NEW ZEALAND DATA SHEET

1. PRODUCT NAME

OMJJARA momelotinib (as momelotinib dihydrochloride monohydrate) 100 mg film-coated tablets

OMJJARA momelotinib (as momelotinib dihydrochloride monohydrate) 150 mg film-coated tablets

OMJJARA momelotinib (as momelotinib dihydrochloride monohydrate) 200 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

OMJJARA 100 mg film-coated tablets

Each film-coated tablet contains momelotinib dihydrochloride monohydrate equivalent to 100 mg momelotinib.

List of excipients with known effect

50.8 mg lactose monohydrate per tablet.

OMJJARA 150 mg film-coated tablets

Each film-coated tablet contains momelotinib dihydrochloride monohydrate equivalent to 150 mg momelotinib.

List of excipients with known effect

76.1 mg lactose monohydrate per tablet.

OMJJARA 200 mg film-coated tablets

Each film-coated tablet contains momelotinib dihydrochloride monohydrate equivalent to 200 mg momelotinib.

List of excipients with known effect

101.5 mg lactose monohydrate per tablet.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

OMJJARA 100 mg film-coated tablets

Brown, round tablets, with an underlined “M” debossed on one side and “100” on the other side.

OMJJARA 150 mg film-coated tablets

Brown, triangle shaped tablets, with an underlined “M” debossed on one side and “150” on the other side.

OMJJARA 200 mg film-coated tablets

Brown, capsule shaped tablets, with an underlined “M” debossed on one side and “200” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Dose and method of administration

Dose

Adults

The recommended dosage of OMJJARA is 200 mg taken orally once daily. OMJJARA may be taken with or without food.

Missed dose

If a dose of OMJJARA is missed, the next scheduled dose should be taken the following day.

Monitoring

Complete blood cell count and liver function tests must be performed before initiating treatment with OMJJARA, periodically during treatment, and as clinically indicated.

Dose modifications

Dose modifications should be considered for haematologic and nonhaematalogic toxicities (Table 1). Discontinue OMJJARA in patients unable to tolerate 100 mg once daily.

Table 1 Dose modifications for adverse reactions

Adverse Reaction	Dose Modification[a]
For clinically significant worsening of thrombocytopenia	Interrupt treatment and/or reduce the daily dose by 50 mg decrements to 150 mg or 100 mg until resolved to platelet count of ≥50 x 10^9L or baseline.
Grade 3 or higher nonhaemotologic toxicities	Interrupt treatment and/or reduce the daily dose by 50 mg decrements to 150 mg or 100 mg until resolved to ≤ Grade 1 or baseline.

[a] Reinitiate or escalate treatment up to 200 mg daily as clinically appropriate.

Special Populations

Elderly

No dose adjustment is required for patients who are aged 65 years and older (see section 4.8 Undesirable effects, Other special population(s)).

Renal impairment

No dose adjustment is required for patients with renal impairment (see section 4.8 Undesirable effects, Other special population(s)).

Hepatic impairment

No dose adjustment is recommended for patients with mild or moderate hepatic impairment. The recommended starting dose of OMJJARA is 150 mg once daily in patients with severe hepatic impairment (Child-Pugh Class C) (see section 4.8 Undesirable effects, Other special population(s)).

Paediatric Population

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

4.3 Contraindications

No contraindications identified.

4.4 Special warnings and precautions for use

Infections

Infections, including serious and sometimes fatal bacterial and viral infections (including COVID-19), have occurred in patients treated with OMJJARA (see section 4.8 Undesirable effects). OMJJARA should not be initiated in patients with active infections. Physicians should monitor patients receiving OMJJARA for signs and symptoms of infection and initiate appropriate treatment promptly.

Hepatitis B reactivation

Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine transaminase (ALT) or aspartate transaminase (AST), have been reported in patients with chronic hepatitis B virus (HBV) infection taking JAK inhibitors, including OMJJARA. The effect of OMJJARA on viral replication in patients with chronic HBV infection is unknown. Patients with chronic HBV infection who receive OMJJARA should have their chronic HBV infection treated and monitored according to clinical HBV guidelines.

Thrombocytopenia

New onset of severe (Grade ≥3) thrombocytopenia was observed in patients treated with OMJJARA (see section 4.8 Undesirable effects). A complete blood count, including platelet count, should be obtained before initiating treatment with OMJJARA, periodically during treatment, and as clinically indicated. Dose interruption or reduction may be required (see 4.2 Dose and method of administration, Dose modifications).

Use in hepatic impairment

See section 4.8 Undesirable effects, Other special population(s).

Use in renal impairment

See section 4.8 Undesirable effects, Other special population(s).

Use in the elderly

See section 4.8 Undesirable effects, Other special population(s).

Paediatric use

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

Effects on laboratory tests

No data available.

4.5 Interaction with other medicines and other forms of interaction

Strong cytochrome P450 (CYP) 3A4 inducers

Coadministration of strong CYP3A4 inducers may lead to decreased exposure of OMJJARA and consequently a risk for reduced efficacy. Therefore, additional monitoring of the clinical signs and symptoms of myelofibrosis is recommended with concomitant use of OMJJARA and strong CYP3A4 inducers (including but not limited to carbamazepine, phenobarbital, phenytoin, and St John’s wort [Hypericum perforatum] (see section 5.2 Pharmacokinetic properties).

Sensitive breast cancer resistance protein (BCRP) substrates

OMJJARA is a BCRP inhibitor. Coadministration of OMJJARA has the potential to increase the plasma concentration of sensitive BCRP substrates, such as rosuvastatin and sulfasalazine. Patients should be monitored for adverse reactions with coadministration.

Transporters

OMJJARA is an organic anion transporting polypeptide (OATP) 1B1/1B3 substrate. Concomitant use with an OATP1B1/1B3 inhibitor may increase OMJJARA exposure, which may increase the risk of adverse reactions with OMJJARA. Therefore, caution and monitoring for adverse reactions is advised with concomitant use of OATP1B1/1B3 inhibitors, including ciclosporin.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data on the effects of OMJJARA in human pregnancy. Based on animal data, OMJJARA may cause embryo-foetal toxicity. In rats and rabbits, abortions, embryonic death, and foetal anomalies were observed in the presence and absence of maternal toxicity at exposures equivalent to the clinical dose of 200 mg daily (see section 5.3 Preclinical safety data).

OMJJARA should only be used during pregnancy if the expected benefits to the mother outweigh the potential risks to the foetus. Females of reproductive potential who are not pregnant should use highly effective contraception during therapy and for at least 1 week after the last dose of OMJJARA.

Breast-feeding

There are no data on the presence of OMJJARA in human milk. OMJJARA was present in rat pups following nursing from treated dams with adverse effects in the offspring (see section 5.3 Preclinical safety data). A risk to the breast-fed child cannot be excluded.

Patients should not breastfeed during treatment with OMJJARA and for at least 1 week after the last dose of OMJJARA.

Fertility

There are no data on the effects of OMJJARA on human male or female fertility. In animal studies, OMJJARA impaired fertility in rats (see section 5.3 Preclinical safety data).

4.7 Effects on ability to drive and use machines

There have been no studies to investigate the effect of OMJJARA on driving performance or the ability to operate machinery. However, patients who experience dizziness or blurred vision after taking OMJJARA should observe caution when driving or using machines (see section 4.8 Undesirable effects).

4.8 Undesirable effects

The safety of OMJJARA, based on three randomised, active-controlled, multicentre studies in adults with myelofibrosis (MOMENTUM, SIMPLIFY-1, SIMPLIFY-2), is presented in Table 2. Subjects were initially randomised to receive OMJJARA 200 mg once daily for 24 weeks (n = 448). The adverse reactions identified for OMJJARA in MOMENTUM, SIMPLIFY-1, SIMPLIFY-2 are listed by body system organ class (SOC) and frequency.

Frequencies are defined as:

Very common: ≥ 1/10
Common: ≥ 1/100 to < 1/10
Uncommon: ≥ 1/1,000 to < 1/100
Rare: ≥ 1/10,000 to < 1/1,000

Table 2 Adverse reactions

MedDRA System Organ Class (SOC)	Frequency Category	Adverse Reaction
Infections and infestations	Very common	Infections[a]
Blood and lymphatic system disorders	Very common	Thrombocytopenia[b]
	Common	Neutropenia[c]
Metabolism and nutrition disorders	Common	Vitamin B1 deficiency
Nervous system disorders	Very common	Dizziness Headache
	Common	Syncope Peripheral neuropathy[d] Paraesthesia
Eye disorders	Common	Blurred vision
Ear and labyrinth disorders	Common	Vertigo
Vascular disorders	Common	Hypotension Haematoma Flushing
Respiratory, thoracic and mediastinal disorders	Very common	Cough
Gastrointestinal disorders	Very common	Diarrhoea Abdominal pain Nausea
	Common	Vomiting Constipation
Musculoskeletal and connective tissue disorders	Common	Arthralgia Pain in extremity
General disorders and administration site conditions	Very common	Asthenia Fatigue
	Common	Pyrexia
Investigations	Common	Alanine transaminase (ALT) increased Aspartate transaminase (AST) increased
Injury, poisoning and procedural complications	Common	Contusion

a Infections includes the preferred terms of the Infections and Infestations SOC such as urinary tract infection, upper respiratory tract infection, COVID-19, herpes zoster; excludes opportunistic infections.
b Thrombocytopenia includes platelet count decreased.
c Neutropenia includes neutrophil count decreased.
d Peripheral neuropathy includes peripheral sensory neuropathy, peripheral motor neuropathy, neuropathy peripheral, peripheral sensorimotor neuropathy, neuralgia, and polyneuropathy.

Infections

In the three randomised clinical studies, 40% (178/448) of patients treated with OMJJARA experienced an infection. The most common infections (≥2%) were urinary tract infection (6%), upper respiratory tract infection (5%), pneumonia (3.6%), nasopharyngitis (2.9%), COVID-19 (2.7%), cystitis (2.7%), bronchitis (2.5%), and oral herpes (2.5%). The majority of infections were mild or moderate, while 10% (47/448) of patients experienced a severe infection (≥ Grade 3). The proportion of patients discontinuing treatment due to an infection was 2% (9/448). Fatal infections were reported in 2.2% (10/448) of patients. In the individual studies of MOMENTUM, SIMPLIFY-1, and SIMPLIFY-2, the rates of infections for OMJJARA were 34%, 36%, and 55%, respectively, compared with 35% for danazol, 43% for ruxolitinib, and 42% for best available therapy.

Thrombocytopenia

In the three randomised clinical studies, 21% (94/448) of patients treated with OMJJARA experienced thrombocytopenia; 12% (54/448) of patients treated with OMJJARA experienced severe thrombocytopenia (≥ Grade 3). The proportion of patients discontinuing treatment due to thrombocytopenia was 2.5% (11/448). In the individual studies of MOMENTUM, SIMPLIFY-1, and SIMPLIFY-2, the rates of thrombocytopenia for OMJJARA were 28%, 19%, and 17%, respectively, compared with 15% for danazol, 29% for ruxolitinib, and 12% for best available therapy.

Paediatric population

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

Other special population(s)

Renal impairment

Momelotinib AUC decreased by 13% in subjects with moderate renal impairment (eGFR 30-59 mL/min/1.73 m^2) and AUC decreased by 16% in subjects with severe renal impairment (eGFR 15-29 mL/min/1.73 m^2) compared to subjects with normal renal function (eGFR ≥90 mL/min/1.73 m^2). The AUC of the active metabolite, M21, increased by 20% and 41%, respectively, in subjects with moderate and severe renal impairment compared to subjects with normal renal function. There are no data in patients with end-stage renal disease (ESRD) receiving dialysis.

Hepatic impairment

Momelotinib AUC increased by 8% and 97% in subjects with moderate (Child-Pugh Class B) and severe (Child-Pugh Class C) hepatic impairment, respectively, compared to subjects with normal hepatic function (see section 4.2 Dose and method of administration).

Age, gender, race, and bodyweight

Age, gender, race, or weight do not have a clinically meaningful effect on the pharmacokinetics of momelotinib based on a population pharmacokinetic analysis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via: https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

There is currently limited experience of overdosage with OMJJARA. If overdose is suspected, the patient should be monitored for any signs or symptoms of adverse reactions or effects, and appropriate standard of care measures should be instituted immediately. Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors

Mechanism of action

OMJJARA is an inhibitor of wild type Janus Kinase 1 and 2 (JAK1/JAK2) and mutant $JAK2^{V617F}$, which contribute to signalling of a number of cytokines and growth factors that are important for haematopoiesis and immune function. JAK1 and JAK2 recruit and activate STAT (signal transducer and activator of transcription) proteins that control gene transcription impacting inflammation, haematopoiesis, and immune regulation. OMJJARA and its major human circulating metabolite, M21, additionally inhibit activin A receptor type 1 (ACVR1), also known as activin receptor-like kinase 2 (ALK2) which subsequently down regulates liver hepcidin expression resulting in increased iron availability and red blood cell production. Myelofibrosis is a myeloproliferative neoplasm associated with constitutive activation and dysregulated JAK signalling that contributes to elevated inflammation and hyperactivation of ACVR1.

Pharmacodynamic effects

OMJJARA inhibits cytokine-induced STAT3 phosphorylation in whole blood from patients with myelofibrosis. Maximal inhibition of STAT3 phosphorylation occurred 2 hours after OMJJARA dosing with inhibition persisting for at least 6 hours. OMJJARA also demonstrated both acute and prolonged reduction of circulating hepcidin in patients with myelofibrosis, resulting in increased iron availability and erythropoiesis.

Cardiovascular effects

At a dose of 4 times the highest recommended starting dosage of 200 mg, OMJJARA did not prolong the QT interval to any clinically relevant extent.

Clinical efficacy and safety

The efficacy of OMJJARA in the treatment of patients with intermediate-1, intermediate-2, or high-risk myelofibrosis, including primary myelofibrosis, post-polycythaemia vera (post-PV) myelofibrosis or post-essential thrombocythaemia (post-ET) myelofibrosis, was established in two randomised, active-controlled Phase 3 studies, MOMENTUM and SIMPLIFY-1. All patients received a starting dose of OMJJARA 200 mg once daily, irrespective of their baseline platelet count (in MOMENTUM study, the minimum platelet count was 25 x 10^9/L; in SIMPLIFY 1 study, the minimum platelet count was 50 x 10^9/L).

MOMENTUM

MOMENTUM was a double-blind, 2:1 randomised, active-controlled study in 195 symptomatic and anaemic patients with myelofibrosis who had previously received a JAK inhibitor. The median age was 71 years (range 38 to 86 years); 79% were 65 years or older and 63% were male. Sixty-four percent (64%) of patients had primary myelofibrosis, 19% had post-PV myelofibrosis, and 17% had post-ET myelofibrosis. Five percent (5%) of patients had intermediate-1 risk, 57% had intermediate-2 risk, and 35% had high-risk disease. Patients were symptomatic with a Myelofibrosis Symptom Assessment Form (MFSAF) v4.0 total symptom score (TSS) of ≥10 at screening (mean MFSAF TSS 27 at baseline), and anaemic with haemoglobin (Hgb) <10 g/dL. The MFSAF daily diary captured the core symptoms of myelofibrosis: night sweats, abdominal discomfort, pain under the left rib, fatigue/tiredness, early satiety, pruritus, and bone pain. Within the 8 weeks prior to enrolment, 79% had red blood cell transfusions. At baseline, 13% and 15% of patients were transfusion independent in the OMJJARA and danazol groups, respectively. The baseline median Hgb was 8 g/dL and the median platelet count was 96 × 10^9/L. The baseline median palpable spleen length was 11.0 cm below the left costal margin; the median spleen volume [measured by magnetic resonance imaging (MRI) or computed tomography (CT)] was 2105 cm^3 (range 610 to 9717 cm^3).

Patients were treated with OMJJARA 200 mg once daily or danazol 300 mg twice daily for 24 weeks, followed by open-label treatment with OMJJARA. The two primary efficacy endpoints were percentage of patients with total symptom score (TSS) reduction of 50% or greater from baseline to week 24 (as measured by the Myelofibrosis Symptom Assessment Form [MFSAF] v4.0), and the percentage of patients who were transfusion independent (TI) at week 24 (defined as no transfusions and all haemoglobin values ≥8 g/dL in the 12 weeks prior to week 24). A key secondary endpoint measured the percentage of subjects with ≥35% reduction in spleen volume from baseline at week 24.

At Week 24, a significantly higher percentage of patients treated with OMJJARA achieved a TSS reduction of 50% or greater from baseline (superiority, one of the primary endpoints) and a spleen volume reduction by 35% or greater from baseline (superiority, one of the secondary endpoints) (Table 3).

Table 3 Efficacy Results of Patients Achieving Symptom Reduction, Transfusion Independence, and Spleen Volume Reduction at Week 24 (MOMENTUM)

	Momelotinib n = 130	**Danazol n = 65**	
	n %	**n %**	**p-value**
Patients with Total Symptom Score Reduction of 50% or greater	32 25%	6 9%	
Treatment Difference (95% CI)	16% (6, 26)		0.0095
Patients with Transfusion Independence[a]	39 30%	13 20%	
Non-inferiority Treatment Difference[b] (95% CI)	14% (2, 25)		0.0116
Patients with Spleen Volume Reduction by 25% or greater	51 39%	4 6%	
Treatment Difference (95% CI)	33% (23, 44)		<0.0001
Patients with Spleen Volume Reduction by 35% or greater	29 22%	2 3%	
Treatment Difference (95% CI)	18% (10, 27)		0.0011
Patients with No Transfusion[c]	46 35%	11 17%	
Treatment Difference (95% CI)	17% (8, 26)		0.0012
	LS Mean[d]	**LS Mean[d]**	
Change from baseline in Total Symptom Score	-9.4	-3.1	
Treatment Difference (95% CI)	-6.22 (-10.0, -2.43)		0.0014

CI = confidence interval; LS = least square.

a Defined as no transfusions and all Hgb values ≥8 g/dL in the 12 weeks prior to Week 24.

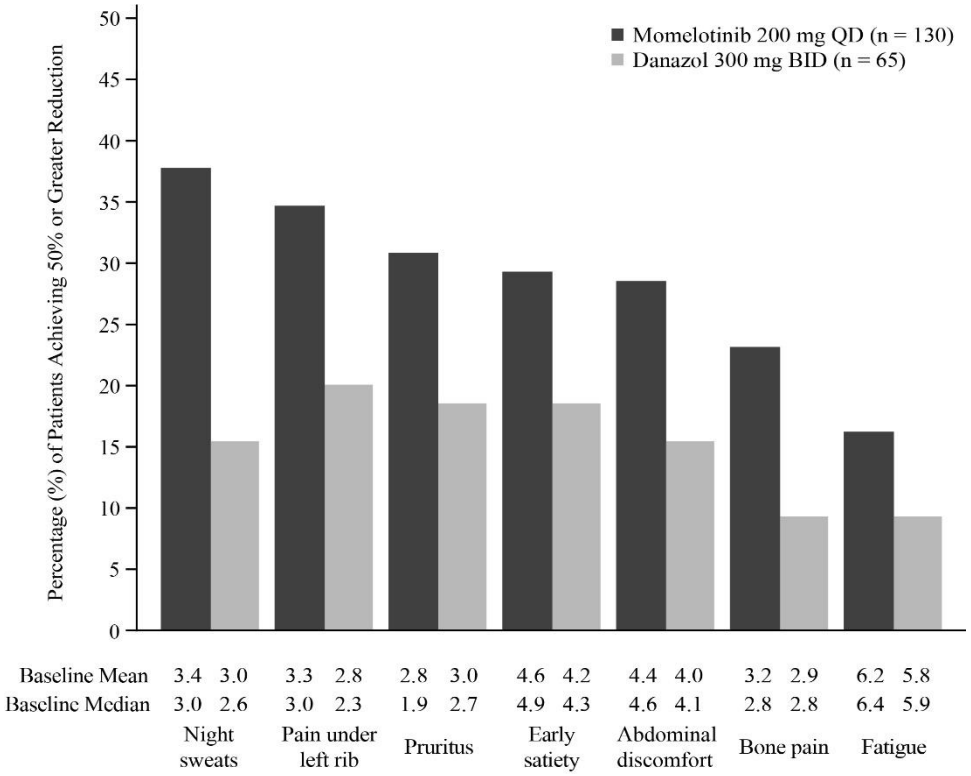
b Non-inferiority difference between momelotinib response rate and 80% of danazol response rate; 1-sided p-value.

c Percentage of patients with zero red blood cell or whole blood units transfused during the 24-week treatment period.

d Least square mean and difference at Week 24 based on a longitudinal mixed effect model for continuous Total Symptom Score change from baseline on a 70-point scale.

Responses based on MFSAF TSS individual components were compared for OMJJARA and danazol (Figure 1). Symptom scores ranged from 0 (absent) to 10 (worst imaginable) for each component. A higher percentage of patients treated with OMJJARA achieved a 50% or greater reduction from baseline compared with danazol for each individual symptom.

Figure 1 Percent of Patients Achieving a 50% or Greater Reduction in Individual Symptom Scores at Week 24 (MOMENTUM)



QD = once daily; BID = twice a day.

Greater improvement was observed for cancer-related fatigue, as measured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30 v3.0) fatigue subscale, for patients treated with momelotinib compared with danazol. At Week 24, the mean change from baseline for cancer-related fatigue showed a reduction of 14.2 points for momelotinib compared with 3.8 points for danazol; these findings were consistent with the TSS fatigue symptom item improvement (mean change from baseline for the MFSAF TSS fatigue symptom score was a reduction of 1.8 points for momelotinib compared with 0.8 points for danazol).

The percentage of patients with Hgb increases of ≥1 g/dL and Hgb increases of ≥1.5 g/dL were 53% and 40% over baseline for those treated with momelotinib, compared with 34% and 23% for those treated with danazol, respectively, by Week 24.

There was a 49% reduction in risk of death in patients treated with momelotinib compared with danazol during the 24-week randomised treatment period (overall survival HR 0.51; 95% CI: 0.24,1.08).

SIMPLIFY-1

SIMPLIFY-1 was a double-blind, randomised, active-controlled study in 432 patients with myelofibrosis who had not previously received a JAK inhibitor. The median age was 66 years (range 25 to 86 years) with 57% of patients older than 65 years and

56% male. Fifty-six percent (56%) of patients had primary myelofibrosis, 23% had post-PV myelofibrosis, and 21% had post-ET myelofibrosis. Twenty-one percent (21%) of patients had intermediate-1 risk, 33% had intermediate-2 risk, and 46% had high-risk disease. TSS response was measured by the modified Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) v2.0 diary (mean TSS 19 at baseline). The MPN-SAF daily diary captured the core symptoms of myelofibrosis: night sweats, abdominal discomfort, pain under the left rib, fatigue/tiredness, early satiety, pruritus, and bone pain. Within the 8 weeks prior to enrolment, 25% of patients had red blood cell transfusions. The baseline median Hgb was 10.4 g/dL and the median platelet count was 243.0 × 10^9/L at baseline. The baseline median palpable spleen length was 12.0 cm below the left costal margin; the median spleen volume (measured by MRI or CT) was 1916 cm^3 (range 206 to 9022 cm^3).

Patients were treated with momelotinib 200 mg or ruxolitinib adjusted dose twice daily for 24 weeks, followed by open-label treatment with momelotinib without tapering of ruxolitinib. The primary efficacy endpoint was percentage of patients with spleen volume response (reduction by 35% or greater) at Week 24; analyses were also conducted in a subset of patients with moderate to severe anaemia (Hgb < 10 g/dL) (Table 4). A similar percentage of patients treated with momelotinib or ruxolitinib achieved a spleen volume response in both populations. Other endpoints included TSS response and red blood cell transfusion requirements.

Table 4 Percent of Overall Patients and Anaemic Patients Achieving Symptom Reduction, Spleen Volume Reduction, and Transfusion Independence at Week 24 (SIMPLIFY-1)

	Overall Population		Anaemic Population (Hgb <10 g/dL)	
	Momelotinib n = 215	**Ruxolitinib n = 217**	**Momelotinib n = 159**	**Ruxolitinib n = 164**
	n %	**n %**	**n %**	**n %**
Patients with Spleen Volume Reduction by 35% or greater	57 27%	64 29%	27 31%	31 33%
Non-inferiority Treatment Difference[a] (95% CI) p value	9% (2, 16) p = 0.014		—	
Patients with Total Symptom Score Reduction of 50% or greater	60/211 28%	89/211 42%	21/84 25%	33/93 35%
Non-inferiority Treatment Difference[b] (95% CI) p value	0% (-8, 8) p = 0.98		—	
Patients with Transfusion Independence[c]	143 67%	107 49%	40 47%	25 27%
Treatment Difference (95% CI) p value	18% (9, 26) p < 0.001[d]		—	

CI = confidence interval.

[a] Non-inferiority difference between momelotinib rate and 60% of ruxolitinib response rate.

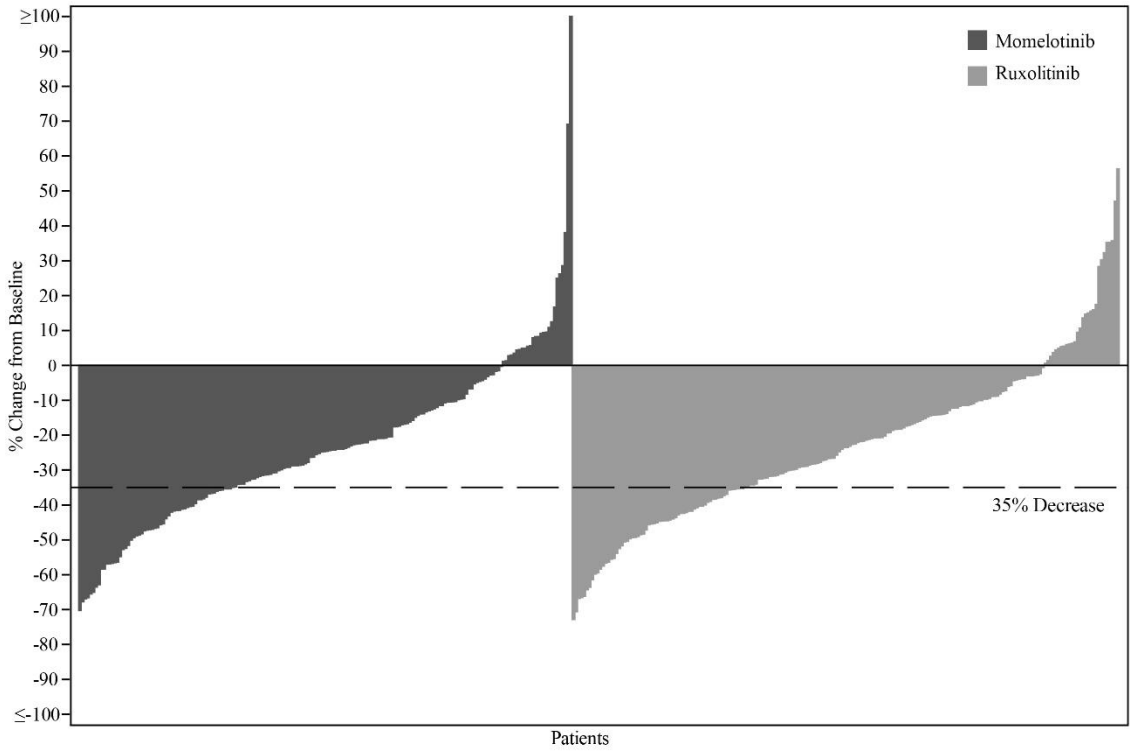
[b] Non-inferiority difference between momelotinib rate and 67% of ruxolitinib response rate.

[c] Defined as no transfusions and all Hgb values ≥8 g/dL in the 12 weeks prior to Week 24.

[d] Nominal p value.

In patients with spleen volume measured at Week 24, the median reduction in spleen volume was 25% in patients treated with momelotinib compared with 24% for ruxolitinib. Figure 2 shows the percent change from baseline in spleen volume for each patient at Week 24.

Figure 2 Percent Change from Baseline in Spleen Volume for Each Patient in the Overall Population at Week 24 (SIMPLIFY-1)



In the overall population, the continuous TSS change from baseline analysis at Week 24 using a longitudinal model shows a mean TSS improvement of 5.9 points for patients treated with momelotinib and 7.1 points for patients treated with ruxolitinib. The least square mean difference of TSS change from baseline was 1.24 points (95% CI: -0.40, 2.88) between momelotinib and ruxolitinib on a 70-point scale.

At baseline for the overall population, 68% and 70% of patients treated with momelotinib or ruxolitinib, respectively, were transfusion independent. At Week 24, the percentage of patients who were transfusion independent was 67% with momelotinib and 49% with ruxolitinib. A higher percentage of patients treated with momelotinib who were not transfusion independent at baseline became transfusion independent at Week 24 (35% for momelotinib; 20% for ruxolitinib). The mean baseline Hgb prior to starting momelotinib and ruxolitinib was 10.6 and 10.7 g/dL, respectively; at Week 24, the mean Hgb was 11.1 and 9.9 g/dL, respectively, for patients receiving momelotinib or ruxolitinib.

Overall, the 1-, 2-, and 3-year survival rates for momelotinib were 93%, 82%, and 71%, respectively.

Paediatric population

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

5.2 Pharmacokinetic properties

Absorption

Momelotinib is rapidly absorbed after oral administration with the maximal plasma concentration (C_{max}) achieved within 3 hours post-dose, with plasma exposures increased in a less than dose proportional manner, at doses above 300 mg. At the dose of 200 mg once daily at steady state, the mean (%CV) momelotinib C_{max} is 479 ng/mL (61%) and AUC is 3288 ng•h/mL (60%) in patients with myelofibrosis.

Following low-fat and high-fat meals in healthy volunteers, the C_{max} of momelotinib was 38% and 28% higher, respectively, and the AUC was 16% and 28% higher, respectively, as compared with those under fasting conditions. These changes in exposure were not clinically meaningful.

Distribution

Plasma protein binding of momelotinib is approximately 91% in human. The mean apparent volume of distribution of momelotinib at steady-state was 984 L in patients with myelofibrosis receiving momelotinib 200 mg daily suggesting extensive tissue distribution.

Biotransformation

Human metabolism of momelotinib is predominantly mediated by CYP enzymes with contributions in the following order: CYP3A4 (36%), CYP2C8 (19%), CYP2C19 (19%), CYP2C9 (17%), and CYP1A2 (9%). M21 is an active human metabolite that has approximately 40% of the pharmacological activity of the parent. M21 Is formed by CYP followed by aldehyde oxidase metabolism of momelotinib. The mean M21 to momelotinib ratio for AUC ranged from 1.4 to 2.1.

Elimination

Following an oral dose of momelotinib 200 mg, the mean terminal half-life (t½) of momelotinib was 4 to 8 hours; the half-life of M21 is similar. The apparent total clearance (CL/F) of momelotinib was 103 L/h in patients with myelofibrosis.

Momelotinib is mainly eliminated through metabolism and then excreted to faeces. Following a single oral dose of [^{14}C]-labelled momelotinib in healthy male subjects, 69% of radioactivity was excreted in the faeces (13% of dose as unchanged momelotinib), and 28% in the urine (<1% of dose as unchanged momelotinib).

5.3 Preclinical safety data

Genotoxicity

Momelotinib was not mutagenic in a bacterial reverse mutation assay or clastogenic in an in vitro chromosomal aberration assay with human peripheral blood lymphocytes or in vivo in a rat bone marrow micronucleus assay.

Carcinogenicity

The carcinogenic potential of momelotinib was assessed in a 6-month rasH2 transgenic mouse study and a 2-year rat carcinogenicity study.

Momelotinib, at exposure levels approximately 28 times the recommended clinical dose of 200 mg once daily (based on AUC at oral doses of 100 mg/kg/day), was not carcinogenic in mice.

In the 2-year carcinogenicity study in Sprague-Dawley rats, oral momelotinib caused benign Leydig cell tumors at a dose of 15 mg/kg/day (approximately 39 times the exposure levels of the recommended clinical dose of 200 mg once daily). An increase to the human health risk is considered unlikely since the increase in Leydig cell adenomas was considered related to a species-specific mechanistic finding (i.e., rat Leydig cell prolactin dependence).

Reproductive Toxicology

Fertility

In fertility studies, momelotinib was administered orally to male and female rats.

In males, momelotinib reduced sperm concentration and motility and reduced testes and seminal vesicle weights at 25 mg/kg/day or greater (exposures 13-times the recommended dose of 200 mg based on combined momelotinib and M21 AUC) leading to reduced fertility at 68 mg/kg/day. In females, momelotinib reduced ovarian function (reproductive cycles and ovulation) at 68 mg/kg/day and decreased the number of pregnant females and increased pre- and post-implantation loss with most pregnant rats having total litter loss at 25 mg/kg/day or greater. Exposures at the no observed adverse effect level in male and female rats at 5 mg/kg/day are approximately 3-times the recommended dose (based on combined momelotinib and M21 AUC).

Pregnancy

In animal reproduction studies, oral administration of momelotinib to pregnant rats during the period of organogenesis caused maternal toxicity at 12 mg/kg/day and was associated with embryonic death, soft tissue anomalies, skeletal variations, and lower mean foetal body weights; skeletal variations were observed at 6 mg/kg/day at exposures 3.5-fold the exposure at the recommended dose of 200 mg daily based on combined momelotinib and M21 (a major human metabolite) AUC. No development toxicity was observed at 2 mg/kg/day at exposures equivalent to the recommended dose (based on combined momelotinib and M21 AUC).

In pregnant rabbits, oral administration of momelotinib during the period of organogenesis caused maternal toxicity and evidence of embryo-foetal toxicity (decreased foetal weight, delayed bone ossification, and abortion) at 60 mg/kg/day at less than the exposure equivalent to the recommended dose (based on combined momelotinib and M21 AUC). No developmental toxicity was observed at 30 mg/kg/day at exposures less than the recommended dose (based on combined momelotinib and M21 AUC).

In a pre- and post-natal development study, pregnant rats received oral momelotinib from organogenesis to end of lactation. Evidence of maternal toxicity, embryo-lethality, and decreased pup body weights were observed at 6 and 12 mg/kg/day. Pup survival was significantly reduced at 12 mg/kg/day from birth to Day 4 of lactation and therefore considered a direct effect of momelotinib via exposure through the milk. Momelotinib exposure in dams at 6 and 12 mg/kg/day were approximately 2 times the exposure at the recommended dose (based on combined momelotinib and M21 AUC). The exposure in dams without developmental toxicity was at a dose of 2 mg/kg/day which was less than the exposure at the recommended dose (based on combined momelotinib and M21 AUC).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Lactose monohydrate
Sodium starch glycolate (type A)
Magnesium stearate
Silica colloidal anhydrous
Propyl gallate
Polyvinyl alcohol
Macrogols
Titanium dioxide (E171)
Talc
Iron oxide yellow (E172)
Iron oxide red (E172)

6.2 Incompatibilities

Incompatibilities were not identified as part of the registration of this medicine.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store below 30°C in the original bottle to protect from moisture. Do not remove the desiccant.

6.5 Nature and contents of container

White, high-density polyethylene (HDPE) bottles with child-resistant polypropylene cap and induction-sealed, aluminium faced liner. Each bottle contains 30 film-coated tablets, silica gel desiccant, and polyester coil packing material.

Not all strengths may be distributed in New Zealand.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of by taking to your local pharmacy.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

GlaxoSmithKline NZ Limited
Private Bag 106600
Downtown
Auckland
New Zealand

Phone: (09) 367 2900
Facsimile: (09) 367 2910

9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine: 27 February 2025

10. DATE OF REVISION OF THE TEXT

First version

Summary table of changes:

Section changed	Summary of new information
All	New Data Sheet

Version 1.0