



# Itovebi®

## Inavolisib

### Film coated tablets

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#### NAME OF THE MEDICINAL PRODUCT

ITOVEBI 3 mg

ITOVEBI 9 mg

#### QUALITATIVE AND QUANTITATIVE COMPOSITION

##### ITOVEBI 3 mg film-coated tablets

Each film-coated tablet contains 3 mg of inavolisib.

*Excipients with known effect*

Each film-coated tablet contains 22 mg of lactose.

##### ITOVEBI 9 mg film-coated tablets

Each film-coated tablet contains 9 mg of inavolisib.

*Excipients with known effect*

Each film-coated tablet contains 66 mg of lactose.

For the full list of excipients, see section 11.

#### PHARMACEUTICAL FORM

Film-coated tablet (tablet).

#### CLINICAL PARTICULARS

##### **Patient safety information card**

The marketing of ITOVEBI is subject to a risk management plan (RMP) including a 'Patient safety information card'. The 'Patient safety information card', emphasizes important safety information that the patient should be aware of before and during treatment.

Please explain to the patient the need to review the card before starting treatment.

## 1 INDICATIONS AND USAGE

ITOVEBI, in combination with palbociclib and fulvestrant, is indicated for the treatment of adults with endocrine-resistant, *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 completing adjuvant endocrine therapy [see *Clinical Studies (14.1)*].

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Patient Selection

Select patients for the treatment of HR-positive, HER2-negative, locally advanced or metastatic breast cancer with ITOVEBI based on the presence of one or more *PIK3CA* mutations in plasma specimens [see *Clinical Studies (14.1)*].

### 2.2 Recommended Evaluation Before Initiating ITOVEBI

Evaluate fasting plasma glucose (FPG)/blood glucose (FBG) and hemoglobin A<sub>1C</sub> (HbA<sub>1C</sub>) and optimize blood glucose prior to starting ITOVEBI and at regular intervals during treatment [see *Warnings and Precautions (5.1)*].

### 2.3 Recommended Dosage

The recommended dosage of ITOVEBI is 9 mg taken orally once daily, with or without food, until disease progression or unacceptable toxicity.

Advise patients to take ITOVEBI at approximately the same time each day.

Swallow ITOVEBI tablet(s) whole. Do not chew, crush, or split prior to swallowing.

If a patient misses a dose, instruct the patient to take the missed dose as soon as possible within 9 hours. After more than 9 hours, instruct the patient to skip the dose and take the next dose at the scheduled time.

If a patient vomits a dose, instruct patients not to take an additional dose on that day and resume the usual dosing schedule the next day.

Administer ITOVEBI in combination with palbociclib and fulvestrant. The recommended dosage of palbociclib is 125 mg taken orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a cycle of 28 days. Refer to the Full Prescribing Information for palbociclib and fulvestrant for dosing information.

For premenopausal and perimenopausal women, administer a luteinizing hormone-releasing hormone (LHRH) agonist in accordance with local clinical practice.

For men, consider administering an LHRH agonist in accordance with local clinical practice.

### 2.4 Dosage Modifications for Adverse Reactions

The recommended dose reduction levels of ITOVEBI for adverse reactions are listed in Table 1. Permanently discontinue ITOVEBI if patients are unable to tolerate the second dose reduction.

**Table 1: Dose Reduction for Adverse Reactions**

Dose Level	Dose and Schedule
Recommended starting dose	9 mg daily
First dose reduction	6 mg daily
Second dose reduction	3 mg daily

The recommended dosage modifications of ITOVEBI for adverse reactions are summarized in Table 2.

**Table 2: Recommended Dosage Modifications for Adverse Reactions**

Adverse Reaction	Severity	Dosage Modification
<b>Hyperglycemia<sup>a</sup></b> <i>[see Warnings and Precautions (5.1)]</i>	Fasting glucose levels (FPG or FBG) > ULN to 160 mg/dL (> ULN – 8.9 mmol/L)	<ul style="list-style-type: none"> <li>No adjustment of ITOVEBI required.</li> <li>Consider dietary modifications and ensure adequate hydration.</li> <li>Initiate or intensify oral anti-hyperglycemic medications for patients with risk factors for hyperglycemia.</li> </ul>
	Fasting glucose levels > 160 to 250 mg/dL (> 8.9 – 13.9 mmol/L)	<ul style="list-style-type: none"> <li>Withhold ITOVEBI until FPG or FBG ≤ 160 mg/dL (≤ 8.9 mmol/L).</li> <li>Initiate or intensify anti-hyperglycemic medications.</li> <li>Resume ITOVEBI at the same dose level.</li> <li>If FPG or FBG persists &gt; 200 – 250 mg/dL (&gt; 11.1 – 13.9 mmol/L) for 7 days under appropriate anti-hyperglycemic treatment, consider consultation with a healthcare professional experienced in the treatment of hyperglycemia.</li> </ul>
	Fasting glucose levels > 250 to 500 mg/dL (> 13.9 – 27.8 mmol/L)	<ul style="list-style-type: none"> <li>Withhold ITOVEBI.</li> <li>Initiate or intensify anti-hyperglycemic medications.</li> <li>Administer appropriate hydration if required.</li> <li>If FPG or FBG decreases to ≤ 160 mg/dL (≤ 8.9 mmol/L) within 7 days, resume ITOVEBI at the same dose level.</li> <li>If FPG or FBG decreases to ≤ 160 mg/dL (≤ 8.9 mmol/L) in ≥ 8 days, resume ITOVEBI at one lower dose level.</li> <li>If FPG or FBG &gt; 250 to 500 mg/dL (&gt; 13.9 – 27.8 mmol/L) recurs within 30 days, withhold ITOVEBI until FPG or FBG decreases to ≤ 160 mg/dL (≤ 8.9 mmol/L). Resume ITOVEBI at one lower dose level.</li> </ul>
	Fasting glucose levels > 500 mg/dL (> 27.8 mmol/L)	<ul style="list-style-type: none"> <li>Withhold ITOVEBI.</li> <li>Initiate or intensify anti-hyperglycemic medications.</li> <li>Assess for volume depletion and ketosis and administer appropriate hydration.</li> <li>If FPG or FBG decreases to ≤ 160 mg/dL (≤ 8.9 mmol/L), resume ITOVEBI at one lower dose level.</li> <li>If FPG or FBG &gt; 500 mg/dL (&gt; 27.8 mmol/L) recurs within 30 days, permanently discontinue ITOVEBI.</li> </ul>
<b>Stomatitis</b> <i>[see Warnings and Precautions (5.2)]</i>	Grade 1 <sup>b</sup>	<ul style="list-style-type: none"> <li>No adjustment of ITOVEBI required.</li> <li>Initiate or intensify appropriate medical therapy (e.g., corticosteroid-containing mouthwash) as clinically indicated.</li> </ul>
	Grade 2 <sup>b</sup>	<ul style="list-style-type: none"> <li>Withhold ITOVEBI until recovery to Grade ≤ 1.</li> <li>Initiate or intensify appropriate medical therapy. Resume ITOVEBI at the same dose level.</li> <li>For recurrent Grade 2 stomatitis, withhold ITOVEBI until recovery to Grade ≤ 1, then resume ITOVEBI at one lower dose level.</li> </ul>
	Grade 3 <sup>b</sup>	<ul style="list-style-type: none"> <li>Withhold ITOVEBI until recovery to Grade ≤ 1.</li> <li>Initiate or intensify appropriate medical therapy. Resume ITOVEBI at one lower dose level.</li> </ul>
	Grade 4 <sup>b</sup>	<ul style="list-style-type: none"> <li>Permanently discontinue ITOVEBI.</li> </ul>

Adverse Reaction	Severity	Dosage Modification
<b>Diarrhea</b> [see Warnings and Precautions (5.3)]	Grade 1 <sup>b</sup>	<ul style="list-style-type: none"> <li>No adjustment of ITOVEBI required.</li> <li>Initiate appropriate medical therapy and monitor as clinically indicated.</li> </ul>
	Grade 2 <sup>b</sup>	<ul style="list-style-type: none"> <li>Withhold ITOVEBI until recovery to Grade <math>\leq 1</math>, then resume ITOVEBI at the same dose level.</li> <li>Initiate or intensify appropriate medical therapy and monitor as clinically indicated.</li> <li>For recurrent Grade 2 diarrhea, withhold ITOVEBI until recovery to Grade <math>\leq 1</math>, then resume ITOVEBI at one lower dose level.</li> </ul>
	Grade 3 <sup>b</sup>	<ul style="list-style-type: none"> <li>Withhold ITOVEBI until recovery to Grade <math>\leq 1</math>, then resume ITOVEBI at one lower dose level.</li> <li>Initiate or intensify appropriate medical therapy and monitor as clinically indicated.</li> </ul>
	Grade 4 <sup>b</sup>	<ul style="list-style-type: none"> <li>Permanently discontinue ITOVEBI.</li> </ul>
<b>Hematologic Toxicities</b> [see Adverse Reactions (6.1)]	Grade 1, 2, or 3 <sup>b</sup>	<ul style="list-style-type: none"> <li>No adjustment of ITOVEBI required.</li> <li>Monitor complete blood count and for signs or symptoms of hematologic toxicities as clinically indicated.</li> </ul>
	Grade 4 <sup>b</sup>	<ul style="list-style-type: none"> <li>Withhold ITOVEBI until recovery to Grade <math>\leq 2</math>.</li> <li>Resume ITOVEBI at the same dose level or reduce to one lower dose level as clinically indicated.</li> </ul>
<b>Other Adverse Reactions</b> [see Adverse Reactions (6.1)]	Grade 1 <sup>b</sup>	<ul style="list-style-type: none"> <li>No adjustment of ITOVEBI required.</li> </ul>
	Grade 2 <sup>b</sup>	<ul style="list-style-type: none"> <li>Consider withholding ITOVEBI, if clinically indicated, until recovery to Grade <math>\leq 1</math>.</li> <li>Resume ITOVEBI at the same dose level.</li> </ul>
	Grade 3 (first event) <sup>b</sup>	<ul style="list-style-type: none"> <li>Withhold ITOVEBI until recovery to Grade <math>\leq 1</math>.</li> <li>Resume ITOVEBI at the same dose level or one lower dose level based on clinical evaluation.</li> </ul>
	Grade 3 (recurrent) <sup>b</sup>	<ul style="list-style-type: none"> <li>Withhold ITOVEBI until recovery to Grade <math>\leq 1</math>.</li> <li>Resume ITOVEBI at one lower dose level.</li> </ul>
	Grade 4 <sup>b</sup>	<ul style="list-style-type: none"> <li>Permanently discontinue ITOVEBI.</li> </ul>
<p><sup>a</sup> Before initiating treatment with ITOVEBI, test FPG or FBG, and HbA<sub>1C</sub> levels, and optimize plasma/blood glucose levels in all patients. After initiating treatment with ITOVEBI, monitor FPG or FBG levels based on the recommended schedule, and as clinically indicated [see Warnings and Precautions (5.1)].</p> <p><sup>b</sup> Based on CTCAE version 5.0.</p>		

## 2.5 Dosage Modification for Moderate Renal Impairment

The recommended starting dosage of ITOVEBI for patients with moderate renal impairment (eGFR 30 to < 60 mL/min based on CKD-EPI) is 6 mg orally once daily [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].

## 3 DOSAGE FORMS AND STRENGTHS

Tablets:

- 3 mg: red and round convex-shaped with an “INA 3” debossing on one side.
- 9 mg: pink and oval-shaped with an “INA 9” debossing on one side.

## 4 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 11

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Hyperglycemia

Severe or fatal hyperglycemia, including ketoacidosis, can occur in patients treated with ITOVEBI. Ketoacidosis with a fatal outcome has occurred in the postmarketing setting. Increased fasting glucose occurred in 85% of patients treated with ITOVEBI, including 22% of patients with Grade 2 (FPG > 160 to 250 mg/dL), 12% with Grade 3 (FPG > 250 to 500 mg/dL), and 0.6% with Grade 4 (FPG > 500 mg/dL) events.

In INAVO120, 46% (74/162) of patients who received ITOVEBI were treated with oral anti-hyperglycemic medications and 7% (11/162) were treated with insulin to manage increased fasting glucose. In patients who experienced increased fasting glucose of > 160 mg/dL, 96% (52/54) had an improvement in fasting glucose of at least one grade level with a median time to improvement of 8 days (range: 2 to 43 days).

Among patients with hyperglycemia, the median time to first onset was 7 days (range: 2 to 955 days). Hyperglycemia led to dose interruption in 28%, to dose reduction in 2.5%, and to discontinuation of ITOVEBI in 1.2% of patients.

The safety of ITOVEBI in patients with Type 1 diabetes mellitus, or Type 2 diabetes mellitus requiring ongoing anti-hyperglycemic treatment have not been studied.

Before initiating treatment with ITOVEBI, test fasting glucose levels (FPG or FBG), HbA<sub>1C</sub> levels, and optimize fasting glucose.

After initiating treatment with ITOVEBI, or in patients who experience hyperglycemia after initiating treatment with ITOVEBI, monitor or self-monitor fasting glucose levels 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. Monitor HbA<sub>1C</sub> every 3 months and as clinically indicated.

Manage hyperglycemia with anti-hyperglycemic medications as clinically indicated. During treatment with anti-hyperglycemic medication, continue monitoring fasting glucose levels. Patients with a history of well-controlled Type 2 diabetes mellitus may require intensified anti-hyperglycemic treatment and close monitoring of fasting glucose levels.

Consider consultation with a healthcare professional experienced in the treatment of hyperglycemia, and initiation of fasting glucose monitoring at home for patients who have risk factors for hyperglycemia or who experience hyperglycemia. Advise patients of the signs and symptoms of hyperglycemia and counsel patients on lifestyle changes.

Based on the severity of the hyperglycemia, ITOVEBI may require dose interruption, reduction, or discontinuation [*see Dosage and Administration (2.4)*].

### 5.2 Stomatitis

Severe stomatitis can occur in patients treated with ITOVEBI.

Stomatitis occurred in 51% of patients treated with ITOVEBI in combination with palbociclib and fulvestrant, including Grade 3 events in 6% of patients. The median time to first onset was 13 days (range: 1 to 610 days).

Stomatitis led to dose interruption in 10%, to dose reduction in 3.7%, and to discontinuation of ITOVEBI in 0.6% of patients.

In patients who received ITOVEBI in combination with palbociclib and fulvestrant, 38% used a mouthwash containing corticosteroid for management or prophylaxis of stomatitis.

Monitor patients for signs and symptoms of stomatitis. Withhold, reduce dose, or permanently discontinue ITOVEBI based on severity [see *Dosage and Administration (2.4)*].

### **5.3 Diarrhea**

Severe diarrhea, including dehydration and acute kidney injury, can occur in patients treated with ITOVEBI.

Diarrhea occurred in 48% of patients treated with ITOVEBI in combination with palbociclib and fulvestrant, including Grade 3 events in 3.7% of patients. The median time to first onset was 15 days (range: 2 to 602 days). Diarrhea led to dose interruptions in 7% of patients, and dose reductions in 1.2% of patients. Anti-diarrheal medicines were used in 28% (46/162) of patients who received ITOVEBI in combination with palbociclib and fulvestrant to manage symptoms.

Monitor patients for signs and symptoms of diarrhea. Advise patients to increase oral fluids and start anti-diarrheal treatment at the first sign of diarrhea while taking ITOVEBI. Withhold, reduce dose, or permanently discontinue ITOVEBI based on severity [see *Dosage and Administration (2.4)*].

### **5.4 Embryo-Fetal Toxicity**

Based on findings in animals and its mechanism of action, ITOVEBI can cause fetal harm when administered to a pregnant woman [see *Clinical Pharmacology (12.1)*]. In an animal reproduction study, oral administration of inavolisib to pregnant rats during the period of organogenesis caused adverse developmental outcomes, including embryo-fetal mortality, structural abnormalities, and alterations to growth at maternal exposures approximately equivalent to the human exposure at the recommended dose of 9 mg/day based on area under the curve (AUC).

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with ITOVEBI and for 1 week after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ITOVEBI and for 1 week after the last dose [see *Use in Specific Populations (8.1 and 8.3)*].

ITOVEBI is used in combination with palbociclib and fulvestrant. Refer to the Full Prescribing Information of palbociclib and fulvestrant for pregnancy and contraception information.

### **5.5 Effects on ability to drive and use machines**

Itovebi has minor influence on the ability to drive or use machines because fatigue has been reported during treatment with ITOVEBI.

## **6 ADVERSE REACTIONS**

The following adverse reactions are discussed in greater detail in other sections of the label:

- Hyperglycemia [see *Warnings and Precautions (5.1)*]
- Stomatitis [see *Warnings and Precautions (5.2)*]
- Diarrhea [see *Warnings and Precautions (5.3)*]

### **6.1 Clinical Trial Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

## Locally Advanced or Metastatic Breast Cancer

### INAVO120

The safety of ITOVEBI was evaluated in a randomized, double-blind, placebo-controlled study (INAVO120) in 324 patients with *PIK3CA*-mutated, HR-positive, HER2-negative, locally advanced or metastatic breast cancer [see *Clinical Studies (14.1)*].

Patients received either ITOVEBI 9 mg (n=162) or placebo (n=162) with palbociclib and fulvestrant. The median duration of treatment with ITOVEBI was 9 months (range: 0 to 39 months) in the ITOVEBI with palbociclib and fulvestrant arm.

Serious adverse reactions occurred in 24% of patients who received ITOVEBI with palbociclib and fulvestrant. Serious adverse reactions in  $\geq 1\%$  of patients included anemia (1.9%), diarrhea (1.2%), and urinary tract infection (1.2%).

Fatal adverse reactions occurred in 3.7% of patients who received ITOVEBI with palbociclib and fulvestrant, including (0.6% each) acute coronary syndrome, cerebral hemorrhage, cerebrovascular accident, COVID-19 infection, and gastrointestinal hemorrhage.

Permanent discontinuation of ITOVEBI due to an adverse reaction occurred in 6% of patients. Adverse reactions which resulted in permanent discontinuation of ITOVEBI included hyperglycemia (1.2%), and (0.6% each) stomatitis, gastric ulcer, intestinal perforation, anal abscess, increased ALT, decreased weight, bone pain, musculoskeletal pain, transitional cell carcinoma, and acute kidney injury.

Dosage interruptions of ITOVEBI due to an adverse reaction occurred in 69% of patients. Adverse reactions which required dosage interruption in  $\geq 2\%$  of patients included hyperglycemia (28%), neutropenia (23%), COVID-19 infection (16%), stomatitis (10%), diarrhea (7%), thrombocytopenia (4.9%), anemia (4.3%), upper respiratory tract infection (4.3%), decreased white blood cell count (3.7%), pyrexia (3.1%), nausea (2.5%), and fatigue (2.5%).

Dose reductions of ITOVEBI due to adverse reactions occurred in 14% of patients. Adverse reactions which required dose reduction of ITOVEBI in  $\geq 2\%$  of patients were stomatitis (3.7%) and hyperglycemia (2.5%).

The most common ( $\geq 20\%$ ) adverse reactions, including laboratory abnormalities, were decreased neutrophils, decreased hemoglobin, increased fasting glucose, decreased platelets, decreased lymphocytes, stomatitis, diarrhea, decreased calcium, fatigue, decreased potassium, increased creatinine, increased ALT, nausea, decreased sodium, decreased magnesium, rash, decreased appetite, COVID-19 infection, and headache.

Adverse reactions and laboratory abnormalities in INAVO120 are summarized in Table 3 and Table 4, respectively. Patient-reported symptoms are summarized in Table 5.

**Table 3: Adverse Reactions ( $\geq 10\%$  with  $\geq 5\%$  [All Grades] or  $\geq 2\%$  [Grade 3-4] Higher Incidence in the ITOVEBI Arm) in INAVO120**

Adverse Reaction	ITOVEBI + Palbociclib + Fulvestrant N=162		Placebo + Palbociclib + Fulvestrant N=162	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
<b>Gastrointestinal Disorders</b>				
Stomatitis <sup>a</sup>	51	6*	27	0
Diarrhea	48	3.7*	16	0
Nausea	28	0.6*	17	0
Vomiting	15	0.6*	5	1.2*
<b>General Disorders and Administration Site Conditions</b>				

Adverse Reaction	ITOVEBI + Palbociclib + Fulvestrant N=162		Placebo + Palbociclib + Fulvestrant N=162	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Fatigue	38	1.9*	25	1.2*
<b>Skin and Subcutaneous Tissue Disorders</b>				
Rash <sup>b</sup>	26	0	19	0
Alopecia	19	0	6	0
Dry skin <sup>c</sup>	13	0	4.3	0
<b>Metabolism and Nutrition Disorders</b>				
Decreased appetite	24	0	9	0
<b>Infections and Infestations</b>				
COVID-19 infection	23	1.9	11	0.6
Urinary tract infection <sup>b</sup>	15	1.2*	9	0
<b>Nervous System Disorders</b>				
Headache <sup>b</sup>	22	0	14	0
<b>Investigations</b>				
Decreased weight	17	3.7*	0.6	0
* No Grade 4 adverse reactions were observed.				
<sup>a</sup> Includes aphthous ulcer, glossitis, glossodynia, lip ulceration, mouth ulceration, mucosal inflammation, and stomatitis.				
<sup>b</sup> Includes other related terms.				
<sup>c</sup> Includes dry skin, skin fissures, xerosis, and xeroderma.				

Clinically relevant adverse reactions occurring in < 10% of patients who received ITOVEBI in combination with palbociclib and fulvestrant included abdominal pain, dry eye, dysgeusia, and dyspepsia.

**Table 4: Select Laboratory Abnormalities (≥ 10% with a ≥ 2% [All Grades or Grade 3-4] Higher Incidence in the ITOVEBI Arm) in INAVO120**

Laboratory Abnormality	ITOVEBI + Palbociclib + Fulvestrant <sup>a</sup>		Placebo + Palbociclib + Fulvestrant <sup>b</sup>	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
<b>Hematology</b>				
Neutrophils (total, absolute) decreased	95	82	97	79
Hemoglobin decreased	88	8*	85	2.5*
Platelets decreased	84	16	71	3.7
Lymphocytes (absolute) decreased	72	9	68	14
<b>Chemistry</b>				
Glucose (fasting) increased <sup>c</sup>	85	12	43	0
Calcium decreased	42	3.1	32	3.7
Potassium decreased	38	6	21	0.6*
Creatinine increased	38	1.9*	30	1.2*
ALT increased	34	3.1*	29	1.2*

Laboratory Abnormality	ITOVEBI + Palbociclib + Fulvestrant <sup>a</sup>		Placebo + Palbociclib + Fulvestrant <sup>b</sup>	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Sodium decreased	28	2.5*	19	2.5
Magnesium decreased	27	0.6	21	0
Lipase (fasting) increased	16	1.4*	7	0

ALT = alanine aminotransferase

\* No Grade 4 laboratory abnormalities were observed.

<sup>a</sup> 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.

<sup>b</sup> 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.

<sup>c</sup> Grading according to CTCAE version 4.03.

In INAVO120, patient-reported symptomatic toxicities (i.e., diarrhea, nausea, vomiting, fatigue, mouth sores, decreased appetite, and rash) were assessed via the Patient-Reported Outcomes – Common Terminology Criteria for Adverse Events (PRO-CTCAE) at baseline, every two weeks through Cycle 3 Day 15, and then Day 1 of every other 28-day cycle until treatment discontinuation.

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

**Table 5: Patient-Reported Symptoms Assessed by PRO-CTCAE in INAVO120**

Symptom (Attribute) <sup>a</sup>	Any Symptom Before Treatment (%) <sup>b</sup>		Any Worsening on Treatment (%) <sup>c</sup>		Worsening to Score 3 or 4 (%) <sup>d</sup>	
	ITOVEBI + P + F (N=148) <sup>e</sup>	Placebo + P + F (N=152) <sup>e</sup>	ITOVEBI + P + F (N=148) <sup>e</sup>	Placebo + P + F (N=152) <sup>e</sup>	ITOVEBI + P + F (N=148) <sup>e</sup>	Placebo + P + F (N=152) <sup>e</sup>
Diarrhea (frequency), %	23	15	78	49	32	8
Nausea (frequency), %	21	21	59	50	20	11
Vomiting (frequency), %	9	6	35	26	6	3.3
Fatigue (severity), %	72	69	72	58	32	22
Mouth sores (severity), %	11	14	74	52	30	9
Decreased appetite (severity), %	38	28	78	55	26	12
Symptom (Attribute)	Baseline Presence		Post-baseline Presence			
	ITOVEBI + P + F (N=148) <sup>e</sup>	Placebo + P + F (N=152) <sup>e</sup>	ITOVEBI + P + F (N=148) <sup>e</sup>	Placebo + P + F (N=152) <sup>e</sup>		
Rash (yes), %	5	5	50	38		

ITOVEBI+P+F = ITOVEBI with palbociclib and fulvestrant arm; Placebo+P+F = placebo with palbociclib and fulvestrant arm.  
<sup>a</sup> 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’.  
<sup>b</sup> The percentage of patients whose symptom score before treatment was 1-4.  
<sup>c</sup> The percentage of patients whose symptom score increased during treatment, with respect to their score before treatment.  
<sup>d</sup> The percentage of patients whose symptom score increased to 3 or 4 during treatment, with respect to their score before treatment.  
<sup>e</sup> The number of patients who provided a score before treatment and at least one on-treatment score.

Patient-reported overall side-effect impact was assessed using the Modified Bother Item (MBI). Patients provided a response to “I am bothered by side effects of treatment,” and at baseline the proportion of patients with MBI responses of “not at all” were 70% in the ITOVEBI with palbociclib and fulvestrant arm and 76% in the placebo with palbociclib and fulvestrant arm. At Cycle 2 Day 15, the proportion of patients with MBI responses of “not at all” were 25% in the ITOVEBI with palbociclib and fulvestrant arm and 53% in the placebo with palbociclib and fulvestrant arm. Through 31 cycles of treatment, patients in the ITOVEBI with palbociclib and fulvestrant arm reported more side effect bother compared to the placebo with palbociclib and fulvestrant arm.

## 6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ITOVEBI. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

*Metabolism and Nutrition Disorders: Ketoacidosis*

## Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: <https://sideeffects.health.gov.il>

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

ITOVEBI is used in combination with palbociclib and fulvestrant. Refer to the Full Prescribing Information of palbociclib and fulvestrant for pregnancy information.

Based on animal data and its mechanism of action, ITOVEBI can cause fetal harm when administered to a pregnant woman [*see Clinical Pharmacology (12.1)*]. There are no available data on the use of ITOVEBI in pregnant women to inform a drug-associated risk. In an animal reproduction study, oral administration of inavolisib to pregnant rats during the period of organogenesis caused adverse developmental outcomes, including embryo-fetal mortality, structural abnormalities, and alterations to growth at maternal exposures approximately equivalent to the human exposure at the recommended dose of 9 mg/day based on AUC (*see Data*). Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown.

#### Data

##### *Animal Data*

In an embryo-fetal development study, pregnant rats received oral doses of inavolisib up to 6 mg/kg/day during the period of organogenesis. Administration of doses  $\geq 2$  mg/kg/day resulted in decreases in fetal body weight and placental weight, post-implantation loss, lower fetal viability, fetal malformations (including kyphosis of vertebral column, fused thoracic arch, microphthalmia) and variations (including dilated renal pelvis, short supernumerary rib, wavy rib). At a dose of 2 mg/kg/day, maternal exposures were 0.9 times the human exposure at the recommended dose of 9 mg/day based on AUC.

### 8.2 Lactation

#### Risk Summary

ITOVEBI is used in combination with palbociclib and fulvestrant. Refer to the Full Prescribing Information of palbociclib and fulvestrant for lactation information.

There are no data on the presence of inavolisib or its metabolites in human milk, its effects on milk production or a breastfed child. Because of the potential for serious adverse reactions in a breastfed child, advise lactating women to not breastfeed during treatment with ITOVEBI and for 1 week after the last dose.

### 8.3 Females and Males of Reproductive Potential

ITOVEBI is used in combination with palbociclib and fulvestrant. Refer to the Full Prescribing Information of palbociclib and fulvestrant for contraception and infertility information.

ITOVEBI can cause fetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1)*].

#### Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating treatment with ITOVEBI.

#### Contraception

##### *Females*

Advise females of reproductive potential to use effective non-hormonal contraception during treatment with ITOVEBI and for 1 week after the last dose.

#### *Males*

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ITOVEBI and for 1 week after the last dose.

#### Infertility

Based on animal studies, ITOVEBI may impair fertility in females and males of reproductive potential [*see Nonclinical Toxicology (13.1)*].

#### **8.4 Pediatric Use**

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

#### **8.5 Geriatric Use**

Of the 162 patients who received ITOVEBI in INAVO120, 15% were  $\geq 65$  years of age, and 3% were  $\geq 75$  years of age.

Dosage modifications or interruptions of ITOVEBI due to adverse reactions occurred at a higher incidence for patients  $\geq 65$  years of age compared to younger patients (79% versus 68%, respectively).

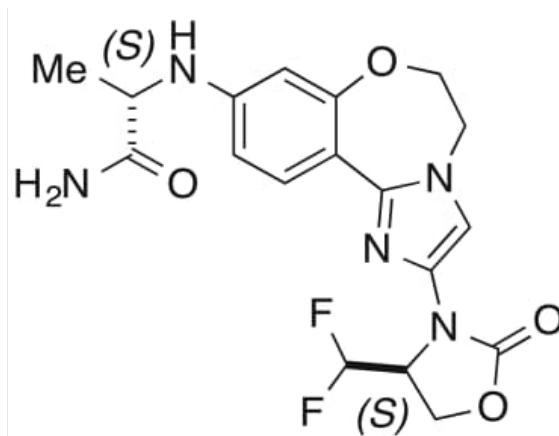
Clinical studies of ITOVEBI did not include sufficient numbers of patients  $\geq 65$  years of age to determine whether they respond differently from younger patients.

#### **8.6 Renal Impairment**

Reduce the dosage in patients with moderate renal impairment (eGFR 30 to  $< 60$  mL/min based on CKD-EPI) [*see Dosage and Administration (2.5)*]. No dosage modification is recommended in patients with mild renal impairment (eGFR 60 to  $< 90$  mL/min). ITOVEBI has not been evaluated in patients with severe renal impairment (eGFR  $< 30$  mL/min).

### **11 DESCRIPTION**

ITOVEBI contains inavolisib, a kinase inhibitor. The chemical name of inavolisib is (2S)-2-[[2-[(4S)-4-(difluoromethyl)-2-oxo-oxazolidin-3-yl]-5,6-dihydroimidazo[1,2-d][1,4]benzoxazepin-9-yl]amino]propanamide. Inavolisib is a white to off-white, greyish pink, greyish orange, or greyish yellow powder or powder with lumps. Inavolisib demonstrates pH-dependent aqueous solubility; the greatest solubility is at low pH, and solubility decreases with increasing pH. The molecular formula for inavolisib is  $C_{18}H_{19}F_2N_5O_4$  and the molecular weight is 407.37 g/mol. The chemical structure of inavolisib is shown below:



ITOVEBI film-coated tablets are supplied for oral administration with two strengths that contain 3 mg and 9 mg of inavolisib. The tablets also contain microcrystalline cellulose, lactose, sodium starch glycolate and magnesium stearate, . The film-coating contains the following inactive ingredients: polyvinyl alcohol (partially

hydrolyzed), titanium dioxide, macrogol/polyethylene glycol, talc, iron oxide red, and iron oxide yellow (in the 9 mg tablet only).

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Inavolisib is an inhibitor of phosphatidylinositol 3-kinase (PI3K) with inhibitory activity predominantly against PI3K $\alpha$ . In vitro, inavolisib induced the degradation of mutated PI3K catalytic alpha subunit p110 $\alpha$  (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 tumor growth in *PIK3CA*-mutated, estrogen receptor-positive, breast cancer xenograft models. The combination of inavolisib with palbociclib and fulvestrant increased tumor growth inhibition compared to each treatment alone or the doublet combinations.

### 12.2 Pharmacodynamics

#### Exposure-Response Relationships

The exposure-response relationship for the efficacy of inavolisib has not been fully characterized. Inavolisib time course of pharmacodynamic response is unknown. Higher systemic exposure of inavolisib was associated with higher incidence of Grade  $\geq 2$  anemia, Grade  $\geq 2$  hyperglycemia, and inavolisib dosage modifications due to adverse reactions.

#### Cardiac Electrophysiology

At the recommended approved dosage, a mean increase in the QTc interval of  $> 20$  ms is unlikely.

### 12.3 Pharmacokinetics

Inavolisib pharmacokinetics are presented as geometric mean (geometric coefficient of variation [geo CV]%) following administration of the approved recommended dosage unless otherwise specified. The inavolisib steady-state AUC is 1,010 h\*ng/mL (25%) and C<sub>max</sub> is 69 ng/mL (27%). Steady-state concentrations are predicted to be attained by day 5.

Inavolisib accumulation is approximately 2-fold.

Inavolisib steady-state AUC is proportional with dose from 6 to 12 mg (0.7 to 1.3 times the approved recommended dosage).

#### Absorption

Inavolisib absolute oral bioavailability is 76%. Inavolisib steady-state median (min, max) time to maximum plasma concentration (T<sub>max</sub>) is 3 hours (0.5, 4 hours).

#### *Effect of Food*

No clinically significant differences in inavolisib pharmacokinetics were observed following administration of inavolisib with a high-fat meal (approximately 1,000 calories, 50% fat).

#### Distribution

Inavolisib apparent (oral) volume of distribution is 155 L (26%). Inavolisib plasma protein binding is 37% and is not concentration-dependent in vitro. Inavolisib blood-to-plasma ratio is 0.8.

#### Elimination

Inavolisib elimination half-life is 15 hours (24%) with a total clearance of 8.8 L/hr (29%).

#### *Metabolism*

Inavolisib is primarily metabolized by hydrolysis. In vitro, inavolisib was minimally metabolized by CYP3A.

#### *Excretion*

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

### Specific Populations

No clinically significant differences in the pharmacokinetics of inavolisib were observed based on age (27 to 85 years), sex, race (Asian or White), body weight (39 to 159 kg), or mild hepatic impairment (total bilirubin > ULN to  $\leq 1.5 \times$  ULN or AST > ULN and total bilirubin  $\leq$  ULN). The effect of moderate to severe hepatic impairment on inavolisib pharmacokinetics is unknown.

#### *Patients with Renal Impairment*

Inavolisib AUC was 73% higher in patients with moderate renal impairment compared to patients with normal renal function (eGFR  $\geq 90$  mL/min).

No clinically significant differences in the pharmacokinetics of inavolisib were observed in patients with mild renal impairment compared to patients with normal renal function. The effect of severe renal impairment (eGFR < 30 mL/min) on the pharmacokinetics of inavolisib is unknown.

### Drug Interaction Studies

#### *Clinical Studies and Model-Informed Approaches*

*Proton Pump Inhibitors:* No clinically significant difference in steady-state inavolisib pharmacokinetics were observed based upon concomitant use of a proton pump inhibitor (lansoprazole, omeprazole, esomeprazole, pantoprazole, or rabeprazole).

#### *In Vitro Studies*

*CYP450 Enzymes:* Inavolisib induces CYP3A and CYP2B6. Inavolisib is a time-dependent inhibitor of CYP3A. Inavolisib does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6.

*Transporter Systems:* 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.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

Carcinogenicity studies with inavolisib have not been conducted.

Inavolisib was not mutagenic in the bacterial reverse mutation (Ames) assay. Inavolisib was clastogenic in an in vitro human lymphocyte micronucleus assay. Inavolisib was not genotoxic in an in vivo rat bone marrow micronucleus test and did not induce DNA break in a liver comet assay.

Fertility studies with inavolisib have not been conducted. In repeat-dose toxicity studies, inavolisib was administered orally once daily for up to 3 months duration in rats and dogs.

In male rats, dose-dependent atrophy of the prostate and seminal vesicle and decreased organ weights of the prostate, seminal vesicle, epididymis and testis were observed at doses  $\geq 1.5$  mg/kg/day ( $\geq 0.4$  times the human exposure at the recommended dose of 9 mg/day based on AUC). In male dogs, focal inspissation of seminiferous tubule contents and multinucleated spermatids in the testis and epithelial degeneration/necrosis in the epididymis were observed following 4 weeks of dosing at  $\geq 1.5$  mg/kg/day ( $\geq 2$  times the human exposure at the recommended dose of 9 mg/day based on AUC) and decreased sperm count was observed following 3 months of dosing at  $\geq 1$  mg/kg/day ( $\geq 1.2$  times the human exposure at the recommended dose of 9 mg/day based on AUC). Findings in dogs were not observed following a recovery period.

In female rats, atrophy in the uterus and vagina, decreased ovarian follicles, and findings suggestive of an interruption/alteration of the estrous cycle were observed following up to 3 months of dosing at doses

≥ 3 mg/kg/day (≥ 1.2 times the human exposure at the recommended dose of 9 mg/day based on AUC). Findings in the uterus, vagina, and estrous cycle observed in the 4-week toxicity study were not observed following recovery. Recovery was not assessed in the 3-month study in rats.

### 13.2 Animal Toxicology and/or Pharmacology

Lens degeneration, characterized by lens fiber swelling, separation of lens fibers, and/or accumulation of subcapsular proteinaceous material, was observed in rats at an oral inavolisib dose of 10 mg/kg/day (6.3 times the human exposure at the recommended dose of 9 mg/day based on AUC). In dogs, lens fiber swelling and lens cortex vacuolation were observed at oral inavolisib doses ≥ 0.3 mg/kg/day (≥ 0.5 times the human exposure at the recommended dose based on AUC) and ≥ 1 mg/kg/day (≥ 1.2 times the human exposure at the recommended dose based on AUC), respectively. Lens degeneration was present in rats following a 4-week recovery period but was not present in dogs following a 12-week recovery period.

## 14 CLINICAL STUDIES

### 14.1 Locally Advanced or Metastatic Breast Cancer

#### INAVO120

INAVO120 (NCT04191499) was a randomized (1:1), double-blind, placebo-controlled trial evaluating the efficacy of ITOVEBI in combination with palbociclib and fulvestrant in adult patients with endocrine-resistant *PIK3CA*-mutated, HR-positive, HER2-negative (defined as IHC 0 or 1+, or IHC 2+/ISH-), 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. Randomization was stratified by presence of visceral disease (yes or no), endocrine resistance (primary or secondary), and geographic region (North America/Western Europe, Asia, other).

Primary endocrine resistance was defined as relapse while on the first 2 years of adjuvant endocrine therapy (ET) and secondary endocrine resistance was defined as relapse while on adjuvant ET after at least 2 years or relapse within 12 months of completing adjuvant ET.

Patients were required to have HbA<sub>1c</sub> < 6% and fasting blood glucose < 126 mg/dL. The study excluded patients with Type 1 diabetes mellitus or Type 2 diabetes mellitus requiring ongoing anti-hyperglycemic treatment at the start of study treatment.

*PIK3CA* mutation status was prospectively determined in a central laboratory using the FoundationOne<sup>®</sup> Liquid CDx assay on plasma-derived circulating tumor DNA (ctDNA) or in local laboratories using various validated polymerase chain reaction (PCR) or next-generation sequencing (NGS) assays on tumor tissue or plasma. All patients were required to provide both a freshly collected pre-treatment blood sample and a tumor tissue sample for central evaluation and determination of *PIK3CA* mutation(s) status.

Patients received either ITOVEBI 9 mg (n=161) or placebo (n=164) orally once daily, in combination with palbociclib 125 mg orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a cycle of 28 days, and fulvestrant 500 mg administered intramuscularly on Cycle 1, Days 1 and 15, and then on Day 1 of every 28-day cycle. Patients received treatment until disease progression or unacceptable toxicity. In addition, all pre/perimenopausal women and men received an LHRH agonist throughout therapy.

The baseline demographic and disease characteristics were: median age 54 years (range: 27 to 79 years); 98% female; 38% pre/perimenopausal; 59% White, 38% Asian, 2.5% unknown, 0.6% Black or African American; 6% Hispanic or Latino; and Eastern Cooperative Oncology Group (ECOG) performance status of 0 (63%) or 1 (36%). Tamoxifen (57%) and aromatase inhibitors (50%) were the most commonly used adjuvant endocrine therapies. Sixty-four percent of patients were considered to have secondary endocrine resistance. Eighty-three percent of patients had received prior chemotherapy (in the neo/adjuvant setting) and 1.2% of patients had been treated with a CDK4/6 inhibitor.

The major efficacy outcome measure was investigator (INV)-assessed progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Additional efficacy outcome measures

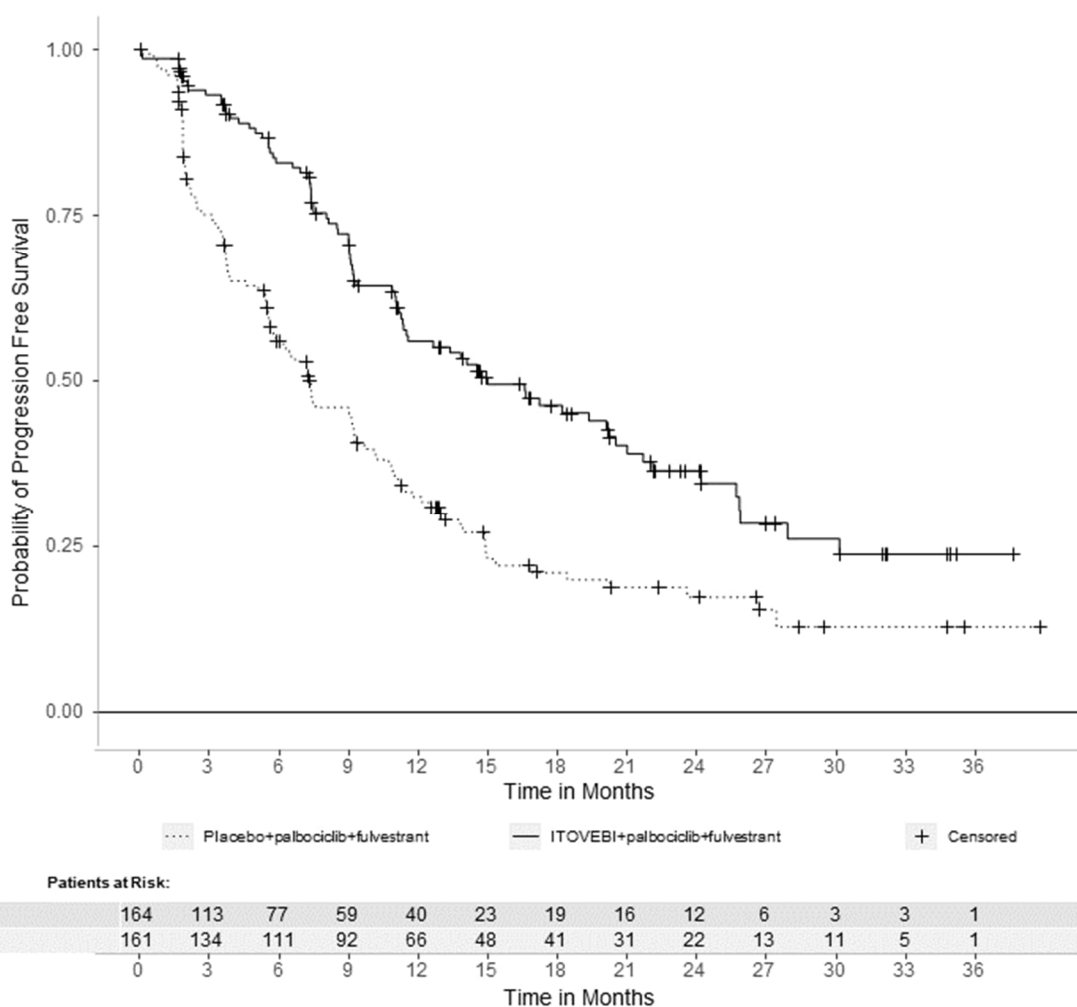
included overall survival (OS), INV-assessed objective response rate (ORR), and INV-assessed duration of response (DOR).

Efficacy results are summarized in Table 6 and Figure 1. INV-assessed PFS results were supported by consistent results from a blinded independent central review (BICR) assessment. At the time of the PFS analysis, OS data were not mature with 30% deaths in the overall population.

**Table 6: Efficacy Results in Patients with Locally Advanced or Metastatic Breast Cancer in INAVO120**

<b>Efficacy Endpoint</b>	<b>ITOVEBI + Palbociclib + Fulvestrant N=161</b>	<b>Placebo + Palbociclib + Fulvestrant N=164</b>
<b>Progression-Free Survival<sup>a,b</sup></b>		
Patients with event, n (%)	82 (51)	113 (69)
Median, months (95% CI)	15.0 (11.3, 20.5)	7.3 (5.6, 9.3)
Hazard ratio (95% CI)	0.43 (0.32, 0.59)	
p-value	< 0.0001	
<b>Objective Response Rate<sup>a,b,c</sup></b>		
Patients with CR or PR, n (%)	94 (58)	41 (25)
95% CI	(50, 66)	(19, 32)
<b>Duration of Response<sup>b</sup></b>		
Median DOR, months (95% CI)	18.4 (10.4, 22.2)	9.6 (7.4, 16.6)
CI = confidence interval; CR = complete response; DOR = duration of response; PR = partial response		
<sup>a</sup> Per RECIST version 1.1.		
<sup>b</sup> Based on investigator assessment.		
<sup>c</sup> Based on confirmed ORR.		

**Figure 1: Kaplan-Meier Curve for Investigator-Assessed Progression-Free Survival in INAVO120**



## 16 HOW SUPPLIED/STORAGE AND HANDLING

ITOVEBI is supplied in the following strengths and package configurations:

Package Configuration	Tablet Strength	Tablet Description
1 carton contains 28 tablets (7 tablets x4 blisters)	3 mg	Red and round convex-shaped with an "INA 3" debossing on one side
1 carton contains 28 tablets (7 tablets x4 blisters)	9 mg	Pink and oval-shaped with an "INA 9" debossing on one side

Store below 30°C

### Shelf life

The expiry date of the product is indicated on the packaging materials.

**17    MARKETING AUTHORISATION HOLDER**

Roche Pharmaceuticals (Israel) Ltd. P.O.B. 6391, Hod Hasharon, 4524079

**18    MARKETING AUTHORISATION NUMBER(S):**

179-69-38289-99

179-70-38290-99

**19    MANUFACTURER**

F. Hoffmann-La Roche Ltd., Basel, Switzerland

Approved on January 2026