Australian Government
Department of Health, Disability and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for ITOVEBI

Active ingredient: Inavolisib

Sponsor: Roche Products Pty Ltd

July 2025

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, Disability and Ageing and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
1L	first-line
AEs	adverse events
ARTG	Australian Register of Therapeutic Goods
BOR	best overall objective response rate
AUC	area under the concentration-time curve
CBR	clinical benefit rate
DOR	duration of response
ET	endocrine therapy
HER2	human epidermal growth factor receptor 2
HR	hormone receptor
ORR	objective response rate
OS	overall survival
PD	pharmacodynamic(s)
PFS	progression-free survival
PI3K	phosphatidylinositol-4,5-bisphosphate 3-kinase
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PI	Product Information
PK	pharmacokinetic(s)
popPK	population pharmacokinetic(s)
RMP	Risk management plan
TEAE	Treatment emergent adverse event
TGA	Therapeutic Goods Administration

ITOVEBI (inavolisib) submission

Type of submission:	New chemical entity
Product name:	ITOVEBI
Active ingredient:	inavolisib
Decision:	Approved
Date of decision:	24 March 2025
Approved therapeutic use for the current submission:	ITOVEBI, in combination with palbociclib and fulvestrant, is 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 within 12 months of completing adjuvant endocrine therapy.
Date of entry onto ARTG:	26 March 2025
ARTG numbers:	ITOVEBI inavolisib 3 mg film-coated tablet blister pack (446750) ITOVEBI inavolisib 9 mg film-coated tablet blister pack (446751)
, *Black Triangle Scheme:*	Yes
Sponsor's name and address:	Roche Products Pty Limited, Level 8, 30-34 Hickson Road, Sydney NSW 2000
Dose form:	film-coated tablet
Strength:	3 mg, 9 mg
Container/pack size:	Cartons of 28 tablets (4 aluminium blister cards, each with 7 tablets, per carton)
Route of administration:	Oral
Dosage:	9 mg once daily For further information regarding dosage refer to the Product Information.
Pregnancy category:	Category D Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. The pregnancy database must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your state or territory.

Proposed indication

This AusPAR describes the submission by Roche Products Pty Ltd (the Sponsor)[1] to register ITOVEBI (inavolisib) for the following proposed indication:

> *ITOVEBI, in combination with palbociclib and endocrine therapy, is 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.*

The condition

Breast cancer is the most commonly diagnosed cancer (excluding skin cancer) in women, with an estimated global incidence of 2.2 million new cases and almost 700,000 deaths reported in 2020. HR+, HER2-negative breast cancer is the most common breast cancer subtype accounting for approximately 70% of all breast cancers; approximately 35-40% of patients with these tumours have phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) mutations. The presence of *PIK3CA* mutation is considered a negative prognostic factor. Advanced or metastatic HR+, HER2-negative breast cancer remains incurable and is associated with a limited life expectancy.

Current treatment options

Treatment with a cyclin-dependent kinase (CDK) 4/6 inhibitor plus endocrine therapy (fulvestrant or aromatase inhibitor) is the standard of care first-line (1L) treatment for patients with advanced HR+, HER2-negative breast cancer. Following progression on 1L therapy, treatment options include: endocrine monotherapy with fulvestrant, aromatase inhibitors (AI) or tamoxifen (if not received as 1L treatment); endocrine therapy (ET) + CDK4/6 inhibitor (if not used in the 1L setting); everolimus in combination with exemestane; alpelisib plus fulvestrant (for those with a *PIK3CA* mutated tumour); capivasertib plus fulvestrant (benefit seen in those with *PIK3CA*/*AKT1*/*PTEN* alterations); poly (ADP-ribose) polymerase (PARP) inhibitors (BRCA1/2 mutations); and chemotherapy/ antibody-drug conjugates (e.g. capecitabine; ENHERTU for HER2-low following previous chemotherapy or ET-resistant; sacituzumab-govitecan 3L+, etc.).

There are no treatments approved specifically for the 1L treatment of patients with endocrine resistant *PIK3CA* mutated, HR+, HER2-negative advanced breast cancer; generally, these patients are treated with currently available options for HR+, HER2-negative breast cancer.

Clinical rationale

Inavolisib (RO7113755, GDC-0077) 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+ breast cancer, often due to activating *PIK3CA* mutations. With its dual mechanisms of

[1] A sponsor is a person or company who does one or more of the following: a) exports therapeutic goods from Australia, b) imports therapeutic goods into Australia, c) manufactures therapeutic goods for supply in Australia or d) elsewhere arranges for another party to import, export or manufacture therapeutic goods

action, inavolisib inhibits the activity of downstream PI3K pathway targets, including protein kinase B (*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 CDK 4 and 6 (CDK4/6) inhibitor (palbociclib) and an endocrine agent.

Regulatory status

Australian regulatory status

This product is a new chemical entity for Australian regulatory purposes.

International regulatory status

At the time the TGA considered this submission, a similar submission had been considered by other regulatory agencies (Table 1).

Table 1. International regulatory status for ITOVEBI

Country/region	Date submitted or intend to submit	Status	Indications (requested)
European Union (Centralised procedure; Rapporteur – Sweden; Co-rapporteur - Germany)	30 April 2024	Pending	*Inavolisib, in combination with palbociclib and fulvestrant, is 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 within 12 months of completing adjuvant endocrine treatment (see section 5.1)*
United States of America	27 March 2024	Pending	*Inavolisib, in combination with palbociclib and endocrine therapy, is 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, as detected by an FDA-approved test, following recurrence on or after completing adjuvant therapy or progression on an endocrine-based regimen in the metastatic setting.*

Registration timeline

Table 2 captures the key steps and dates for this submission.

Table 2: Registration timeline for ITOVEBI (inavolisib), submission PM-2024-01518-1-4

Description	Date
Submission dossier accepted and evaluation commenced	31 May 2024
Evaluation completed	4 February 2025

Description	Date
Registration decision (Outcome)	24 March 2025
Registration in the ARTG completed	26 March 2025
Number of working days from submission dossier acceptance to registration decision*	208 days

*Statutory timeframe for standard submissions is 255 working days

Assessment overview

Quality evaluation summary

There were no significant issues identified from the quality evaluation of the submitted data that would indicate the product should not be registered on the basis of quality, or safety-related issues arising from the quality of the product. The Sponsor had satisfied all requirements with respect to:

- stability and release specifications,
- appropriately conducted stability studies that support the proposed shelf life/storage conditions,
- validation of analytical procedures utilised to assess drug specifications,
- appropriate choice/synthesis and validation of reference standards and reference materials,
- appropriate in-process controls within the manufacturing process and identification of critical manufacturing steps,
- consistency of medicine manufacture verified by process validation and demonstrated through batch analysis,
- satisfactory control of impurities,
- adequate characterisation and justification of excipients,
- medicine sterility/appropriate control of infectious disease & adventitious agents,
- appropriate/compatible container closure systems,
- labelling that conformed to Therapeutic Goods Order 91,
- GMP compliance.

Nonclinical evaluation summary

The submitted nonclinical dossier was in accordance with the relevant ICH guideline for the nonclinical evaluation of anticancer pharmaceuticals (ICH S9).[2] The overall quality of the nonclinical dossier was high. All pivotal safety-related studies were GLP compliant.

[2] International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH S9 Non-clinical evaluation for anticancer pharmaceuticals - Scientific guideline. 2018

In vitro, inavolisib inhibited recombinant PI3Kα with picomolar potency, within expected clinical plasma concentrations. Inavolisib induced degradation of p110α in cell lines expressing breast cancer-associated PI3KA mutants (H1047R and E545K but not wild type PI3Kα). Inavolisib inhibited proliferation of breast cancer cell lines (low nanomolar IC_{50}), and weakly synergised with fulvestrant and palbociclib in this effect. In vivo mouse studies using human tumour xenografts demonstrated that inavolisib–alone or in combination with fulvestrant and/or palbociclib–decreased tumour growth. Greater tumour growth inhibition was achieved using the triplet combination than using single agents or doublet combinations. Thus, the pharmacology program supports the use of inavolisib as a specific PI3Kα inhibitor in combination with palbociclib and endocrine therapy for the proposed indication.

Inavolisib also had inhibitory activity against PI3Kδ and PI3Kγ at clinically relevant concentrations.

Safety pharmacology studies assessed effects on respiratory, central nervous and cardiovascular systems. No adverse effects were seen on central nervous system function in rats or respiratory function in dogs. No significant inhibition of hERG K+ channel tail current, Nav1.5 sodium, or Cav1.2 calcium currents was observed at clinically relevant concentrations. Inavolisib lengthened QTc interval (~5%) in dogs at 10× the clinical C_{max}. However, it is not predicted to prolong the QT interval in patients.

Overall, the pharmacokinetic profile in animals was qualitatively similar to that of humans. Any differences are only minor. Inavolisib was rapidly absorbed in rats and dogs but more slowly in humans. Half-life values were similar in rats and dogs but longer in humans. Plasma protein binding of inavolisib was similarly low in humans and animal species used in the toxicity studies. Following oral dosing, tissue distribution of drug-related material was moderate in rats with limited penetration into brain and spinal cord and retention of drug-related material to melanin-containing tissues. Minimal metabolism was seen in liver microsomes from dogs, rats and humans with unchanged inavolisib the main circulating drug-related component in the latter two species. Drug-related material was excreted primarily via faeces in rats (due to low absorption with some excretion into bile) and equally in faeces and urine in humans.

Inavolisib could potentially affect exposure to co-administered drugs that are CYP2B6 or 3A4 substrates.

Inavolisib had a low to moderate order of acute oral toxicity in rats and dogs.

Repeat-dose toxicity studies by the oral route were conducted in rats and dogs (up to 13 weeks). Maximum exposures (AUC) in the pivotal studies were low. Hyperglycaemia occurred in both species, accompanied by hypercholesterolemia and glucosuria, and correlated with adaptive changes in the pancreas (islet hypertrophy and vacuolation). Other target organs for toxicity were the lymphoid organs (lymphoid depletion of the thymus, spleen, lymph nodes and/or GALT), eye (vacuolation at the equatorial region of the lens cortex, and lens degeneration with lens fibre swelling, separation of lens fibres and accumulation of subcapsular proteinaceous material), liver (inflammation correlated with expected pathology markers), and reproductive organs (focal inspissation of seminiferous tubule contents and multinucleated spermatids, decreased ovarian follicle number correlated with interruptions in oestrous cycling).

Inavolisib was not mutagenic in the bacterial mutation assay. Inavolisib was clastogenic in vitro (in human lymphocytes) but not in vivo (in the rat micronucleus test). No carcinogenicity studies were conducted, which is considered acceptable given the indication.

Increased embryofetal death and teratogenicity, lower fetal weights, and increased skeletal and visceral variations were seen in a pilot embryofetal development study in rats. No fertility and early embryonic studies were conducted; however, in repeat dose toxicity studies in rats and

dogs, histopathological changes observed in reproductive organs suggest that inavolisib has the potential to impair male and female fertility.

Inavolisib is not expected to have phototoxic potential upon exposure to visible/UV light after repeat dosing.

The proposed limit for two impurities in the drug substance have been adequately qualified by submitted toxicity data.

There are no nonclinical objections to the registration of ITOVEBI.

Clinical evaluation summary

This evaluation was facilitated through Project Orbis, an initiative of the United States Food and Drug Administration (FDA) Oncology Center of Excellence. Under this project, the FDA, and the TGA collaboratively reviewed the submission. This evaluation process provided a framework for process alignment and management of evaluation issues in real-time across jurisdictions. Each regulator made independent decisions regarding approval (market authorisation) of the new medicine.

Pharmacology

Mechanism of action

Inavolisib is an inhibitor of PI3K with inhibitory activity predominantly against PI3Kα. In vitro, inavolisib induced the degradation of mutated PI3K catalytic alpha subunit p110α (encoded by the *PIK3CA* gene), inhibited phosphorylation of the downstream target *AKT*, reduced cellular proliferation, and induced apoptosis in *PIK3CA*-mutated breast cancer cell lines. In vivo, inavolisib reduced tumour growth in *PIK3CA*-mutated, estrogen receptor(ER)-positive, breast cancer xenograft models. The combination of inavolisib with palbociclib and fulvestrant increased tumour growth inhibition compared to each treatment alone or the doublet combinations.

Absorption

- Absolute oral bioavailability = 76%
- Steady-state median (min, max) time to maximum plasma concentration (T_{max}) is 3 hours
- No clinically significant differences in pharmacokinetics (PK) were observed following administration of inavolisib with a high fat meal

Distribution

- Volume of distribution is 155L
- Mean plasma protein binding is 37%

Elimination

- Elimination half-life is 15hrs
- Total clearance is 8.8L/hr (29%)

Metabolism

- By hydrolysis; in vitro, inavolisib was minimally metabolised by CYP3A.

Excretion

- Following oral administration of a single radiolabelled dose, 49% of the administered dose was recovered in urine (40% unchanged) and 48% in faeces (11% unchanged).

Specific populations

- No clinically significant differences in the PK of inavolisib was observed based on age, race, sex, body weight or mild hepatic impairment. The effect of moderate to severe hepatic impairment on inavolisib PK is unknown.

Patients with renal impairment

- Inavolisib AUC was 73% higher in patients with moderate renal impairment compared to patients with normal renal function.
- C_{max} values were similar between patients with normal renal function and moderate renal impairment.
- No clinically significant differences in the PK of inavolisib was observed in patients with mild renal impairment compared to patients with normal renal function.
- The effect of severe renal impairment (estimated glomerular filtration rate <30ml/min) on the PK of inavolisib is unknown.

Drug-drug interactions

- No clinically significant differences in steady-state PK were observed based on the concomitant use of a PPI.
- Inavolisib induces CYP3A and CYP2B6. Inavolisib is a time-dependent inhibitor of CYP3A. Inavolisib does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6.
- Inavolisib is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), but is not a substrate of OATP1B1, OATP1B3, OCT1, OCT2, MATE1, MATE2K, OAT1, OAT2. Inavolisib does not inhibit P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, or MATE2K.

Efficacy

The pivotal data for efficacy come from study WO41554 (INAVO120).

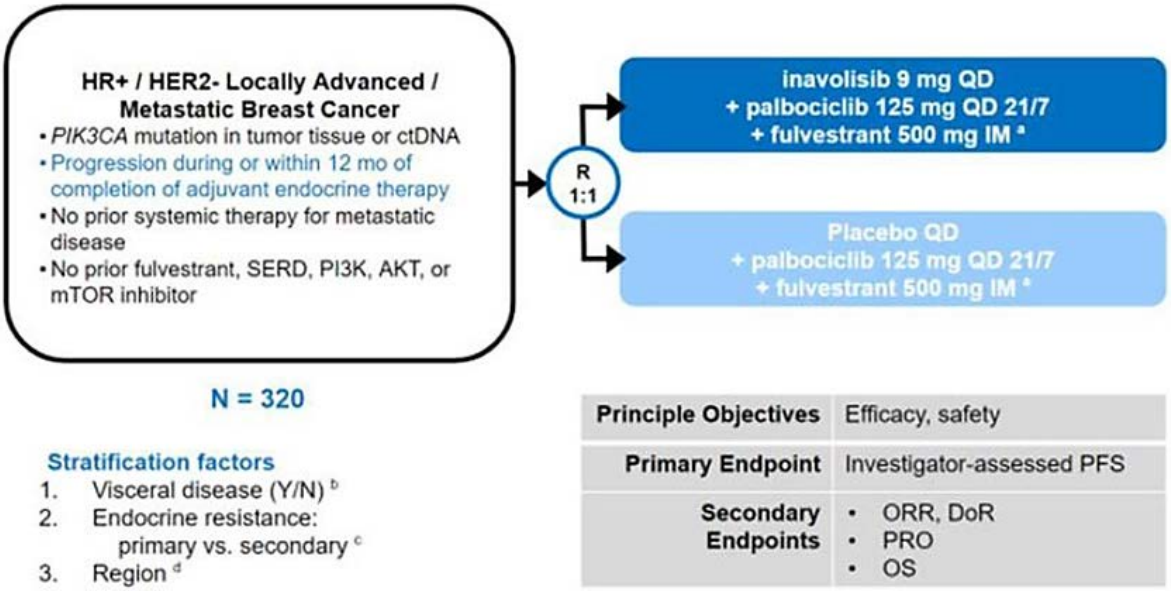
INAVO120 (Study W041554)

INAVO120 is a phase 3, randomised, double-blind placebo-controlled study that assessed inavolisib with palbociclib + fulvestrant compared with placebo with palbociclib + fulvestrant in patients with *PIK3CA*-mutated HR+, HER2- advanced breast cancer who recurred on or within 12 months of adjuvant endocrine therapy and who have not received prior systemic therapy for advanced disease.

Design

Phase 3 randomised, double-blind, placebo-controlled, multi-centre, global study designed to compare the efficacy as measured by investigator assessed progression-free survival (PFS) and the safety of the triplet combination of inavolisib with palbociclib and fulvestrant versus placebo with palbociclib and fulvestrant in patients with *PIK3CA*-mutated, HR+, HER- locally advanced or metastatic breast cancer whose disease progressed during treatment or within 12 months of completing adjuvant ET and who had not received prior systemic therapy for locally advanced or metastatic disease.

Figure 1. INAVO120 (Study W041554) study design



Trial location

The study was conducted at 123 study centres in 28 countries, including Australia.

Diagnostic criteria

Table 3. Diagnostic criteria

Patients	Efficacy evaluation (n = 325) **Key inclusion criteria:** • Histologically or cytologically confirmed adenocarcinoma of the breast that is locally advanced or metastatic and not amenable to surgery or RT with curative intent • Estrogen receptor and/or progesterone receptor positive • HER-2 negative • ***PIK3CA*** mutated tumour (central testing of blood or local testing of blood or tumour tissue) • If female: post-menopausal, otherwise on treatment with luteinizing hormone-releasing hormone (LHRH) agonist • If male: on treatment with LHRH agonist • Progressive disease during adjuvant ET or within 12 months of completing ET with an aromatase inhibitor or tamoxifen • If CDK4/6 inhibitor received as part of (neo)adjuvant therapy, progression event >12 months since completion of CDK4/6 inhibitor portion of (neo)adjuvant therapy • Treatment with endocrine-based therapy (e.g. palbociclib and fulvestrant) was recommended at time of study entry • Measurable disease by RECIST 1.1

	• Adequate organ function including fasting glucose <7.0 mmol/L and HbA1c <6.0% **Key exclusion criteria** • Any prior systemic therapy for metastatic breast cancer • Prior treatment with fulvestrant or selective estrogen receptor degrader • Prior treatment with any PI3K, AKT or mTOR inhibitor • Type 1 diabetes mellitus, or Type 2 diabetes mellitus requiring ongoing systemic therapy at the start of study treatment • Any history of leptomeningeal disease • Known and untreated, or active CNS metastases • Active bowel inflammation • Symptomatic active lung disease • Clinically significant and active liver disease • Clinically significant cardiovascular dysfunction • Chronic corticosteroid therapy of ≥10mg of prednisolone per day or equivalent, for a chronic disease
Intervention	Randomisation 1:1* Arm A (n=161): Inavolisib 9mg orally once daily, in combination with palbociclib 125mg orally once daily for 21 days on/7 days off (28 day cycle) and fulvestrant (500mg) IM on C1D1, C1D15 and C1 of every 28 day cycle thereafter. Patients received treatment until progression or unacceptable toxicity
Comparator	Arm B (n=164) Placebo orally once daily, in combination with palbociclib 125mg orally once daily for 21 days on/7 days off (28 day cycle) and fulvestrant (500mg) IM on C1D1, C1D15 and C1 of every 28 day cycle thereafter.
Endpoints	**Primary endpoint** • PFS (per investigator); prospectively planned sensitivity analysis of PFS (by blinded independent central review) **Key Secondary endpoints** • OS • ORR • DOR • BOR • CBR • PRO

*Stratified by presence of visceral disease (Y/N), endocrine resistance (primary or secondary) and geographic region (N America/Western Europe/Asia/Other).

Patient disposition

At clinical cutoff date 29 September 2023, the median duration of follow-up for all patients was 21.3 months and was similar in both arms. A lower proportion of patients in the inavolisib arm (58.4%) in comparison to the placebo arm (70.1%) had discontinued from all study treatment. The most common reason for study drug discontinuation was progressive disease, which occurred at a higher frequency in the placebo arm.

A lower proportion of patients in the inavolisib arm (35.4%) in comparison to the placebo arm (40.91%) had discontinued from the study; death was the main reason for study discontinuation in both arms.

Protocol violations

Major protocol violations likely did not impact on the outcome or interpretation of study results.

Baseline characteristics

In general, the two arms were well balanced across baseline characteristics.

- Female: 98.2% (all patients)
- Age median: 54.0 years (range: 27, 79)
- White: 58.8.%; Asian 38.2%
- Region: Europe 49.8%; Asia 36.9%; Australia 2.2%
- Endocrine resistance: primary 34.2%; secondary 65.5%
- Visceral disease: 80%; Liver metastases: 51.7%
- Prior therapy: (neo)adjuvant chemotherapy 82.8%; (neo)adjuvant endocrine therapy: 99.4%; adjuvant CDK4/6 inhibitor: 1.2%.

Table 4. Study WO41554 demographic data, full analysis set.

Demographic Parameters	Inavo+Palbo+Fulv (N=161) n (%)	Pbo+Palbo+Fulv (N=164) n (%)	All Patients (N=325) n (%)
Sex			
Male	5 (3.1%)	1 (0.6%)	6 (1.8%)
Female	156 (96.9%)	163 (99.4%)	319 (98.2%)
Age			
Mean years (SD)	53.8 (10.9)	54.1 (11.2)	54.0 (11.1)
Median (years)	53.0	54.4	54.0
Min, max (years)	27,77	29,79	27,79
Age Group			
< 18 years	0	0	0
< 65 years	136 (84.5%)	130 (79.3%)	266 (81.8%)
≥ 65 years	19 (11.8%)	28 (17.1%)	47 (14.5%)
≥ 75 years	6 (3.7%)	6 (3.6%)	12 (3.7%)
Race			
White	94 (58.4%)	97 (59.1%)	191 (58.8%)
Black or African American	1 (0.6%)	1 (0.6%)	2 (0.6%)
Asian	61 (37.9%)	63 (38.4%)	124 (38.2%)
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Other	5	3	8
Ethnicity			
Hispanic or Latino	10 (6.2%)	10 (6.1%)	20 (6.2%)
Not Hispanic or Latino	145 (90.1%)	149 (90.9%)	294 (90.5%)
Not Reported/Unknown	6 (3.7%)	5 (3.0%)	11 (3.3%)
Region			
United States	7 (4.3%)	9 (5.5%)	16 (4.9%)
Rest of the World*	1 (0.6%)	0	1 (0.3%)
Canada	10 (6.2%)	4 (2.4%)	14 (4.3%)
South America	4 (2.5%)	1 (0.6%)	5 (1.5%)
Europe	77 (47.8%)	85 (51.8%)	162 (49.8%)
Asia	58 (36.0%)	62(37.8%)	120 (36.9%)
Australia	4 (2.5%)	3 (1.8%)	7 (2.2%)

*New Zealand

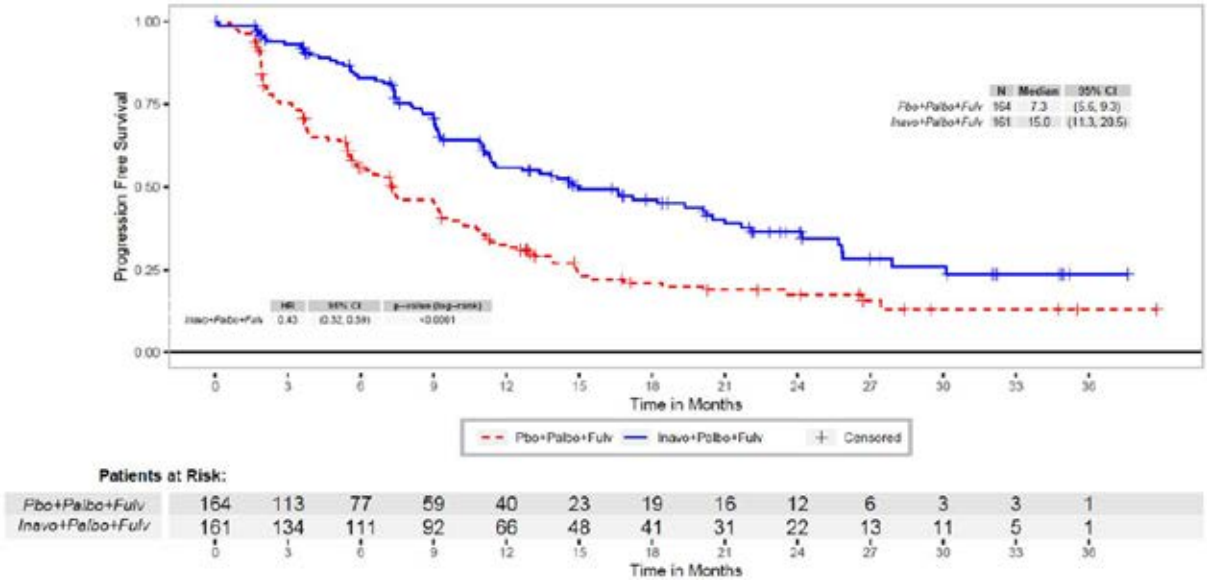
The racial and ethnic minorities appear to be reflective of the Australian population.

Results

Table 5. Overview of study WO41554 efficacy, full analysis set.

	Inavo + Palbo + Fulv N = 161	Pbo + Palbo + Fulv N = 164
Primary Efficacy Endpoints		
Progression-Free Survival (Investigator) per RECIST v1.1		
Patients with event (%)	82 (50.9%)	113 (68.9%)
Median (months) (95% CI)	15.0 (11.3, 20.5)	7.3 (5.6, 9.3)
Stratified HR (95% CI)	0.43 (0.32, 0.59)	
p-value (log-rank)	<0.0001	
Secondary Efficacy Endpoints		
Overall Survival		
Patients with event (%)	42 (26.1%)	55 (33.5%)
Median (months) (95% CI)	NE (27.3, NE)	31.1 (22.3, NE)
Stratified HR (95% CI)	0.64 (0.43, 0.97)	
p-value (log-rank) [a]	0.0338	
Objective Response Rate (Investigator)		
Responders (n) (%)	94 (58.4%)	41 (25.0%)
95% CI (Clopper-Pearson)	50.4, 66.1	18.6, 32.3
Difference in Response rate (%) (95% CI)	33.4 (23.3, 43.5)	
Best Overall Response (Investigator)		
Responders (n) (%)	103 (64.0%)	49 (29.9%)
95% CI (Clopper-Pearson)	56.0, 71.4	23.0, 37.5
Difference in Response rate (%) (95% CI)	34.1 (23.9, 44.3)	
Clinical Benefit Rate (Investigator)		
Responders (n) (%)	121 (75.2%)	77 (47.0%)
95% CI (Clopper-Pearson)	67.7, 81.6	39.1, 54.9
Difference in Response rate (%) (95% CI)	28.2 (18.1, 38.3)	
Duration of Response (Investigator)		
Number of evaluable patients	94	41
Patients with event (%)	46 (48.9%)	27 (65.9%)
Median (months) (95% CI)	18.4 (10.4, 22.2)	9.6 (7.4, 16.6)

Figure 2. Kaplan-Meier plot for PFS by investigator, FAS.



Patients at Risk:

Pbo+Palbo+Fulv	164	113	77	59	40	23	19	16	12	6	3	3	1
Inavo+Palbo+Fulv	161	134	111	92	66	48	41	31	22	13	11	5	1

0 3 6 9 12 15 18 21 24 27 30 33 36

Time in Months

The inavolisib arm demonstrated statistically significant efficacy results over the placebo arm for the primary endpoint of PFS per investigator assessment:

- PFS hazard ratio = 0.43 (95% CI: 0.32, 0.59); p<0.001
- Median PFS = 15.0 months (inavolisib arm) vs 7.3 months (placebo arm) PFS by blinded independent central review results were supportive of the primary endpoint.

PFS results were mostly consistent within subgroups but varied somewhat by age and region, with North America/Western Europe regions performing the worst of the three regions; sample sizes of these groups were small and therefore subgroup analyses should be interpreted with caution.

The efficacy results for the secondary endpoints of overall survival (OS), objective response rate (ORR), best overall objective response rate (BOR), duration of response (DOR) and clinical benefit rate (CBR) are shown in Table 5. It is noted that CBR is not an endpoint evaluated for regulatory decision- making.

Interim analysis of OS at the time of PFS analysis was not statistically significant (none of the remaining secondary endpoints in the pre-specified testing hierarchy were formally tested and results should be considered descriptive). OS data is immature; the final OS analysis is expected in Q2 2025.

Safety

Table 6. Overview of adverse events (safety analysis set):

	Inavo+Palbo+Fulv (N=162)	Pbo+Palbo+Fulv (N=162)
Total number of patients with at least one AE	160 (98.8%)	162 (100%)
Total number of AEs	3298	2058
Total number of deaths	43 (26.5%)	54 (33.3%)
Total number of patients with at least one treatment-related AE		
Inavolisib/Placebo	142 (87.7%)	116 (71.6%)
Palbociclib	152 (93.8%)	153 (94.4%)
Fulvestrant	84 (51.9%)	72 (44.4%)
Any Treatment	158 (97.5%)	153 (94.4%)
Total number of patients with at least one		
AE with fatal outcome	6 (3.7%)	2 (1.2%)
Serious AE	39 (24.1%)	17 (10.5%)
Grade 3-4 AE	143 (88.3%)	133 (82.1%)
AE leading to withdrawal from treatment		
Inavolisib/Placebo	10 (6.2%)	1 (0.6%)
Palbociclib	8 (4.9%)	0
Fulvestrant	5 (3.1%)	0
Any Treatment	11 (6.8%)	1 (0.6%)
AE leading to dose modification/interruption		
Inavolisib/Placebo	113 (69.8%)	57 (35.2%)
Palbociclib	125 (77.2%)	116 (71.6%)
Fulvestrant	52 (32.1%)	34 (21.0%)
Any Treatment	134 (82.7%)	121 (74.7%)

Investigator text for AEs encoded using MedDRA version 26.1.

Treatment emergent adverse events

- All-grade: inavolisib + palbociclib + fulvestrant arm = 99% vs placebo + palbociclib + fulvestrant arm = 100%
- Grade 5 (due to adverse events [AEs]): inavolisib + palbociclib + fulvestrant arm = 4% vs placebo + palbociclib + fulvestrant arm = 1%
- Grade 3-4: inavolisib + palbociclib + fulvestrant arm =86% vs placebo + palbociclib + fulvestrant arm = 82%
- Serious adverse events (SAEs): inavolisib + palbociclib + fulvestrant arm = 24% vs placebo + palbociclib + fulvestrant arm = 10%.

Inavolisib drug discontinuation: inavolisib + palbociclib + fulvestrant arm = 6% vs placebo + palbociclib + fulvestrant arm = 1%.

Inavolisib drug interrupted: inavolisib + palbociclib + fulvestrant arm = 69% vs placebo + palbociclib + fulvestrant arm = 35%.

Inavolisib dose reduced: inavolisib + palbociclib + fulvestrant arm = 14% vs placebo + palbociclib + fulvestrant arm = 3%.

Palbociclib drug discontinuation: inavolisib + palbociclib + fulvestrant arm = 5% vs placebo + palbociclib + fulvestrant arm = 0.

Palbociclib drug interrupted: inavolisib + palbociclib + fulvestrant arm = 71% vs placebo + palbociclib + fulvestrant arm = 61%.

Palbociclib dose reduced: inavolisib + palbociclib + fulvestrant arm = 36% vs placebo + palbociclib + fulvestrant arm = 30%.

Fulvestrant drug discontinuation: inavolisib +palbociclib + fulvestrant arm = 3% vs placebo + palbociclib + fulvestrant arm = 0.

Fulvestrant drug interrupted: inavolisib + palbociclib + fulvestrant arm = 32% vs placebo + palbociclib + fulvestrant arm = 21%.

Adverse events ≥20%

In the inavolisib + palbociclib + fulvestrant arm, the commonest AEs were neutropenia (all grades 89%, grades 3-4 80%), hyperglycaemia (all grades 59%, grades 3-4 6%), stomatitis (all grades 51%, grades 3-4 6%), diarrhoea (all grades 48%, grades 3-4 4%), fatigue (all grades 38%, grades 3-4 2%), anaemia (all grades 36%, grades 3-4 6%), musculoskeletal pain (all grades 29%, grades 3-4 2%), nausea (all grades 28%, grades 3-4 1%), rash (all grades 26%, grades 3-4 0), decreased appetite (all grades 23%, grades 3-4 0), covid-19 (all grades 23%, grades 3-4 2%), thrombocytopenia (all grades 22%, grades 3-4 5%), headache (all grades 22%, grades 3-4 0), and leukopenia (all grades 17%, grades 3-4 6%).

In comparison, the frequencies of these AEs in the placebo + palbociclib + fulvestrant arm were as follows: neutropenia (all grades 90%, grades 3-4 78%), hyperglycaemia (all grades 9%, grades 3-4 0), stomatitis (all grades 27%, grades 3-4 0), diarrhoea (all grades 16%, grades 3-4 0), fatigue (all grades 25%, grades 3-4 2%), anaemia (all grades 36%, grades 3-4 2%), musculoskeletal pain (all grades 25%, grades 3-4 0), nausea (all grades 17%, grades 3-4 0), rash (all grades 19%, grades 3-4 0), decreased appetite (all grades 23%, grades 3-4 0), covid-19 (all grades 10%, grades 3-4 1%), thrombocytopenia (all grades 25%, grades 3-4 2%), headache (all grades 14%, grades 3-4 0), and leukopenia (all grades 25%, grades 3-4 10%).

Deaths

Six deaths due to AEs vs 2 deaths due to AEs in the inavolisib + palbociclib + fulvestrant arm vs placebo + palbociclib + fulvestrant arm, respectively. These were not considered to be due to study drugs.

Adverse events of special interest/submission specific safety issues

Hyperglycaemia, stomatitis/diarrhoea and ocular toxicities (dry eye, blurred vision).

Inclusion of stomatitis and diarrhoea (in addition to hyperglycaemia) in the Warnings and Precautions section of the PI is recommended based on the incidence of these events and the occurrence of severe cases for both stomatitis and diarrhoea in INAVO120.

Risk management plan evaluation summary

Safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 7.

Table 7. Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Hyperglycaemia	P	-	P	P*

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
Important potential risks	None	-	-	-	-
Missing information	Safety in patients with renal impairment	P	P†	P	-
	Safety in patients with type 2 diabetes mellitus	P	P‡	P	-

*patient card

†GP44944

‡PASS

The summary of safety concerns and the pharmacovigilance plan in the Australia-specific annex aligns with the EU-RMP.

The summary of safety concerns is acceptable. Routine and additional pharmacovigilance activities were proposed. Additional pharmacovigilance included a single dose study (GP44944) in moderate to severe renal impairment patients and a PASS to further elucidate safety in patients with Type 2 diabetes mellitus.

Routine and additional risk minimisation activities are proposed. The additional risk minimisation activity is a Patient Card to highlight the Important Identified Risk of hyperglycaemia. The proposed Patient Card includes appropriate information but should also include the Black Triangle Symbol and wording (abbreviated).

Risk-benefit analysis

Treatment with a CDK4/6 inhibitor plus endocrine therapy (fulvestrant or aromatase inhibitor) is the standard of care 1L treatment for patients with advanced HR+, HER2-negative breast cancer. Following progression on 1L therapy, treatment options include: endocrine monotherapy with fulvestrant, AI or tamoxifen (if not received as 1L treatment); ET+CDK4/6 inhibitor (if not used in the 1L setting); everolimus in combination with exemestane; alpelisib plus fulvestrant (for those with a *PIK3CA* mutated tumour); capivasertib plus fulvestrant (*PIK3CA*/*AKT1*/*PTEN* alterations); PARP inhibitor (BRCA1/2 mutations); and chemotherapy/ADCs (e.g. capecitabine; Enhertu for HER2-low following previous chemotherapy in metastatic setting; sacituzumab-govitecan 3L+, etc.).

There are no treatments approved specifically for the 1L treatment of patients with endocrine resistant *PIK3CA* mutated, HR+, HER2-negative advanced breast cancer; generally, these patients are treated with currently available options for HR+, HER2-negative breast cancer. Alpelisib and everolimus (both targeting the PI3K-*AKT*-mTOR pathway) are recommended in 2L+ setting. Capivasertib is approved for use in combination with fulvestrant for the treatment of patients with HR+, HER2-negative advanced breast cancer following recurrence or progression on or after an endocrine based regimen (PFS benefit seen mainly attributed to those whose tumours have a *PIK3CA*, *AKT1* or *PTEN* alteration).

More effective treatments are required for patients with *PIK3CA*-mutated HR+, HER2- advanced breast cancer.

PIK3α inhibitors to date have faced challenges with safety and tolerability. 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 (acts as a mutant degrader).

Benefits/uncertainties of benefit

The Sponsor provided efficacy data from the pivotal study WO41554 (INAVO120), a phase III, global, randomised, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of inavolisib in combination with palbociclib and fulvestrant versus placebo in combination with palbociclib and fulvestrant in patients with *PIK3CA*-mutated, HR+, HER2-negative LA/mBC whose disease progressed during treatment or within 12 months of completing adjuvant ET.

INAVO120 enrolled 325 patients with *PIK3CA*-mutated, HR+, HER2-negative, advanced or metastatic breast cancer, following recurrence on or within 12 months of adjuvant ET and who have not received prior therapy for locally advanced or metastatic disease. Patients were randomised 1:1 to either inavolisib + palbociclib + fulvestrant or placebo + palbociclib + fulvestrant. The primary endpoint was PFS by investigator.

The addition of inavolisib to the combination of palbociclib and fulvestrant demonstrated a statistically significant and clinically meaningful improvement in PFS (compared to Pbo + Palbo + Fulv), by reducing the risk of disease progression or death by 57% in patients with *PIK3CA*-mutated, HR+, HER2- locally advanced/metastatic breast cancer (hazard ratio = 0.43 [95% CI:0.32, 0.59], p < 0.0001). A 7.7 month improvement in median PFS was demonstrated with an increase from 7.3 months in the Pbo + Palbo + Fulv group (95% CI: 5.6, 9.3 months) to 15.0 months (95% CI: 11.3, 20.5) in the Inavo + Palbo + Fulv group. PFS results by blinded independent central review were consistent with results of PFS by investigators. ORR and DOR results were supportive of PFS findings.

OS results were immature at interim analysis (63% maturity), but no detriment seen (hazard ratio =0.64; 95 %CI: 0.43, 0.97; p=0.035); the final OS analysis is expected in Q2 2025.

Uncertainties

Whilst pre-clinical data and early phase clinical data suggest that the combination of inavolisib + palbociclib + fulvestrant may be efficacious in a patient population that is broader than the patient population in INAVO120, currently available data from the pivotal study only supports its use in those with endocrine-therapy resistant disease. The trial specifically enriched for patients with clinicopathologic characteristics associated with a poor prognosis. The indication should reflect this – i.e. in alignment with the INAVO120 study population, use of the inavolisib combination should be restricted to patients who have recurrent disease whilst on (or within 12 months of completing) adjuvant endocrine therapy. The phrase “or progression on an endocrine-based regimen in the metastatic setting” should be removed from the indication.

Note: although other regulatory agencies have accepted the term “endocrine resistant” in the wording of the indication (to reflect the intended population), this terminology is somewhat inconsistent and therefore the Delegate requests that the indication be specifically restricted to those who have disease recurrence on or within 12 months of completing adjuvant endocrine therapy.

The trial was designed to assess the use of only one of the three CDK4/6 inhibitors (specifically palbociclib) currently approved for the treatment of HR+, HER2-negative advanced breast cancer. Data regarding the efficacy and safety of combination treatment with ribociclib or abemaciclib with inavolisib + fulvestrant in patients with advanced breast cancer is limited; ongoing studies are noted e.g. NCT034240005.

Fulvestrant was the endocrine therapy used in the inavolisib arm of the pivotal study; there is limited clinical data available for the use of other endocrine therapy in combination with inavolisib + palbociclib. The Delegate advises that the wording of the indication be revised to reflect this.

OS data remains immature, follow up is ongoing. No OS detriment seen at interim OS analysis. Completion of study and submission of final dataset/analysis including final OS results is expected and will be proposed as one of the conditions of registration.

Very few patients in INAVO120 had previously received adjuvant CDK4/6 inhibitor therapy (1.2%), given timing of the study and availability of adjuvant CDK4/6 inhibitors. It remains to be seen whether previous exposure to CDK4/6 inhibitors as adjuvant therapy affects the efficacy of a CDK4/6 inhibitor as a component of therapy for advanced disease. This does not preclude registration of inavolisib for the intended population within context of this submission.

Patients with diabetes that required ongoing treatment were excluded – further data are required to define the benefit-risk profile in this population.

Diversity among patients was limited, especially in relation to the proportion of Black or African American patients as noted. The FDA corresponding post-marketing commitment aims to address this limitation.

Risks / uncertainties of risk

Overall, the addition of inavolisib to palbociclib and fulvestrant resulted in increased toxicity; however, the median relative dose intensity of palbociclib and fulvestrant was similar between the two treatment arms in INAVO120. Therefore, the triplet combination including inavolisib did not have a significant impact on the ability to administer the full dose of palbociclib + fulvestrant; the discontinuation rate of inavolisib treatment due to adverse events was low (6.2%) demonstrating good tolerability of the triplet regimen.

The safety profile of inavolisib in combination with palbociclib and fulvestrant in INAVO120 demonstrated that the treatment regimen was tolerable, the toxicities were consistent with the known safety profiles of the individual study treatment.

A higher incidence of hyperglycaemia, stomatitis and diarrhoea, including severe cases, was observed in the inavolisib arm. These AEs can be controlled with supportive care and dose modifications. The Warnings and Precautions section of the PI should include hyperglycaemia, stomatitis and diarrhoea to better inform clinicians and to provide guidance for dose modifications.

AE profile:

- Neutropenia 89% vs 90% (inavolisib arm vs placebo arm respectively)
- Stomatitis 51% vs 26% (no grade 4 or 5 events or SAEs)
- Hyperglycaemia 58% vs 8% (no grade 5 events, no DKA or HONK states)
- Diarrhoea 48% vs 16% (no grade 4 or 5 events; 2 events of SAEs, both resolved by DCO)
  Rash 25% vs 17% (no grade 4 or 5 events or SAEs)
- Ocular toxicity 22% vs 13% (mostly dry eye, blurred vision, or increased lacrimation)

Discontinuation of treatment due to AEs: 6.8% vs 0.6%

- Inavolisib or placebo 6% vs 0.6%
- Palbociclib 5% vs 0

- Fulvestrant 3% vs 0

Dose modification/interruption of treatment due to AEs: 82.7% vs 74.7%

- Inavolisib or placebo 69.8% vs 35.2%
- Palbociclib 77.2% vs 71.6%
- Fulvestrant 32.1% vs 21.0%

Safety data from the supportive phase 1 study was limited; however, the safety profile of inavolisib in combination with palbociclib and ET as observed in arms B, E, and F of the supportive study GO39374 was generally consistent with what was seen in INAVO120.

No unexpected safety findings were identified in either study, and the overall safety profile of inavolisib in combination with palbociclib and ET was manageable.

Uncertainties

Fulvestrant was the endocrine therapy used in the inavolisib arm of the pivotal study; there is limited safety data available for other endocrine therapies (in particular aromatase inhibitors) in combination with inavolisib + palbociclib. The wording of the indication should be revised to reflect this, i.e. restricted to inavolisib in combination with palbociclib + fulvestrant.

Risk/benefit balance

Inavolisib in combination with Palbociclib + fulvestrant demonstrated a statistically significant and clinically meaningful improvement in PFS in patients with *PIK3CA*-mutated HR+, HER2- advanced breast cancer who recurred on or within 12 months of adjuvant ET, and who have not received prior systemic therapy for metastatic disease. Median PFS increased from 7.3 to 15.0 months, with a hazard ratio of 0.43 (95% CI 0.32, 0.59; p<0.0001). At 1IA, there appears to be no OS detriment (hazard ratio 0.64; 95% CI: 0.43, 0.97).

The safety profile in the evaluated patient population was manageable, with no new safety signals and a low discontinuation rate.

Overall, the benefit-risk assessment for inavolisib for the patient population as assessed in INAVO120 is favourable.

Conclusions

The benefit risk assessment for inavolisib for the population evaluated is considered to be favourable; consequently, the Delegate supports registration of inavolisib for the following indication:

> *ITOVEBI, in combination with palbociclib and fulvestrant, is 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 within 12 months of completing adjuvant endocrine therapy.*

This wording of the indication was preferred by the Delegate as it better reflected the inclusion criteria of INAVO120 and the intended treatment population. The Sponsor was agreeable to this wording.

Assessment outcome

Based on a review of quality, safety, and efficacy, the TGA decided to register (ITOVEBI) inavolisib for the following indication:

> *"ITOVEBI, in combination with palbociclib and fulvestrant, is 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 within 12 months of completing adjuvant endocrine therapy".*

Specific conditions of registration

ITOVEBI (inavolisib)] is to be included in the Black Triangle Scheme. The PI and CMI for ITOVEBI must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date of first supply of the product.

The ITOVEBI EU-Risk Management Plan (RMP) (version 1.1, dated 2 December 2024, data lock point 15 March 2024), with Australia-Specific Annex (ASA) (version 1.2, dated 13 January 2025), included with submission PM-2024-001518-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

If the product is approved in the EU during the three years period, reports can be provided in line with the published list of EU reference dates no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must be submitted within ninety calendar days of the data lock point for that report.

Conduct, and submit the final report for, a multicentre, randomized clinical trial to further characterize known serious risks with inavolisib including severe hyperglycaemia, stomatitis/mucosal inflammation, and diarrhea, and compare the safety and activity of inavolisib 9 mg daily versus a lower daily dose in patients with *PIK3CA*-mutant, HR+ HER2-negative locally advanced or metastatic breast cancer.

Complete, and submit the final report for, the ongoing renal impairment clinical trial and evaluate the pharmacokinetics and safety of inavolisib in participants with normal renal function and patients with severe renal impairment, to evaluate the serious potential risk of increased drug exposure. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labelling."

Conduct, and submit the final report for, a hepatic impairment clinical trial to evaluate the serious potential risk of increased drug exposure and determine a safe and appropriate dose of inavolisib in patients with moderate and severe hepatic impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labelling."

Conduct, and submit the final report for, a clinical pharmacokinetic trial to evaluate the effect of repeat doses of inavolisib on the single dose pharmacokinetics of a sensitive CYP3A substrate to inform appropriate management strategies for clinically relevant drug interactions. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies — Cytochrome P450 Enzyme-and Transporter-Mediated Drug Interactions."

Conduct, and submit the final report for, a clinical pharmacokinetic trial to evaluate the effect of repeat doses of inavolisib on the single dose pharmacokinetics of a CYP2B6 substrate to inform appropriate management strategies for clinically relevant drug interactions. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies — Cytochrome P450 Enzyme-and Transporter-Mediated Drug Interactions."

Complete and submit the final report for the ongoing clinical trial, INAVO120 (Study WO41554), entitled "A Phase III, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Inavolisib plus Palbociclib and Fulvestrant versus Placebo plus Palbociclib and Fulvestrant in Patients with *PIK3CA*-Mutant, Hormone Receptor-Positive, HER2-Negative Locally Advanced or Metastatic Breast Cancer", to provide the final overall survival (OS) analysis.

Conduct, and submit the final report for, an integrated analysis containing data from clinical trials and post-marketing reports, observational studies (e.g., real-world evidence), and other sources to further characterize the pharmacokinetics (PK), pharmacodynamics (PD), safety and efficacy of inavolisib in racial and ethnic minority patients and older patients age >65 years with *PIK3CA*-mutant, HR+, HER2-negative locally advanced or metastatic breast cancer. The analyses should support comparative safety and efficacy outcome analyses and characterization of potential differences in PK and PD between racial and ethnic minority patients and White patients, and older and younger patients.

Product Information and Consumer Medicines Information

For the most recent Product Information (PI) and Consumer Medicines Information (CMI), please refer to the TGA PI/CMI search facility.

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