Product Monograph

Including Patient Medication Information

Pr **PIMJETMI®**

Pimicotinib capsules

For oral use

25 mg pimicotinib (as pimicotinib hydrochloride)

Kinase inhibitor

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Recent Major Label Changes

None at the time of the most recent authorization.

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Part 1: Healthcare Professional Information

1. Indication

PIMJETMI (pimicotinib) is indicated for the treatment of adult patients with symptomatic tenosynovial giant cell tumour (TGCT) for which surgical resection will potentially cause worsening functional limitation or severe morbidity.

1.1. Pediatrics

Pediatrics (< 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of PIMJETMI in pediatric patients have not been established; therefore, Health Canada has not authorized an indication for pediatric use (see 7.1.3 Pediatrics).

1.2. Geriatrics

Geriatrics (> 65 years of age): Clinical studies of PIMJETMI did not include a sufficient number of patients > 65 years of age to determine whether they respond differently from younger patients (see 7.1.4. Geriatrics).

2. Contraindications

PIMJETMI is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6. Dosage Forms, Strengths, Composition, and Packaging.

4. Dosage and Administration

4.1. Dosing Considerations

Patients with moderate hepatic impairment require PIMJETMI dose adjustment (see 4.2 Recommended Dose and Dosage Adjustment, and 10. Clinical Pharmacology).

Verify the pregnancy status of females of reproductive potential prior to initiating treatment with PIMJETMI (see 7. Warnings and Precautions, Reproductive Health and 7.1.1. Pregnancy).

4.2. Recommended Dose and Dosage Adjustment

The recommended dose of PIMJETMI is 50 mg orally once daily (two 25 mg capsules).

Dose Modification

The management of adverse reactions of PIMJETMI may require either temporary interruption or dose reduction to 25 mg once daily. Treatment with PIMJETMI should be continued as long as benefits are observed or until unacceptable toxicity.

Recommended dose modifications of PIMJETMI for elevated liver transaminases are provided in Table

1 (see 7. Warnings and Precautions, 8. Adverse Reactions).

Table 1 – Recommended PIMJETMI Dosage Modifications for Elevated Liver Transaminases

Adverse Reaction	Treatment and monitoring recommendation
AST and/or ALT elevations > 5 × ULN	• Withhold PIMJETMI. • Confirm elevation with repeat testing. Monitor at least once weekly until recovery to ≤ 3 x ULN or patient's baseline (whichever is greater). • Resume treatment at reduced dose of 25 mg once daily if ALT and AST decreased to ≤ 3 x ULN or patient's baseline (whichever is greater) and monitor the patient.
AST and/or ALT elevations > 3 × ULN and concurrent total bilirubin elevations > 2 × ULN	• Withhold PIMJETMI. • Perform further assessment to investigate drug-induced liver injury or alternative causes. • If drug-induced liver injury confirmed, permanently discontinue PIMJETMI. • Resume treatment at reduced dose of 25 mg once daily if drug-induced liver injury is definitively ruled out, and ALT and AST decreased to ≤ 3 x ULN or patient's baseline (whichever is greater) and total bilirubin decreased to baseline. Monitor the patient.
AST and/or ALT elevations > 5 x ULN and concurrent total bilirubin elevation > 1.5 x ULN	• Permanently discontinue PIMJETMI.
AST and/or ALT elevations > 8 × ULN	• Permanently discontinue PIMJETMI.
Any and total bilirubin elevation > 3 x ULN	• Permanently discontinue PIMJETMI.

ALT - alanine aminotransferase; AST - aspartate aminotransferase; ULN - upper limit of normal

Pediatrics (< 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of PIMJETMI in pediatric patients < 18 years of age have not been established; therefore, Health Canada has not authorized an indication for pediatric use (see 7.1.3 Pediatrics).

Geriatrics (> 65 years of age): Based on the limited data available, no dosage modification is considered necessary in patients over 65 years of age (see 7.1.4. Geriatrics, 10. Clinical Pharmacology and 14. Clinical Trials).

Hepatic Impairment: Reduce the PIMJETMI starting dosage to 25 mg once daily for patients with moderate (Child-Pugh class B) hepatic impairment. Monitor for adverse reactions and further modify dose as recommended in Table 1. No dosage adjustment is recommended for patients with mild hepatic impairment (Child-Pugh class A) (see 10. Clinical Pharmacology).

PIMJETMI has not been studied in patients with severe hepatic impairment (total bilirubin > 3 to 10 × ULN and any AST or Child-Pugh class C).

Renal Impairment: No dosage modification is necessary for patients with mild to moderate renal impairment (creatinine clearance [CRCL] 30 to 89 mL/min) (see 10. Clinical Pharmacology).

PIMJETMI has not been studied in patients with severe renal impairment (CRCL < 30 mL/min).

Strong CYP3A Inhibitors: Avoid concomitant use of strong CYP3A inhibitors with PIMJETMI. If concomitant use cannot be avoided, monitor patients closely for adverse reactions and modify dose as recommended in Table 1 (see 9. Drug Interactions).

4.4. Administration

PIMJETMI is for oral use. The capsules can be taken with or without food. The capsules should be swallowed whole with water and should not be opened, broken, dissolved, or chewed. PIMJETMI should be taken at the same time each day, whenever possible.

4.5. Missed Dose

If a patient misses a dose of PIMJETMI or vomits after taking a dose, the patient should be instructed to take the next dose at its scheduled time.

5. Overdose

There is limited experience with cases of overdose reported in clinical studies with PIMJETMI.

No specific antidotes for PIMJETMI are known. Should an overdose occur, the patient should be closely monitored for adverse reactions and treated with appropriate supportive care until recovery.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

Table 2 – Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form/ Strength/Composition	Non-Medicinal Ingredients
oral	Capsule / 25 mg pimicotinib (as pimicotinib hydrochloride)	Black iron oxide, colloidal silicon dioxide, croscarmellose sodium, gelatin, lactose monohydrate, magnesium stearate, microcrystalline cellulose, potassium hydroxide, shellac, and titanium dioxide.

Description

PIMJETMI is a white opaque hard capsule imprinted with “PIMI 25” in black ink.

PIMJETMI is supplied in a high-density polyethylene (HDPE) bottle and polypropylene child resistant (PPCR) cap. Each bottle contains 30 capsules and a silica gel desiccant.

7. Warnings and Precautions

Driving and Operating Machinery

Based on its pharmacodynamic properties, PIMJETMI is anticipated to have no or negligible influence on the ability to drive and use machines. However, during treatment with PIMJETMI, fatigue and dizziness have been reported. Patients who experience these symptoms should be advised to use caution when driving or using machines.

Hepatic/Biliary/Pancreatic

Elevation of hepatic transaminases

In the pooled safety population (see 8.1 Adverse Reaction Overview), all patients had total bilirubin, AST, ALT, and alkaline phosphatase (ALP) ≤ 1.5 x ULN at baseline. The adverse event (AE) of elevation of aminotransferase was reported in 59.5% of patients. One patient (0.6%), with a medical history of hepatic steatosis, had a Grade 3 AE of ALT elevation. Adverse events of AST and/or ALT increased led to temporary interruption in 4 patients (2.4%) and dosage reduction in 1 patient (0.6%). The median time to first onset for AST and/or ALT increase of any grade was 20.5 days and the median time to resolution after treatment discontinuation was 10 days.

Monitor hepatic enzymes (AST, ALP, gammaglutamyl transferase [GGT]) and total bilirubin prior to, 1 month and 3 months after the initiation of PIMJETMI, and as clinically indicated thereafter. Withhold and reduce the dose or permanently discontinue PIMJETMI based on severity of the hepatic transaminase elevations (see 4.2. Recommended Dose and Dosage Adjustment).

Monitoring and Laboratory Tests

Verify the pregnancy status of females of reproductive potential prior to initiating treatment with PIMJETMI (see 7. Warnings and Precautions, Reproductive Health and 7.1.1. Pregnancy).

Monitor hepatic enzymes (AST, ALP, gammaglutamyl transferase [GGT]) and total bilirubin prior to, 1 month and 3 months after the initiation of PIMJETMI, and as clinically indicated thereafter. Withhold and reduce the dose or permanently discontinue PIMJETMI based on severity of the hepatic transaminase elevations (see 4.2. Recommended Dose and Dosage Adjustment).

During PIMJETMI treatment, use alternative measures that are not based on serum creatinine to assess renal function (see 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry, and Other Quantitative Data).

Reproductive Health

- **Contraception**

  Based on animal studies and its mechanism of action, pimicotinib can cause fetal harm when administered to a pregnant woman (see 16. Non-Clinical Toxicology). Women should be advised to avoid pregnancy during treatment with PIMJETMI.

  Before initiation of treatment, women of childbearing potential and males who could potentially father a child should be counselled regarding the potential for serious risk to the fetus.

  Pregnancy testing is recommended in women of childbearing potential prior to initiating treatment with PIMJETMI. Women of childbearing potential should use an effective method of contraception during treatment and for 2 weeks after the last dose of PIMJETMI.

  Educational materials for healthcare professionals are available on EMD Serono's website https://medinfo.emdserono.ca/en or by calling EMD Serono at 1-888-737-6668.

- **Fertility**

  Based on findings from animal studies, pimicotinib does not impair female fertility. However, pimicotinib may impair male fertility. Male patients, including males who have had a vasectomy, with female partners of childbearing potential should use effective contraception during PIMJETMI treatment and for 2 weeks after the last dose.

7.1. Special Populations

7.1.1. Pregnancy

PIMJETMI should not be used during pregnancy.

There are no available data on PIMJETMI use in pregnant women. Based on data from animal studies and its mechanism of action, pimicotinib can cause fetal harm when administered to a pregnant woman. In a rat pre- and postnatal development study, animals showed increased mortality and developmental retardation, including at doses lower than human exposure at the therapeutic dose (see 16. Non-Clinical Toxicology and 10.1 Mechanism of Action).

Women of childbearing potential or male patients with female partners of childbearing potential should be advised of the potential risk to a fetus. Patients should be advised on the importance of immediately informing their healthcare professional of any pregnancy that occurs (or is suspected) during treatment with PIMJETMI. If a pregnancy occurs during treatment with PIMJETMI, the benefits of therapy versus the potential risk to the fetus should be assessed by the healthcare professional and the treatment options should be discussed with the patient.

Women of childbearing potential who wish to become pregnant while receiving PIMJETMI should discontinue treatment and use effective contraception for at least 2 weeks after the last dose before attempting conception.

7.1.2. Breastfeeding

There are no data on the presence of pimicotinib or its metabolites in human milk. Based on animal data, there is potential for presence of pimicotinib in breast milk (see 16. Non-Clinical Toxicology). When a drug is present in animal milk, it is likely to be present in human milk. Because of the potential for serious adverse reactions in the breastfed child, women should not breastfeed during treatment with PIMJETMI and for 2 weeks after the final dose of PIMJETMI.

7.1.3. Pediatrics

Pediatrics (< 18 years of age): Health Canada has not authorized an indication for pediatric use.

Based on the limited data submitted (three adolescents [14-17 years]) weighing at least 40 kilograms and who had reached puberty and skeletal maturity) and reviewed by Health Canada, the safety and efficacy of PIMJETMI in post pubertal pediatric patients have not been established.

PIMJETMI has not been studied in children from birth to pre-pubertal age. Based on the mechanism of action of PIMJETMI, findings in animals, and clinical pharmacology results, there are potential concerns for bone, tooth, and reproductive organ development and function in pediatric patients who have not completed longitudinal growth and puberty (see 10. Clinical Pharmacology and 16. Non-Clinical Toxicology).

7.1.4. Geriatrics

Geriatrics (> 65 years of age): No overall differences in safety were observed between patients > 65 years of age and patients ≤ 65 years of age; however, the total number of patients with TGCT > 65 years of age treated with PIMJETMI 50 mg once daily in the pooled safety population (11 of 158 [7.0%]) is small, limiting interpretability of results.

8. Adverse Reactions

8.1. Adverse Reaction Overview

The pooled safety population described in 7. Warnings and Precautions reflects exposure to PIMJETMI in 158 patients with TGCT treated with PIMJETMI 50 mg once daily, including 94 patients from the Phase 3 MANEUVER study (i.e., 63 patients randomized to PIMJETMI in the double-blind part and 31 patients who crossed over from placebo to PIMJETMI in the open-label part) (see 14. Clinical Trials) and 64 patients from a single arm Phase 1 study. The median total duration of exposure to PIMJETMI was 12.7 months, with 80.4% of patients exposed for 6 months or longer, 53.2% exposed for one year or longer, and 17.1% exposed for 2 years or longer.

Adverse reactions comprise treatment-emergent adverse events that met adverse drug reaction criteria. Adverse reactions were reported by 155 (98.1%) patients. The most common (> 10%) adverse reactions by preferred term were pruritus (43.0%), face edema (41.1%), rash (36.1%), periorbital edema (25.3%), fatigue (20.9%), nausea (20.3%), skin indentation (19.0%), headache (16.5%), dizziness (13.9%), hypertension (12.7%), and edema peripheral (10.8%).

The most common (> 20%) laboratory abnormalities adverse reactions were blood lactate dehydrogenase increased (96.8%), blood creatine phosphokinase increased (96.2%), aspartate aminotransferase increased (82.9%), cholesterol increased (56.8%), lipase increased (54.1%), serum

amylase increased (51.3%), alanine aminotransferase increased (42.4%), white blood cell decreased (30.6%), creatinine increased (29.1%), neutrophil count decreased (27.4%), and lymphocyte count decreased (22.9%).

Skin indentation (a clustered term including skin indentation, skin atrophy, mid-dermal elastolysis, and skin dystrophy) was reported in 22.8% of patients treated with PIMJETMI in the pooled safety population compared with one (1.6%) patient in the PIMJETMI group in the double-blind part of MANEUVER (see 8.3 Less Common Clinical Trial Adverse Reactions), indicating a delayed onset of this adverse reaction.

Grade 3 or higher adverse reactions were reported in 48 (30.4%) patients. Grade 3 or higher adverse reactions reported in > 2% of patients by preferred term were rash (2.5%), hypertension (5.7%), and blood pressure increased (5.1%).

Grade 3 or higher laboratory abnormalities adverse reactions reported in > 2% of patients were blood CPK increase (16.6%), lipase increase (2.8%) and neutrophil count decreased (3.2%).

There was no adverse reaction leading to death.

Serious adverse reactions were reported in 3 (1.9%) patients (1 patient each with an event of blood pressure increase, hypertension and headache).

Permanent discontinuation due to an adverse reaction occurred in 4 (2.5%) patients who received PIMJETMI. Adverse reactions requiring permanent discontinuation included 2 (1.3%) patients with fatigue and 1 (0.6%) patient each with nausea, pruritus, face edema, headache, and rash.

Dose reduction due to adverse reaction occurred in 18.4% of patients who received PIMJETMI. Most frequent adverse reactions (> 1%) requiring a dosage reduction were skin indentation (3.8%), rash (3.2%), blood creatine phosphokinase increased (2.5%), pruritus (2.5%), face edema (1.9%), rash maculo-papular (1.3%), and headache (1.3%).

Treatment interruptions due to adverse reaction occurred in 46.8% of patients who received PIMJETMI. Most frequent adverse reactions (> 2%) requiring a dosage interruption were blood creatine phosphokinase increased (13.3%), rash (10.1%), pruritus (7.0%), face edema (5.1%), periorbital edema (4.4%), skin indentation (3.8%), eyelid edema (2.5%), headache (2.5%), hypertension (2.5%), and neutrophil count decreased (2.5%).

8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

The safety of PIMJETMI was evaluated in 63 adult patients with TGCT randomized to PIMJETMI in the double-blind part of the Phase 3 MANEUVER study (see 14. Clinical Trials).

The most common (> 20%) adverse reactions, including laboratory abnormalities, were blood lactate dehydrogenase increased, blood creatine phosphokinase increased, aspartate aminotransferase increased, cholesterol high, lipase increased, amylase increased, pruritus, face edema, alanine aminotransferase increased, rash, creatinine increased, white blood cell decreased, neutrophil count decreased, fatigue, nausea, headache, peripheral edema and periorbital edema.

Table 3 summarizes the adverse reactions in MANEUVER during the double-blind part through Week 25.

Table 3: Adverse Reactions Occurring in ≥ 10% of Patients Receiving PIMJETMI with a Difference Between Arms of > 5% Compared to Placebo Through Week 25 in the MANEUVER Study*

	PIMJETMI N = 63		Placebo N = 31	
System organ class Adverse reaction#	**All Grades %**	**Grade 3 or 4 %**	**All Grades %**	**Grade 3 or 4 %**
Eye disorders				
Periorbital edema[a]	41.3	0	9.7	0
Gastrointestinal disorders				
Nausea	27.0	0	6.5	0
General disorders and administration site conditions				
Face edema	47.6	0	0	0
Fatigue[b]	36.5	0	22.6	0
Peripheral edema[c]	20.6	0	6.5	0
Nervous system disorders				
Headache[d]	22.2	0	6.5	0
Dizziness	15.9	0	3.2	0
Psychiatric disorders				
Insomnia	14.3%	0	6.5%	0
Skin and subcutaneous tissue disorders				
Pruritus	52.4	3.2	3.2	0
Rash[e]	47.6	6.3	9.7	0
Vascular disorders				
Hypertension[f]	19.0	9.5	6.5	0

*Excludes laboratory treatment-emergent abnormalities reported as adverse reactions
The severity of adverse reactions was assessed using CTCAE v5.0.
a. Periorbital edema (including periorbital edema, eyelid edema)
b. Fatigue (including fatigue, asthenia)
c. Peripheral edema (including edema peripheral, generalised edema, edema, swelling)
d. Headache (including headache, migraine)
e. Rash (including rash, rash maculo-papular, dermatitis, rash erythematous, rash macular, eczema, rash papulosquamous, intertrigo)
f. Hypertension (including hypertension, blood pressure increased)

8.3. Less Common Clinical Trial Adverse Reactions

Gastrointestinal disorders: vomiting (6.3%)

Metabolism and nutrition disorders: decreased appetite (9.5%)

Musculoskeletal and connective tissue disorders: myalgia (6.3%)

Skin and subcutaneous tissue disorders: dermatitis acneiform (6.3%); skin indentation (1.6%)

8.4. Abnormal Laboratory Findings: Hematologic, Clinical Chemistry, and Other Quantitative Data

Table 4 summarizes the laboratory treatment-emergent abnormalities in MANEUVER during the double-blind part through Week 25.

Table 4: Laboratory Abnormalities Worsening from Baseline in ≥ 10% of Patients Receiving PIMJETMI with a Difference Between Arms of > 5% Compared to Placebo Through Week 25 in the MANEUVER Study

	PIMJETMI N = 63		Placebo N = 31	
Laboratory Abnormality[a, #]	**All Grades %**	**Grade 3 or 4 %**	**All Grades %**	**Grade 3 or 4 %**
Chemistry				
Creatine phosphokinase increased[+]	96.8	15.9*	19.4	0
Blood lactate dehydrogenase increased[+]	95.2	0	6.5	0
Aspartate aminotransferase increased[+]	82.5	0	12.9	0
Lipase increased[+]	58.3	4.2	26.1	0
Cholesterol increased[b]	52.6	0	29.6	0
Serum amylase increased[+]	51.6	0	3.3	0
Alanine aminotransferase increased[+]	36.5	0	25.8	0
Creatinine increased[+]	25.4	0	0	0
Hematology				
White blood cell decreased	27.0	0	3.2	0
Neutrophil count decreased	20.6	1.6	0	0
Lymphocyte count decreased	14.3	0	3.2	0

+ Additional information on the respective adverse reaction is provided below

The severity of adverse reactions was assessed using CTCAE v5.0.

* Includes Grade 4 events

a The denominator used to calculate the rate varied from 48 to 63 for PIMJETMI and from 23 to 31 for Placebo based on the number of patients with a baseline value and at least one post-treatment value. Represents the incidence of laboratory findings, not of reported adverse reactions
b. Most patients with cholesterol increased had concurrent high-density lipoprotein (HDL) increased, suggesting that events of increased cholesterol may primarily be due to HDL increases

Elevation of certain serum enzymes

Elevation of serum enzymes (e.g., creatine phosphokinase [CPK], lactate dehydrogenase [LDH], liver transaminases [ALT, AST], lipase or amylase) have been reported for the CSF-1R inhibitor drug class, including PIMJETMI. These elevations were generally mild to moderate, asymptomatic, and reversible following treatment interruption or discontinuation. The majority of elevations occurred within 1 or 2 months of starting PIMJETMI treatment.

Increased creatinine

In MANEUVER study Part 1, a maximum mean increase in serum creatinine of 11.4 µmol/L was observed 5 weeks after initiation of treatment with PIMJETMI. The serum creatinine increases persisted throughout treatment and were reversible upon treatment completion. These increases in serum creatinine may not be associated with changes in renal function.

9. Drug Interactions

9.2. Drug Interactions Overview

PIMJETMI is a CYP3A substrate.

Concomitant use of a strong CYP3A inducer decreases PIMJETMI exposure, which may decrease the efficacy of PIMJETMI. Avoid concomitant use of PIMJETMI with strong CYP3A inducers.

Concomitant use of a strong or moderate CYP3A inhibitor increases PIMJETMI exposure, which may increase the risk of PIMJETMI adverse reactions. Avoid concomitant use of strong CYP3A inhibitors. Monitor patients for adverse reactions when used with strong or moderate CYP3A inhibitors and modify dose as recommended for adverse reactions.

PIMJETMI is an inhibitor of P-gp and increases the plasma concentration of P-gp substrate, which may increase the risk of adverse reactions associated with P-gp substrates with narrow therapeutic index. If concomitant use cannot be avoided, monitor for adverse reactions of substrate (see P-gp substrate product label).

9.3. Drug-Behaviour Interactions

The interaction of PIMJETMI with individual behavioural risks (e.g. cigarette smoking, cannabis use, and/or alcohol consumption) has not been studied.

9.4. Drug-Drug Interactions

The drugs listed in Table 5 are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction.

Table 5 – Established or Potential Drug-Drug Interactions

Proper/ common name	Source of evidence	Effect	Clinical comment
Strong CYP3A inhibitors (e.g., itraconazole)	CT	Co-administration of a strong CYP3A inhibitor (itraconazole) increased pimicotinib total exposure ($AUC_{0-\infty}$) by 57% and did not impact pimicotinib C_{max}, which may increase the risk of PIMJETMI adverse reactions (see 10. Clinical Pharmacology).	Avoid concomitant use of strong CYP3A inhibitors. If concomitant use cannot be avoided, monitor patients closely for adverse reactions and modify dose as recommended in Table 1 (see 4. Dosage and Administration).
Moderate CYP3A Inhibitors (e.g., fluconazole, erythromycin)	PBPK	Co-administration of a moderate CYP3A inhibitor (fluconazole or erythromycin) is predicted to increase pimicotinib systemic exposure (AUC ratios of ≤ 1.5-fold), which may increase the risk of PIMJETMI adverse reactions (see 10. Clinical Pharmacology)	Monitor patients for adverse reactions. Modify dose as recommended for adverse reactions in Table 1 (see 4. Dosage and Administration).
Strong CYP3A inducers (e.g., rifampin)	CT	Co-administration of a strong CYP3A inducer (rifampicin) decreased pimicotinib peak plasma concentration (C_{max}) by 28% and total exposure ($AUC_{0-\infty}$) by 69%, which may decrease the efficacy of PIMJETMI (see 10. Clinical Pharmacology).	Avoid concomitant use of strong CYP3A inducers.

Proper/ common name	Source of evidence	Effect	Clinical comment
P- glycoprotein (P-gp) Substrates with narrow therapeutic index (e.g., fexofenadine, digoxin)	CT	Co-administration of fexofenadine (P-gp substrate) led to increased systemic exposures of fexofenadine where C_{max} increased by 82% and $AUC_{0-\infty}$ increased by 57% (see 10. Clinical Pharmacology). Co-administration of P-gp substrates with narrow therapeutic index (e.g. digoxin) may increase the risk of substrate adverse reactions.	If concomitant use cannot be avoided, monitor for adverse reactions of substrate (see P-gp substrate product label).

CT = Clinical Trial; PBPK = Physiologically based pharmacokinetic modeling

Other Clinical studies and Model-Informed Approaches

CYP3A Inducers: Based on PBPK modeling, coadministration of efavirenz (moderate CYP3A inducer) decreased pimicotinib C_{max} by 22% and $AUC_{0-\infty}$ by 52%.

Acid-Reducing Agents: Co-administration of Omeprazole (proton pump inhibitor) delayed t_{max} by approximately 1 h and decreased C_{max} of pimicotinib by 42% while the total exposure of pimicotinib was not affected.

Effect of pimicotinib on MATE1 substrates: Coadministration of metformin (MATE1 substrate) led to increases in the systemic exposures of metformin where C_{max} increased by 29% and $AUC_{0-\infty}$ increased by 42%.

Effect of pimicotinib on BRCP substrates: Coadministration of rosuvastatin (BCRP substrate) led to increases in the systemic exposures of rosuvastatin where C_{max} increased by 45% and $AUC_{0-\infty}$ increased by 39%.

In-vitro studies

Effect of pimicotinib on CYP substrates: In vitro studies suggest pimicotinib is not likely to be a direct inhibitor of CYP3A, CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2C8 and CYP2D6 at clinically relevant concentrations. In vitro, pimicotinib demonstrated time-dependent inhibition (TDI) of CYP2C8 and TDI for CYP3A4/5 (however only for testosterone but not for midazolam as substrate). Based on additional in vitro investigations and PBPK modeling, this is not expected to result in clinically meaningful interactions with CYP2C8 or CYP3A4 substrates, respectively.

Pimicotinib is not likely to induce CYP3A, CYP1A2 and CYP2B6 at clinically relevant concentrations.

Effect of pimicotinib on substrates of transporters: In vitro studies suggest pimicotinib is not likely to

inhibit OATP1B1, OATP1B3, OAT1, OAT3, OCT2, and MATE2-K at clinically relevant concentrations.

Effect of transporters on pimicotinib: Based on in vitro studies, pimicotinib is not likely to be a substrate of P-gp, BCRP, OAT1, OAT3, OCT2, OATP1B1, OATP1B3, MATE1, or MATE2-K at clinically relevant concentrations.

Effect of Metabolites on CYP substrates: In vitro studies suggest M281 and M113 are not likely to inhibit CYP1A2, CYP2B6, CYP3A, CYP2C9, CYP2C19, CYP2C8 and CYP2D6 in both direct and TDI manner at clinically relevant concentrations. M281 has a low risk for clinically relevant CYP1A2 induction, while not likely to induce CYP3A and CYP2B6 at clinically relevant concentrations. M113 has no induction potential on CYP1A2, CYP2B6 and CYP3A4 enzymes at clinically relevant concentrations.

Effect of Metabolites on substrates of transporters: In vitro studies suggest that M281 is not likely to inhibit OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE2-K at clinically relevant concentrations. M281 shows a potential inhibition risk on MATE1 at clinically relevant concentrations. M113 is not likely to inhibit to OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1 and MATE2-K at clinically relevant concentrations.

9.5. Drug-Food Interactions

PIMJETMI may be taken with or without food (see 10. Clinical Pharmacology). Avoid coadministration of PIMJETMI with strong CYP3A inhibitors, including grapefruit or grapefruit juice (See 9.4 Drug-Drug Interactions).

9.6. Drug-Herb Interactions

Avoid coadministration of PIMJETMI with strong CYP3A inducers, including St. John's wort (See 9.4 Drug-Drug Interactions).

9.7. Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10. Clinical Pharmacology

10.1. Mechanism of Action

Pimicotinib is a small molecule tyrosine kinase inhibitor that inhibits colony stimulating factor 1 receptor (CSF-1R). In vitro, pimicotinib inhibited CSF-1R kinase activity and proliferation of cells expressing CSF-1R.

10.2. Pharmacodynamics

Effects on Non-classical monocytes, Colony-stimulating factor 1 and C-terminal telopeptide

Across the dose range of 25 mg to 100 mg, pimicotinib treatment led to a decrease in non- classical monocytes (NCMs) in the peripheral blood and an increase in colony-stimulating factor 1 (CSF-1) levels in the plasma of patients with solid tumours. Maximum decrease of NCM was observed at a dose of 25 mg once daily and higher, and treatment-related changes in CSF-1 concentrations were saturated at 50

mg. In patients with TGCT, those given pimicotinib 50 mg once daily exhibited more pronounced changes in CSF-1 and C-terminal telopeptide (CTx) compared to those given 25 mg once daily.

Cardiac Electrophysiology

The effect of pimicotinib on the QTc interval was analyzed in 32 patients who received multiple doses ranging from 25 mg to 75 mg once daily with matching PK and QTcF samples from the multicentered, open-label, uncontrolled Phase 1 study using a linear mixed-effects modeling approach. At an exposure of 1.29-fold of the mean steady state C_{max} of the recommended dose (50 mg once daily), a mean increase in the QTc interval of > 20 msec is unlikely.

Exposure-Response Relationships

Higher pimicotinib exposure is associated with an increased risk of amylase increase, increased AST, face edema, pruritus, periorbital edema, any TEAE leading to dose reduction/dose interruption, and time to first Grade ≥ 3 CPK increased.

The probability of response (objective response rate [ORR] by blinded independent review committee (BIRC) per Response Evaluation Criteria in Solid Tumors (RECIST)) increased with increasing pimicotinib exposure.

10.3. Pharmacokinetics

Over the dose range from 25 to 75 mg, pimicotinib steady state exposure increased approximately dose proportionally. Steady state was achieved within 15 days of once daily dosing. The geometric mean steady-state accumulation ratio based on AUC_{tau} was 3.43 after 50 mg once daily.

Table 6 – Summary of pimicotinib pharmacokinetic parameters in TGCT patients

	$C_{max,ss}$	T_{max}	$t_{½}$ (h)	$AUC_{24,ss}$	CL/F	$V_{central}/F$
Steady State Mean (50 mg once daily)	577 (24.8) ng/mL[a]	0.93 h (0.45, 3.50)[b]	47.8 h (31.0)[b]	6990 (28.8) h*ng/mL[a]	7.97 L/h (2.83)[c]	110 L (3.87)[c]

[a] Values (derived from popPK analysis estimates/simulations) are given as GeoMean (geoCV%), %CV=percent coefficient
[b] $T_{max,ss}$ is given as median (minimum, maximum) values, $t_{1/2}$ is given as GeoMean (geoCV%)
[c] Parameter estimates of the final pimicotinib plasma PK model given as values (%RSE)

Absorption

Pimicotinib median time to achieve C_{max} was approximately 1 hour following a single dose of pimicotinib 50 mg.

Following a high-fat, high calorie meal in healthy subjects, pimicotinib AUC_T was not affected and C_{max} decreased by approximately 60% as compared to fasted conditions. The t_{max} was delayed by approximately 4 hours. These differences were not clinically relevant.

Distribution

Human plasma protein binding of pimicotinib is 95.4%. The apparent volume of distribution after a single 50 mg dose is 730 L.

Metabolism

The metabolic pathways of pimicotinib include hydrolysis, oxidation, dehydrogenation, demethylation, O-dealkylation, glucuronidation, and sulfation. Hydrolysis reactions mediated by human carboxylesterase 1 (CES1) were identified as the primary routes of metabolism accounting for 63.25% of the drug's elimination. Oxidation reactions accounted for 20.51% of the drug's elimination. Oxidative metabolism occurred mainly via CYP3A4. Two major circulating pharmacologically inactive metabolites (M281 and M113) were identified.

Elimination

Following single doses of 25 mg to 100 mg the apparent clearance of pimicotinib was low. After a single 50 mg dose, geometric mean CL/F is 11.6 L/h (CV%: 52.7). The geometric mean terminal half-life ($t_{1/2}$) after a single 50 mg dose is 43.6 hours (CV%: 33.5). Following a single radiolabeled dose of pimicotinib 50 mg to healthy participants, 57.6% of the dose was recovered in urine (0.06% unchanged) and 37.9% in feces (0.15% unchanged).

Special populations and conditions

- **Age**

  No clinically meaningful differences in the pharmacokinetics of pimicotinib was observed based on age (18 to 82 years) from the population pharmacokinetic analysis.

- **Sex**

  No clinically meaningful differences in the pharmacokinetics of pimicotinib was observed based on sex from the population pharmacokinetic analysis.

- **Ethnic origin**

  No clinically meaningful differences in the pharmacokinetics of pimicotinib was observed based on race (Asian, Black, White/Other) and region (China or rest of the world) from the population pharmacokinetic analysis.

- **Hepatic Insufficiency**

  In a dedicated hepatic impairment study, pimicotinib exposure was evaluated in participants with varying degrees of liver function given a single 25 mg dose. Pimicotinib exposure ($AUC_{0-\infty}$) increased by 45% (unbound $AUC_{0-\infty}$ increased by 84%) in participants with moderate hepatic impairment (n=8) (Child-Pugh class B) compared to participants with normal liver function (n=8). Similar results were observed when classifying patients using the NCI-ODWG criteria in participants with moderate hepatic impairment (n=8; total bilirubin > 1.5 to 3 x ULN, with any AST) and normal liver function (n=15). Pimicotinib exposure is comparable in patients with mild hepatic impairment (n=8; Child-Pugh class A) compared to participants with normal liver function (n=8). Reduce the PIMJETMI starting dosage to 25 mg once daily for patients with moderate (Child-Pugh class B) hepatic impairment. Monitor for adverse reactions and further modify dose as recommended in Table 1. No dosage adjustment is recommended for patients with mild hepatic impairment (Child-Pugh class A) (see 4. Dosage and Administration; 4.2 Recommended Dose and Dosage Adjustment Hepatic Impairment).

  Hepatic impairment was also tested as a covariate in the population pharmacokinetic model. Twenty-seven (8.8%) patients had mild (NCI-ODWG classification; total bilirubin ≤upper limit of normal [ULN] with AST > ULN or total bilirubin > 1 to 1.5 × ULN with any AST) hepatic

impairment. Population pharmacokinetic modeling indicated similar pimicotinib exposure between patients with mild hepatic impairment and patients with normal liver function.

Pimicotinib has not been studied in patients with severe hepatic impairment (total bilirubin >3 to 10 × ULN and any AST or Child-Pugh class C).

- **Renal Insufficiency**

  Renal clearance of pimicotinib is negligible and renal impairment is not expected to have a relevant effect on the pharmacokinetics of pimicotinib. No formal pharmacokinetic study has been conducted. Based on population pharmacokinetic analysis no clinically relevant pharmacokinetic difference was observed in subjects with mild (n=57) and moderate (n=17) renal impairment (CRCL between 30 and 89 mL/min).

  Pimicotinib has not been studied in patients with severe renal impairment (CRCL < 30 mL/min).

- **Body Weight**

  In the population pharmacokinetic analysis, baseline body weight was included in the base model as a mechanistic covariate. Patients with body weight corresponding to the 5^{th} and 95^{th} percentiles (48 kg and 94 kg, respectively) had approximately 26% higher and 24% lower $C_{avg,ss}$ relative to a patient with median body weight (65 kg). Similarly, participants with body weight corresponding to the 5^{th} and 95^{th} percentiles had approximately 30% higher and 27% lower $C_{max,ss}$ relative to a patient with median body weight. The differences in pimicotinib exposure ($C_{avg,ss}$ and $C_{max,ss}$) are not clinically relevant.

11. Storage, Stability, and Disposal

Store PIMJETMI at room temperature (15°C to 30°C). Store in the original package to protect from moisture. Do not discard the desiccant.

Part 2: Scientific Information

13. Pharmaceutical Information

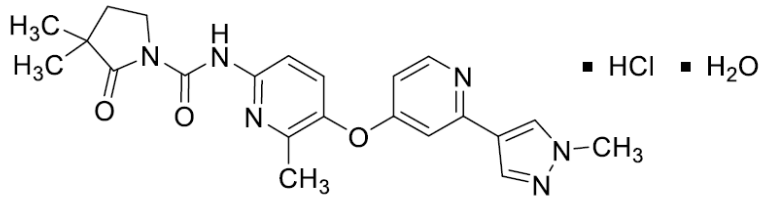
Drug Substance

Non-proprietary name of the drug substance(s): pimicotinib hydrochloride

Chemical name: 3,3-dimethyl-N-(6-methyl-5-{[2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl]oxy}pyridin-2-yl)-2-oxopyrrolidine-1-carboxamide hydrochloride hydrate

Molecular formula and molecular mass: $C_{22}H_{24}N_6O_3 \bullet HCl \bullet H_2O$
474.94 g/mol (pimicotinib hydrochloride monohydrate)
420.47 g/mol (pimicotinib)

Structural formula:



Physicochemical properties: The solubility of pimicotinib hydrochloride in aqueous solutions and bio-relevant media decreases with increasing pH. The pKa was determined to be 5.0 (base). Pimicotinib hydrochloride is freely soluble in ethanol and practically insoluble or insoluble in water.

Product Characteristics:

Pimicotinib is a kinase inhibitor for oral use.

14. Clinical Trials

14.1. Clinical Trials by Indication

Tenosynovial Giant Cell Tumour (TGCT)

Table 7 – Summary of Patient Demographics for Clinical Study ABSK021-301 in TGCT

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Age (range)	Sex
ABSK021-301 (MANEUVER)	Phase 3, double-blind, randomized, placebo-controlled international multicentre study in patients with TGCT	Part 1: 50 mg orally once daily or placebo for 24 weeks; Part 2 (open-label): 50 mg orally once daily for 24 weeks	Part 1: PIMJETMI: n=63; placebo: n=31 Part 2: PIMJETMI: n=83 (received blinded PIMJETMI [n=52] or blinded placebo [n=31] in Part 1 before their first dose of PIMJETMI in Part 2)	18-69 years	Female: 68.1% Male: 31.9%

The efficacy of PIMJETMI was evaluated in MANEUVER, a double-blind, randomized, placebo-controlled, international, multicentre, Phase 3 clinical study in adult patients with symptomatic (at least moderate pain and/or moderate stiffness), unresectable TGCT (i.e., surgical resection may cause dysfunction or serious complications and/or complete resection was not possible based on location in a complex anatomical site and extensive invasion). Eligible patients had a histologically confirmed diagnosis of TGCT with measurable disease as per Response Evaluation Criteria in Solid Tumors (RECIST v1.1), with at least one lesion with a minimum size of two centimetres. Patients with known metastatic disease were excluded.

Patients were randomized in a 2:1 ratio to PIMJETMI or a matching placebo. Randomization was stratified by geographic region (China versus non-China). Patients received PIMJETMI 50 mg once daily or placebo until completion of treatment administration at Week 24 and completion of the Week 25 follow-up visit including magnetic resonance imaging, or until their withdrawal from study. After completion of the double-blind, randomized part of the study, patients who continued to meet eligibility criteria were offered to continue at their current dose or start treatment with PIMJETMI 50 mg once daily in the open-label treatment phase of the study.

The primary efficacy endpoint was the objective response rate (ORR), evaluated by a blinded independent review committee (BIRC) at Week 25, based on RECIST v1.1 criteria (i.e., the proportion of patients who achieved the best overall response of either complete response or partial response within 25 weeks). Key secondary efficacy endpoints at Week 25 were ORR evaluated by BIRC using the tumour volume score (TVS); mean change from baseline in the active range of motion (ROM) (presented as

relative ROM) of the affected joint, according to the reference criteria for the same joint; and mean change from baseline in patient reported outcome measures including Worst Stiffness Numeric Rating Scale (NRS) score, the Brief Pain Inventory (BPI) Worst Pain NRS score, and the Patient-reported Outcomes Measurement Information System Physical Functioning (PROMIS-PF) Short Form. Other secondary efficacy endpoints at Week 25 included the duration of response (DOR) evaluated by BIRC based on RECIST v1.1.

In the MANEUVER study, TVS was defined as the estimated volume of the maximally distended synovial cavity or tendon sheath involved, measured in 10% increments. The range of motion was measured as a percentage of the normal reference range for the affected joint. Clinical assessors performed these range of motion assessments using a goniometer. Stiffness NRS, Pain NRS, and PROMIS-PF are patient-reported outcomes (PROs) collected through fixed questionnaires every 4 weeks. The content of the PROMIS-PF questionnaire was selected based on whether the affected joint was located in the upper or lower limbs.

A total of 94 patients were randomized to either PIMJETMI (N=63) or placebo (N=31); 88.3% (83/94) of the patients entered the open-label treatment phase of the study, including 52 from the PIMJETMI group and 31 from the placebo group, and 82 received treatment with PIMJETMI.

The median age was 40.0 years (range: 18-69), with 7.4% of patients aged ≥ 65 years; 51.1% were Asian, 39.4% were White, 5.3% were Black or African American, and 4.3% selected Other. A total of 47.9% were enrolled in China, with the remainer enrolled in Europe, the United States, and Canada (29.8%, 11.7%, and 10.6%, respectively). Baseline disease characteristics included 85.1% with diffuse TGCT, 11.7% with localized TGCT; 59.6% with prior surgery and 6.4% who had previously been treated with systemic therapy. Disease locations were the knee (50%), ankle (14.9%), hip (13.8%), foot (8.5%), wrist (7.4%), and other (5.3%). The Eastern Cooperative Oncology Group Performance Status was 0 and 1 in 35.1% and 64.9% of patients, respectively.

MANEUVER demonstrated a statistically significant improvement in ORR and all key secondary endpoints in patients randomized to PIMJETMI compared with placebo.

Efficacy results are summarized in Table 8.

Table 8 – Results of Efficacy Endpoints at Week 25 in the MANEUVER Study

	PIMJETMI (N = 63)	Placebo (N = 31)
Primary endpoint		
Overall response rate[a,b,c] (ORR) by BIRC per RECIST v1.1		
ORR, n (%)	34 (54.0)	1 (3.2)
(95% CI)	(40.9, 66.6)	(0.1, 16.7)
Complete response	1 (1.6)	0
Partial response	33 (52.4)	1 (3.2)
p-value	< 0.0001	
Key secondary endpoints[c]		
ORR by BIRC per tumour volume score (TVS)[a,b]		
ORR, n (%)	39 (61.9)	1 (3.2)
(95% CI)	(48.8, 73.9)	(0.1, 16.7)
Complete response	1 (1.6)	0
Partial response	38 (60.3)	1 (3.2)
p-value	< 0.0001	
Range of Motion (ROM) (%)[d]		
Patients with data at baseline and Week 25, n	56	28
at baseline, mean (SD)	70.60 (20.748)	66.07 (21.757)
at Week 25, mean (SD)	84.94 (21.355)	67.55 (23.587)
Change from baseline, LS mean (95% CI)[e]	15.64 (10.3, 20.91)	-0.07 (-7.02, 6.88)
Difference from placebo (95% CI)	15.72 (7.33, 24.10)	
p-value	0.0003	
Worst Stiffness NRS[f]		
Patients with data at baseline and Week 25, n	56	29
at baseline, mean (SD)	5.28 (1.906)	5.59 (1.700)
at Week 25, mean (SD)	2.33 (1.801)	4.78 (2.256)
Change from baseline, LS mean (95% CI)[g]	-3.00 (-3.46, -2.55)	-0.57 (-1.21, 0.07)
Difference from placebo (95% CI)	-2.44 (-3.22, -1.65)	
p-value	< 0.0001	
BPI Worst Pain NRS[h]		
Patients with data at baseline and Week 25, n	56	29
at baseline, mean (SD)	4.76 (2.148)	4.75 (2.562)
at Week 25, mean (SD)	2.50 (1.889)	4.40 (2.484)
Change from baseline, LS mean (95% CI)	-2.32 (-2.73, -1.91)	-0.23 (-0.80, 0.34)
Difference from placebo (95% CI)[i]	-2.09 (-2.79, -1.39)	
p-value	< 0.0001	
PROMIS Physical Function T-Score[j]		
Patients with data at baseline and Week 25, n	57	29
at baseline, mean (SD)	41.20 (7.122)	39.75 (5.994)

	PIMJETMI (N = 63)	Placebo (N = 31)
at Week 25, mean (SD)	46.55 (7.848)	42.63 (7.757)
Change from baseline, LS mean (95% CI)	5.63 (4.21, 7.06)	2.23 (0.23, 4.24)
Difference from placebo (95% CI)[k]	3.40 (0.94, 5.86)	
p-value	0.0074	

NR – not reached; NA – not applicable; BPI - Brief Pain Inventory; CI - confidence interval; LS - least squares; MMRM - mixed model for repeated measures; N - number of patients in treatment group in analysis set and denominators for all percentages; n - number of patients in analysis with data available; NRS - numerical rating scale; PROMIS-PF - Patient-reported Outcomes Measurement Information System- Physical Function; ROM - range of motion; SD – standard deviation.

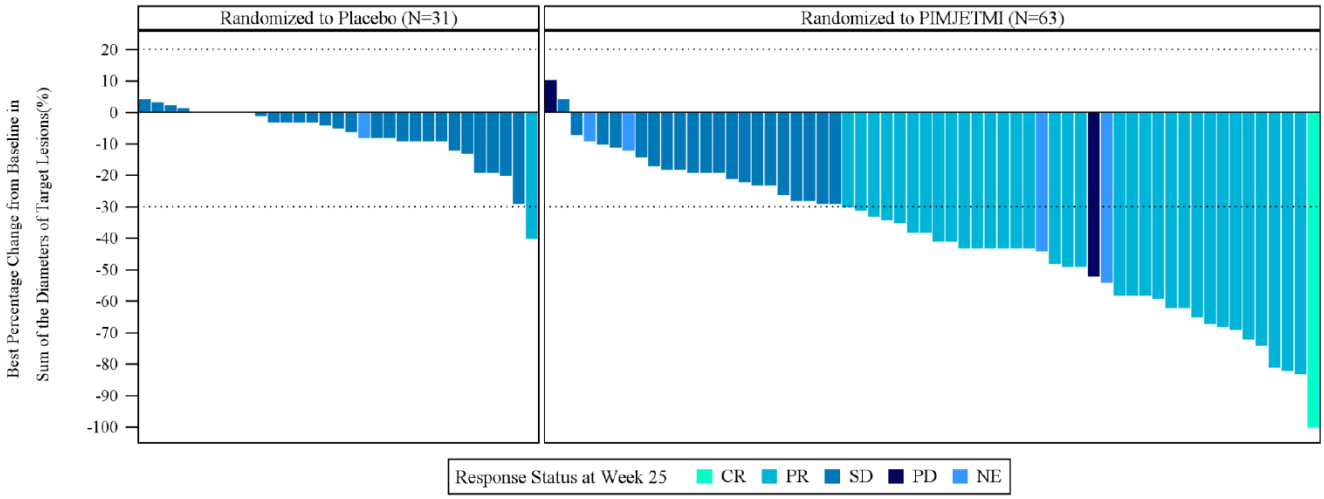
a Assessed by a blinded independent review committee.
b Estimate using Kaplan-Meier method.
c A hierarchical gatekeeping testing procedure was applied to first test the treatment effect on the primary endpoint followed by all five key secondary endpoints.
d Active ROM was normalized to the American Medical Association reference standard.
e Estimated using MMRM with fixed effects for treatment, baseline, visit, stratification-factor of China vs. non-China sites, and treatment-by-visit interaction, baseline-by-visit interaction, joint-type-category (knee, ankle and others). An unstructured variance-covariance matrix is used.
f Measured by Worst Stiffness Numeric Rating Scale (NRS), based on a scale of 0 to 10. Low number on scale indicates less stiffness.
g Estimated using MMRM with fixed effects for treatment, baseline, visit, stratification-factor of China vs. non-China sites, and treatment-by-visit interaction, baseline-by-visit interaction. An unstructured variance-covariance matrix is used
h Measured by BPI Worst Pain Numeric Rating Scale (NRS), based on a scale of 0 to 10. Low number on scale indicates less pain.
i Estimated using MMRM with fixed effects for treatment, baseline, visit, stratification-factor of China vs. non-China sites, and treatment-by-visit interaction, baseline-by-visit interaction. An unstructured variance-covariance matrix is used.
j Measured by PROMIS-PF T-score (15-Item score; ranges from 0-100); higher scores of PROMIS-PF indicate better physical functioning; data for PROMIS-PF are largely based on lower limb extremity assessment due to tumour location as described above.
k Estimated using MMRM with fixed effects for treatment arm, visit, baseline, region, treatment by visit interaction, baseline by visit interaction based on pre-specified model in SAP.

With an additional 6 months of follow-up from the time of the primary analysis of ORR at Week 25 and a median duration of treatment of 14.2 months (range 1.8 to 22.5 months), the median DOR (based on the number of patients with complete response or partial response in Part 1 per RECIST v1.1 [N=38]) was not reached and ranged from 0.03 to 19.81 months (both censored observations).

PIMJETMI showed response onset at Week 13 with an ORR by BIRC per RECIST v1.1 of 41.3% (95% CI: 29.0, 54.4).

Figure 1 shows the best percentage change from baseline in the sum of the diameters of target lesions at Week 25 in the Intent-to-treat (ITT) Analysis Set.

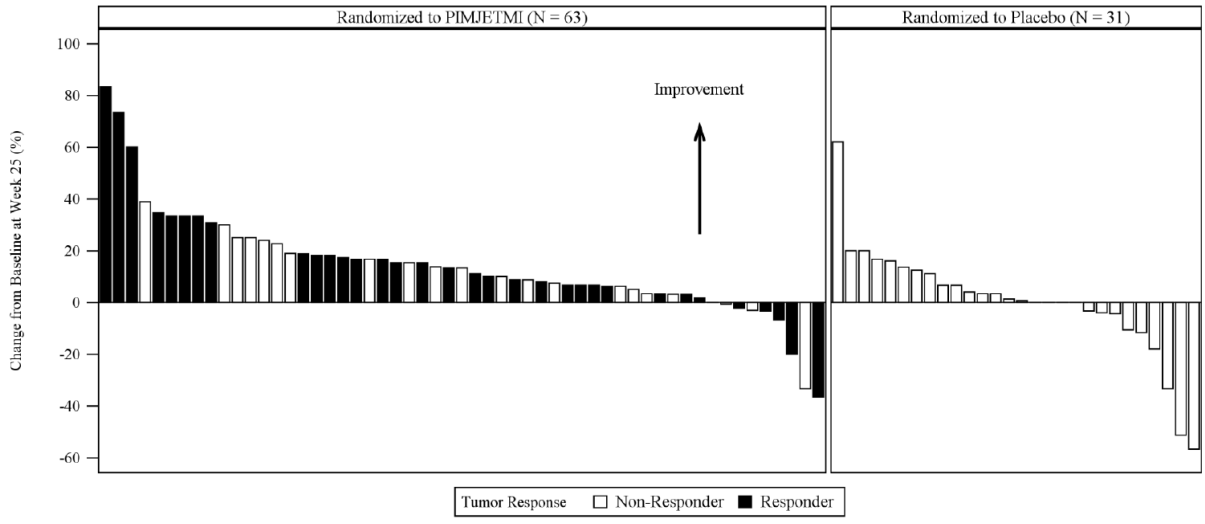
Figure 1 – Best Percentage Change from Baseline in the Sum of the Diameters of Target Lesions (by BIRC based on RECIST v1.1) at Week 25 for MANEUVER (ITT Analysis Set)



CR = complete response; N = number of patients in treatment group in analysis set; NE= not evaluable; PD = progressive disease; PR = partial response; SD = stable disease

Figure 2 shows the change from baseline in active range of motion for each patient at Week 25.

Figure 2 – Change from Baseline (%) in Active Range of Motion at Week 25 by BIRC ORR Response Status (based on RECIST v1.1) and Treatment Group for MANEUVER (ITT Analysis Set)



N = number of patients in treatment group in analysis set
Note: Range of Motion was measured as a percentage of the standard full range of motion for the affected joint.

16. Non-Clinical Toxicology

General toxicology

In the 26-week rat repeat-dose study, pimicotinib-related mortality was noted at ≥3 mg/kg/day (6.8-fold human exposure at the recommended dose based on AUC) with histopathology findings of minimal to severe glomerulonephritis. Glomerulonephritis was also observed at 1 mg/kg/day (2.3-fold human exposure at the recommended dose based on AUC) along with myxomatous changes in the skin and tongue and vascular inflammation. Bone changes, including increased bone thickness and increased trabecular bone that correlated with decreased systemic calcium and phosphate levels were reported at ≥ 3 mg/kg/day, along with tooth abnormalities. The findings were fully or partially reversed after a 4-week recovery except for glomerulonephritis. The no-observed-adverse-effect level (NOAEL) was not established in this study.

In the 39-week monkey repeat-dose study, there were no pimicotinib related deaths at up to 5 mg/kg/day (1.4-fold human exposure at the recommended dose based on AUC). In other studies in monkeys, deaths were reported at exposures ≥ 19-fold human exposure at the recommended dose based on AUC. Significant increases in liver enzymes (ALT and AST) and creatine kinase (CK) without correlated microscopic findings were observed at 5 mg/kg/day. One animal at that dose had vascular inflammation and multifocal mineralization at the end of the recovery phase, which was likely pimicotinib-related. The NOAEL was 1.5 mg/kg/day (0.3-fold human exposure at the recommended dose based on AUC).

Genotoxicity

Pimicotinib and its major human circulating metabolites, M281 and M113 were not mutagenic in the bacterial reverse mutation test (Ames) or clastogenic in the in vitro chromosomal aberrations assay. Pimicotinib and M113 were not clastogenic or aneugenic in vivo.

Carcinogenicity

Pimicotinib was not carcinogenic in a 6-month rasH2-Tg mice study at oral dose up to 40 mg/kg/day, resulting in exposure approximately 50-fold human exposure at the recommended dose based on AUC.

Reproductive and developmental toxicology

A fertility and early embryonic development study was conducted in rats at oral pimicotinib doses of 5, 10, or 20 mg/kg/day. Male rats were dosed 9 weeks prior to mating and throughout mating to termination and female rats were dosed 2 weeks prior to mating and continued throughout mating to gestation day 7. No effects on fertility or reproductive capacities were observed in male or female rats at up to20 mg/kg/day (> 37-fold human exposure at the recommended dose based on AUC). However, small in magnitude, non-adverse, non-statistically significant effects on sperm, testis, and epididymis were noted.

In a 26-week rat repeat-dose toxicity study, adverse effects on the testis and epididymis were observed at ≥ 3 mg/kg/day (6.8-fold of human exposure at the recommended dose based on AUC), attributed to the presence of spermatic granulomas.

In embryo-fetal development studies, pimicotinib was orally administered to rats and rabbits during the period of organogenesis. In rats, external malformation and subcutaneous edema were observed at 10 mg/kg/day (18.4-fold human exposure at the recommended dose based on AUC). In rabbits, administration of pimicotinib resulted in development retardation (including decreased fetal weight and crown-rump length and increased visceral variation) at 20 mg/kg/day (14.7-fold human exposure at

the recommended dose based on AUC) and external and/or visceral malformation were observed at ≥ 5 mg/kg/day (3.3-fold human exposure at the recommended dose based on AUC).

In a pre-and post-natal developmental study in rats, pimicotinib was orally administered to pregnant rats during organogenesis, parturition and lactation. Developmental retardation (delays in tooth eruption, testes descent, preputial separation, and vaginal opening) and pup deaths were observed at ≥ 1 mg/kg/day (0.8-fold human exposure at the recommended dose based on AUC). Mortality of dams was noted at ≥ 1 mg/kg/day, of which the dams at 1 mg/kg/day were terminated early due to pup deaths.

Pimicotinib was detected in pups at low levels on post-natal days 4 and 21. The presence of pimicotinib in maternal milk was not measured, but the presence of pimicotinib in pups suggests prolonged persistence of pimicotinib in pups and/or presence of pimicotinib in maternal milk.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr] PIMJETMI®

Pimicotinib capsules

This Patient Medication Information is written for the person who will be taking PIMJETMI. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about PIMJETMI, talk to a healthcare professional.

What PIMJETMI is used for:

PIMJETMI is used to treat adults with symptoms of a joint disease called tenosynovial giant cell tumour (TGCT). PIMJETMI is used when removing TGCT by surgery may make your symptoms worse or cause other severe health problems.

How PIMJETMI works:

PIMJETMI works by blocking the activity of certain proteins that are involved in the growth of TGCTs.

The ingredients in PIMJETMI are:

Medicinal ingredient(s): pimicotinib hydrochloride

Non-medicinal ingredients: Black iron oxide, colloidal silicon dioxide, croscarmellose sodium, gelatin, lactose monohydrate, magnesium stearate, microcrystalline cellulose, potassium hydroxide, shellac, and titanium dioxide.

PIMJETMI comes in the following dosage form(s):

Capsules: 25 mg of pimicotinib (as pimicotinib hydrochloride)

Do not use PIMJETMI if:

- you are allergic (hypersensitive) to pimicotinib or any of the other ingredients of PIMJETMI or the container.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take PIMJETMI. Talk about any health conditions or problems you may have, including if you:

- have or had liver problems

Other warnings you should know about:

Family Planning
Female Patients: Pregnancy and Breastfeeding:

- If you are pregnant, able to get pregnant or think you are pregnant, there are specific risks you should discuss with your healthcare professional.
- Do not take PIMJETMI if you are pregnant or are planning to become pregnant. PIMJETMI may harm your unborn baby.
- If you are able to get pregnant:

    - Your healthcare professional will do a pregnancy test before you start treatment with PIMJETMI. This is to ensure that you are not pregnant.
- Use effective birth control (contraception) during treatment and for 2 weeks after you stop taking PIMJETMI.
- Tell your healthcare professional right away if you become pregnant, you think you may be pregnant, or wish to become pregnant during treatment with PIMJETMI.
- Do not breastfeed your baby while you are taking PIMJETMI and for 2 weeks after you stop taking it.

Male patients:

- If you are able to father a child, there are specific risks you should discuss with your healthcare professional.
- Male patients, including males with a vasectomy (permanent birth control):
    - Use effective birth control (contraception) during treatment and for 2 weeks after you stop taking PIMJETMI.
- Tell your healthcare provider right away if your female partner becomes pregnant or thinks she may be pregnant during treatment with PIMJETMI.
- PIMJETMI may affect your ability to father a child.

Your healthcare professional should provide you with patient educational materials for pregnancy and family planning. These are available on EMD Serono's website https://www.emdserono.ca/ca-en/products.html or by calling EMD Serono at 1-888-737-6668.

Driving and using machines: PIMJETMI can cause fatigue and dizziness. If you have these symptoms, be careful when driving or using machines.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with PIMJETMI:

- medicines to treat fungal infections such as itraconazole, fluconazole;
- medicines to treat bacterial infections such as rifampin, erythromycin;
- digoxin, a medicine used to treat heart problems;
- fexofenadine, a medicine used to treat allergy symptoms;
- grapefruit juice;
- St. John's Wort, an herbal product primarily used to treat depression.

How to take PIMJETMI:

- Take PIMJETMI exactly as your healthcare professional tells you to take it. Check with your healthcare professional if you are not sure.
- Do NOT change your dose or stop taking it unless your healthcare professional tells you to.
- Take PIMJETMI capsules, with or without food, at the same time each day.
- Swallow PIMJETMI capsules whole with a glass of water. Do not open, break, dissolve, or chew the capsules.

Usual dose:

- **Adults:** 50 mg (two 25 mg capsules) by mouth once a day.

Overdose:

If you think you, or a person you are caring for, have taken too much PIMJETMI, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:

If you missed a dose of this medication, take it as soon as you remember. But if it is almost time for your next dose, skip the missed dose and continue with your next scheduled dose. Go back to the regular dosing schedule. Do not take two doses at the same time to make up a missed dose.

If you vomit after taking a dose of PIMJETMI, take the next dose at its scheduled time.

Possible side effects from using PIMJETMI:

These are not all the possible side effects you may have when taking PIMJETMI. If you experience any side effects not listed here, tell your healthcare professional.

Common side effects of PIMJETMI are:

- itching (pruritus)
- rash
- acne-like bumps on your skin
- skin indents or pitting
- swelling: face, around your eyes, hands and feet
- tiredness, trouble sleeping
- nausea, vomiting
- headache
- dizziness
- decreased appetite
- muscle pain
- change in certain blood tests

PIMJETMI can cause abnormal blood test results. Your healthcare professional will do blood tests to check your liver and do other blood tests before, during and after treatment with PIMJETMI as needed.

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Get immediate medical help
	Only if severe	In all cases	
Very common			
Hypertension (high blood pressure): shortness of breath, fatigue, dizziness or fainting, chest pain or pressure, blurred vision, racing pulse or heart palpitations		X	

Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store PIMJETMI at room temperature (15°C to 30°C).
- Store in the original package to protect from moisture. Do not discard the desiccant.
- Keep out of reach and sight of children.

If you want more information about PIMJETMI:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (Drug Product Database: Access the database); EMD Serono's website (http://www.emdserono.ca); or by calling EMD Serono at 1-888-737-6668.

This leaflet was prepared by EMD Serono, a Division of EMD Inc., Canada. EMD Serono is the healthcare business of Merck KGaA, Darmstadt, Germany in Canada.

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