NEW ZEALAND DATA SHEET

1. PRODUCT NAME

ITOVEBI® inavolisib 3 mg film-coated tablet
ITOVEBI® inavolisib 9 mg film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ITOVEBI inavolisib 3 mg
ITOVEBI inavolisib 9 mg

Excipients with known effect: Lactose.

For the full list of excipients, see section *6.1 List of excipients.*

3. PHARMACEUTICAL FORM

ITOVEBI inavolisib 3 mg film-coated tablet is red and round convex-shaped with an "INA 3" debossing on one side. Each 3 mg film-coated tablet contains 3 mg inavolisib.

ITOVEBI inavolisib 9 mg film-coated tablet is pink and oval-shaped with an "INA 9" debossing on one side. Each 9 mg film-coated tablet contains 9 mg inavolisib.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ITOVEBI 3 mg and 9 mg film coated tablets, in combination with palbociclib and endocrine therapy, are indicated for the treatment of adult patients with *PIK3CA*-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, following recurrence on or after adjuvant therapy or progression on an endocrine-based regimen in the metastatic setting.

4.2 Dose and method of administration

General

Patients with HR-positive, HER2-negative, locally advanced or metastatic breast cancer should be selected for treatment with ITOVEBI based on the presence of one or more *PIK3CA* mutations using a validated assay. *PIK3CA* mutation status should be established prior to initiation of ITOVEBI therapy.

Dose Recommendation

The recommended dose of ITOVEBI is 9 mg taken orally once daily with or without food.

ITOVEBI should be administered in combination with palbociclib and endocrine therapy. The recommended dose of palbociclib is 125 mg taken orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days. The endocrine therapy being used should be administered according to the recommended dose in the prescribing information. Refer to the prescribing information for palbociclib and the endocrine therapy being used for complete dosing information.

Treatment of pre/perimenopausal women with ITOVEBI should also include a luteinizing hormone-releasing hormone (LHRH) agonist in accordance with local clinical practice.

For male patients, consider treatment with an LHRH agonist according to local clinical practice.

Duration of Treatment

It is recommended that patients are treated with ITOVEBI until disease progression or unacceptable toxicity.

Delayed or Missing Doses

Patients should be encouraged to take their dose at approximately the same time each day. If a dose of ITOVEBI is missed, it can be taken within 9 hours after the time it is usually taken. After more than 9 hours, the dose should be skipped for that day. On the next day, ITOVEBI should be taken at the usual time. If the patient vomits after taking the ITOVEBI dose, the patient should not take an additional dose on that day and should resume the usual dosing schedule the next day at the usual time.

Dose Modification

Management of adverse reactions may require temporary interruption, dose reduction, or discontinuation of treatment with ITOVEBI.

The recommended dose reduction guidelines for adverse reactions are listed in Table 1.

Table 1 Dose Reduction Guidelines for Adverse Reactions

Dose Reduction Schedule	Dose Modified
Starting dose	9 mg daily
First dose reduction	6 mg daily
Second dose reduction	3 mg daily [a]
[a] Itovebi treatment should be permanently discontinued if patients are unable to tolerate the 3 mg daily dose.	

The dose of ITOVEBI may be re-escalated to a maximum daily dose of 9 mg based on clinical evaluation of the patient by the treating physician.

Hyperglycaemia

Before initiating treatment with ITOVEBI, fasting plasma glucose (FPG)/blood glucose (FBG) and HbA_{1C} levels should be tested, and plasma/blood glucose levels should be optimised in all patients. Evaluate patients for renal impairment prior to treatment with Itovebi (see section 4.2 Dose and method of administration-Renal Impairment and section 5.2 Pharmacokinetic Properties). After initiating treatment with ITOVEBI, patient fasting glucose (FPG or FBG) levels should be monitored or self-monitored based on the recommended schedule (see *section 4.4 Special warnings and precautions for use - General).*

Table 2 Dose Modification and Management for Hyperglycaemia

Fasting Glucose Levels[a]	Recommendation[b]
> ULN to 8.9 mmol/L	• No adjustment of ITOVEBI required.

Fasting Glucose Levels[a]	Recommendation[b]
	• Consider dietary modifications (e.g., low carbohydrate diet) and ensure adequate hydration. • Consider initiating or intensifying oral anti-hyperglycaemic medications[c] for patients with risk factors for hyperglycaemia[d].
> 8.9 – 13.9 mmol/L	• Interrupt ITOVEBI until fasting glucose level decreases to ≤ 160 mg/dL (≤ 8.9 mmol/L). • Initiate or intensify anti-hyperglycaemic medication[c,e]. • Resume ITOVEBI at the same dose level. • If fasting glucose level persists > 200 – 250 mg/dL (> 11.1 – 13.9 mmol/L) for 7 days under appropriate anti-hyperglycaemic treatment, consultation with a healthcare professional experienced in the treatment of hyperglycaemia is recommended.
> 13.9 – 27.8 mmol/L	• Interrupt ITOVEBI. • Initiate or intensify anti-hyperglycaemic medication[c,e]. • Administer appropriate hydration if required. • If fasting glucose level decreases to ≤ 8.9 mmol/L within 7 days, resume ITOVEBI at the same dose level. • If fasting glucose level decreases to ≤ 8.9 mmol/L in ≥ 8 days, resume ITOVEBI at one lower dose level (see Table 1). • If fasting glucose level > 13.9 – 27.8 mmol/L recurs within 30 days, interrupt ITOVEBI until fasting glucose level decreases to ≤ 8.9 mmol/L. Resume ITOVEBI at one lower dose level (see Table 1).
> 27.8 mmol/L	• Interrupt ITOVEBI. • Initiate or intensify anti-hyperglycaemic medication[c,e]. • Assess for volume depletion and ketosis and administer appropriate hydration. • If fasting glucose level decreases to ≤ 160 mg/dL (≤ 8.9 mmol/L), resume ITOVEBI at one lower dose level (see Table 1). • If fasting glucose level > 27.8 mmol/L recurs within 30 days, permanently discontinue ITOVEBI.

ULN = upper limit of normal

[a] Fasting glucose levels (FPG or FBG) should be checked prior to dosing. Fasting glucose levels referenced in this table reflect hyperglycaemia grading according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

[b] Metformin prophylaxis was recommended for patients with risk factors in the INAVO120 study (see section *4.4 Special warnings and precautions for use - General*).

[c] Initiate applicable anti-hyperglycaemic medications, such as metformin, sodium-glucose cotransporter-2 (SGLT2) inhibitors, dipeptidyl peptidase-4 [DPP-4] inhibitors, or insulin sensitizers (such as thiazolidinediones), and review the respective prescribing information for dosing and dose titration recommendations, including local hyperglycaemia treatment guidelines. Metformin was recommended in the INAVO120 study as the preferred initial agent. See se*ction 4.8 Undesirable effects - Clinical Trials - Description of Selected Adverse Drug Reactions*.

[d] Risk factors for hyperglycaemia include, but are not limited to, (pre)diabetes, $HbA_{1C} \geq 5.7\%$, BMI ≥ 30 kg/m^2, ≥ 45 years of age, history of gestational diabetes, and family history of diabetes mellitus (see section *4.4 Special warnings and precautions for use - General*).

[e] In the INAVO120 study, short-term insulin was allowed to control blood glucose levels with a goal of maintaining blood glucose levels on oral agents only once the acute episode resolves.

Stomatitis

Table 3: Dose Modification and Management for Stomatitis

Grade[a]	**Recommendation**
Grade 1	• No adjustment of Itovebi required. • Initiate or intensify appropriate medical therapy (e.g., corticosteroid-containing mouthwash) as clinically indicated.
Grade 2	• Withhold Itovebi until recovery to Grade < 1. • Initiate or intensify appropriate medical therapy. Resume Itovebi at the same dose level. • For recurrent Grade 2 stomatitis, withhold Itovebi until recovery to Grade < 1, then resume Itovebi at one lower dose level.
Grade 3	• Withhold Itovebi until recovery to Grade < 1. • Initiate or intensify appropriate medical therapy. Resume Itovebi at one lower dose level.
Grade 4	• Permanently discontinue Itovebi.
[a] Based on CTCAE version 5.0.	

Other Adverse Reactions

Table 4 Dose Modification and Management for Other Adverse Reactions

Grade[a]	**Recommendation**
For all grades: Initiate supportive therapy and monitor as clinically indicated.	
Grade 1	• No adjustment of ITOVEBI required.
Grade 2	• Consider interruption of ITOVEBI, if clinically indicated, until recovery to Grade ≤ 1. • Resume ITOVEBI at the same dose level.
Grade 3, first event	• Interrupt ITOVEBI until recovery to Grade ≤ 1. • Resume ITOVEBI at the same dose level or at one lower dose level based on clinical evaluation (see Table 1).
Grade 3, recurrent OR Grade 4, non-life-threatening	• Interrupt ITOVEBI until recovery to Grade ≤ 1. • Resume ITOVEBI at one lower dose level (see Table 1).
Grade 4, life-threatening	• Permanently discontinue ITOVEBI.
[a] Based on CTCAE version 5.0.	

Special Dosage Instructions

Paediatric Population

The safety and efficacy of ITOVEBI has not been established in children and adolescents (< 18 years).

Elderly

No dose adjustment of ITOVEBI is required in patients ≥ 65 years of age. For details on geriatric data, see *section 4.4 Special warnings and precautions for use - Use in Special Populations - Elderly*.

Renal Impairment

No dose adjustment is required in patients with mild renal impairment (eGFR ≥ 60 to < 90 mL/min). The recommended starting dose of Itovebi for patients with moderate renal impairment (eGFR 30 to < 60 mL/min) is 6 mg orally once daily. The safety and efficacy of ITOVEBI have not been established in patients with severe renal impairment. For details on renal impairment data, see *section 4.4 Special warnings and precautions for use - Use in Special Populations - Renal impairment.*

Hepatic Impairment

No dose adjustment is required in patients with mild hepatic impairment (total bilirubin > ULN to ≤ 1.5 x ULN or AST > ULN and total bilirubin ≤ ULN). The safety and efficacy of ITOVEBI have not been studied in patients with moderate to severe hepatic impairment. For details on hepatic impairment data, see *section 4.4 Special warnings and precautions for use - Use in Special Populations - Hepatic Impairment*.

4.3 Contraindications

ITOVEBI is contraindicated in patients with a known hypersensitivity to inavolisib or any of the excipients.

4.4 Special warnings and precautions for use

General

Hyperglycaemia

Severe cases of hyperglycaemia, including complications such as life-threatening ketoacidosis, have been reported in patients treated with ITOVEBI.

The safety of Itovebi in patients with Type 1 diabetes mellitus or Type 2 diabetes mellitus requiring ongoing systemic therapy has not been studied. Patients with a history of well-controlled Type 2 diabetes mellitus may require intensified anti-hyperglycaemic treatment and close monitoring of fasting glucose levels as clinically indicated. Itovebi should not be administered until fasting glucose levels are optimized. Consultation with a healthcare professional experienced in the treatment of hyperglycaemia should be considered before initiating Itovebi.

Hyperglycaemia was managed with anti-hyperglycaemic medication (see *section 4.8 Undesirable effects - Clinical Trials - Description of Selected Adverse Reactions*).

Before initiating treatment with ITOVEBI, fasting glucose levels (FPG or FBG) and HbA1C levels should be tested, and fasting glucose levels should be optimized in all patients. Patients should also be advised of the signs and symptoms of hyperglycaemia (e.g., excessive thirst, urinating more often, blurred vision, mental confusion, difficulty breathing, or increased appetite with weight loss) and to immediately contact a healthcare professional if these symptoms occur. Optimal hydration should be maintained prior to and during treatment.

After initiating treatment with ITOVEBI, fasting glucose levels should be monitored or self-monitored once every 3 days for the first week (Day 1 to 7), then once every week for the next 3 weeks (Day 8 to 28), then once every 2 weeks for the next 8 weeks, then once every 4 weeks thereafter, and as clinically indicated. HbA1C should be monitored every 3 months and as clinically indicated, according to the instructions of a healthcare professional.

In patients with risk factors for hyperglycaemia including, but not limited to, (pre)diabetes, HbA1C ≥ 5.7%, BMI ≥ 30 kg/m2, ≥ 45 years of age, history of gestational diabetes, and family history of diabetes mellitus, fasting glucose levels should be monitored or self-monitored more frequently as clinically indicated. Anti-hyperglycaemic treatment should be initiated or adjusted as required (see *section 4.2 Dose and method of administration - Dose Modification*). Metformin prophylaxis was recommended for patients with risk factors for hyperglycaemia in the INAVO120 study.

If a patient experiences hyperglycaemia after initiating treatment with ITOVEBI, fasting glucose levels should be monitored more closely as clinically indicated. During treatment with anti-hyperglycaemic medication, fasting glucose levels should continue to be monitored at least once a week for 8 weeks, followed by once every 2 weeks, and as clinically indicated. Fasting glucose monitoring at home should be considered for patients who have risk factors for hyperglycaemia or who experience hyperglycaemia.

Based on the severity of the hyperglycaemia, ITOVEBI may require dose interruption, reduction, or discontinuation as described in Table 2 (see *section 4.2 Dose and method of administration - Dose Modification*). All patients should be instructed on lifestyle changes (e.g., dietary modifications, physical activity).

Stomatitis

Stomatitis has been reported in patients treated with Itovebi (see section 4.8 Undesirable effects - Description of selected adverse drug reactions). Based on the severity of stomatitis, Itovebi dosing may be interrupted, reduced, or permanently discontinued (see Table 3).

Corticosteroid mouthwash was recommended for prophylaxis of stomatitis for all patients in clinical studies.

Patients should be advised to start alcohol-free corticosteroid mouthwash at the first sign of stomatitis and to avoid alcohol- or peroxide-containing mouthwashes as they may exacerbate the condition (see section 4.8 Undesirable effects - Description of selected adverse drug reactions). Dietary modifications (e.g., avoiding spicy foods) should be considered.

Embryo-foetal toxicity

Based on the animal studies and pharmacological activity of inavolisib, ITOVEBI is expected to cause foetal harm when administered to pregnant women (see *section 5.3 Preclinical safety data - Developmental Toxicity*). Pregnant women should be advised of potential risk to the fetus. Females of reproductive potential and male patients should be advised to use effective contraception during treatment with ITOVEBI and for 2 weeks after the last dose of ITOVEBI (see *section 4.6 Fertility, pregnancy and lactation - Females and Males of Reproduction Potential*).

Drug Abuse and Dependence

There is no evidence that ITOVEBI has the potential for drug abuse or dependence.

Use in Special Populations

Paediatric Use

The safety and efficacy of ITOVEBI in paediatric patients have not been established.

Elderly

The safety and efficacy of ITOVEBI have been studied in geriatric patients up to 79 years of age. Of the 162 patients who received ITOVEBI in INAVO120, 14.8% were ≥ 65 years of age and 3% were ≥ 75 years of age.

The available data on the efficacy of ITOVEBI in patients 65 years and older do not suggest overall differences compared to younger patients. Analysis of the safety of ITOVEBI comparing patients ≥ 65 years of age to younger patients suggest a higher incidence of ITOVEBI dosage modifications/ interruptions (79.2% versus 68.1%). There are an insufficient number of patients ≥ 75 years of age to assess whether there are differences in safety or efficacy.

Renal Impairment

No dose adjustment is required in patients with mild renal impairment (eGFR ≥ 60 to < 90 mL/min) based on population pharmacokinetic analysis. The recommended starting dose of Itovebi for patients with moderate renal impairment (eGFR 30 to < 60 mL/min based on CKD-EPI) is 6 mg orally once daily. The safety and efficacy of ITOVEBI have not been established in patients with severe renal impairment. See *section 4.2 Dose and method of administration- Renal impairment* and section *5.2 Pharmacokinetic properties - Renal impairment*.

ITOVEBI is known to be excreted by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function.

Hepatic Impairment

No dose adjustment is required in patients with mild hepatic impairment (total bilirubin > ULN to ≤ 1.5 x ULN or AST > ULN and total bilirubin ≤ ULN). The safety and efficacy of ITOVEBI in patients with moderate to severe hepatic impairment have not been studied. See *section 4.2 Dose and method of administration - Special Dosage Instructions* and *section 5.2 Pharmacokinetic properties - Pharmacokinetics in Special Populations*.

4.5 Interaction with other medicines and other forms of interaction

No pharmacokinetic drug-drug interaction studies have been conducted with ITOVEBI.

Effects of Inavolisib on Other Drugs

CYP Substrates

In vitro studies suggest a low likelihood of time-dependent inhibition and induction of CYP3A4, and no potential to inhibit or induce the other CYP enzymes tested (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6) at clinically relevant concentrations. Physiologically based pharmacokinetic modelling predicted that inavolisib has no clinically relevant impact on the exposure of a sensitive CYP3A4 substrate, midazolam.

Transporters

In vitro studies have shown that inavolisib does not appear to have the potential to inhibit any of the transporters tested (P-glycoprotein [P-gp], breast cancer resistance protein [BCRP], OATP1B1, OATP1B3, OCT1, OCT2, MATE1, MATE2K, OAT1, or OAT3) at clinically relevant concentrations.

Effects of Other Drugs on Inavolisib

CYP Inhibitors/Inducers

Clinical study results show that the predominant metabolites of inavolisib are not mediated by CYP enzymes, suggesting a low likelihood of interaction between inavolisib and CYP inhibitors or inducers.

Transporters

In vitro studies have shown that inavolisib is not a substrate of OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT2, MATE1, or MATE2K, but is a substrate of P-gp and BCRP. However, based on the pharmacokinetic profile of inavolisib, inhibitors or inducers of P-gp and/or BCRP are not expected to have a clinically relevant drug-drug interaction with inavolisib.

Acid-reducing Agents

In clinical studies, concomitant use of proton pump inhibitors did not have a clinically meaningful effect on inavolisib exposure.

4.6 Fertility, pregnancy and lactation

Females and Males of Reproductive Potential

Fertility

There are no clinical studies conducted to evaluate the effect of ITOVEBI on fertility. Based on animal studies, inavolisib may impact fertility in females and males of reproductive potential (see section *4.6 Fertility, pregnancy and lactation - Fertility*).

Pregnancy testing

The pregnancy status of females of reproductive potential should be verified prior to initiating ITOVEBI therapy. Pregnant women should be clearly advised of the potential risk to the fetus.

Contraception

Female

Patients should be advised to use effective non-hormonal contraception during treatment with ITOVEBI and for 2 weeks after the last dose of ITOVEBI (see *section 4.4 Special warnings and precautions for use - General*).

Male

It is not known if ITOVEBI is present in semen. To avoid potential foetal exposure during pregnancy, male patients with female partners of childbearing potential or pregnant female partners should use a condom during treatment with ITOVEBI and for 2 weeks after the last dose of ITOVEBI (see *section 4.4 Special warnings and precautions for use - General*).

Pregnancy

Pregnancy Category D

ITOVEBI is not recommended during pregnancy.

No clinical studies of ITOVEBI in pregnant women have been performed. Based on animal studies and the pharmacological activity of inavolisib, ITOVEBI is expected to cause foetal harm when

administered to pregnant women, including teratogenicity and miscarriage (see *section 5.3 Preclinical safety data - Developmental Toxicity*).

Labour and Delivery

The use of ITOVEBI during labour and delivery has not been established.

Lactation

It is not known whether inavolisib is excreted in human breast milk.

No studies have been conducted to assess the impact of inavolisib on milk production or its presence in breast milk. Because of the potential for serious adverse reactions in the breastfed infant, it is recommended that women should not breastfeed during ITOVEBI treatment.

4.7 Effects on ability to drive and use machines

ITOVEBI has no or negligible influence on the ability to drive or use machines.

4.8 Undesirable effects

Clinical Trials

Summary of Safety Profile

The overall safety profile of ITOVEBI is based on data from 162 patients with locally advanced or metastatic breast cancer who received ITOVEBI in combination with palbociclib and fulvestrant in the INAVO120 Phase 3, randomised study. The median duration of ITOVEBI treatment at the time of the analysis was 9.2 months (range: 0 to 38.8 months).

The safety of ITOVEBI was also evaluated in the GO39374 Phase 1, dose-escalation study in patients with *PIK3CA*-mutated, HR-positive, HER2-negative, locally advanced or metastatic breast cancer who were enrolled to receive ITOVEBI in combination with palbociclib and fulvestrant (n=20); in combination with palbociclib, fulvestrant, and metformin (n=20); and in combination with palbociclib and letrozole (n=33). The safety profile of ITOVEBI in Study GO39374 was generally consistent with that observed in INAVO120.

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from the INAVO120 study are listed by MedDRA system organ class in Table 5. The corresponding frequency category for each adverse drug reaction is based on the following convention: 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), very rare (< 1/10,000).

Table 5 Adverse Drug Reactions with ≥ 5% (All Grades) or ≥ 2% (Grade 3-4) Higher Incidence in the ITOVEBI Arm in INAVO120

System Organ Class **Adverse Reaction**	**ITOVEBI + Palbociclib + Fulvestrant N=162**			**Placebo + Palbociclib + Fulvestrant N=162**	
	Frequency Category (All Grades)	**All Grades (%)**	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
Infections and Infestations					

Urinary Tract Infection	Very Common	13	1.2*	7.4	0
Blood and Lymphatic System Disorders					
Thrombocytopenia[a]	Very Common	48.1	14.2	45.1	4.3
Anaemia[b]	Very Common	37	6.2*	36.4	1.9*
Metabolism and Nutrition Disorders					
Hyperglycaemia[c]	Very Common	59.9	5.6*	9.9	0
Decreased appetite	Very Common	23.5	0	8.6	0
Hypokalaemia	Very Common	16	2.5	6.2	0
Hypocalcaemia	Common	8.6	1.2*	2.5	0.6*
Nervous System Disorders					
Headache	Very Common	21	0	13.6	0
Eye Disorders					
Dry eye	Common	8.6	0	3.1	0
Gastrointestinal Disorders					
Stomatitis[d]	Very Common	51.2	5.6*	26.5	0
Diarrhoea	Very Common	48.1	3.7*	16	0
Nausea	Very Common	27.8	0.6*	16.7	0
Vomiting	Very Common	14.8	0.6*	4.9	1.2*
Dyspepsia	Common	8	0	2.5	0
Skin and Subcutaneous Tissue Disorders					
Rash[e]	Very Common	25.3	0	17.3	0
Alopecia	Very Common	18.5	0	5.6	0
Dry skin[f]	Very Common	13	0	4.3	0
General Disorders and Administration Site Conditions					
Fatigue	Very Common	37.7	1.9*	25.3	1.2*
Investigations					
Alanine aminotransferase increased	Very Common	17.3	3.7*	13	1.2*
Weight decreased	Very Common	17.3	3.7*	0.6	0
Blood insulin increased	Common	6.2	0	0.6	0

Grading according to CTCAE version 5.0.

* No Grade 4 events were observed.

[a] Includes platelet count decreased and thrombocytopenia.

[b] Includes anaemia and haemoglobin decreased.

[c] Includes hyperglycaemia, blood glucose increased, hyperglycaemic crisis, glycated serum protein increased, glucose tolerance impaired, diabetes mellitus, Type 2 diabetes mellitus, and glycosylated haemoglobin increased.

[d] Includes aphthous ulcer, glossitis, glossodynia, lip ulceration, mouth ulceration, mucosal inflammation, and stomatitis.

[e] Includes dermatitis, dermatitis acneiform, dermatitis bullous, erythema, folliculitis, rash, rash erythematous, rash maculo-papular, rash popular, rash pruritic, and rash pustular.

[f] Includes dry skin, skin fissures, xerosis, and xeroderma.

Other adverse reactions with < 5% (all grades) or < 2% (Grade 3-4) greater incidence reported in patients in the ITOVEBI arm than the placebo arm are presented below.

Gastrointestinal disorders
Abdominal pain, including abdominal pain, abdominal pain upper, abdominal pain lower (all grades: 15.4%; Grade 3: 0.6%; no Grade 4 events); dysgeusia, including dysgeusia, ageusia, and hypogeusia (all grades: 8.6%; Grade 3-4: 0%)

Description of selected adverse drug reactions

Hyperglycaemia
In the INAVO120 study, hyperglycaemia of any grade was reported in 59.9% of patients treated with ITOVEBI in combination with palbociclib and fulvestrant; Grade 2 and Grade 3 events were reported in 38.3% and 5.6% of patients, respectively, and no Grade 4 events were reported (based on CTCAE version 5.0). Among the patients who experienced hyperglycaemia, the rate of new onset of hyperglycaemia events was highest during the first two months of treatment (range: 1 to 32 months) with a median time to first onset of 7 days (range: 2 to 955 days).

In patients who received ITOVEBI in combination with palbociclib and fulvestrant, 43.8% were managed with anti-hyperglycaemic medication including metformin as a single agent or in combination with other anti-hyperglycaemic medication (i.e., insulin, DPP-4 inhibitors, and sulfonylureas), SGLT2 inhibitors, thiazolidinediones, and DPP-4 inhibitors. In patients with fasting glucose levels > 8.9 mmol/L with at least one level (see Table 2) improvement in fasting glucose levels (n=52), the median time to improvement was 8 days (range: 2 to 43 days).

Hyperglycaemia led to interruption of ITOVEBI in 27.8%, to dose reduction of ITOVEBI in 2.5%, and to discontinuation of ITOVEBI in 1.2% of patients.

Stomatitis
Stomatitis was reported in 51.2% of patients treated with ITOVEBI in combination with palbociclib and fulvestrant; Grade 1 events were reported in 32.1% of patients, Grade 2 events in 13.6% of patients, and Grade 3 events in 5.6% of patients. No Grade 4 stomatitis events were reported. The median time to first onset was 13 days (range: 1 to 610 days).

Stomatitis led to interruption of ITOVEBI in 9.9%, to dose reduction of ITOVEBI in 3.7%, and to discontinuation of ITOVEBI in 0.6% of patients.

In patients who received ITOVEBI in combination with palbociclib and fulvestrant, 24.1% used a mouthwash containing dexamethasone for management of stomatitis.

Corticosteroid mouthwash was recommended for prophylaxis of stomatitis in the INAVO120 study. Among patients who received ITOVEBI in combination with palbociclib and fulvestrant, prophylaxis containing dexamethasone or triamcinolone was used in 19.1% and 1.2% of patients, respectively.

Diarrhoea
Diarrhoea was reported in 48.1% of patients treated with ITOVEBI in combination with palbociclib and fulvestrant; Grade 1 events were reported in 27.8% of patients, Grade 2 events in 16.7% of patients, and Grade 3 events in 3.7% of patients. No Grade 4 diarrhoea events were reported. The median time to first onset was 15 days (range: 2 to 602 days).

Diarrhoea led to interruption of ITOVEBI in 6.8%, to dose reduction of TRADENAME] in 1.2%, and did not lead to discontinuation of ITOVEBI in any patients.

Anti-diarrhoeal medicines (e.g., loperamide) were used in 28.4% of patients who received ITOVEBI in combination with palbociclib and fulvestrant to manage symptoms.

Laboratory Abnormalities

Table 6 summarises treatment-emergent shifts from baseline in laboratory abnormalities in the INAVO120 study.

Table 6 Laboratory Abnormalities with a ≥ 2% (All Grades or Grade 3-4) Higher Incidence in the ITOVEBI Arm in INAVO120

Laboratory Abnormality	**ITOVEBI + Palbociclib + Fulvestrant[a]**		**Placebo + Palbociclib + Fulvestrant[b]**	
	All Grades (%)	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
Haematology				
Neutrophils (total, absolute) decreased	95.1	82	97	78.8
Haemoglobin decreased	87.5	7.5*	85.1	2.5*
Glucose (fasting) increased[c]	85.4	12.1	42.9	0
Platelets decreased	83.8	15.6	71.4	3.7
Lymphocytes (absolute) decreased	72.1	9	68.2	14.4
Chemistry				
Calcium decreased	41.9	3.1	31.7	3.7
Potassium decreased	37.5	6.2	20.5	0.6*
Creatinine increased	37.5	1.9*	29.8	1.2*
ALT increased	34.4	3.1*	28.6	1.2*
Sodium decreased	27.5	2.5*	18.6	2.5
Magnesium decreased	26.9	0.6	20.5	0
Albumin decreased	25	0.6*	18.1	0
Lipase (fasting) increased	16	1.4*	6.9	0
Glucose (fasting) decreased[c]	6.4	0	3.2	0

ALT = alanine aminotransferase

Grading according to CTCAE version 5.0.

*No Grade 4 events were observed.

[a] The denominator used to calculate the rate varied from 122 to 160 based on the number of patients with a baseline value and at least one post-treatment value.

[b] The denominator used to calculate the rate varied from 131 to 161 based on the number of patients with a baseline value and at least one post-treatment value.

[c] Grading according to CTCAE version 4.03.

Post-marketing Experience

The following adverse drug reactions have been identified from postmarketing experience with Itovebi (Table 7) based on spontaneous case reports and literature cases. Adverse drug reactions are listed according to system organ classes in MedDRA and the corresponding frequency category estimation for each adverse drug reaction is based on the following convention: 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); very rare (<1/10,000).

Table 7: Adverse Drug Reactions Reported from Post-Marketing Experience

System Organ Class **Adverse Reaction**	**Frequency Category**	**CDS Reference**
Metabolism and Nutrition Disorders		
Ketoacidosis	Rare[a]	[12]
[a] This adverse reaction was from postmarketing experience outside the clinical trial dataset. The frequency category was estimated as the upper limit of the 95% confidence interval calculated on the basis of the total number of patients exposed to inavolisib in clinical trials.		

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 https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

There is limited experience of overdose with ITOVEBI in clinical trials. In clinical studies, ITOVEBI was administered at doses up to 12 mg once daily.

The highest dose administered in the INAVO120 study was 18 mg in one patient. The event of accidental overdosage was resolved in one day and did not require treatment or lead to dose modification of any study drugs.

Patients who experience overdose should be closely supervised and supportive care instituted. There are no known antidotes for ITOVEBI.

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

Not yet assigned

ATC code

Not yet assigned.

Mechanism of Action

Inavolisib is a highly potent and selective inhibitor of the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) catalytic subunit alpha isoform protein (p110α; encoded by the *PIK3CA* gene). In addition, inavolisib promotes the degradation of mutated p110α (mutant degrader). The PI3K signaling pathway is commonly dysregulated in HR-positive breast cancer, often due to activating *PIK3CA* mutations. With its dual mechanism of action, inavolisib inhibits the activity of downstream PI3K pathway targets, including AKT, resulting in reduced cellular proliferation and induction of

apoptosis in *PIK3CA*-mutated breast cancer cell lines. In *PIK3CA*-mutated breast cancer xenograft models, inavolisib reduced tumour growth, which was more pronounced in combination with a CDK4/6 inhibitor (palbociclib) and endocrine therapy.

Clinical/Efficacy Studies

Locally Advanced or Metastatic Breast Cancer

INAVO120

The efficacy of ITOVEBI in combination with palbociclib and fulvestrant was evaluated in a Phase III, randomised, double-blind, placebo-controlled study in adult patients with *PIK3CA*-mutated, HR-positive, HER2-negative, locally advanced or metastatic breast cancer whose disease progressed during or within 12 months of completing adjuvant endocrine therapy and who have not received prior systemic therapy for locally advanced or metastatic disease. The study excluded patients with Type 1 diabetes mellitus or Type 2 diabetes mellitus requiring ongoing systemic therapy at the start of study treatment.

PIK3CA mutation status was prospectively determined through testing of plasma-derived circulating tumour DNA (ctDNA) using a next-generation sequencing (NGS) assay at a central laboratory, or in local laboratories using various validated polymerase chain reaction (PCR) or NGS assays on tumour tissue or plasma.

A total of 325 patients were randomised 1:1 to receive either ITOVEBI 9 mg (n=161) or placebo (n=164) orally once daily, in combination with palbociclib and fulvestrant, until disease progression or unacceptable toxicity. In addition, pre/perimenopausal women and men received an LHRH agonist throughout therapy. Randomisation was stratified by presence of visceral disease (yes or no), endocrine resistance (primary or secondary), and geographic region (North America/Western Europe, Asia, other).

The baseline demographic and disease characteristics were: median age 54 years (range: 27 to 79 years); 98.2% female, 38.2% pre/perimenopausal; 58.8% White, 38.2% Asian, 2.5% unknown, 0.6% Black or African American; 6.2% Hispanic or Latino; and Eastern Cooperative Oncology Group (ECOG) performance status of 0 (63.4%) or 1 (36.3%). Tamoxifen (56.9%) and aromatase inhibitors (50.2%) were the most commonly used adjuvant endocrine therapies. The demographics and baseline disease characteristics were balanced and comparable between study arms.

The primary efficacy outcome measure was investigator (INV)-assessed progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. The secondary efficacy outcome measures included overall survival (OS), objective response rate (ORR), best overall response (BOR), clinical benefit rate (CBR), duration of response (DOR), and time to confirmed deterioration (TTCD) in pain, physical function, role function, and global health status/health-related quality of life (HRQoL).

Efficacy results are summarised inTable 8, Figure 1, and Figure 2. INV-assessed PFS results were supported by consistent results from blinded independent central review (BICR) assessment.

Table 8 Efficacy Results in Patients with Locally Advanced or Metastatic Breast Cancer in INAVO120

Efficacy Endpoint	**ITOVEBI + Palbociclib + Fulvestrant N=161**	**Placebo + Palbociclib + Fulvestrant N=164**
Primary Endpoint		
INV-Assessed Progression-Free Survival[a]		

Patients with event, n (%)	82 (50.9)	113 (68.9)
Median, months (95% CI)	15 (11.3, 20.5)	7.3 (5.6, 9.3)
Hazard ratio (95% CI)	0.43 (0.32, 0.59)	
p-value	< 0.0001	
Secondary Endpoints		
Overall Survival[b]		
Patients with event, n (%)	42 (26.1)	55 (33.5)
Median, months (95% CI)	NE (27.3, NE)	31.1 (22.3, NE)
Hazard ratio (95% CI)	0.64 (0.43, 0.97)	
p-value	0.0338	
Objective Response Rate[a,c]		
Patients with CR or PR, n (%)	94 (58.4)	41 (25)
95% CI	(50.4, 66.1)	(18.6, 32.3)
Best Overall Response[a,d]		
Patients with CR or PR, n (%)	103 (64)	49 (29.9)
95% CI	(56, 71.4)	(23, 37.5)
Duration of Response		
Median DOR, months (95% CI)	18.4 (10.4, 22.2)	9.6 (7.4, 16.6)
Clinical Benefit Rate		
Patients, n (%)	121 (75.2)	77 (47)
95% CI	(67.7, 81.6)	(39.1, 54.9)

CI = confidence interval; CR = complete response; NE = not evaluable; PR = partial response

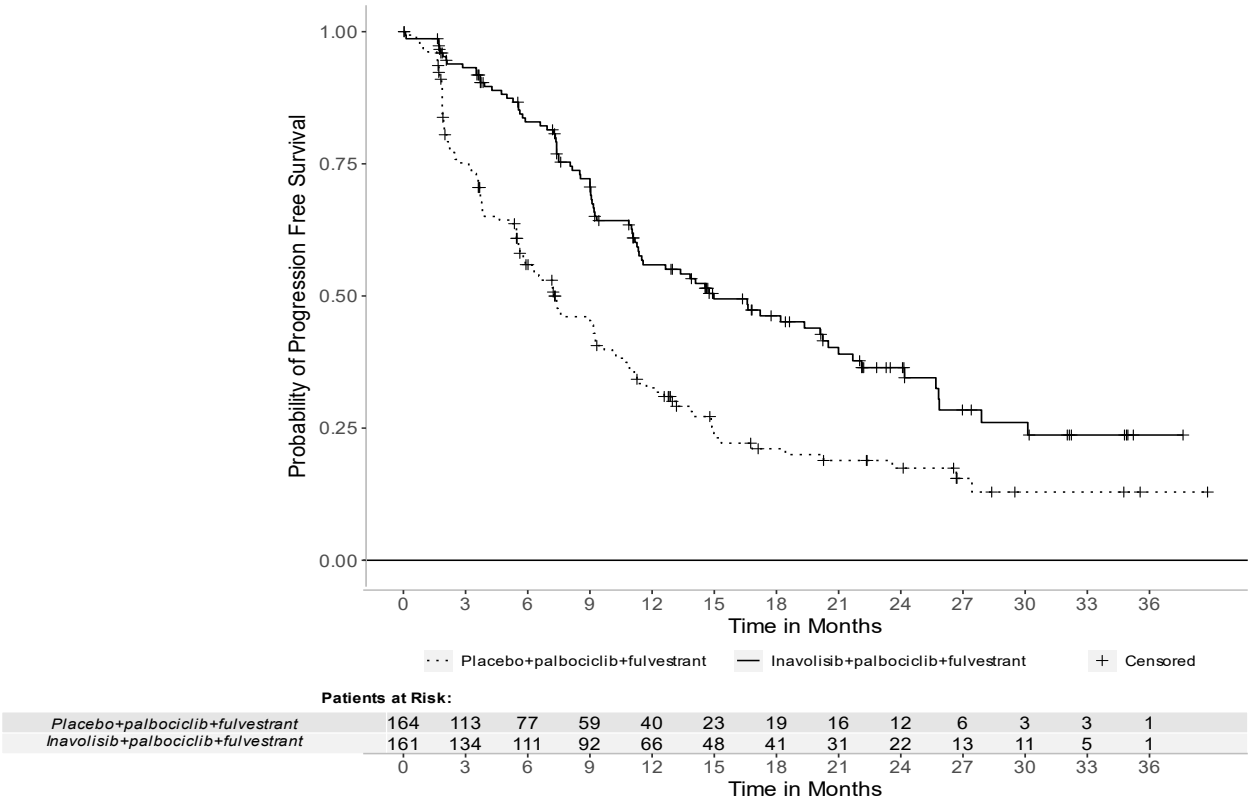
[a] Per RECIST version 1.1.

[b] Based on interim analysis. Under the interim analysis stopping boundary ($p \leq 0.0098$), statistical significance was not reached.

[c] ORR is defined as the proportion of patients with a CR or PR on two consecutive occasions ≥ 4 weeks apart, as determined by the investigator.

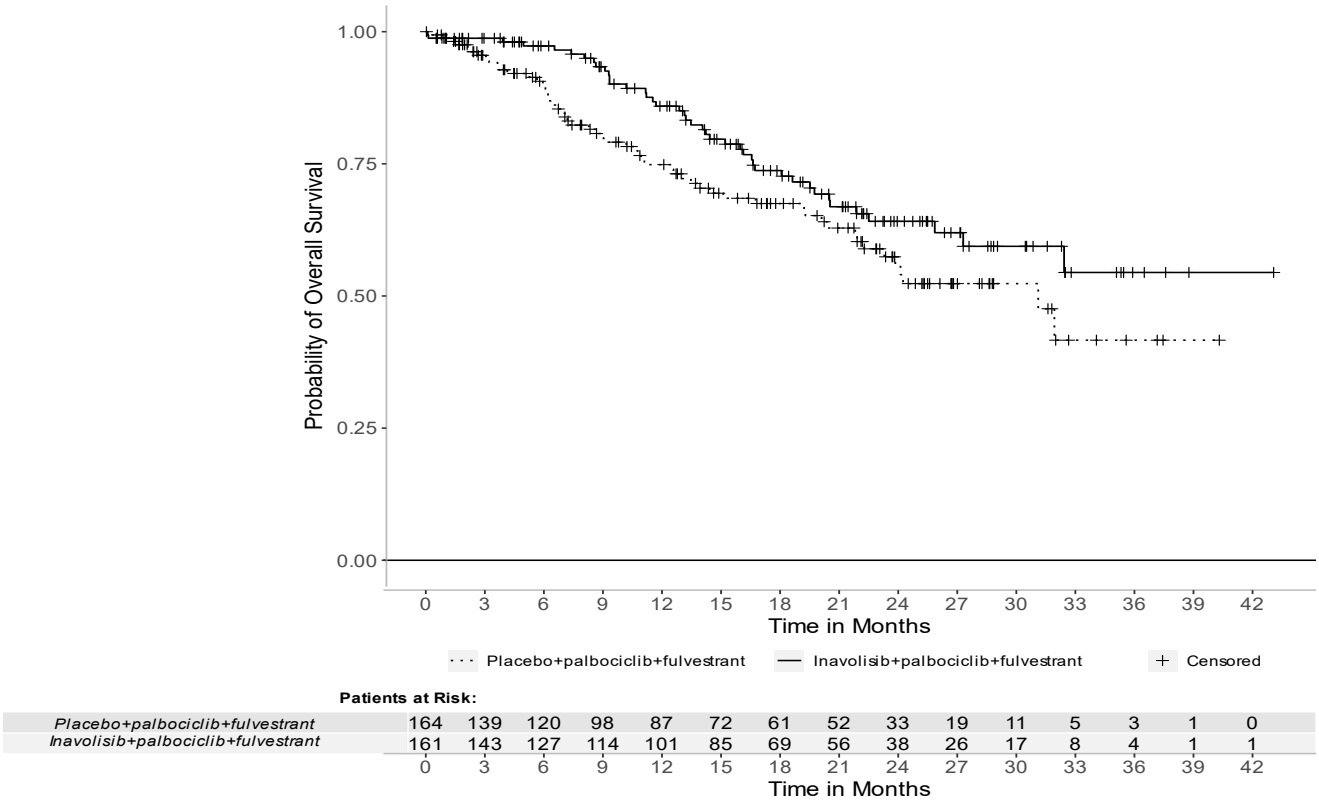
[d] BOR is defined as the proportion of patients with a CR or PR, as determined by the investigator.

Figure 1 INV-Assessed Progression-Free Survival in Patients with Locally Advanced or Metastatic Breast Cancer in INAVO120



Prespecified PFS analyses per investigator assessment showed a generally consistent treatment effect in favour of the ITOVEBI arm in patient subgroups including age, sex, ethnicity, race, ECOG performance status, menopausal status, presence of visceral disease (yes or no), presence of liver metastases (yes or no), number of metastatic organ sites, and endocrine resistance (primary or secondary).

Figure 2 Overall Survival in Patients with Locally Advanced or Metastatic Breast Cancer in INAVO120 (Interim Analysis)



Patient-reported outcomes

PFS results were supported by a longer time to clinically meaningful deterioration in patient-reported worst pain severity, defined as an increase of 2 or more points from baseline on the Brief Pain Inventory worst pain item score, favouring the ITOVEBI arm (median 30.9 months [95% CI: 16.6, NE] versus 18.1 months [95% CI: 13.1, NE]).

Other patient-reported endpoints measured by the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) suggest that patients maintained their baseline levels of HRQoL, physical functioning, and role functioning while on treatment. Mean scores at baseline for HRQoL (65.5 and 66.3), physical function (80.4 and 80.1), and role function (80.2 and 79) in the ITOVEBI and placebo arms, respectively, were comparable with no changes of 10 points or greater from baseline mean score observed during the course of treatment. Additionally, no differences in the median time to a confirmed ≥ 10-point, clinically meaningful deterioration in HRQoL (29 [95% CI: 15.8, NE] and 27.4 [95% CI: 15, NE] months), physical function (23.7 [95% CI: 18.4, 28.4] and 22.7 [95% CI: 13.3, 27.4] months), or role function (25.7 [95% CI: 18.4, NE] and 24.2 [95% CI: 7.4, NE] months) were observed between the ITOVEBI and placebo arms, respectively, indicating that patients in both arms maintained their day-to-day functioning and HRQoL for a similar duration of time.

Patients also reported on seven selected symptomatic toxicities (diarrhoea, nausea, vomiting, fatigue, mouth sores, decreased appetite, and rash) via the Patient-Reported Outcomes – Common Terminology Criteria for Adverse Events (PRO-CTCAE) corresponding to the known, reportable side effects of ITOVEBI, palbociclib, and fulvestrant, as well as their overall level of bother due to treatment side effects via a single item/question.

Completion rates in both arms were > 90% at baseline and > 80% at subsequent time points where > 50% of randomised patients were on treatment.

In both arms, worst post-baseline levels of 'moderate'/'somewhat' or less were reported by > 70% of patients for decreased appetite, nausea, and vomiting, and by > 60% of patients for mouth sores, diarrhoea, and fatigue. Greater proportions of patients in the ITOVEBI arm reported post-baseline symptomatic toxicities at 'severe'/'frequently' or 'very severe'/'almost constantly' levels; these differences were greatest for mouth sores, decreased appetite, and diarrhoea (Table 9 Proportion of Patients Reporting Worst Post-baseline Levels of PRO-CTCAE Symptoms Items in INAVO120). Rash was reported in 53.9% and 40.5% of patients in the ITOVEBI and placebo arms, respectively, post-baseline.

Table 9 Proportion of Patients Reporting Worst Post-baseline Levels of PRO-CTCAE Symptoms Items in INAVO120

Symptom (Attribute)[a]	**Baseline Score ≤ 1[a]**		**Post-baseline Score ≤ 2[a]**		**Post-baseline Score ≥ 3[a]**	
	Inavo+P+F (N=148)	**Pbo+P+F (N=152)**	**Inavo+P+F (N=152)**	**Pbo+P+F (N=158)**	**Inavo+P+F (N=152)**	**Pbo+P+F (N=158)**
Mouth sores (severity), %	97.3	97.4	69.7	91.1	30.2	8.9
Decreased appetite (severity), %	89.9	91.5	73	87.4	27	12.7
Nausea (frequency), %	89.2	91.4	80.3	86.7	19.7	13.3
Vomiting (frequency), %	95.9	98	94.1	96.8	5.9	3.2
Diarrhoea (frequency), %	91.2	93.5	67.1	89.9	32.9	10.1
Fatigue (severity), %	73.6	73	63.2	72.8	36.8	27.2

Symptom (Attribute)	**Baseline Presence**		**Post-baseline Presence**	
	Inavo+P+F (N=148)	**Pbo+P+F (N=152)**	**Inavo+P+F (N=152)**	**Pbo+P+F (N=158)**
Rash (yes/no), %	94.6 (No)	95.4 (No)	53.9 (Yes)	40.5 (Yes)

Inavo+P+F = ITOVEBI plus palbociclib and fulvestrant arm; N/A = not applicable; Pbo+P+F = placebo plus palbociclib and fulvestrant arm

[a] The symptom attribute scoring is defined by amount/frequency/severity with a score of 0 = 'not at all'/'never'/'none'; 1 = 'a little bit'/'rarely'/'mild'; 2 = 'somewhat'/'occasionally'/'moderate'; 3 = 'quite a bit'/'frequently'/'severe'; 4 = 'very much'/'almost constantly'/'very severe'.

Patients reported low levels of overall bother from treatment side effects (i.e., 'not at all' or 'a little bit') at baseline in both the ITOVEBI arm (91.2%) and placebo arm (94.1%). During the course of treatment, a similar proportion of patients in both arms (≥ 90% in each arm) reported increased levels of bother, mostly at levels 'moderate'/'somewhat' or less, suggesting that ITOVEBI did not increase treatment burden when added to palbociclib and fulvestrant.

GO39374

The efficacy of ITOVEBI was evaluated in Study GO39374, a Phase I, open-label, dose escalation study evaluating the safety, tolerability, and pharmacokinetics of ITOVEBI in combination with standard-of-care endocrine and/or targeted therapies in patients with *PIK3CA*-mutated, locally advanced or metastatic breast cancer. *PIK3CA* mutation status was determined on the basis of local or central test results in a Clinical Laboratory Improvement Amendments (CLIA)- or equivalently-certified laboratory.

Female patients with *PIK3CA*-mutated, HR-positive, HER2-negative, locally advanced or metastatic breast cancer were enrolled in Arms B (n=33), E (n=20), and F (n=21) of this study. In Arm B, patients received ITOVEBI in combination with palbociclib and letrozole. In Arms E and F, patients received ITOVEBI in combination with palbociclib and fulvestrant. In Arm F, patients were required to have BMI ≥ 30 kg/m2 and/or HbA_{1C} ≥ 5.7% and < 7% at baseline, and were also treated with metformin. In Arms E and F, pre/perimenopausal women received an LHRH agonist throughout therapy; all patients enrolled in Arm B were postmenopausal.

The median age was 57 years (range: 37 to 80 years) in Arm B, 55 years (range: 33 to 73 years) in Arm E, and 65 years (range: 33 to 77 years) in Arm F.

The majority (97%) of patients in Arm B, 60% in Arm E, and all patients in Arm F had received at least one prior anti-cancer therapy in the metastatic setting. Among these patients, the median number of lines of prior anti-cancer therapy in the metastatic setting was 2 lines (range: 1 to 4 lines) in Arm B, 1 line (range: 1 to 4 lines) in Arm E, and 3 lines (range: 1 to 9 lines) in Arm F. In all patients, 21.2% in Arm B, none in Arm E, and 66.7% in Arm F had received prior treatment with a CDK4/6 inhibitor; 42.4% in Arm B, 15% in Arm E, and 71.4% in Arm F had received a prior selective estrogen receptor degrader; and 39.4% in Arm B, 15% in Arm E, and 66.7% in Arm F had received prior fulvestrant.

The median duration of ITOVEBI treatment was 15.7 months (range: 1.3 to 66.5 months) in Arm B, 20.8 months (range: 1.8 to 47.6 months) in Arm E, and 7.2 months (range: 1.1 to 35.4 months) in Arm F.

In Study GO39374, ORR and PFS were assessed by investigators per RECIST version 1.1. In Arm B, the ORR was 60% (15/25) in patients with measurable disease; the median DOR was 42.3 months (95% CI: 14.7, NE); and the median PFS was 23.3 months (95% CI: 9.2, 44.4). In Arm E, the ORR was 40% (6/15) in patients with measurable disease; the median DOR was 11.9 months (95% CI: 7.6, 33.4); and the median PFS was 35 months (95% CI: 17.7, NE). In Arm F, the ORR was 16.7% (3/18) in patients with measurable disease; the median DOR was 9.2 months (95% CI: 9.1, NE); and the median PFS was 10.8 months (95% CI: 3.4, 12.5).

5.2 Pharmacokinetic properties

The pharmacokinetics of inavolisib were characterised in patients with locally advanced or metastatic *PIK3CA*-mutated solid tumours, including breast cancer, under an oral dosing regimen ranging from 6 mg to 12 mg daily and in healthy subjects at 9 mg single dose.

Inavolisib exhibited dose-proportional pharmacokinetics in patients with locally advanced or metastatic breast cancer over a dose range of 6 mg to 12 mg.

The exposure-response correlation for the efficacy of inavolisib was not observed. Exposure-response relationships were observed for hyperglycaemia (CTCAE Grade ≥ 2) at doses of 3 mg to 12 mg (0.3 to 1.3 times the recommended dosage) and anaemia (CTCAE Grade ≥ 2) at the recommended dosage of 9 mg.

Absorption

The time to maximum plasma concentration (T_{max}) was reached after a median of 3 hours (range: 0.5 to 4 hours) at steady state following 9 mg once daily dosing of inavolisib, under fasted conditions.

With 9 mg once daily dosing, the geometric mean accumulation ratio was 2.04.

The absolute bioavailability of inavolisib was 76%.

No clinically significant effect of food on inavolisib exposure was observed. The geometric mean ratio (GMR) (90% CI) for AUC_{0-24} comparing the fed to the fasted state was 0.895 (0.737 – 1.09) after a single dose and 0.876 (0.701 – 1.09) at steady state. The GMR (90% CI) for C_{max} comparing the fed to the fasted state was 0.925 (0.748 – 1.14) after a single dose and 0.910 (0.712 – 1.16) at steady state.

Distribution

Plasma protein binding of inavolisib ranged from 27% to 75% bound (mouse, 75%; rat, 40%; rabbit, 47%; dog, 31%; monkey, 27%; and human, 37%) and did not appear to be concentration-dependent over the concentration range tested (0.1 - 10 μM). In humans, the estimated steady state oral volume of distribution is 155 L and the blood-to-plasma ratio is approximately 0.794.

Biotransformation

Minimal metabolism of inavolisib was detected *in vitro* in rat, dog, and human liver microsome incubations.

Following oral administration of a single radiolabelled 9 mg dose of inavolisib to healthy subjects, parent drug was the most prominent drug-related compound in plasma and urine. Total metabolites in the excreta accounted for 42% (35% in faeces and 7% in urine) of the dose. Hydrolysis was the major metabolic pathway.

Elimination

Following oral administration of a single radiolabelled 9 mg dose of inavolisib to healthy subjects, 48.5% of the administered dose was recovered in urine (40.4% unchanged) and 48% in faeces (10.8% unchanged).

In clinical studies, the geometric mean of the individual elimination half-life estimate for inavolisib was 16.4 hours following a single 9 mg dose. The estimated total clearance of inavolisib is 8.83 L/hr.

Pharmacokinetics in Special Populations

Paediatric Population

No studies have been conducted to investigate the pharmacokinetics of inavolisib in paediatric patients.

Elderly

No differences in inavolisib pharmacokinetics were noted between patients 65 years of age and older and those under 65 years based on population pharmacokinetic analysis.

Renal Impairment

Population pharmacokinetic analyses indicated that mild renal impairment is not a significant covariate on ITOVEBI exposure. The pharmacokinetics of inavolisib in patients with mild renal impairment (CrCl 60 to < 90 mL/min) were similar to those in patients with normal renal function. Inavolisib AUC and C_{max} were 73% and 11% higher in patients with moderate renal impairment compared to patients with normal renal function (eGFR ≥ 90 mL/min), respectively. The effect of severe renal impairment on ITOVEBI pharmacokinetics has not been established.

Hepatic Impairment

Population pharmacokinetic analyses indicated that mild hepatic impairment is not a significant covariate on ITOVEBI exposure. The pharmacokinetics of inavolisib in patients with mild hepatic impairment (total bilirubin > ULN to ≤ 1.5 x ULN or AST > ULN and total bilirubin ≤ ULN) were similar to those in patients with normal hepatic function. The effect of moderate to severe hepatic impairment on ITOVEBI pharmacokinetics has not been studied.

5.3 Preclinical safety data

Genotoxicity and Mutagenicity

Inavolisib was not mutagenic in the bacterial mutagenesis assay.

Inavolisib showed clastogenicity *in vitro*; however, there was no evidence of inavolisib induced *in vivo* genotoxicity (clastogenicity, aneugenicity, or DNA damage) in the micronucleus and comet study in rats at doses up to a maximum tolerated dose (MTD) of 16.1 times the exposure at a clinical dose of 9 mg.

Carcinogenicity

No carcinogenicity studies with inavolisib have been conducted.

Developmental Toxicity

An embryo-foetal development study in Sprague Dawley rats identified inavolisib-related dose dependent effects on embryo-foetal development (at ≥ 0.8 times the exposure at a clinical dose of 9 mg) that included decreases in foetal body weight and placental weight, post-implantation loss, lower foetal viability, and teratogenicity (foetal external, visceral, and skeletal malformations).

Fertility

No dedicated fertility studies with inavolisib have been conducted.

In male rats, dose-dependent atrophy of the prostate and seminal vesicle and decreased organ weights without microscopic correlate in the epididymis and testis were observed (at ≥ 0.4 times the exposure at a clinical dose of 9 mg). In the 1-month toxicity study in dogs, focal inspissation of seminiferous

tubule contents and multinucleated spermatids in the testis and epithelial degeneration/necrosis in the epididymis were observed (at ≥ 2 times the exposure at a clinical dose of 9 mg). However, there were no inavolisib-related microscopic findings in the testes or epididymides or effects on sperm concentration, motility, or morphology in the 3-month dog toxicity study at similar exposures.

In female rats, minimal to mild and reversible atrophy in the uterus and vagina and decreased ovarian follicles were observed (at ≥ 1.1 times the exposure at a clinical dose of 9 mg) in the 4-week rat toxicity study. Findings suggestive of an interruption/alteration of the oestrus cycle were observed (at ≥ 1.5 times the exposure at a clinical dose of 9 mg) in the 3-month rat toxicity study. Potential effects on female reproductive system cycling are expected to be reversible in a clinical setting.

Other

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use, included inflammation in dogs and eye lens degeneration in rats. The inflammation is consistent with the anticipated pharmacologic effects of PI3K inhibition, was generally dose-dependent and reversible, and is considered to be clinically monitorable and/or manageable. Lens fibre degeneration observed in some rats (at ≥ 3.6 times the exposure at a clinical dose of 9 mg) was considered irreversible.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Lactose
Sodium starch glycollate
Magnesium stearate
Polyvinyl alcohol
Titanium dioxide
Macrogol/polyethylene glycol
Purified talc
Iron oxide red
Iron oxide yellow (9 mg tablet only)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

This medicine should not be used after the expiry date (EXP) shown on the blister packaging.

6.4 Special precautions for storage

Store below 30°C

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

Alu/alu (aluminium/aluminium) blister sealed into a blister card containing 7 film-coated tablets. Each carton contains 28 film-coated tablets (4 blister cards per carton).

6.6 Special precautions for disposal <and other handling>

The release of pharmaceuticals in the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription only medicine

8. SPONSOR

Roche Products (New Zealand) Limited
PO Box 109113
Newmarket
Auckland 1149
NEW ZEALAND

Medical enquiries: 0800 276 243

9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:
30 October 2025

10. DATE OF REVISION OF THE TEXT

28 April 2026

SUMMARY TABLE OF CHANGES

Section Changed	**Summary of new information**
6.3	Shelf life extension to 36 months