10 (3.8%)	3 (4.6%)	30 (5.0%)	38 (5.2%)
Vitamin B1 deficiency	14 (3.1%)	14 (5.3%)	0	26 (4.3%)	37 (5.1%)
Bone pain	9 (2.0%)	21 (8.0%)	3 (4.6%)	22 (3.6%)	31 (4.3%)
Hyponatraemia	9 (2.0%)	1 (0.4%)	4 (6.2%)	16 (2.6%)	23 (3.2%)

Shading indicates events that met the ≥ 5% threshold.
DAN, danazol; MMB, momelotinib; RUX, ruxolitinib.

Treatment-Related Adverse Events

Table 84: Integrated Commonly Reported Treatment-Related Adverse Events in ⩾ 5% of Subjects in Any Group by Preferred Term by Study Period and Treatment (Safety Population)

	Randomized Treatment			Open-Label	Overall
Preferred Term	MMB (N = 448)	RUX (N = 262)	DAN (N = 65)	MMB (N = 604)	MMB (N = 725)
Any treatment-related adverse event, n (%)	290 (64.7%)	161 (61.5%)	29 (44.6%)	328 (54.3%)	497 (68.6%)
Thrombocytopenia	69 (15.4%)	59 (22.5%)	3 (4.6%)	74 (12.3%)	127 (17.5%)
Diarrhoea	53 (11.8%)	20 (7.6%)	2 (3.1%)	33 (5.5%)	83 (11.4%)
Nausea	49 (10.9%)	3 (1.1%)	3 (4.6%)	29 (4.8%)	75 (10.3%)
Peripheral sensory neuropathy	24 (5.4%)	5 (1.9%)	1 (1.5%)	46 (7.6%)	68 (9.4%)
Anaemia	29 (6.5%)	69 (26.3%)	1 (1.5%)	44 (7.3%)	63 (8.7%)
Dizziness	40 (8.9%)	9 (3.4%)	0	21 (3.5%)	60 (8.3%)
Headache	38 (8.5%)	19 (7.3%)	0	19 (3.1%)	55 (7.6%)
Fatigue	23 (5.1%)	10 (3.8%)	1 (1.5%)	22 (3.6%)	45 (6.2%)
Paraesthesia	26 (5.8%)	5 (1.9%)	0	14 (2.3%)	38 (5.2%)
Asthenia	14 (3.1%)	4 (1.5%)	1 (1.5%)	23 (3.8%)	36 (5.0%)
Alanine aminotransferase increased	14 (3.1%)	4 (1.5%)	5 (7.7%)	9 (1.5%)	23 (3.2%)

Source: Table 2.7.4.2.5.2
Shading indicates events that met the ⩾ 5% threshold.
DAN, danazol; MMB, momelotinib; RUX, ruxolitinib.

All Grade ≥ 3 Adverse Events

Table 85: Integrated Adverse Events of Grade ⩾ 3 Severity in ⩾ 5% of Subjects in Any Group by System Organ Class and Preferred Term by Study Period and Treatment (Safety Population)

	Randomized Treatment			Open-Label	Overall
System Organ Class Preferred Term	MMB (N = 448)	RUX (N = 262)	DAN (N = 65)	MMB (N = 604)	MMB (N = 725)
Any grade ≥ 3 adverse event, n (%)	207 (46.2%)	113 (43.1%)	42 (64.6%)	357 (59.1%)	484 (66.8%)
Blood and lymphatic system disorders	92 (20.5%)	70 (26.7%)	16 (24.6%)	156 (25.8%)	221 (30.5%)
Thrombocytopenia	48 (10.7%)	13 (5.0%)	5 (7.7%)	70 (11.6%)	110 (15.2%)
Anaemia	37 (8.3%)	57 (21.8%)	7 (10.8%)	77 (12.7%)	105 (14.5%)
Infections and infestations	47 (10.5%)	11 (4.2%)	11 (16.9%)	112 (18.5%)	154 (21.2%)
Pneumonia	12 (2.7%)	4 (1.5%)	6 (9.2%)	49 (8.1%)	61 (8.4%)
Renal and urinary disorders	13 (2.9%)	5 (1.9%)	8 (12.3%)	42 (7.0%)	52 (7.2%)
Acute kidney injury	4 (0.9%)	1 (0.4%)	6 (9.2%)	13 (2.2%)	17 (2.3%)

Shading indicates events that met the ⩾ 5% threshold.
DAN, danazol; MMB, momelotinib; RUX, ruxolitinib.

2.6.8.3. Serious adverse event/deaths/other significant events

Deaths

Table 86: Integrated Fatal Adverse Events in ⩾ 2 Subjects in Any Group by System Organ Class and Preferred Term by Study Period and Treatment (Safety Population)

System Organ Class Preferred Term	Randomized Treatment			Open-Label	Overall
	MMB (N = 448)	RUX (N = 262)	DAN (N = 65)	MMB (N = 604)	MMB (N = 725)
Any fatal adverse event, n (%)	29 (6.5%)	9 (3.4%)	11 (16.9%)	73 (12.1%)	102 (14.1%)
Infections and infestations	10 (2.2%)	3 (1.1%)	0	22 (3.6%)	32 (4.4%)
Pneumonia	1 (0.2%)	1 (0.4%)	0	8 (1.3%)	9 (1.2%)
Sepsis	1 (0.2%)	2 (0.8%)	0	4 (0.7%)	5 (0.7%)
COVID-19	3 (0.7%)	0	0	0	3 (0.4%)
COVID-19 pneumonia	3 (0.7%)	0	0	0	3 (0.4%)
Septic shock	1 (0.2%)	0	0	1 (0.2%)	2 (0.3%)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	5 (1.1%)	3 (1.1%)	2 (3.1%)	9 (1.5%)	14 (1.9%)
Acute myeloid leukaemia	3 (0.7%)	1 (0.4%)	1 (1.5%)	3 (0.5%)	6 (0.8%)
Transformation to acute myeloid leukaemia	2 (0.4%)	0	1 (1.5%)	1 (0.2%)	3 (0.4%)
General disorders and administration site conditions	4 (0.9%)	0	2 (3.1%)	10 (1.7%)	14 (1.9%)
Death	1 (0.2%)	0	1 (1.5%)	3 (0.5%)	4 (0.6%)
Sudden death	2 (0.4%)	0	0	1 (0.2%)	3 (0.4%)
Disease progression	0	0	1 (1.5%)	3 (0.5%)	3 (0.4%)
Multiple organ dysfunction syndrome	0	0	0	2 (0.3%)	2 (0.3%)
Cardiac disorders	1 (0.2%)	0	2 (3.1%)	10 (1.7%)	11 (1.5%)
Cardiac arrest	1 (0.2%)	0	0	3 (0.5%)	4 (0.6%)
Cardiac failure	0	0	0	4 (0.7%)	4 (0.6%)
Myocardial infarction	0	0	0	2 (0.3%)	2 (0.3%)
Respiratory, thoracic and mediastinal disorders	2 (0.4%)	0	0	7 (1.2%)	9 (1.2%)
Respiratory failure	2 (0.4%)	0	0	2 (0.3%)	4 (0.6%)
Renal and urinary disorders	1 (0.2%)	0	0	4 (0.7%)	5 (0.7%)
Renal failure	1 (0.2%)	0	0	1 (0.2%)	2 (0.3%)

System Organ Class Preferred Term	Randomized Treatment			Open-Label	Overall
	MMB (N = 448)	RUX (N = 262)	DAN (N = 65)	MMB (N = 604)	MMB (N = 725)
Blood and lymphatic system disorders	0	0	3 (4.6%)	3 (0.5%)	3 (0.4%)
Anaemia	0	0	3 (4.6%)	1 (0.2%)	1 (0.1%)

Shading indicates events that met the ≥ 2 subjects threshold.
DAN, danazol; MMB, momelotinib; RUX, ruxolitinib.

Table 87: Summary of Related Treatment-Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	Randomized Treatment			Open-Label	Overall
	MMB (N = 448)	RUX (N = 262)	DAN (N = 65)	MMB (N = 607)	MMB (N = 726)
Any related TEAE leading to death, n (%)	2 (0.4)	0	2 (3.1)	5 (0.8)	7 (1.0)
Infections and infestations	0	0	0	3 (0.5)	3 (0.4)
Gastroenteritis rotavirus	0	0	0	1 (0.2)	1 (0.1)
Infection	0	0	0	1 (0.2)	1 (0.1)
Pneumonia staphylococcal	0	0	0	1 (0.2)	1 (0.1)
Cardiac disorders	1 (0.2)	0	1 (1.5)	0	1 (0.1)
Cardiac arrest	1 (0.2)	0	0	0	1 (0.1)
Cardiogenic shock	0	0	1 (1.5)	0	0
Respiratory, thoracic and mediastinal disorders	1 (0.2)	0	0	0	1 (0.1)
Respiratory failure	1 (0.2)	0	0	0	1 (0.1)
General disorders and administration site conditions	0	0	0	1 (0.2)	1 (0.1)
Death	0	0	0	1 (0.2)	1 (0.1)
Renal and urinary disorders	0	0	0	1 (0.2)	1 (0.1)
Nephritis	0	0	0	1 (0.2)	1 (0.1)
Injury, poisoning and procedural complications	0	0	1 (1.5)	0	0
Subdural haematoma	0	0	1 (1.5)	0	0

Note: DAN, danazol; MMB, momelotinib; OL, open label/extended treatment; RT, randomized treatment; RUX, ruxolitinib.
- Adverse event was coded to system organ class and preferred term using MedDRA coding dictionary version 24.0
- Subject was counted only once in each system organ class and preferred term.
- Exposure-adjusted event rate in 100 person years was calculated as 100*number of AEs/total person-time follow-up in years.

Abbreviations: DAN, danazol; MMB, momelotinib; RUX, ruxolitinib.
Source: Table 40.005

Serious Adverse Events

Table 88: Integrated Serious Adverse Events Reported in ⩾ 2 Subjects in Any Group During Randomized Treatment by System Organ Class and Preferred Term by Study Period and Treatment (Safety Population)

System Organ Class Preferred Term	Randomized Treatment			Open-Label	Overall
	MMB (N = 448)	RUX (N = 262)	DAN (N = 65)	MMB (N = 604)	MMB (N = 725)
Any serious adverse event, n (%)	131 (29.2%)	48 (18.3%)	26 (40.0%)	257 (42.5%)	347 (47.9%)
Infections and infestations	44 (9.8%)	12 (4.6%)	11 (16.9%)	111 (18.4%)	148 (20.4%)
Pneumonia	10 (2.2%)	3 (1.1%)	6 (9.2%)	44 (7.3%)	54 (7.4%)
Sepsis	4 (0.9%)	2 (0.8%)	0	13 (2.2%)	15 (2.1%)
Urinary tract infection	2 (0.4%)	2 (0.8%)	0	13 (2.2%)	15 (2.1%)
Cellulitis	4 (0.9%)	0	1 (1.5%)	5 (0.8%)	8 (1.1%)
COVID-19 pneumonia	3 (0.7%)	0	0	3 (0.5%)	6 (0.8%)
COVID-19	3 (0.7%)	0	0	0	3 (0.4%)
Cystitis	3 (0.7%)	0	1 (1.5%)	0	3 (0.4%)
Gastroenteritis	0	2 (0.8%)	0	3 (0.5%)	3 (0.4%)
Cardiac disorders	21 (4.7%)	7 (2.7%)	3 (4.6%)	46 (7.6%)	65 (9.0%)
Atrial fibrillation	7 (1.6%)	1 (0.4%)	0	10 (1.7%)	17 (2.3%)
Cardiac failure	5 (1.1%)	2 (0.8%)	0	12 (2.0%)	17 (2.3%)
Cardiac failure congestive	2 (0.4%)	1 (0.4%)	0	7 (1.2%)	9 (1.2%)
Acute myocardial infarction	3 (0.7%)	0	0	4 (0.7%)	7 (1.0%)
Angina unstable	2 (0.4%)	0	0	1 (0.2%)	3 (0.4%)
Supraventricular tachycardia	2 (0.4%)	0	0	0	2 (0.3%)
Gastrointestinal disorders	24 (5.4%)	10 (3.8%)	0	39 (6.5%)	58 (8.0%)
Diarrhoea	5 (1.1%)	1 (0.4%)	0	4 (0.7%)	9 (1.2%)
Upper gastrointestinal haemorrhage	3 (0.7%)	0	0	3 (0.5%)	6 (0.8%)
Ascites	1 (0.2%)	2 (0.8%)	0	5 (0.8%)	5 (0.7%)
Gastrointestinal haemorrhage	2 (0.4%)	0	0	3 (0.5%)	3 (0.4%)
Small intestinal obstruction	2 (0.4%)	0	0	1 (0.2%)	3 (0.4%)
Abdominal pain	1 (0.2%)	3 (1.1%)	0	2 (0.3%)	3 (0.4%)

System Organ Class Preferred Term	Randomized Treatment			Open-Label	Overall
	MMB (N = 448)	RUX (N = 262)	DAN (N = 65)	MMB (N = 604)	MMB (N = 725)
Blood and lymphatic system disorders	21 (4.7%)	9 (3.4%)	6 (9.2%)	34 (5.6%)	54 (7.4%)
Anaemia	13 (2.9%)	8 (3.1%)	3 (4.6%)	20 (3.3%)	32 (4.4%)
Splenic infarction	2 (0.4%)	0	2 (3.1%)	6 (1.0%)	8 (1.1%)
Thrombocytopenia	3 (0.7%)	3 (1.1%)	0	4 (0.7%)	7 (1.0%)
Renal and urinary disorders	16 (3.6%)	2 (0.8%)	3 (4.6%)	41 (6.8%)	53 (7.3%)
Acute kidney injury	7 (1.6%)	1 (0.4%)	3 (4.6%)	18 (3.0%)	25 (3.4%)
Renal failure	4 (0.9%)	0	0	5 (0.8%)	9 (1.2%)
Nephrolithiasis	2 (0.4%)	1 (0.4%)	0	1 (0.2%)	3 (0.4%)
Respiratory, thoracic and mediastinal disorders	12 (2.7%)	5 (1.9%)	1 (1.5%)	38 (6.3%)	49 (6.8%)
Dyspnoea	2 (0.4%)	0	0	7 (1.2%)	9 (1.2%)
Respiratory failure	3 (0.7%)	0	0	4 (0.7%)	7 (1.0%)
Pneumonia aspiration	2 (0.4%)	0	0	4 (0.7%)	5 (0.7%)
Chronic obstructive pulmonary disease	2 (0.4%)	0	0	1 (0.2%)	3 (0.4%)
General disorders and administration site conditions	15 (3.3%)	8 (3.1%)	5 (7.7%)	33 (5.5%)	47 (6.5%)
Pyrexia	7 (1.6%)	3 (1.1%)	0	12 (2.0%)	18 (2.5%)
General physical health deterioration	4 (0.9%)	2 (0.8%)	2 (3.1%)	2 (0.3%)	6 (0.8%)
Sudden death	2 (0.4%)	0	0	1 (0.2%)	3 (0.4%)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	10 (2.2%)	2 (0.8%)	4 (6.2%)	29 (4.8%)	38 (5.2%)
Transformation to acute myeloid leukaemia	2 (0.4%)	0	2 (3.1%)	1 (0.2%)	3 (0.4%)
Acute myeloid leukaemia	2 (0.4%)	0	1 (1.5%)	1 (0.2%)	3 (0.4%)
Nervous system disorders	10 (2.2%)	1 (0.4%)	2 (3.1%)	25 (4.1%)	35 (4.8%)
Syncope	4 (0.9%)	0	0	4 (0.7%)	8 (1.1%)
Presyncope	2 (0.4%)	0	0	1 (0.2%)	3 (0.4%)
Metabolism and nutrition disorders	6 (1.3%)	3 (1.1%)	2 (3.1%)	19 (3.1%)	25 (3.4%)
Hyperkalaemia	2 (0.4%)	1 (0.4%)	1 (1.5%)	3 (0.5%)	5 (0.7%)

System Organ Class Preferred Term	Randomized Treatment			Open-Label	Overall
	MMB (N = 448)	RUX (N = 262)	DAN (N = 65)	MMB (N = 604)	MMB (N = 725)
Fluid overload	2 (0.4%)	0	0	0	2 (0.3%)
Vascular disorders	8 (1.8%)	3 (1.1%)	1 (1.5%)	14 (2.3%)	22 (3.0%)
Hypotension	2 (0.4%)	0	0	3 (0.5%)	5 (0.7%)
Investigations	3 (0.7%)	1 (0.4%)	1 (1.5%)	1 (0.2%)	4 (0.6%)
Blood creatinine increased	2 (0.4%)	0	0	0	2 (0.3%)
Immune system disorders	2 (0.4%)	0	0	1 (0.2%)	3 (0.4%)
Hypersensitivity	2 (0.4%)	0	0	0	2 (0.3%)
Ear and labyrinth disorders	0	3 (1.1%)	0	1 (0.2%)	1 (0.1%)
Vertigo	0	2 (0.8%)	0	1 (0.2%)	1 (0.1%)

Shading indicates events that met the ≥ 2 subjects threshold in any group.
DAN, danazol; MMB, momelotinib; RUX, ruxolitinib.

Adverse Events of Clinical Importance

Table 89: Integrated Overall Summary of All Adverse Events of Clinical Importance by Study Period and Treatment (Safety Population)

Important Event, n (%)	Randomized Treatment			Open-Label	Overall
	MMB (N = 448)	RUX (N = 262)	DAN (N = 65)	MMB (N = 604)	MMB (N = 725)
Infections	178 (39.7%)	112 (42.7%)	23 (35.4%)	299 (49.5%)	402 (55.4%)
Malignancies	25 (5.6%)	15 (5.7%)	5 (7.7%)	77 (12.7%)	97 (13.4%)
Opportunistic infections	10 (2.2%)	11 (4.2%)	1 (1.5%)	31 (5.1%)	40 (5.5%)
AML/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	31 (5.1%)	35 (4.8%)
MACE	14 (3.1%)	7 (2.7%)	4 (6.2%)	46 (7.6%)	57 (7.9%)
Thrombocytopenia	94 (21.0%)	69 (26.3%)	10 (15.4%)	114 (18.9%)	181 (25.0%)
Neutropenia	27 (6.0%)	15 (5.7%)	3 (4.6%)	30 (5.0%)	49 (6.8%)
Anemia	63 (14.1%)	92 (35.1%)	11 (16.9%)	128 (21.2%)	170 (23.4%)
Peripheral neuropathy	39 (8.7%)	12 (4.6%)	1 (1.5%)	74 (12.3%)	107 (14.8%)
Thromboembolism	15 (3.3%)	2 (0.8%)	6 (9.2%)	51 (8.4%)	64 (8.8%)
Hemorrhage	95 (21.2%)	52 (19.8%)	12 (18.5%)	136 (22.5%)	207 (28.6%)

Shading indicates adverse events ≥ 5 percentage points higher than 1 or more group during randomized treatment.
AML, acute myeloid leukemia; DAN, danazol; MACE, major adverse cardiovascular events; MMB, momelotinib; RUX, ruxolitinib.

2.6.8.4. Laboratory findings

Parameter During 24 Weeks of Randomized Treatment (Safety Population)

Table 90: Integrated Hematology – Shift From Baseline Grade 0, 1, or 2 to Worst Postbaseline Grade 3 or 4 by Key abnormality

Laboratory Abnormality	Shift From Baseline to Worst Postbaseline	MMB (N = 448)	RUX (N = 262)	DAN (N = 65)
Anemia	0 to 3	1 (0.2%)	5 (1.9%)	0
	1 to 3	5 (1.1%)	22 (8.4%)	0
	2 to 3	48 (10.7%)	59 (22.5%)	10 (15.4%)
Lymphocyte count decreased	0 to 3	11 (2.5%)	14 (5.3%)	4 (6.2%)
	1 to 3	5 (1.1%)	2 (0.8%)	2 (3.1%)
	2 to 3	25 (5.6%)	14 (5.3%)	14 (21.5%)
	0 to 4	3 (0.7%)	0	0
Neutrophil count decreased	0 to 3	6 (1.3%)	4 (1.5%)	1 (1.5%)
	1 to 3	7 (1.6%)	4 (1.5%)	0
	2 to 3	7 (1.6%)	5 (1.9%)	2 (3.1%)
	0 to 4	0	2 (0.8%)	0
	2 to 4	2 (0.4%)	0	1 (1.5%)
Platelet count decreased	0 to 3	11 (2.5%)	3 (1.1%)	0
	1 to 3	11 (2.5%)	6 (2.3%)	1 (1.5%)
	2 to 3	23 (5.1%)	3 (1.1%)	5 (7.7%)
	0 to 4	1 (0.2%)	1 (0.4%)	0
	1 to 4	3 (0.7%)	0	0
	2 to 4	6 (1.3%)	2 (0.8%)	1 (1.5%)
WBC count decreased	0 to 3	7 (1.6%)	7 (2.7%)	0
	1 to 3	4 (0.9%)	2 (0.8%)	1 (1.5%)
	2 to 3	5 (1.1%)	12 (4.6%)	2 (3.1%)
	0 to 4	1 (0.2%)	0	0

Baseline was the most recent assessment prior to or on the first dose date during randomized treatment.
DAN, danazol; MMB, momelotinib; RUX, ruxolitinib; WBC, white blood cell.

Abnormal Liver Function Laboratory Findings

Table 91: Integrated Summary of Abnormal Liver Function Laboratory Findings by Study Period and Treatment (Safety Population)

	Randomized			Open-Label	Overall
Laboratory Abnormality	MMB	RUX	DAN	MMB	MMB
ALT, n	443	259	64	579	710
≥ 3 × ULN	16 (3.6%)	7 (2.7%)	4 (6.3%)	29 (5.0%)	41 (5.8%)
≥ 5 × ULN	8 (1.8%)	1 (0.4%)	2 (3.1%)	11 (1.9%)	17 (2.4%)
≥ 10 × ULN	1 (0.2%)	0	0	5 (0.9%)	6 (0.8%)
≥ 20 × ULN	1 (0.2%)	0	0	1 (0.2%)	2 (0.3%)
AST, n	442	259	63	579	709
≥ 3 × ULN	7 (1.6%)	2 (0.8%)	1 (1.6%)	12 (2.1%)	17 (2.4%)
≥ 5 × ULN	1 (0.2%)	0	1 (1.6%)	6 (1.0%)	7 (1.0%)
≥ 10 × ULN	1 (0.2%)	0	0	3 (0.5%)	4 (0.6%)
≥ 20 × ULN	0	0	0	2 (0.3%)	2 (0.3%)
AST or ALT, n	443	259	64	579	710
≥ 3 × ULN	17 (3.8%)	8 (3.1%)	4 (6.3%)	29 (5.0%)	42 (5.9%)
≥ 5 × ULN	8 (1.8%)	1 (0.4%)	2 (3.1%)	11 (1.9%)	17 (2.4%)
≥ 10 × ULN	1 (0.2%)	0	0	5 (0.9%)	6 (0.8%)
≥ 20 × ULN	1 (0.2%)	0	0	2 (0.3%)	3 (0.4%)
Total bilirubin, n	443	259	64	579	710
> 2 × ULN	15 (3.4%)	10 (3.9%)	3 (4.7%)	24 (4.1%)	33 (4.6%)
Alkaline phosphatase, n	443	259	64	579	711
> 1.5 × ULN	75 (16.9%)	31 (12.0%)	4 (6.3%)	88 (15.2%)	142 (20.0%)
Elevated ALT or AST and elevated total bilirubin, n	433	259	64	579	710
ALT or AST ≥ 3 × ULN and total bilirubin > 1.5 × ULN	0	0	0	7 (1.2%)	7 (1.0%)
ALT or AST ≥ 3× ULN and total bilirubin > 2.0 × ULN	0	0	0	2 (0.3%)	2 (0.3%)
Hy's Law, n [1]	433	259	64	578	710
	0	0	0	2 (0.3%)	2 (0.3%)

Denominators were the number of subjects with nonmissing postbaseline values for a parameter.
[1] ALT or AST ≥ 3 × ULN, total bilirubin > 2 × ULN, and alkaline phosphatase < 2 × ULN.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; DAN, danazol; MMB, momelotinib; RUX, ruxolitinib, ULN, upper limit of normal.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.6. Safety in special populations

Table 92: Integrated Overall Summary of Adverse Events by Sex (Male, Female; Randomized Treatment)

Adverse Event Category	MMB		RUX		DAN	
	Male (N = 271)	Female (N = 177)	Male (N = 141)	Female (N = 121)	Male (N = 44)	Female (N = 21)
Any adverse event, n (%)	257 (94.8%)	163 (92.1%)	133 (94.3%)	115 (95.0%)	43 (97.7%)	19 (90.5%)
Related	171 (63.1%)	119 (67.2%)	86 (61.0%)	75 (62.0%)	22 (50.0%)	7 (33.3%)
Grade 3 or 4	133 (49.1%)	61 (34.5%)	59 (41.8%)	54 (44.6%)	29 (65.9%)	12 (57.1%)
Related	65 (24.0%)	42 (23.7%)	38 (27.0%)	32 (26.4%)	12 (27.3%)	4 (19.0%)
Serious	93 (34.3%)	38 (21.5%)	29 (20.6%)	19 (15.7%)	16 (36.4%)	10 (47.6%)
Related	30 (11.1%)	8 (4.5%)	9 (6.4%)	6 (5.0%)	4 (9.1%)	1 (4.8%)
Fatal	22 (8.1%)	7 (4.0%)	6 (4.3%)	3 (2.5%)	6 (13.6%)	5 (23.8%)
Leading to study drug modification	57 (21.0%)	43 (24.3%)	44 (31.2%)	43 (35.5%)	15 (34.1%)	4 (19.0%)
Leading to study drug discontinuation	46 (17.0%)	26 (14.7%)	8 (5.7%)	5 (4.1%)	11 (25.0%)	4 (19.0%)

DAN, danazol; MMB, momelotinib; RUX, ruxolitinib.

Table 93: Integrated Overall Summary of Adverse Events by Age (18-64, ⩾ 65, 18-74, ⩾ 75 Years; Randomized Treatment)

Adverse Event Category	MMB				RUX				DAN			
	18-64 (N = 159)	≥ 65 (N = 289)	18-74 (N = 353)	≥ 75 (N = 95)	18-64 (N = 106)	≥ 65 (N = 156)	18-74 (N = 218)	≥ 75 (N = 44)	18-64 (N = 11)	≥ 65 (N = 54)	18-74 (N = 44)	≥ 75 (N = 21)
Any adverse event, n (%)	144 (90.6%)	276 (95.5%)	329 (93.2%)	91 (95.8%)	95 (89.6%)	153 (98.1%)	205 (94.0%)	43 (97.7%)	11 (100%)	51 (94.4%)	41 (93.2%)	21 (100%)
Related	104 (65.4%)	186 (64.4%)	225 (63.7%)	65 (68.4%)	63 (59.4%)	98 (62.8%)	136 (62.4%)	25 (56.8%)	9 (81.8%)	20 (37.0%)	22 (50.0%)	7 (33.3%)
Grade 3 or 4	59 (37.1%)	135 (46.7%)	146 (41.4%)	48 (50.5%)	36 (34.0%)	77 (49.4%)	88 (40.4%)	25 (56.8%)	8 (72.7%)	33 (61.1%)	28 (63.6%)	13 (61.9%)
Related	31 (19.5%)	76 (26.3%)	77 (21.8%)	30 (31.6%)	29 (27.4%)	41 (26.3%)	54 (24.8%)	16 (36.4%)	5 (45.5%)	11 (20.4%)	12 (27.3%)	4 (19.0%)
Serious	33 (20.8%)	98 (33.9%)	98 (27.8%)	33 (34.7%)	13 (12.3%)	35 (22.4%)	36 (16.5%)	12 (27.3%)	4 (36.4%)	22 (40.7%)	16 (36.4%)	10 (47.6%)
Related	5 (3.1%)	33 (11.4%)	25 (7.1%)	13 (13.7%)	6 (5.7%)	9 (5.8%)	13 (6.0%)	2 (4.5%)	1 (9.1%)	4 (7.4%)	2 (4.5%)	3 (14.3%)
Fatal	7 (4.4%)	22 (7.6%)	23 (6.5%)	6 (6.3%)	2 (1.9%)	7 (4.5%)	7 (3.2%)	2 (4.5%)	1 (9.1%)	10 (18.5%)	5 (11.4%)	6 (28.6%)
Leading to study drug modification	26 (16.4%)	74 (25.6%)	73 (20.7%)	27 (28.4%)	31 (29.2%)	56 (35.9%)	73 (33.5%)	14 (31.8%)	4 (36.4%)	15 (27.8%)	14 (31.8%)	5 (23.8%)
Leading to study drug discontinuation	21 (13.2%)	51 (17.6%)	56 (15.9%)	16 (16.8%)	4 (3.8%)	9 (5.8%)	11 (5.0%)	2 (4.5%)	4 (36.4%)	11 (20.4%)	10 (22.7%)	5 (23.8%)

DAN, danazol; MMB, momelotinib; RUX, ruxolitinib.

Table 94: Integrated Overall Summary of Adverse Events by Baseline Prognostic Score (Intermediate 1, Intermediate 2, High Risk; Randomized Treatment

Adverse Event Category	MMB			RUX			DAN		
	Int-1 (N = 70)	Int-2 (N = 201)	High (N = 177)	Int-1 (N = 55)	Int-2 (N = 92)	High (N = 115)	Int-1 (N = 1)	Int-2 (N = 31)	High (N = 32)
Any adverse event, n (%)	66 (94.3%)	184 (91.5%)	170 (96.0%)	49 (89.1%)	88 (95.7%)	111 (96.5%)	1 (100%)	29 (93.5%)	31 (96.9%)
Related	53 (75.7%)	128 (63.7%)	109 (61.6%)	28 (50.9%)	58 (63.0%)	75 (65.2%)	0	16 (51.6%)	13 (40.6%)
Grade 3 or 4	23 (32.9%)	84 (41.8%)	87 (49.2%)	12 (21.8%)	39 (42.4%)	62 (53.9%)	0	22 (71.0%)	19 (59.4%)
Related	15 (21.4%)	48 (23.9%)	44 (24.9%)	7 (12.7%)	28 (30.4%)	35 (30.4%)	0	10 (32.3%)	6 (18.8%)
Serious	17 (24.3%)	56 (27.9%)	58 (32.8%)	5 (9.1%)	16 (17.4%)	27 (23.5%)	0	15 (48.4%)	11 (34.4%)
Related	5 (7.1%)	21 (10.4%)	12 (6.8%)	1 (1.8%)	5 (5.4%)	9 (7.8%)	0	4 (12.9%)	1 (3.1%)
Fatal	1 (1.4%)	13 (6.5%)	15 (8.5%)	1 (1.8%)	5 (5.4%)	3 (2.6%)	0	7 (22.6%)	4 (12.5%)
Leading to study drug modification	10 (14.3%)	44 (21.9%)	46 (26.0%)	16 (29.1%)	27 (29.3%)	44 (38.3%)	0	10 (32.3%)	9 (28.1%)
Leading to study drug discontinuation	9 (12.9%)	30 (14.9%)	33 (18.6%)	1 (1.8%)	6 (6.5%)	6 (5.2%)	0	12 (38.7%)	3 (9.4%)

DIPSS scores were used for the analysis of baseline prognostic risk.

DAN, danazol; DIPSS, Dynamic International Prognostic Scoring System; Int-1, intermediate-1; Int-2, intermediate-2; MMB, momelotinib; RUX, ruxolitinib.

Table 95: Integrated Overall Summary of Adverse Events by Baseline Hemoglobin Value (< 8 g/dL, ⩾ 8 g/dL, < 10 g/dL, ⩾ 10 g/dL; Randomized Treatment)

	MMB				RUX				DAN			
Adverse Event Category	< 8 g/dL (N = 100)	≥ 8 g/dL (N = 347)	< 10 g/dL (N = 275)	≥ 10 g/dL (N = 172)	< 8 g/dL (N = 24)	≥ 8 g/dL (N = 237)	< 10 g/dL (N = 130)	≥ 10 g/dL (N = 131)	< 8 g/dL (N = 32)	≥ 8 g/dL (N = 33)	< 10 g/dL (N = 65)	≥ 10 g/dL (N = 0)
Any adverse event, n (%)	94 (94.0%)	325 (93.7%)	262 (95.3%)	157 (91.3%)	22 (91.7%)	225 (94.9%)	123 (94.6%)	124 (94.7%)	31 (96.9%)	31 (93.9%)	62 (95.4%)	0
Related	59 (59.0%)	230 (66.3%)	176 (64.0%)	113 (65.7%)	13 (54.2%)	148 (62.4%)	73 (56.2%)	88 (67.2%)	14 (43.8%)	15 (45.5%)	29 (44.6%)	0
Grade 3 or 4	52 (52.0%)	141 (40.6%)	137 (49.8%)	56 (32.6%)	13 (54.2%)	100 (42.2%)	68 (52.3%)	45 (34.4%)	19 (59.4%)	22 (66.7%)	41 (63.1%)	0
Related	24 (24.0%)	83 (23.9%)	71 (25.8%)	36 (20.9%)	6 (25.0%)	64 (27.0%)	39 (30.0%)	31 (23.7%)	7 (21.9%)	9 (27.3%)	16 (24.6%)	0
Serious	37 (37.0%)	94 (27.1%)	91 (33.1%)	40 (23.3%)	5 (20.8%)	43 (18.1%)	30 (23.1%)	18 (13.7%)	11 (34.4%)	15 (45.5%)	26 (40.0%)	0
Related	9 (9.0%)	29 (8.4%)	27 (9.8%)	11 (6.4%)	2 (8.3%)	13 (5.5%)	10 (7.7%)	5 (3.8%)	2 (6.3%)	3 (9.1%)	5 (7.7%)	0
Fatal	11 (11.0%)	18 (5.2%)	21 (7.6%)	8 (4.7%)	3 (12.5%)	6 (2.5%)	6 (4.6%)	3 (2.3%)	5 (15.6%)	6 (18.2%)	11 (16.9%)	0
Leading to study drug modification	24 (24.0%)	76 (21.9%)	69 (25.1%)	31 (18.0%)	7 (29.2%)	80 (33.8%)	41 (31.5%)	46 (35.1%)	7 (21.9%)	12 (36.4%)	19 (29.2%)	0
Leading to study drug discontinuation	21 (21.0%)	51 (14.7%)	52 (18.9%)	20 (11.6%)	4 (16.7%)	9 (3.8%)	7 (5.4%)	6 (4.6%)	10 (31.3%)	5 (15.2%)	15 (23.1%)	0

DAN, danazol; MMB, momelotinib; RUX, ruxolitinib.

2.6.8.7. Immunological events

Not applicable.

2.6.8.8. Safety related to drug-drug interactions and other interactions

Potential for Other Medicinal Products to Affect MMB Exposure

MMB is not a sensitive substrate of cytochrome P450 (CYP) 3A, P glycoprotein (P gp), or breast cancer resistance protein (BCRP) and can be coadministered with inhibitors of CYP3A without dose modification.

Coadministration of single dose rifampin (600 mg), a potent inhibitor of the hepatic uptake transporters organic anion transporting polypeptide (OATP) 1B1/1B3, and MMB resulted in a moderate increase in MMB plasma exposure in a study of healthy adult volunteers; however, the extent of this interaction does not suggest dose modification of MMB is warranted when coadministered with inhibitors of OATP1B1/1B3.

Coadministration of multiple dose rifampin treatment (600 mg once daily), a strong inducer of CYP3A/2C8/2C19, and MMB (200 mg single dose) resulted in a slight decrease in MMB plasma exposure in a study of healthy adult volunteers; thus, MMB can be coadministered with rifampin without dose modification. However, coadministration of other strong CYP3A inducers may decrease MMB exposure, and therefore result in reduced effective drug exposure. If coadministration of other strong CYP3A inducers is necessary, the patient should be monitored frequently.

Coadministration of multiple dose omeprazole (20 mg once daily), a proton pump inhibitor, resulted in a moderate decrease in MMB exposure in a study of healthy adult volunteers administered MMB 200 mg single dose. However, the extent of this interaction does not suggest that dose modification is warranted when MMB is coadministered with an acid reducing agent.

Potential for MMB to Affect Exposure to Other Medicinal Products

MMB did not alter the PK of midazolam (a sensitive probe CYP3A substrate), and no dose modification is needed for sensitive CYP3A substrates when coadministered with MMB.

MMB is a BCRP inhibitor *in vitro* and significantly increased the plasma exposure of the BCRP substrate rosuvastatin 10 mg when coadministered with a single dose of MMB 200 mg (3.2 fold increase in maximum plasm concentration [Cmax] and 2.7 fold increase in area under the concentration time curve [AUCinf]) in a study of healthy adult volunteers. When clinically appropriate, dose modification or alternative medications for rosuvastatin should be considered when coadministered with MMB.

2.6.8.9. Discontinuation due to adverse events

Table 96: Integrated Grade ⩾ 3 Adverse Events Leading to Study Drug Discontinuation in ⩾ 1% of Subjects in Any Group by System Organ Class and Preferred Term by Study Period and Treatment (Safety Population)

System Organ Class Preferred Term	Randomized Treatment			Open-Label	Overall
	MMB (N = 448)	RUX (N = 262)	DAN (N = 65)	MMB (N = 604)	MMB (N = 725)
Any adverse event leading to study drug discontinuation, n (%)	56 (12.5%)	13 (5.0%)	11 (16.9%)	120 (19.9%)	176 (24.3%)
Blood and lymphatic system disorders	17 (3.8%)	4 (1.5%)	4 (6.2%)	31 (5.1%)	48 (6.6%)
Thrombocytopenia	10 (2.2%)	3 (1.1%)	0	16 (2.6%)	26 (3.6%)
Anaemia	2 (0.4%)	0	2 (3.1%)	5 (0.8%)	7 (1.0%)
Splenomegaly	2 (0.4%)	0	1 (1.5%)	4 (0.7%)	6 (0.8%)
Neutropenia	0	0	1 (1.5%)	4 (0.7%)	4 (0.6%)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	10 (2.2%)	3 (1.1%)	2 (3.1%)	18 (3.0%)	28 (3.9%)
Acute myeloid leukaemia	4 (0.9%)	1 (0.4%)	1 (1.5%)	7 (1.2%)	11 (1.5%)
Transformation to acute myeloid leukaemia	1 (0.2%)	1 (0.4%)	1 (1.5%)	2 (0.3%)	3 (0.4%)
Infections and infestations	8 (1.8%)	2 (0.8%)	0	20 (3.3%)	28 (3.9%)
Pneumonia	2 (0.4%)	1 (0.4%)	0	6 (1.0%)	8 (1.1%)
General disorders and administration site conditions	5 (1.1%)	0	2 (3.1%)	13 (2.2%)	18 (2.5%)
Disease progression	1 (0.2%)	0	0	6 (1.0%)	7 (1.0%)
Death	1 (0.2%)	0	1 (1.5%)	1 (0.2%)	2 (0.3%)
Chest pain	0	0	1 (1.5%)	0	0
Nervous system disorders	1 (0.2%)	0	1 (1.5%)	11 (1.8%)	12 (1.7%)
Cerebrovascular accident	0	0	1 (1.5%)	2 (0.3%)	2 (0.3%)
Cardiac disorders	2 (0.4%)	0	1 (1.5%)	5 (0.8%)	7 (1.0%)
Coronary artery stenosis	0	0	1 (1.5%)	0	0
Hepatobiliary disorders	1 (0.2%)	0	1 (1.5%)	3 (0.5%)	4 (0.6%)
Jaundice	0	0	1 (1.5%)	0	0

Shading indicates events that met the ≥ 1% threshold.

UPDATED INFORMATION:

Updated overall AE summaries are presented for the subjects participating in the MOMENTUM OLE treatment period in tables below. For MOMENTUM, the data cut for this updated analysis was based on the overall study last patient last visit date of 29 December 2022, when all subjects had discontinued treatment or had transitioned to XAP after at least 24 weeks of participation in the OLE treatment phase of the study. The updated analysis of the XAP study, with a data cut of 02 September 2022, included subjects who entered this long-term extension study after initiating momelotinib on one of the Phase 3 studies (SIMPLIFY-1, SIMPLIFY-2, or MOMENTUM).

Table 97: Updated Overall Summary of Treatment-emergent Adverse Events Over the MOMENTUM OLE Treatment Period (Safety Analysis Set)

	OLE		
Subjects with at least 1, n (%)	**MMB → MMB (N=93)**	**DAN → MMB (N=41)**	**Total (N=134)**
TEAE	83 (89.2)	35 (85.4)	118 (88.1)
≥Grade 3 TEAE	48 (51.6)	20 (48.8)	68 (50.7)
Related TEAE	35 (37.6)	17 (41.5)	52 (38.8)
≥ Grade 3 related TEAE	16 (17.2)	10 (24.4)	26 (19.4)
TEAE leading to treatment discontinuation	17 (18.3)	5 (12.2)	22 (16.4)
TEAE leading to treatment interruption and/or dose reduction	26 (28.0)	15 (36.6)	41 (30.6)
SAE	30 (32.3)	12 (29.3)	42 (31.3)
Related SAE	3 (3.2)	1 (2.4)	4 (3.0)
Fatal TEAE	10 (10.8)	5 (12.2)	15 (11.2)

	XAP			
Subjects with at least 1, n (%)	**SIMPLIFY-1 (N=96)**	**SIMPLIFY-2 (N=22)**	**MOMENTUM (N=85)**	**Total (N=203)**
TEAE	79 (82.3)	20 (90.9)	38 (44.7)	137 (67.5)
≥Grade 3 TEAE	47 (49.0)	13 (59.1)	21 (24.7)	81 (39.9)
Related TEAE	33 (34.4)	7 (31.8)	10 (11.8)	50 (24.6)
≥Grade 3 related TEAE	9 (9.4))	4 (18.2	5(5.9)	18 (8.9)
TEAE leading to treatment discontinuation	16 (16.7)	5 (22.7)	6 (7.1)	27 (13.3)
TEAE leading to treatment interruption and/or dose reduction	25 (26.0)	7 (31.8)	8 (9.4)	40 (19.7)
SAE	35 (36.5)	11 (50.0)	17 (20.0)	63 (31.0)
Related SAE	4 (4.2)	0	0	4 (2.0)
Fatal TEAE	15 (15.6)	4 (18.2)	3 (3.5)	22 (10.8)

Adverse events

MOMENTUM OLE

The most commonly reported adverse events during MOMENTUM OLE are summarized by preferred term in table below. Commonly reported adverse events are defined as those reported in ≥ 5% of subjects in any group. Shading indicates events that met the ≥ 5% threshold.

Certain adverse events met the ≥ 5% incidence threshold in both subjects who continued MMB from randomized treatment (MMB to MMB) and subjects who started MMB after randomized treatment with DAN (DAN to MMB), including diarrhea, thrombocytopenia, pyrexia, weight decreased, anemia, asthenia, blood creatinine increased, and fatigue, consistent with underlying MF disease signs and symptoms. The only PT with a difference ≥ 10% between treatment groups was asthenia (MMB to MMB 12/93 [12.9%]; DANto MMB 0/41).

During the MOMENTUM OLE treatment period, the updated exposure-adjusted incidence of subjects with at least one TEAE was 176.65 per 100 person-years overall; in the treatment groups, the incidence was 176.60 per 100 person-years in MMB to MMB and 176.77 per 100 person-years in DAN to MMB.

Table 98: Commonly Reported Treatment-emergent Adverse Events in ⩾ 5% of Subjects in Any Group by Preferred Term During OLE Treatment Period (Safety Analysis Set)

	MMB→MMB (N=93)	DAN→MMB (N=41)	Total (N=134)
Subjects with at least one event, n (%)	83 (89.2)	35 (85.4)	118 (88.1)
Diarrhoea	16 (17.2)	5 (12.2)	21 (15.7)
Thrombocytopenia	13 (14.0)	7 (17.1)	20 (14.9)
Pyrexia	13 (14.0)	4 (9.8)	17 (12.7)
Weight decreased	9 (9.7)	7 (17.1)	16 (11.9)
Anaemia	10 (10.8)	4 (9.8)	14 (10.4)
Asthenia	12 (12.9)	0	12 (9.0)
Blood creatinine increased	7 (7.5)	4 (9.8)	11 (8.2)
Cough	8 (8.6)	2 (4.9)	10 (7.5)
Fatigue	6 (6.5)	3 (7.3)	9 (6.7)
COVID-19	8 (8.6)	0	8 (6.0)
Hypertension	3 (3.2)	5 (12.2)	8 (6.0)
Nausea	8 (8.6)	0	8 (6.0)
Dyspnoea	7 (7.5)	0	7 (5.2)
Neutropenia	5 (5.4)	2 (4.9)	7 (5.2)
Pruritus	6 (6.5)	1 (2.4)	7 (5.2)
Acute kidney injury	3 (3.2)	3 (7.3)	6 (4.5)
Hyperuricaemia	3 (3.2)	3 (7.3)	6 (4.5)
Urinary tract infection	5 (5.4)	1 (2.4)	6 (4.5)
Dizziness	1 (1.1)	4 (9.8)	5 (3.7)
Hyperkalaemia	2 (2.2)	3 (7.3)	5 (3.7)
Arthralgia	1 (1.1)	3 (7.3)	4 (3.0)
Epistaxis	1 (1.1)	3 (7.3)	4 (3.0)

Source: Table 14.3.1.2c

XAP

The most commonly reported adverse events during the long-term extension study XAP are summarized by parent Phase 3 study and preferred term in below. The overall TEAE rate was lower in the MOMENTUM study (44.7%) than in SIMPLIFY-1 and SIMPLIFY-2 (82.3% and 90.9%, respectively), likely due to the shorter duration of follow up.

Commonly reported adverse events are defined as those reported in ≥ 5% of subjects in any group. Shading indicates events that met the ≥ 5% threshold. Anemia and COVID-19 were observed in ≥ 5% of subject across studies. There were no notable differences in the types of common AEs between groups during the XAP.

Table 99: Commonly Reported Adverse Events in ⩾ 5% of Subjects in Any Group by Preferred Term During XAP Treatment (Safety Population)

Preferred Term	SIMPLIFY-1 (N=96) n (%)		SIMPLIFY-2 (N=22) n (%)		MOMENTUM (N=85) n (%)		Overall (N=203) n (%)	
Any Treatment-Emergent Adverse Event (TEAE)	79	(82.3)	20	(90.9)	38	(44.7)	137	(67.5)
Anaemia	22	(22.9)	4	(18.2)	6	(7.1)	32	(15.8)
COVID-19	10	(10.4)	2	(9.1)	7	(8.2)	19	(9.4)
Thrombocytopenia	8	(8.3)	1	(4.5)	4	(4.7)	13	(6.4)
Diarrhoea	4	(4.2)	4	(18.2)	2	(2.4)	10	(4.9)
Platelet count decreased	5	(5.2)	2	(9.1)	3	(3.5)	10	(4.9)
Pneumonia	6	(6.3)	3	(3.6)	1	(1.2)	10	(4.9)
Urinary tract infection	7	(7.3)	3	(13.6)	0		10	(4.9)
Asthenia	2	(2.1)	3	(13.6)	4	(4.7)	9	(4.4)
Abdominal pain	4	(4.2)	2	(9.1)	2	(2.4)	8	(3.9)
Acute kidney injury	6	(6.3)	2	(9.1)	0		8	(3.9)
Cough	6	(6.3)	2	(9.1)	0		8	(3.9)
Arthralgia	3	(3.1)	3	(13.6)	1	(1.2)	7	(3.4)
COVID-19 pneumonia	3	(3.1)	2	(9.1)	2	(2.4)	7	(3.4)
Disease progression	3	(3.1)	1	(4.5)	3	(3.5)	7	(3.4)
Dizziness	3	(3.1)	2	(9.1)	2	(2.4)	7	(3.4)
Nausea	4	(4.2)	2	(9.1)	1	(1.2)	7	(3.4)
Pruritus	3	(3.1)	4	(18.2)	0		7	(3.4)
Pyrexia	5	(5.2)	2	(9.1)	0		7	(3.4)
Upper respiratory tract infection	6	(6.3)	1	(4.5)	0		7	(3.4)
Back pain	5	(5.2)	0		1	(1.2)	6	(3.0)
Fatigue	4	(4.2)	2	(9.1)	0		6	(3.0)
Peripheral sensory neuropathy	4	(4.2)	2	(9.1)	0		6	(3.0)
Squamous cell carcinoma of skin	5	(5.2)	1	(4.5)	0		6	(3.0)
Abdominal pain upper	1	(1.0)	4	(18.2)	0		5	(2.5)
Bronchitis	3	(3.1)	2	(9.1)	0		5	(2.5)
Decreased appetite	0		2	(9.1)	3	(3.5)	5	(2.5)
Insomnia	3	(3.1)	2	(9.1)	0		5	(2.5)
Pain in extremity	1	(1.0)	3	(13.6)	1	(1.2)	5	(2.5)
Paraesthesia	2	(2.1)	2	(9.1)	1	(1.2)	5	(2.5)
Vomiting	2	(2.1)	3	(13.6)	0		5	(2.5)
Constipation	0		3	(13.6)	1	(1.2)	4	(2.0)
Fall	0		3	(13.6)	1	(1.2)	4	(2.0)
Gout	2	(2.1)	2	(9.1)	0		4	(2.0)
Oedema peripheral	2	(2.1)	2	(9.1)	0		4	(2.0)
Oropharyngeal pain	1	(1.0)	2	(9.1)	1	(1.2)	4	(2.0)
Sinusitis	0		3	(13.6)	0		3	(1.5)
Skin laceration	0		3	(13.6)	0		3	(1.5)
Subdural haematoma	0		2	(9.1)	1	(1.2)	3	(1.5)
Oral herpes	0		2	(9.1)	0		2	(1.0)
Rhinitis	0		2	(9.1)	0		2	(1.0)
Stomatitis	0		2	(9.1)	0		2	(1.0)

Source: Table 14.3.2.11

First Dose Effects

During the MOMENTUM OLE, AEs occurring within 24 hours after the first dose of study drug were reported for 21.6% of subjects overall. As the MMB to MMB group continued treatment with momelotinib into the OLE, only AEs occurring in the DAN to MMB will be considered here. In the DAN to MMB group, there were 10/41 subjects (24.4%) who experienced at least one AE in the first 24 hours

after the first dose of momelotinib in the OLE period. Diarrhea, dizziness, and hypocalcemia were reported in 2/41 subjects (4.9%) each; all other PTs were reported in single subjects.

During the MOMENTUM OLE, AEs considered related to study drug and occurring within the 24 hours after the first dose of open label MMB were reported for 3.7% of subjects overall. In the DAN to MMB group, there were 3/41 subjects (7.3%) who experienced at least one AE in the first 24 hours after the first dose of open-label MMB; 2 subjects experienced diarrhea and 1 subject each experienced vomiting, dizziness, headache, and hypertension.

Treatment-related adverse events

MOMENTUM OLE

Overall, 38.8% of subjects in OLE experienced at least 1 related TEAE. The most commonly reported treatment related AEs during MOMENTUM OLE were thrombocytopenia in 11.2% (MMB to MMB 10/93 [10.8%]; DAN to MMB 5/41 [12.2%]) and diarrhea in 6.7% (MMB to MMB 6/93 [6.5%]; DAN to MMB 3/41 [7.3%]).

During the MOMENTUM OLE treatment period, the incidence of subjects with at least one TEAE assessed as related to study drug was 77.84 per 100 person-years overall; in the treatment groups, the incidence was 74.47 per 100 person-years in MMB to MMB and 85.86 per 100 person-years in DAN to MMB.

XAP

Overall, 50 subjects (24.6%) experienced a treatment-related AE during XAP (SIMPLIFY-1 33/96 [34.4%]; SIMPLIFY-2 7/22 [31.8%]; MOMENTUM 10/85 [11.8%]). No PT was experienced by ≥ 5% of subjects overall. The only PTs experienced by ≥ 5% of subjects by study were anemia (SIMPLIFY-1 6/96 [6.3%]; SIMPLIFY-2 1/22 [4.5%]; MOMENTUM 1/85 [1.2%]), paresthesia (SIMPLIFY-1 1/96 [1.0%]; SIMPLIFY-2 2/22 [9.1%]; MOMENTUM 1/85 [1.2%]), and stomatitis (SIMPLIFY-1 0; SIMPLIFY-2 2/22 [9.1%]; MOMENTUM 0).

Grade ≥ 3 adverse events

MOMENTUM OLE

During the MOMENTUM OLE, 68 subjects overall (50.7%) experienced at least one Grade ≥ 3 AE; these occurred with similar frequency between treatment groups (MMB to MMB 48/93 [51.6%]; DAN to MMB 20/41 [48.8%]). Grade ≥ 3 AEs by PT occurring in ≥ 5% subjects overall included thrombocytopenia in 10.4% (MMB to MMB 8/93 [8.6%]; DAN to MMB 6/41 [14.6%]) and anemia in 6.7% (MMB to MMB 8/93 [8.6%]; DAN to MMB 1/41 [2.4%]). Grade ≥ 3 AEs that occurred in ≥ 5% subjects in either treatment group included Grade ≥ 3 acute kidney injury(MMB to MMB 2/93 [2.2%]; DAN to MMB 3/41 [7.3%]) and neutropenia (MMB to MMB 5/93 [5.4%]; DAN to MMB 0).

The exposure-adjusted incidence of Grade ≥ AEs during the MOMENTUM OLE was 101.80 per 100 person-years overall: 102.13 per 100 person-years in the MMB ≥ MMB group and 101.01 per 100 person-years in the DAN□MMB group.

During the MOMENTUM OLE, Grade ≥ 3 adverse events assessed as related to study treatment were reported in 16/93 subjects (17.2%) in the MMB to MMB treatment group and in 10/41 subjects (24.4%) in the DAN□MMB treatment group.

The most frequently reported PTs with Grade ≥ 3 related AEs were thrombocytopenia (MMB to MMB 6/93 [6.5%]; DAN to MMB 5/41 [12.2%]), neutropenia (MMB to MMB 3/93 [3.2%]; DAN to MMB 0/41), platelet count decreased (MMB to MMB 3/93 [3.2%];DAN to MMB 0/41), and anemia (MMB□MMB 3/93 [3.2%]; DAN to MMB 1/41 [2.4]).

The exposure-adjusted incidence of Grade ≥ 3 AEs assessed as related to study treatment during the MOMENTUM OLE was 26 per 100 person-years overall: 16 per 100 person years in the MMB ≥ MMB group and 10 per 100 person-years in the DAN to MMB group.

XAP

During the XAP, 39.9% of subjects overall experienced a Grade ≥ 3 AE; 47 subjects (49.0%) from SIMPLIFY-1, 13 subjects (59.1%) from SIMPLIFY-2, and 21 subjects (24.7%) from MOMENTUM. The only PT occurring in ≥ 5% subjects overall was anemia in 7.9% of subjects (SIMPLIFY-1, 8/96 [8.3%]; SIMPLIFY-2, 3/22 [13.6%]; and MOMENTUM, 5/85 [5.9%]).

Overall, 8.9% of subjects in XAP experienced a Grade ≥3 AE assessed as related by the investigator. Thrombocytopenia was the only PT occurring in more than 1 subject per study group, occurring in 6 subjects (3.0%) overall (SIMPLIFY-1, 3/96 [3.1%]; SIMPLIFY-2, 1/22 [4.5%]; and MOMENTUM, 2/85 [2.4%]).

Serious adverse events

MOMENTUM OLE

During treatment in the OLE period, 31.3% of subjects overall experienced at least 1 SAE (MMB to MMB 30/93 [32.3%]; DAN to MMB 12/41 [29.3%]). The SAEs by PT experienced by ≥2 subjects overall were: COVID-19 pneumonia 4/134 subjects (MMB to MMB 4/93 [4.3%]; DAN to MMB 0); acute kidney injury 4/134 subjects (MMB to MMB 2/93 [2.2%]; DAN to MMB 2/41 [4.9%]); urinary tract infection 3/134 subjects (MMB to MMB 2/93 [2.2%]; DAN to MMB 1/41 [2.4%]); febrile neutropenia and squamous cell carcinoma of the skin 2/134 subjects each (MMB to MMB 2/93 [2.2%]; DAN to MMB 0); and anemia, pneumonia, basal cell carcinoma, and pulmonary edema in 2/134 subjects each (MMB to MMB 1/93 [1.1%]; DAN to MMB 1/41 [2.4%]).Four subjects experienced SAEs assessed as related to study treatment. In the MMB to MMB group, related SAEs of edema peripheral, gastroenteritis rotavirus, and pneumonia staphylococcal were experienced in 1 subject each. In the DAN to MMB group, 1 subject experienced a related SAE of anemia.

Over the MOMENTUM OLE treatment period, the exposure-adjusted incidence of SAEs was 62.87 per 100 person-years overall: 63.83 per 100 person-years in the MMB to MMB group and 60.61 per 100 person-years in the DAN to MMB group. The exposure-adjusted incidence of SAEs assessed as Grade ≥ 3 was 55.39 per 100 person-years overall: 55.32 per 100 person-years in the MMB to MMB group and 55.56 per 100 person-years in the DAN to MMB group. The exposure-adjusted incidence of SAEs considered to be related to study drug was 5.99 per 100 person-years: 6.38 per 100 person-years in the MMB to MMB group and 5.05 per 100 person-years in the DAN to MMB group.

XAP

During treatment in XAP, 63 subjects (31.0%) overall experienced an SAE. SAEs occurring in 2 or more subjects overall are presented in Table below.

Table 100: Serious Adverse Events occurring in ⩾ 2 subjects overall in the XAP

Preferred Term	SIMPLIFY-1 (N=96) n (%)		SIMPLIFY-2 (N=22) n (%)		MOMENTUM (N=85) n (%)		Overall (N=203) n (%)	
Any Serious Treatment-Emergent Adverse Event (TEAE)	35	(36.5)	11	(50.0)	17	(20.0)	63	(31.0)
Pneumonia	5	(5.2)	2	(9.1)	1	(1.2)	8	(3.9)
COVID-19 pneumonia	2	(2.1)	2	(9.1)	2	(2.4)	6	(3.0)
Acute kidney injury	3	(3.1)	2	(9.1)	0		5	(2.5)
Anaemia	1	(1.0)	1	(4.5)	2	(2.4)	4	(2.0)
Cellulitis	1	(1.0)	1	(4.5)	2	(2.4)	4	(2.0)
Septic shock	2	(2.1)	1	(4.5)	0		3	(1.5)
Subdural haematoma	0		2	(9.1)	1	(1.2)	3	(1.5)
Abdominal pain	1	(1.0)	0		1	(1.2)	2	(1.0)
Ascites	2	(2.1)	0		0		2	(1.0)
Atrial fibrillation	2	(2.1)	0		0		2	(1.0)
COVID-19	0		0		2	(2.4)	2	(1.0)
Cardiac failure congestive	0		0		2	(2.4)	2	(1.0)
Death	2	(2.1)	0		0		2	(1.0)
Dyspnoea	1	(1.0)	0		1	(1.2)	2	(1.0)
Pneumonia bacterial	1	(1.0)	0		1	(1.2)	2	(1.0)
Pyrexia	1	(1.0)	1	(4.5)	0		2	(1.0)
Sepsis	2	(2.1)	0		0		2	(1.0)
Squamous cell carcinoma of skin	2	(2.1)	0		0		2	(1.0)
Urinary tract infection	1	(1.0)	1	(4.5)	0		2	(1.0)

Source: Table 14.3.2.15

Four subjects experienced SAEs that were assessed as related to study treatment. All of the SAEs assessed as related to study treatment were reported in subjects from SIMPLIFY-1. PTs include squamous cell carcinoma of the skin in 2 subjects; and dehydration, hyperkalemia, infection, and skin lesion in 1 subject each.

Deaths

MOMENTUM OLE

During treatment in the MOMENTUM OLE treatment period, there were 15 fatal AEs overall (MMB to MMB 10/93 [10.8%]; DAN to MMB 5/41 [12.2%]).

No PT occurred in more than 1 subject. In the MMB to MMB group, fatal AEs occurred in the PTs of anemia, arrhythmia, cerebral hemorrhage, Escherichia infection, gastroenteritis rotavirus, general physical health deterioration, multiple organ dysfunction syndrome, pneumonia staphylococcal, splenic abscess, and urosepsis; gastroenteritis rotavirus and pneumonia staphylococcal were assessed by the investigator to be related to study treatment. In the DAN to MMB group, fatal AEs occurred in the PTs of adenocarcinoma, cardiac arrest, Enterobacter sepsis, sudden death, and transformation to AML; no event was considered to be related to study treatment.

During the MOMENTUM OLE treatment period, fatal AEs occurred at an exposure-adjusted incidence rate of 22.46 events per 100 person-years. Fatal AEs considered to be related to study drug occurred at an exposure-adjusted incidence rate of 2.99 events per 100 person-years.

XAP

During treatment in the XAP, there were 25 deaths, including 21 on-study deaths (SIMPLIFY-1, 14/96 [14.6%]; SIMPLIFY-2, 4/22 [18.2%]; and MOMENTUM, 3/85 [3.5%]). Adverse event was listed as the most frequent cause of death for each study group (21 subjects [10.3%] overall; 13 subjects [13.5%]

in SIMPLIFY-1; 5 subjects [22.7%] in SIMPLIFY-2; and 3 subjects [3.5%] in MOMENTUM). Two subject deaths in SIMPLIFY-1 were due to progressive disease, 1 subject in SIMPLIFY-1 had an unexpected sudden death, and 1 subject in SIMPLIFY-2 had a death due to worsening of a medical condition. The only death considered by the investigator to be related to study treatment was in MOMENTUM due to infection.

Adverse events leading to study treatment discontinuation

MOMENTUM OLE

During the OLE treatment period, 16.4% of subjects overall experienced an AE leading to discontinuation. In the MMB to MMB group, 17 subjects (18.3%) reported AEs leading to discontinuation. The only PT occurring in >1 subject was anemia (2 subjects [2.2%]). In the DAN to MMB group, 5 subjects (12.2%) experienced an AE leading to treatment discontinuation; no PT was reported in more than 1 subject.

Over the MOMENTUM OLE treatment period, the incidence of subjects with at least 1 exposure-adjusted TEAE leading to study drug discontinuation was 32.93 per 100 person-years overall; in the treatment groups, the incidence was 36.17 per 100 person-years in MMB to MMB and 25.25 per 100 person-years in DAN to MMB.

XAP

During the XAP, 13.3 % of subjects overall experienced a TEAE leading to study drug discontinuation; (SIMPLIFY-1, 16 subjects [16.7%]; SIMPLIFY-2, 5 subjects [22.7%]; MOMENTUM, 6 subjects [7.1%]). Of these, 9 (4.4%) were due to Grade 3 or 4 events. The most common PT leading to study drug discontinuation was disease progression (SIMPLIFY-1, 3 subjects [3.1%]; SIMPLIFY-2, 1 subject [4.5%]; MOMENTUM, 3 subjects [3.5%]).

Adverse events leading to study drug modification

MOMENTUM OLE

During the OLE treatment period, 30.6% of subjects overall experienced an AE leading to dose modification (MMB to MMB 26 subjects [28.0%]; DAN to MMB 15 subjects [36.6%]). PTs occurring in 2 or more subjects per treatment group included: thrombocytopenia (6 subjects each), neutropenia and platelet count decreased (MMB to MMB 2 subjects; DAN to MMB 0 subjects each), chronic kidney disease (MMB to MMB 2 subjects; DAN to MMB 1 subject), and diarrhea (MMB to MMB 1 subject; DAN to MMB 2 subjects).

During the MOMENTUM OLE treatment period, the incidence of subjects with at least 1 exposure-adjusted TEAE leading to dose modification was 61.38 per 100 person-years overall; in the treatment groups, the incidence was 55.32 per 100 person-years in MMB to MMB and 75.76 per 100 person-years in DAN to MMB.

XAP

During the XAP, 19.7 % of subjects overall experienced a TEAE leading to study drug interruption and/or dose modification; (SIMPLIFY-1, 25 subjects [26.0%]; SIMPLIFY-2, 7 subjects [31.8%]; MOMENTUM, 8 subjects [9.4%]). Of these, 28 subjects (13.8%) experienced Grade 3 or 4 events. The most common PTs leading to study drug interruption and/or dose modification were thrombocytopenia (SIMPLIFY-1, 3 subjects [3.1%]; SIMPLIFY-2, 1 subject [4.5%]; MOMENTUM, 2 subjects [2.4%]); COVID-19 (SIMPLIFY-1, 1 subject [1.0%]; SIMPLIFY-2, 1 subject [4.5%]; MOMENTUM, 2 subjects [2.4%]); and platelet count decreased (SIMPLIFY-1, 2 subjects [2.1%]; SIMPLIFY-2, 1 subject [4.5%]; MOMENTUM, 1 subject [1.2%]).

XAP

During the XAP, 13.3 % of subjects overall experienced a TEAE leading to study drug discontinuation; (SIMPLIFY-1, 16 subjects [16.7%]; SIMPLIFY-2, 5 subjects [22.7%]; MOMENTUM, 6 subjects [7.1%]). Of these, 9 (4.4%) were due to Grade 3 or 4 events. The most common PT leading to study drug discontinuation was disease progression (SIMPLIFY-1, 3 subjects [3.1%]; SIMPLIFY-2, 1 subject [4.5%]; MOMENTUM, 3 subjects [3.5%]).

Adverse events leading to study drug modification

MOMENTUM OLE

During the OLE treatment period, 30.6% of subjects overall experienced an AE leading to dose modification (MMB to MMB 26 subjects [28.0%]; DAN to MMB 15 subjects [36.6%]). PTs occurring in 2 or more subjects per treatment group included: thrombocytopenia (6 subjects each), neutropenia and platelet count decreased (MMB to MMB 2 subjects; DAN to MMB 0 subjects each), chronic kidney disease (MMB to MMB 2 subjects; DAN to MMB 1 subject), and diarrhea (MMB to MMB 1 subject; DAN□MMB 2 subjects).

During the MOMENTUM OLE treatment period, the incidence of subjects with at least 1 exposure-adjusted TEAE leading to dose modification was 61.38 per 100 person-years overall; in the treatment groups, the incidence was 55.32 per 100 person-years in MMB to MMB and 75.76 per 100 person-years in DAN to MMB.

XAP

During the XAP, 19.7 % of subjects overall experienced a TEAE leading to study drug interruption and/or dose modification; (SIMPLIFY-1, 25 subjects [26.0%]; SIMPLIFY-2, 7 subjects [31.8%]; MOMENTUM, 8 subjects [9.4%]). Of these, 28 subjects (13.8%) experienced Grade 3 or 4 events. The most common PTs leading to study drug interruption and/or dose modification were thrombocytopenia (SIMPLIFY-1, 3 subjects [3.1%]; SIMPLIFY-2, 1 subject [4.5%]; MOMENTUM, 2 subjects [2.4%]); COVID-19 (SIMPLIFY-1, 1 subject [1.0%]; SIMPLIFY-2, 1 subject [4.5%]; MOMENTUM, 2 subjects [2.4%]); and platelet count decreased (SIMPLIFY-1, 2 subjects [2.1%]; SIMPLIFY-2, 1 subject [4.5%]; MOMENTUM, 1 subject [1.2%]).

COVID-19 Adverse Events

MOMENTUM OLE

During the MOMENTUM OLE, 12 subjects (MMB to MMB 11 subjects; DAN to MMB 1 subject) were diagnosed with COVID-19 infection. Of those, 8/12 subjects (66.7%) experienced an SAE. All subjects with COVID-19 with reported SAEs were in the MMB to MMB treatment group. All events were Grade ≥ 3. COVID-19 pneumonia was reported in 4/12 subjects (33.3%); all other events were reported in single subjects (abscess limb, coronary artery stenosis, depression, dyspnoea, febrile neutropenia, gastroenteritis rotavirus, haemorrhagic erosive gastritis, infective exacerbation of chronic obstructive airways disease, periprosthetic fracture, pneumonia bacterial, pulmonary embolism, pulmonary oedema, restrictive pulmonary disease, splenic infarction, and upper gastrointestinal haemorrhage).

XAP

During treatment in the XAP, 19 subjects (9.4%) were diagnosed with COVID-19 (10 subjects [10.4%] in SIMPLIFY-1; 2 subjects [9.1%] in SIMPLIFY-2, and 7 subjects [8.2%] in MOMENTUM) and 7 subjects (3.4%) were diagnosed with COVID-19 pneumonia (3 subjects [3.1%] in SIMPLIFY-1; 2 subjects in SIMPLIFY-2; and 2 subjects [2.4%] in MOMENTUM). No COVID-19 events were considered to be related to study treatment. Two subjects experienced COVID-19 events in MOMENTUM and 6 subjects experienced COVID-19 pneumonia events (2 subjects in each study) that were considered to be SAEs.

2.6.8.10. Post marketing experience

Not applicable.

2.6.9. Discussion on clinical safety

The clinical safety data of MMB in patients with PMF or post polycythaemia vera and post essential thrombocythemia MF is derived for 4 clinical studies (the phase 3 program including 3 RCTs: MOMENTUM, SIMPLIFY-1 and SIMPLIFY-2, and a long term safety study XAP which rolled-over patients from Ph 3 program). The cut-off for MOMENTUM and XAP is 03 Dec 2021.

The safety database includes 725 adults with a total follow-up of 1260.93 person-years. The randomized 24 week MMB treatment period includes 448 subjects. Open label data include 604 subjects who crossed over to MMB after RUX, BAT or DAN treatment in the context of the respective Phase 3 studies or those who received MMB in the long term extension safety study XAP.

In the integrated safety analysis, the median duration of exposure to MMB in the open-label period and overall is approximately double (11.3 months and 11.0 months) than the duration of exposure to RUX and DAN (5.5 months each).

In all Phase 3 studies all patients received at least 1 dose of study drug. In the MMB arms, the majority of patients completed the RT period i.e. 72.3 %, 81.8 % and 66.3 % in MOMENTUM, SIMPLIFY-1 and SIMPLIFY-2 respectively. The main reason for discontinuation of MMB in the RT period across all three studies are adverse events. The rate of adverse events leading to discontinuation is higher in the MMB RT than in control arm in SIMPLIFY-1 (8.9% in MMB vs 4.2% RUX) and SIMPLIFY-2 (12.5% in MMB vs 0% in BAT). In MOMENTUM study, the discontinuation due to AEs in the RT period is lower in MMB than in DAN while in the open-label period there is an inverse trend. In the open-label period the main reason for discontinuation is 'study terminated by sponsor' in SIMPLIFY-1 and SIMPLIFY-2.

Overall approximately a third (28.6%) of patients who received MMB (during RT and in the open-label period/roll-over in the XAP) discontinued the treatment due to adverse events.

The majority of patients in the phase 3 studies had at least one AE.

During RT, the incidence of all SAEs were higher in MMB than in the control arm in SIMPLIFY-1 (22.9% MMB vs 18.1% RUX) and in SIMPLIFY-2 (35.6% in MMB vs 23.18% BAT). In MOMENTUM the SAEs incidence was lower in MMB than in DAN (34.6% vs 40.0%).

However, the incidence for related SAEs was higher in MMB arms than in the control (8.5% vs 7.7% in MOMENTUM, 7.0% vs 6.0% in SIMPLIFY-1 and 11.5% vs 3.8% in SIMPLIFY-2, the latter not being subject to the current application).

In MOMENTUM study (open-label phase), the rate of fatal adverse events is higher in the patient population who switched from DAN to MMB (7.5%) than for patients who continued MMB (5.4%). In SIMPLIFY-1 study, the rate of TEAEs, G3 or 4 AEs, SAEs are higher in patients who switched from RUX to MMB than in patients who continued MMB in the open label phase. Similarly, in study SIMPLIFY-2, the rate of AEs are higher in patients who switched from BAT to MMB than those who continued treatment with MMB. Overall in the three studies, 7 patients had fatal AEs considered related to MMB by the investigator (including RT and open label period).

Diarrhoea, nausea, cough and dizziness incidence was higher in MMB RT group than in RUX or DAN.

Of note, the incidence of anaemia was lower during the RT period in patients receiving MMB (13.8%) than those receiving RUX (34.4%) or DAN (15.4%). All grade thrombocytopenia incidence was lower in MMB group (19.4%) than in RUX (26.3%) but higher than in DAN (10.8%).

During the RT period the most frequent AEs reported as related to treatment were thrombocytopenia, diarrhoea and nausea for MMB, anaemia and thrombocytopenia for RUX and ALT increased for DAN.

Peripheral sensory neuropathy, dizziness and paresthesia considered related to treatment were also more frequent during MMB RT period than in RUX and DAN.

The most frequent Grade 3 adverse events in the RT period were thrombocytopenia and anaemia for MMB and RUX, and for DAN anaemia, pneumonia and acute kidney injury.

The incidence of Grade 3 thrombocytopenia in the MMB RT period was approximately two times higher than in RUX while anaemia incidence was approximately half in MMB than in RUX in the RT period.

Although thrombocytopenia (all grades) marginally less frequent in MMB RT period than in RUX, the severity of thrombocytopenia appears to be higher in MMB than in RUX.

Death rate due to AEs was low during the MMB RT treatment, however it was higher in the MMB RT period (6.5%) than in RUX (3.4%) and lower than in DAN (16.6%), the latter probably associated with more advanced comorbidities and disease.

Deaths due to infection and infestations were higher in the MMB RT period (2.2%) than in both RUX (1.1%) and DAN (0%). There were 6 deaths associated with COVID-19 infection

Seven cases of sudden, unexplained or unspecified death occurred in the clinical trials with MMB. For some of the cases, risk factors associated with cardiovascular events were described in the clinical history; the age of these patients was overall low, however all had 65 years of age or more, male and female. Two cases had no known risk factors associated with cardiovascular events. Some cases are insufficiently documented to unequivocally assess causality.

The most frequent SAEs during the MMB RT were in the SOC Infections and infestations'. Pneumonia was the most frequent PT infection in the MMB RT period and was higher than in RUX but lower than the rate observed in DAN.

SAEs in SOC 'Cardiac disorders' were higher during the RT period in MMB than in RUX or DAN; the most frequent PT in cardiac disorders is atrial fibrillation. Considering risk factors associated with myelofibrosis population and the class effect of JAK inhibitors, MACE are a topic of concern for momelotinib and will need to be closely monitored in post-marketing provided favourable outcome of the marketing authorisation from the CHMP. MACE has been added as requested in the RMP as important potential risk. The majority of patients with MACE had over 60 years of age and had associated cardiovascular conditions (including but not limited to hypertension, ischemia) however for several patients there was no known pre-existent risk factors or cardiovascular known condition associated with MACE. The causality of the event was considered possibly related to trial medication by the investigator in few patients.

Of note, more frequent severe haemorrhages of gastrointestinal origin (including one fatal event in SIMPLIFY-1 study) were reported in the MMB arm during RT period (n=5) than in either RUX or DAN (no cases). It cannot be excluded that patients with haemorrhages may have had low thrombocyte levels. The frequency of thrombocyte count monitoring during the clinical trials, the threshold selected for stopping the treatment, or the low adherence to the stopping rules could explain the incidence of serious haemorrhagic events during the MMB RT.

Broad 'gastrointestinal haemorrhages' SMQ term AE analysis has been performed by the applicant in response to question. In overall incidence of GI haemorrhages are higher in the MMB arm than in the

control arm in all of the 3 studies. Although there is a numerical difference in term of AEs between MMB and control arms, the overall incidence is low and multiple factors may have contributed to the haemorrhages and among these severe thrombocytopenia is a key factor. Thrombocytopenia, anaemia and haemorrhage were the most frequent (>10%) AEs of clinical significance during the MMB treatment period

Despite the fact that anaemia is a common toxicity of JAK inhibitors, including momelotinib, the latter could also improve anaemia by inhibiting hepcidin production which promote erythropoiesis and by decreasing inflammation via inhibition of inflammatory cytokines signaling which improve anaemia.

The incidence of peripheral neuropathy was higher in MMB during the RT than in RUX and DAN. During RT period, the incidence of adverse events of clinical significance were generally similar between MMB and DAN with the exception of thrombocytopenia (higher incidence in RUX than in MMB). The incidence of thromboembolism was higher in MMB RT than in RUX.

With regard to time to onset, generally the adverse events of clinical importance occurred more frequently during the first 24 weeks of treatment and the incidence decreased after. When adjusted per exposure, the rate of AEs of clinical importance were lower during the open label treatment than in the randomized treatment period.

Peripheral neuropathy incidence is higher in MMB than in RUX and DAN during the RT. The most frequently reported preferred term is peripheral sensory neuropathy however a small percentage is specifically reported as peripheral motor or sensorimotor neuropathy.

Overall, the majority of the events are grade 1 and 2 in severity, however there were 9 cases of grade 3 peripheral neuropathy and discontinuations did occur in 18 patients overall. There were no fatal cases, however two cases were considered serious.

Adverse events occurring in the MMB RT appear to resolve in approximately half of the patients. The average duration of the events is around 100 days (1-471 days).

The incidence of peripheral neuropathy is higher in open-label period though the exposure-adjusted event rate in 100 person years is higher in the RT period than in open label period. During the clinical development of with MMB, peripheral neuropathy has been reported in clinical studies in up to 58.3% eg in study CCL09101E.

Peripheral neuropathy was included the list of adverse events of clinical importance in the MMB due to an early signal in early clinical development (as of phase I/II dose escalation trial).

Neurologic adverse events have been reported with JAK inhibitors, including acute neurological adverse events (Wernicke's encephalopathy), however peripheral neuropathy is not considered as an ADR for other JAK inhibitors in the respective SmPCs (e.g. tofacitinib, ruxolitinib). Anecdotal case reports of peripheral neuropathy to other JAK inhibitors are described in the literature.

The mechanistic rationale is not elucidated. In contrast to other JAK inhibitors, MMB has an inhibitory activity against ACVR1. ACVR1 is a member of the type I bone morphogenetic protein (BMP) receptors and is involved in a wide variety of biological processes, including nervous system development and regulation.

Overall, the total incidence of peripheral neuropathy reported in the clinical trials as PT/narrow SMQ grouping might be underestimated.

Safety data on peripheral neuropathy according to a broad SMQ definition shown that the preferred term for AES according to the broad SMQ definition is peripheral sensory neuropathy. The next most frequent AEs are paraesthesia and muscle weakness, respectively. It appears that peripheral neuropathy reported in MMB trials can be either sensory, motor or both, without a clear dominance for

either sensory or motor. Of note, muscle atrophy has also been reported. Nevertheless, the majority of the events were mild and moderate in severity.

The incidence of infections were overall comparable during the RT with MMB, RUX and DAN; the rate of infections leading to death was low, a slightly higher incidence of infections leading to death were observed in MMB (2.2%) than in RUX (1.1%) or DAN (0%). With regards to opportunistic infections, no prominent difference was observed during the RT for MMB and RUX and DAN, respectively.

The incidence of malignancies is overall similar between MMB, RUX and DAN during RT. The most frequent malignancy was AML/transformation were reported for 1.8% MMB, 1.1% RUX, and 4.6% DAN. The greatest proportions of subjects had grade $\geq$ 3 events and were fatal.

According to literature, the frequency of leukemic evolution varies according to myeloproliferative neoplasms subtype. It is highest in primary myelofibrosis, where it is estimated to be approximately 10–20% at 10 years, following by polycythemia vera, with a risk of 2.3% at 10 years. The rate of transformation or survival does not appear to be influenced by JAK inhibitors treatment. With regard to malignancy and AML transformation; the data presented are in line with what has been previously reported in the literature for patients with MF and JAKi.

There is a prominent difference in term of COVID-19 AEs, including fatal events incidence, between MMB and DAN during the RT period in MOMENTUM STUDY.

There is no known potential mechanism to explain a higher risk of severe disease or death due to COVID-19 in patients receiving MMB. The majority of COVID-19 cases had pre-existing comorbidities commonly associated with risk of developing more severe COVID-19 disease and were not vaccinated against COVID-19.

Due to prominent imbalance of COVID-19 cases in MMB vs DAN, it cannot be excluded that MMB treatment may be associated with a higher risk of SARS-CoV-2 infection and a more severe risk of severe COVID-19. One of the possible mechanisms cited by the applicant in RTQ is that JAK inhibition can block the production of certain cytokines, such as type I interferons and interferon γ, which may interfere with the natural immune response (Adas, 2022). At longer term, vaccines may have had a mitigating effect in all patients since few serious/fatal COVID-19 infection cases were reported after the vaccination became widespread.

Shift from baseline of haematology parameters in the MMB RT period are similar to RUX and DAN with the exception of platelet decreased with a more prominent trend toward shift from grade 0 to 2 at baseline to grade 3 to 4 in the MMB compared with RUX and DAN. This is consistent with observations regarding the increased incidence in thrombocytopenia grade 3 and 4 adverse events and SAEs in MMB RT period.

DILI cases occurred in the phase 3 studied with MMB. The SmPC includes elevated liver enzymes as ADRs. Healthy volunteer QT study has been performed and no indication of MMB effect on QTcF has been reported. Routine postbaseline ECGs were discontinued in SIMPLIFY-1 and SIMPLIFY-2 studies and not formally analysed. In MOMENTUM ECGs were read locally and assessed predose and post baseline.

Overall, the rate of AEs are similar in males vs females who received either MMB, RUX or DAN in the RT period. In DAN treatment, males have higher incidence of G3 and G4 AES and fatal AEs than females. In MMB RT group; males had higher number of certain adverse vents than females as following: Grade 3 or 4 49.1% vs 34.5%, SAEs 34.3% vs 21.5%, SAE related 11.1% vs 4.5% and fatal 8.1% vs 4.0%.

Overall, patients who received MMB in the RT period and who were aged 65 or 75 and above years old have slightly higher incidence of grade 3 or 4, serious, fatal and adverse events leading to drug

modification and discontinuation that patients between 18-64 and 18-74 years old. This trend is also observed in patients receiving DAN or RUX and may be due to comorbidities, disease progression associated with age rather than with study medication.

The majority of patients in the Ph III clinical program with MMB were White, followed by Asians and Blacks. Due to the low number of patients in the different race subgroups (ie each group includes less than 10% of the total population) no strong conclusion can be made regarding a different safety profile in Asians or Black than in White population.

For patients with creatinine clearance lower than 60 mL/min the incidence of adverse events (grade 3 or 4, serious, fatal or leading to drug discontinuation) were higher than for in patients with ≥ 60 mL/min for MMB, RUX and DAN.

For patients Grade 3 or 4, serious, fatal and AEs leading to drug discontinuation, the proportions of the MMB and RUX groups were consistently smaller for the higher baseline Hgb subgroups (≥ 8 and ≥ 10 g/dL) compared with the lower subgroups (< 8 and < 10 g/dL).

In the MMB RT group, the proportion of native and previously treated patients are similar. There is clear trend toward a higher incidence of Grade 3 or 4 (overall and related), serious (overall and related), fatal and who lead to study discontinuation/study drug modification. There is no such trend in the RUX treated patients for whom the rate of above mentioned types of adverse events in previously treated patients are similar or lower than in treatment-naïve patients in the MMB RT period.

DDI have been addressed in the PK section of the report. More patients in MMB received PPIs during treatment when compared to control treatment (RUX, DAN).

The rate of discontinuations due to G3 or above AEs in the MMB RT group was higher than RUX and lower than in DAN. The most frequent adverse events leading to discontinuation of MMB are haematology AE, namely thrombocytopenia.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics

2.6.10. Conclusions on the clinical safety

The safety profile of momelotinib has been characterised across a number of studies in patients with myeloproliferative disorders and healthy volunteers. A total of 725 patients have been exposed to momelotinib in these studies.

The information for safety assessment includes patients from three randomised controlled studies in patients with no prior JAK inhibitor treatment (SIMPLIFY-1), prior treatment with ruxolitinib (SIMPLIFY-2), and prior treatment with an approved JAK inhibitor (ruxolitinib or fedratinib) in MOMENTUM study.

The safety profile is characterised by haematological adverse events (thrombocytopenia, anaemia) and gastrointestinal adverse events (diarrhoea, nausea), in line with the underlying disease and other JAK inhibitors. The incidence of thrombocytopenia is comparable with control (RUX, DAN), however it appears more severe with momelotinib.

Peripheral neuropathy was an adverse event of clinical importance and has been identified early in the clinical development of momelotinib. Infections and infestations are not unexpected in patients with the underlying disease or treatment.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 101: Summary of safety concerns

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

2.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.7.3. Risk minimisation measures

Table 102: 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
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.

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.
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.

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.2 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 15.09.2023. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Omjjara (momelotinib) is included in the

additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

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.

3.1.2. Available therapies and unmet medical need

MF is a rare, chronic, life-threatening disease that may arise de novo as primary (PMF) belonging to the group of myeloproliferative neoplasms (MPN) or develop from other pre-existing MPNs, namely PV or ET (post PV or post ET MF) grouped to secondary MF (SMF). MF is a heterogeneous disease with key clinical features that include anaemia, constitutional symptoms, and splenomegaly. All patients eventually become anaemic due to ineffective haematopoiesis, often associated with RBC transfusion dependency and worsening of thrombocytopenia.

The aim of therapy with JAK inhibitors is mainly symptomatic, there is currently no evidence regarding disease-modifying effects and impact on long-term efficacy outcomes such as overall survival.

The etiology of anaemia in MF is multifactorial, that could be distinguished as MF-associated anaemia with contributions from bone marrow fibrosis, direct effects of inflammation on the bone marrow microenvironment, splenomegaly with splenic sequestration; anaemia due to other causes than MF, such as indirect effects due to elevated hepcidin or concomitant factors or deficiencies that contribute to anaemia, and treatment-related anaemia (e.g., following treatment with JAK inhibitors). Anaemia is cardinal feature of this progressive disease and an important risk factor for poor survival at diagnosis, as determined by prognostic scores in patients not previously treated with JAK inhibitors. The impact of anaemia management on prognosis in JAK inhibitor-treated patients remains uncertain. Ruxolitinib and fedratinib are thought to exacerbate disease-related cytopenias (thrombocytopenia, anaemia, neutropenia) due to their myelosuppressive effect attributed mainly to JAK2 inhibition mechanism, necessitating dose modification, interruption, or discontinuation. Compromised dose intensity can limit treatment effects on disease related splenomegaly and symptoms. Therapies with a distinct safety profile potentially improving anaemia specific outcomes, along with control and alleviation of symptoms and reduction in spleen volume in patients with MF, may address a medical need for MF patients with anaemia, in particular in patients requiring RBC transfusions or being defined as transfusion-dependent. There are currently no approved options for patients with MF who have moderate to severe anaemia.

3.1.3. Main clinical studies

The main evidence of efficacy submitted in patients with primary and secondary myelofibrosis is coming from two phase 3 randomised controlled studies (MOMENTUM and SIMPLIFY-1), supported by the results of one additional randomised phase 3 trial (SIMPLIFY-2) and one single-arm Phase 2 trial (GU-US-352-1672).

These trials support respectively the indications:

- in patients that have been treated with ruxolitinib
  - SRA-MMB-301 (MOMENTUM) study with 24 weeks randomized, double-blind treatment period and 24 weeks open-label period, with cross-over allowed after 24 weeks
  - GS-US-352-1214 (SIMPLIFY-2) with 24 weeks randomised open-label treatment period and open-label extended treatment phase (up to 168 weeks) with momelotinib treatment in both arms
- in JAK inhibitor naïve patients
  - GU-US-352-0101 (SIMPLIFY-1) with 24 weeks randomized, double-blind period and up to 5 years open-label, with momelotinib monotherapy after 24 weeks in both arms
  - GU-US-352-1672 open-label, single-arm trial with momelotinib monotherapy.

Patients have been randomised at 2:1 or 1:1 ratio to momelotinib or active controls in

- MOMENTUM trial (195 patients: 130 to momelotinib arm and 65 to danazol arm),
- SIMPLIFY-2 trial (156 patients: 104 to momelotinib arm and 52 to best available therapy arm)
- SIMPLIFY-1 trial (432 patients: 215 to momelotinib arm and 217 to ruxolitinib arm)

or treated in a single-arm GU-US-352-1672 trial (41 patients).

SRA-MMB-301 (MOMENTUM) study is the main pivotal trial in patients previously treated with JAK inhibitors while GS-US-352-1214 (SIMPLIFY-2) is the supportive study. In JAK inhibitor naïve patients GU-US-352-0101 (SIMPLIFY-1) is the main study supported by data from GU-US-352-1672 trial.

The primary and secondary endpoints differed in SRA-MMB-301 (MOMENTUM) study from SIMPLIFY-1 and SIMPLIFY-2 studies. MOMENTUM has two primary endpoints, i.e. the assessment of improvement of symptoms, by evaluating the MFSAF total symptom score (TSS) response rate at week 24, and assessment of anaemia-related outcomes, by evaluating the transfusion independency (TI) response at week 24. These two primary endpoints were however not co-primary endpoints. The study considered meeting both primary endpoints if superiority of TSS 24 was significant and at least non-inferiority of TI 24 was significant.

Both GS-US-352-1214 (SIMPLIFY-2) and GU-US-352-0101 (SIMPLIFY-1) studies had a primary endpoint of Spleen response rate at week 24 (defined as the proportion of subjects who achieves a $\geq$ 35% reduction in spleen volume at wk 24 from baseline as measured by MRI or CT) and 4 secondary endpoints: response rate in TSS at Week 24, rate of RBC transfusion in the RT phase, RBC transfusion independence (TI) rate at Week 24 and RBC transfusion dependence (TD) rate at Week 24 as secondary endpoints. The SIMPLIFY-1 study was designed to demonstrate non-inferiority in the primary endpoint of splenic response rate (compared to ruxolitinib), while the SIMPLIFY-2 study was designed to demonstrate superiority in that endpoint (compared to best available therapy).

All phase 3 trials included adults who were required to have confirmed diagnosis of PMF in accordance with the World Health Organization (WHO) criteria, or Post-PV/ET MF in accordance with the IWG-MRT

criteria. In addition, prognostic scoring systems were considered for eligibility, with haemoglobin < 10 g/dL being an important variable contributing to the score (1 or 2 points) and to the consequently defined prognostic risk category. In MOMENTUM trial, eligible patients were required to having received prior treatment with an approved JAK inhibitor after a wash-out period of at least 2 weeks. Eligible patients also had baseline splenomegaly, were symptomatic [defined as total symptom score ≥ 10 (on a total score of 70)] and had at least moderate anaemia (defined as haemoglobin < 10 g/dL). This study also allowed enrolment of patients with severe thrombocytopenia (defined as platelet counts ≤ 50 x 10^9/L, however not lower than 25 x 10^9/L). In SIMPLIFY-2 trial, a similar population as in the MOMENTUM study was included, i.e. patients who received current or prior treatment with ruxolitinib that was complicated with hematologic toxicity. However, patients were not required to respect a wash-out of prior JAK inhibitor therapy.

In SIMPLIFY-1 trial, only patients with no prior treatment with a JAK inhibitor were eligible. Similar as for the SIMPLIFY-2 study, inclusion of non-anaemic patients was allowed. Patients were also not required to be symptomatic.

3.2. Favourable effects

Symptom response

In the MOMENTUM study, the MFSAF TSS response rate at 24 weeks was 24.62% (95% CI: 17.49, 32.94) for the momelotinib group and 9.23% (95% CI: 3.46, 19.02) for the danazol group, with a treatment difference of 15.67% (95% CI: 5.54, 25.81), p <0.001.

This result for a primary endpoint in the MOMENTUM study was supported by the results from a secondary endpoint of change in MFSAF Total Symptom Score From Baseline at week 24. The absolute mean (SD) change from baseline in MFSAF TSS at week 24 was respectively -11.52 (12.86) and -3.93 (11.94) for the MMB and DAN group, with an LS (least squares) mean difference of -6.22 (95% CI: -10.0, -2.43), p <0.01.

In the SIMPLIFY-1 study, in the post-hoc defined subgroup of patients with at least moderate anaemia, TSS response rate was consistent (25.0%). In the overall population, the TSS response rate was 28.4%, consistently with 24.6% and 26.2% in the MOMENTUM and SIMPLIFY-2, respectively.

Spleen volume response

In SRA-MMB-301 (MOMENTUM) study, as the results for secondary endpoint measured at 24 weeks, 22.31% of patients treated with momelotinib reached a reduction in spleen volume of ≥ 35%. In the DAN group, 3.08% reached a reduction in spleen volume of ≥ 35%. The treatment difference was 18.18% (95% CI: 9.77, 26.59; p =0.0011).

In the SIMPLIFY-1 trial, in the post-hoc defined subgroup of JAK inhibitor naïve patients with at least moderate anaemia, the SRR at Week 24 was numerically similar for MMB compared to RUX (31.4% versus 32.6% RUX). In the overall population, the primary endpoint of non-inferiority of MMB over RUX in SRR at week 24 was met [26.5% (95%CI: 20.74, 32.94) versus 29.5% (95% CI: 23.51, 36.04); p = 0.014].

Anaemia-related outcomes

Results for anaemia-related outcomes are considered as supportive. In the MOMENTUM study, a numerically higher percent of patients treated with Omjjara (30%; 39/130) achieved transfusion independence (defined as no transfusions and all Hgb values ≥8 g/dL in the 12 weeks prior to week 24) compared with 20% (13/65) for danazol at week 24.

In the SIMPLIFY-1 trial, in the post-hoc defined subgroup of patients with at least moderate anaemia, a numerically higher TI rate at week 24 has been observed for MMB (46.5%) versus RUX (27.4%).

Follow-up data of TSS response rate, TI rate and SRR at Week 48 from the MOMENTUM study supported the results at 24 weeks, with the majority of patients maintaining their response to MMB (72% for symptom response, 76% for splenic response and 88.2% for TI response).

3.3. Uncertainties and limitations about favourable effects

The proportion of missing data at Week 24 was substantial in the MOMENTUM and SIMPLIFY-2 studies in JAKi-treated patients, mainly due to early discontinuation of treatment before completing the double-blind phase at Week 24, while such proportion is lower in SIMPLIFY-1 in JAKi naïve patients (MOMENTUM: 26.2% MMB, 40.0% DAN; SIMPLIFY-2: 22.1% MMB, 19.2% BAT, SIMPLIFY-1: 12.6% MMB, 4.1% RUX). In the primary analyses, these patients with missing data at Week 24 were considered non-responders, which introduces uncertainty on the estimation of MMB treatment effects, in particular in case of important imbalances in proportion of missing data at Week 24 (MOMENTUM and SIMPLIFY-1). Post-hoc sensitivity analyses using various missing data handling methods and assumptions were, however, overall consistent with the primary analyses and indicated that neither the information loss nor the methods used to handle missing data had a substantial impact on the study conclusions and therefore are reassuring for the reliability and the validity of the primary analysis results.

The data for the duration of symptom response, splenic response and for longer-term data for anaemia-related endpoints across the studies are confounded by the cross-over of patients from the control groups to MMB after week 24, not allowing to draw conclusions on comparisons for response durations.

In the SIMPLIFY-1 study, although double-blinded, the frequent protocol-mandated dose modifications for ruxolitinib compared to momelotinib and investigator experience with ruxolitinib may have confounded assessments, in particular for symptom response.

Symptom response

In the SIMPLIFY-1, non-inferiority of MMB over RUX in the secondary endpoint of modified MPN-SAF v2.0 TSS response rate at Week 24 could not be demonstrated, it was 28.4% (95% CI: 22.45, 35.03) versus 42.2% (95% CI: 35.43, 49.15) for ruxolitinib. A similar observation was made in the post-hoc defined subgroup of subjects with at least moderate anaemia (25.0% MMB, 36.2% RUX), hence lower TSS response rates were observed in the RUX arm for this subgroup compared to ITT, resulting in numerically smaller differential treatment effects in favour of ruxolitinib. Several limitations to the SIMPLIFY-1 design might have contributed in failing to meet non-inferiority, however missing data sensitivity analyses suggest an important contribution of the imbalance in early discontinuation to the unmet TSS response rate results in SIMPLIFY-1, as they favoured the RUX study control arm.

Spleen volume response

There was inconsistency in splenic response between two phase 3 studies in patients treated with JAK inhibitors. In the SIMPLIFY-2 study, the primary efficacy endpoint of superiority of MMB over BAT in SRR at week 24 was not met in ruxolitinib-treated patients which were exposed to momelotinib without a wash-out period after ruxolitinib exposure, and explained by maintenance of the effect of ongoing JAKi therapy. Lack of wash-out period for patients receiving MF therapy at screening was reported as 74% for MMB and 75% for BAT. The proportion of subjects with a $\geq$ 35% reduction from baseline in spleen volume at week 24 was 6.7% for the MMB group and 5.8% for the BAT group.

Anaemia-related outcomes

In the MOMENTUM study, superiority could not be demonstrated for a second primary endpoint of transfusion independency rate at week 24, which was 30.00% (95% CI: 22.28, 38.66) for the MMB group and 20.00% (95% CI: 11.10, 31.77) for the DAN group, with a treatment difference of 9.80% (95% CI: -2.03, 21.62). Moreover, given the absence of well-controlled data supporting danazol as active comparator, inference of efficacy based on non-inferiority with respect to transfusion independency rate is not supported. In addition, the observed treatment difference in TI rate (10%) is lower than expected (24%) and thus the clinical relevance of data for transfusion dependency rate is uncertain.

The numerical improvements in transfusion burden endpoints reported in the SIMPLIFY-1 and SIMPLIFY-2 studies are only of nominal significance due to missed statistical significance in the previous endpoint in the hierarchical testing. Results should thus be seen as exploratory.

In addition, the clinical relevance of the observed effects on anaemia-related endpoints in the SIMPLIFY-1 study are uncertain. Transfusion independency endpoint was measured at the time of a nadir in haematology values during ruxolitinib treatment in the comparator arm, after which recovery is known to occur. Due to the option of cross-over, no data is available on the persistence of the transfusion independency effect of momelotinib compared to ruxolitinib after Week 24. Though cross-trial comparisons support the maintenance of momelotinib advantage over ruxolitinib in reducing transfusion needs and anemia-related benefits after Week 24, the limitations related to such indirect comparisons should be considered.

Survival

No definite conclusion of the effect of MMB on overall survival (OS) and leukemia-free survival (LFS) versus their respective comparator can be drawn across the three phase 3 studies, as the comparisons with their respective control groups were heavily confounded because of the high rate of cross-over from the control groups to the MMB group after Week 24 assessments.

3.4. Unfavourable effects

Non-haematological toxicity

Peripheral sensory neuropathy was overall reported in 6.9% of patients in the pooled safety analyses, with 4.6% and 1.5% of patients experiencing this AE when treated with ruxolitinib and danazol, respectively. The elevated incidence of peripheral neuropathy events was reported in the early open-label phase studies and about 50% of cases were irreversible/unresolved.

Anaemia all grades was reported as AE in 13.8% of patients in MMB during RT period; of these, 8.5% were AEs of grade 3 or more in severity.

Infections: the incidence of all grade infections in RT was 39% in MMB (42.7% in RUX and 35.4% in DAN). Of these, 9.8% were SAEs (comparing to 4.6% for RUX and 16.9% for DAN) and 2.2% were fatal events (comparing to 1.1% for RUX and 0 for DAN). Of note, 6/10 cases of fatal infections were related to COVID-19 infection.

Haematological toxicity

Thrombocytopenia was reported in 19.4% treated with MMB versus 26.3% for ruxolitinib and 10.8% for danazol. Frequent G3 and G4 were reported and thrombocytopenia was the most frequent AE leading to discontinuation of treatment. This AE is related to mechanism of action of JAK inhibitors.

3.5. Uncertainties and limitations about unfavourable effects

Peripheral sensory neuropathy

An uncertainty remains as regards the incidence which reported to be higher in the earlier studies (up to 50% in different trials).

Hy's law criteria

There were 2 cases meeting Hy's law criteria; there is uncertainty on a potentially increased risk of serious hepatotoxic effects.

Upper GI haemorrhages

Five SAEs of upper GI/GI haemorrhage were reported in the MMB, none for RUX or DAN.

Severe hepatic impairment

As hepatic elimination is a major route of excretion for momelotinib, hepatic impairment may result in increased plasma momelotinib concentrations. In this context, the applicant provided the results of a dedicated study of momelotinib and its main metabolites in patients with moderate and severe hepatic impairment. The applicant considered the reduced exposure of the pharmacologically active metabolite, M21, to guide the dose adjustment recommendation. The overall 37% (based on geometric mean ratio) increase of AUC for the combined exposure justifies the recommended dose reduction of 25% of the starting dose from 200mg to 150mg once daily to account for the increase in plasma exposures of momelotinib and the decrease in plasma exposures of M21 in subjects with severe hepatic impairment.

Drug-drug interactions

Without an *in vivo* dedicated DDI study studying the impact of momelotinib on oral contraceptives, a risk of induction of other non-CYP3A enzymes cannot be completely excluded. The effectiveness of concomitant administration of oral contraceptives may be reduced and given that embryo-foetal toxicity has been shown with momelotinib in studies in animals, female patients of child-bearing potential receiving momelotinib must use highly effective contraceptive methods during treatment. In this context, The applicant agreed to update sections 4.4, 4.6, and 5.2 to reflect that women using oral hormonal contraceptives should add an additional barrier method during OMJJARA treatment and for at least one week after the last dose. The updates were also made in the product information leaflet.

Cardiac disorders

This is a class effect, incidence of serious cardiac disorders was 4.7% with the most frequent is atrial fibrillation. The incidence of 2.7% and 4.6% was reported for RUX and DAN respectively.

In addition, imbalance in frequency of COVID-19 cases in MMB was reported compared with DAN. In addition, there is no known mechanism to explain the higher incidence of COVID-19 in patients receiving MMB.

3.6. Effects Table

Effects Table for Omjjara in primary and secondary myelofibrosis (for favourable effects the data cut-off for MOMENTUM trial is 03 Dec 2021 and for SIMPLIFY-1 trial is 01 Jul 2019. For unfavourable effects the data cut-off is 03 Dec 2021)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	Ref
Favourable Effects Study SRA-MMB-301 (MOMENTUM) – prior JAK inhibitor treatment						
			MMB + DAN matched placebo n = 130	DAN + MMB matched placebo n = 65		
Symptom RR	proportion of subjects with a ≥ 50% reduction in mean Myelofibrosis Symptom Assessment Form(MFSAF)version 4.0 TSS at w24	% (95% CI)	24.62% (17.49, 32.94)	9.23% (3.46, 19.02)		
SRR at Week 24 [≥35% reduction in spleen volume]	proportion of subjects who had splenic response based on ⩾ 35% reduction in spleen volume from baseline	% (95% CI)	22.31 (15.48, 30.44)	3.08 (0.37, 10.68)		
Favourable Effects Study GU-US-352-0101 (SIMPLIFY-1) – JAK inhibitor naïve, anaemic subgroup (Hgb values <10 g/dL)						
			MMB + RUX matched placebo n = 86	RUX + MMB matched placebo n = 95		
Spleen RR	proportion of subjects who had splenic response based on ≥ 35% reduction in spleen volume from baseline at 24w	% (95% CI)	31.4 (21.81, 42.30)	32.6 (23.36, 43.02)	Post-hoc subgroup analysis	

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	Ref
Symptom RR	proportion of subjects with a ≥ 50% reduction in mean Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) version 2.0 TSS	% (95% CI)	25.0 (16.19, 35.64)	36.2 (26.51, 46.73)	Post-hoc subgroup analysis Non-inferiority compared to RUX not demonstrated in the overall population	
Unfavourable Effects						
			MMB n=448	RUX n=262 DAN n=65		
Peripheral sensory neuropathy	Incidence of peripheral sensory neuropathy	%	6.9	4.6 1.5	Infrequent G3 and G4, two serious cases	
Thrombocytopenia	Incidence of thrombocytopenia	%	19.4	26.3 10.8	Frequent G3 and G4, related to MoA; thrombocytopenia was the most frequent AE leading to discontinuation of treatment	
Anaemia	Incidence of anaemia	%	18.4	34.4 15.4	Grade 3 and above anaemia in MMB RT group was 8.3% (21.8 in RUX and 10.8% in DAN)	
Upper GI haemorrhages	Cases of upper GI bleeding	n	5	0 0	5 SAEs of upper GI/GI hemorrhage in the MMB, none in RUX or DAN	
Infections	Infections incidence	%	39.7	42.7 35.4	9.8 were SAEs (comparing to 4.6% for RUX and 16.9% for DAN) 2.2% were fatal events (comparing to 1.1% for RUX and 0% for DAN); 6/10 cases of fatal infections were related to COVID-19 infection of uncertain causality	
Hy's law cases	Cases of Hy's law	n	2	0 0	ALT/AST increases are known JAKi effect	
Cardiac disorders	Serious cardiac disorders incidence	%	4.7	2.7 4.6	Known JAKi effect	

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The alleviation of symptoms associated with MF, either constitutional or related to organomegaly is of clinical relevance for patients and are of direct benefit.

In the JAK inhibitor pretreated patient population, the benefit of momelotinib on disease-related symptoms is considered clinically meaningful, mainly based on the results of the MOMENTUM trial in the JAK inhibitor pre-treated patient population with at least moderate anemia (haemoglobin <10 g/dL, per protocol eligibility).

The results of the MOMENTUM trial are also in favor of momelotinib for disease-related splenomegaly. However, a lower magnitude of response was observed in the SIMPLIFY-2 trial compared to the MOMENTUM trial. This may be explained by differences in wash-out period after prior JAK inhibitor therapy (absent in SIMPLIFY-2), likely resulting in confounded treatment effect due maintenance of the effect of ongoing JAKi therapy in the majority of patients in both treatment arms. Superiority for MMB vs BAT was not met for SRR, although splenic volume control was maintained.

In JAK inhibitor naïve patients, while non-inferiority of MMB to RUX was met for the primary endpoint of splenic response rate, it was not met for the first secondary endpoint of TSS response rate. Missing data sensitivity analyses conducted post hoc suggest an important contribution of the imbalance in the proportion of patients who early discontinued study treatment due to protocol defined safety-based dose modification scheme differences. These imbalances were favouring the RUX study control arm. In addition, with the limits intrinsic to cross-trial comparisons, consistency in magnitude of the MMB TSS response across phase 3 studies suggests a clinically meaningful magnitude of effect for MMB. Although this effect is numerically lower for MMB compared to that reported for the other JAK inhibitors as ruxolitinib (SIMPLIFY-1 and COMFORT-1) and fedratinib (JAKARTA-1) in JAKi naïve patients, it supports the overall effect of MMB on other clinically relevant endpoints and contributes to the totality of supportive data.

As regards the anaemia-related outcomes, it is acknowledged that overall consistent results were observed across studies and that overall data support the reduced requirements for transfusions. Moreover, the myelosuppressive effects of prior JAK inhibitors might be counteracted by additional mechanisms. While inhibiting JAK2, momelotinib appears to have less worsening effect for cytopenias. Its distinct mechanism of action through inhibiting the ACVR1 SMAD signaling pathway was associated with reduced hepcidin levels, thus potentially increasing iron availability for erythropoiesis.

However, the evidence supporting the anaemia-related outcomes can only be considered of non-confirmatory nature in both the JAKi treated and JAKi naïve population, mainly due to methodological issues, either for non-inferiority testing for TI rate over danazol or hierarchical multiplicity control, respectively. Hence, the claim of "anaemia treatment" was not supported. The restricted indication for adult patients with moderate to severe anaemia in both JAKi treated and JAKi naïve patients relies, respectively, on the results of the pivotal MOMENTUM trial in patients with at least moderate anaemia per eligibility criteria (ITT population) and on post-hoc subgroup analysis of the SIMPLIFY-1 trial in anaemic patients with more advanced disease, progressively compromised erythropoiesis and in need of therapy not worsening and potentially counteracting anaemia.

As regards the observed safety profile, derived in a relatively large number of patients with rare disease and with longer follow-up data from earlier studies available, it does no outweigh the clinically meaningful effects and allows treatment in more advanced patients. Manageable safety profile was observed with acceptable incidence and severity of adverse events in the intended clinical setting.

Some non-hematologic toxicities were reported, mainly known JAK inhibitor class effects and were either of relatively low incidence or with high grade in a limited proportion of patients. Some haematological toxicities were observed, such as thrombocytopenia, which could result in early treatment discontinuations of this long-term treatment. However patients with low platelet counts (until $25x10^9$) could be treated in the MOMENTUM trial, with few serious adverse events of bleeding reported. One of the notable toxicities is peripheral sensory neuropathy, which is generally of low grade but irreversible or reported as ongoing in about half of patients, it resulted in treatment discontinuation in early studies. Inconsistent incidence was reported peripheral sensory neuropathy between early and later trials. Class effects of JAK inhibitors include among others risk of severe infections and secondary malignancies, but overall safety profile show some differences with other JAK inhibitors. There is an uncertainty on the MACE incidence and severity, it is considered as important potential risk.

The effect of momelotinib on disease-related splenomegaly (SRR of 22.3%) and symptoms (TSS response rate of 24.6%) in JAK inhibitor treated patients as demonstrated in the MOMENTUM study is considered of clinical relevance in this advanced myelofibrosis setting. With the limits intrinsic to indirect comparison, the observed splenic and symptom response rates are in the same order of magnitude as that of the 22.7% and 21.5% reported respectively for similar endpoints in ruxolitinib-pretreated patients who received treatment with fedratinib 400 mg QD in the JAKARTA-2 study.

With regard to the JAK inhibitor treated population, all patients in the SIMPLIFY-2 study and MOMENTUM previously received ruxolitinib. Only few patients in the MOMENTUM study (n = 9) additionally received prior fedratinib, not allowing to make definite conclusions on the benefit of momelotinib in the subgroup of patients previously treated with fedratinib and not supporting extrapolation to the entire pharmaceutical class, taking into account differential targeting of kinases with differences in underlying mechanism of action, with potential differences in cross-resistance mechanisms.

Based on the totality of data, MMB is considered to provide benefits in the JAKi naïve setting: the effect on disease-related splenomegaly is considered clinically meaningful and the magnitude of effect on disease-related symptoms is consistent across momelotinib trials, although lower when compared to approved JAK inhibitors.

In addition, in the JAKi pretreated setting, momelotinib might be a valuable treatment option in MF patients with moderate or severe anaemia, where both disease-related and treatment-related anaemia are of significant burden for patients as it is frequently associated with requirements for RBC transfusions and transfusion dependency. In JAKi-naïve setting, patients with manifestation of at least moderate anaemia may also derive benefit at longer term, due to potentially reduced RBC transfusion requirements of particular relevance in this subgroup. The totality of evidence suggests a relevant safety and efficacy profile, with sparing and potentially improving effect on erythropoiesis.

3.7.2. Balance of benefits and risks

The benefit-risk for the indications "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" is positive.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall benefit/risk balance of Omjjara is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Omjjara is not similar to Inrebic within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Omjjara is favourable in the following indication:

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.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that momelotinib is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.