PT. Pfizer Indonesia
Local Product Document

Generic Name: Palbociclib
Trade Name: Ibrance
CDS Effective Date: January 4, 2023
Supersedes: November 4, 2019

1. NAME OF THE MEDICINAL PRODUCT

1.1. Product name

IBRANCE®

1.2. Strength

75 mg, 100 mg, and 125 mg

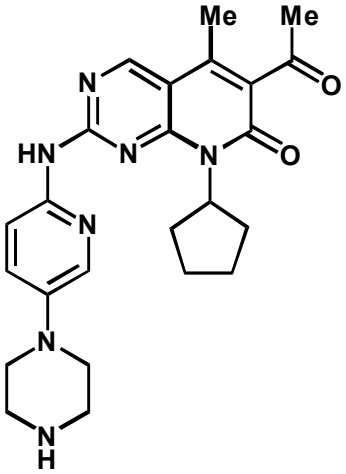
1.3. Pharmaceutical dosage form

Film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1. Qualitative declaration

Each film-coated tablet contains 75 mg or 100 mg or 125 mg of palbociclib freebase.



Palbociclib is a yellow to orange powder with a pKa of 7.4 (the secondary piperazine nitrogen) and 3.9 (the pyridine nitrogen).

2.2. Quantitative declaration

Excipients: see Section 6.1 (List of excipients) for the full list of excipients.

3. PHARMACEUTICAL FORM

Ibrance 75 mg: Round light purple film-coated tablet with "Pfizer" debossed on one tablet face and "PBC 75" debossed on the opposite tablet face.

Ibrance 100 mg: Oval green film-coated tablet with "Pfizer" debossed on one tablet face and "PBC 100" debossed on the opposite tablet face.

Ibrance 125 mg: Oval light purple film-coated tablet with "Pfizer" debossed on one tablet face and "PBC 125" debossed on the opposite tablet face.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

IBRANCE is indicated for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer:

- in combination with letrozole with proven diagnosis of adenocarcinoma of the breast with evidence of loco regionally recurrent or metastatic disease not amenable to resection or radiation.
- in combination with fulvestrant in women who have received prior endocrine therapy (see section 5.1).

In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinizing hormone-releasing hormone (LHRH) agonist.

4.2. Posology and method of administration

Treatment with IBRANCE should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

The recommended dose of IBRANCE is a 125 mg tablet taken orally once daily for 21 consecutive days followed by 7 days off treatment (Schedule 3/1) to comprise a complete cycle of 28 days.

When co-administered with palbociclib, the recommended dose of letrozole is 2.5 mg taken orally once daily continuously throughout the 28-day cycle. Please refer to the full prescribing information of letrozole.

When co-administered with palbociclib, the recommended dose of fulvestrant is 500 mg administered intramuscularly on Days 1, 15, 29, and once monthly thereafter. Please refer to the full prescribing information of fulvestrant.

Treatment of pre/perimenopausal women with the combination of palbociclib plus an aromatase inhibitor/fulvestrant should always be combined with an LHRH agonist (see Section 4.4 Special warnings and precautions for use).

Patients should be encouraged to take their dose at approximately the same time each day. Continue the treatment as long as the patient is deriving clinical benefit from therapy.

If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time. IBRANCE tablets should be swallowed whole (do not chew, crush, or split the tablets prior to swallowing). No tablet should be ingested if it is broken, cracked, or otherwise not intact.

Method of administration

IBRANCE is for oral use. IBRANCE tablets may be taken with or without food. Palbociclib should not be taken with grapefruit or grapefruit juice (see Section 4.5 Interaction with other medicinal products and other forms of interaction). IBRANCE tablets should be swallowed whole (should not be chewed, crushed, or split the tablets prior to swallowing). No tablet should be ingested if it is broken, cracked, or otherwise not intact.

Dose modifications

Dose modification of IBRANCE is recommended based on individual safety and tolerability.

Management of some adverse reactions may require temporary dosing interruptions/cycle delays, and/or dose reductions, or permanent discontinuation as per dose reduction schedules provided in Tables 1, 2, and 3 (see Section 4.4 Special warnings and precautions for use and Section 4.8 Undesirable effects).

Table 1. IBRANCE Recommended Dose Modifications for Adverse Events

Dose Level	Dose
Recommended dose	125 mg/day
First dose reduction	100 mg/day
Second dose reduction	75 mg/day[a]

[a] If further dose reduction below 75 mg/day is required, discontinue the treatment.

Table 2. IBRANCE Dose Modification and Management – Hematologic Toxicities[a]

Monitor complete blood counts prior to the start of IBRANCE therapy and at the beginning of each cycle, as well as on Day 15 of the first 2 cycles, and as clinically indicated. For patients who experience a maximum of Grade 1 or 2 neutropenia in the first 6 cycles, monitor complete blood counts for subsequent cycles every 3 months, prior to the beginning of a cycle and as clinically indicated. Absolute neutrophil counts (ANC) of ≥1000/mm^3 and platelet counts of ≥50,000/mm^3 are recommended to receive IBRANCE.	
CTCAE Grade	**Dose Modifications**
Grade 1 or 2	No dose adjustment is required.
Grade 3[a]	Day 1 of cycle: Withhold IBRANCE, until recovery to Grade ≤2, and repeat complete blood count monitoring within 1 week. When

	recovered to Grade ≤2, start the next cycle at the *same dose*. Day 15 of first 2 cycles: If Grade 3 on Day 15, continue IBRANCE at the *current dose* to complete cycle and repeat complete blood count on Day 22. If Grade 4 on Day 22, see Grade 4 dose modification guidelines below. Consider dose reduction in cases of prolonged (>1 week) recovery from Grade 3 neutropenia or recurrent Grade 3 neutropenia on Day 1 of the subsequent cycles.
Grade 3 ANC[b] (<1000 to 500/mm^3) + fever ≥38.5°C and/or infection	At any time: Withhold IBRANCE until recovery to Grade ≤2. Resume at the *next lower dose.*
Grade 4[a]	At any time: Withhold IBRANCE until recovery to Grade ≤2. Resume at the *next lower dose.*

Grading according to CTCAE 4.0 (Grade 1: ANC < LLN - 1500/mm^3; Grade 2: ANC 1000 - <1500/mm^3; Grade 3: ANC 500 - <1000/mm^3; Grade 4: ANC <500/mm^3).
ANC=absolute neutrophil count; CTCAE=Common Terminology Criteria for Adverse Events; LLN=lower limit of normal.

[a] Table applies to all hematologic adverse reactions except lymphopenia (unless associated with clinical events, e.g., opportunistic infections).

[b] ANC: Grade 1: ANC < LLN - 1500/mm^3; Grade 2: ANC 1000 - <1500/mm^3; Grade 3: ANC 500 - <1000/mm^3; Grade 4: ANC <500/mm^3.

Table 3. IBRANCE Dose Modification and Management – Non-hematologic Toxicities

CTCAE Grade	Dose Modifications
Grade 1 or 2	No dose adjustment is required.
Grade ≥3 non-hematologic toxicity (if persisting despite medical treatment)	Withhold until symptoms resolve to: Grade ≤1; Grade ≤2 (if not considered a safety risk for the patient) Resume at the *next lower dose*.

Grading according to CTCAE 4.0
CTCAE=Common Terminology Criteria for Adverse Events.

No dose modifications are required on the basis of patient's age, sex, or body weight (see Section 5.2 Pharmacokinetic properties).

Permanently discontinue IBRANCE in patients with severe interstitial lung disease (ILD) or pneumonitis (see Section 4.4 Special warnings and precautions for use).

Special populations

Elderly population: No dose adjustment is necessary in patients ≥65 years of age (see Section 5.2 Pharmacokinetic properties).

Pediatric population: The safety and efficacy of IBRANCE in children and adolescents ≤18 years of age have not been established.

Hepatic impairment: No dose adjustment is required for patients with mild or moderate hepatic impairment (Child-Pugh classes A and B). For patients with severe hepatic impairment (Child-Pugh class C), the recommended dose of IBRANCE is 75 mg once daily on Schedule 3/1 (see Section 5.2 Pharmacokinetic properties).

Renal impairment: No dose adjustment is required for patients with mild, moderate or severe renal impairment (creatinine clearance [CrCl] ≥15 mL/min). Insufficient data are available in patients requiring hemodialysis to provide any dosing recommendation in this patient population (see Section 5.2 Pharmacokinetic properties).

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 List of excipients.

Use of preparations containing St. John's Wort (see Section 4.5 Interaction with other medicinal products and other forms of interaction).

4.4. Special warnings and precautions for use

Myelosuppression

- **Neutropenia**

  Decreased neutrophil counts have been observed very commonly in clinical studies with IBRANCE. In patients receiving IBRANCE in combination with letrozole (PALOMA-1 and PALOMA-2) and in combination with fulvestrant (PALOMA-3), Grade 3 (ANC 500 <1000/mm^3) and Grade 4 (ANC <500/mm^3) decreased neutrophil counts were reported.

  In PALOMA-1 and PALOMA-2 the median time to first episode of any grade neutropenia was 15 days (12-700 days) and 28 days (range 12-854) for Grade ≥3 neutropenia. The median duration of Grade ≥3 neutropenia was 33 days (range 1-534).

  In PALOMA-3 the median time to first episode of neutropenia was 15 days (13-317 days) for any grade and 16 days (range 13-587) for Grade ≥3 neutropenia. The median duration for Grade ≥3 neutropenia was 21 days (range 1-167).

  An increase in palbociclib exposure has been associated with more severe neutropenia; in Asian subjects, frequency of Grade ≥3 neutropenia is higher

than in White subjects (see Section 5.2 Pharmacokinetic properties, Special Populations – Asian race).

Febrile neutropenia has been reported in 1.6% of patients receiving palbociclib in combination with letrozole in PALOMA-2 and in 0.9% of patients receiving palbociclib in combination with fulvestrant in PALOMA-3. One death due to neutropenic sepsis was reported in PALOMA-3.

Febrile neutropenia has not been reported in PALOMA-1. Febrile neutropenia has been reported in about 2% of patients exposed to IBRANCE across the overall clinical program (see Section 4.4 Special warnings and precautions for use - Infection).

Monitor complete blood count prior to the start of IBRANCE therapy and at the beginning of each cycle, as well as on Day 15 of the first 2 cycles, and as clinically indicated.

Dosing interruption, dose reduction or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia. Appropriate monitoring should be performed (see Section 4.2 Posology and method of administration, Table 2).

- **Anaemia**

  Anaemia has been observed very commonly in clinical studies with IBRANCE. In patients receiving IBRANCE in combination with letrozole (PALOMA-1 and PALOMA-2) and in combination with fulvestrant (PALOMA-3), Grade 3 and Grade 4 anaemia was observed. In PALOMA-1 and PALOMA-2 the median time to first episode of any grade anaemia was 29 days (range 1-777 days) and 195 days (range 14-760) for Grade ≥3 anaemia. The median duration of Grade ≥3 anaemia was 7 days (range 1-125). In PALOMA-3 the median time to first episode of anaemia was 25 days (12-378 days) for any grade and 52 days (range 15-363) for Grade ≥3 anaemia. The median duration for Grade ≥3 anaemia was 7 days (range 1-125). Across both studies, supportive treatment with red blood cell growth factors and transfusions was administered.

- **Thrombocytopenia**

  Thrombocytopenia has been observed very commonly in clinical studies with IBRANCE. In patients receiving IBRANCE in combination with letrozole (PALOMA-1 and PALOMA-2) and in combination with fulvestrant (PALOMA-3), Grade 3 and Grade 4 thrombocytopenia was observed. In PALOMA-1 and PALOMA-2 the median time to first episode of any grade thrombocytopenia was 27 days (range 2-875 days) and 256 days (range 21-652 days) for Grade ≥3 thrombocytopenia. The median duration of Grade ≥3 thrombocytopenia was 7 days (range 1-28 days). In PALOMA-3 the median time to first episode of thrombocytopenia was 15 days (13-422 days) for any

grade and 23 days (range 15-57) for Grade ≥3 thrombocytopenia. The median duration for Grade ≥3 thrombocytopenia was 7 days (range 1-9 days).

Interstitial lung disease/pneumonitis

Severe, life-threatening, or fatal ILD and/or pneumonitis can occur in patients treated with cyclin-dependent kinase 4/6 (CDK 4/6) inhibitors, including IBRANCE when taken in combination with endocrine therapy.

Across clinical trials, 1.4% of IBRANCE -treated patients had ILD/pneumonitis of any grade, 0.1% had Grade 3, and no Grade 4 or fatal cases were reported. Additional cases of ILD/pneumonitis have been observed in the post-marketing setting (see Section 4.8 Undesirable effects), with fatalities reported.

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis (e.g., hypoxia, cough, dyspnea). In patients who have new or worsening respiratory symptoms and are suspected to have developed ILD/pneumonitis, interrupt IBRANCE immediately and evaluate the patient. Permanently discontinue IBRANCE in patients with severe ILD or pneumonitis (see Section 4.2 Posology and method of administration).

Infections

Since IBRANCE has myelosuppressive properties, it may predispose to infections.

Infections have been reported at a higher rate in patients treated with IBRANCE in randomized clinical studies compared to patients treated in the respective comparator arm. Grades 3 and 4 infections occurred in 4.4% and 0.7%, respectively, in patients treated with IBRANCE in either combination compared to patients treated in the respective comparator arms (2.5% and 0%, respectively).

Monitor patients for signs and symptoms of infection and treat as medically appropriate (see Section 4.8 Undesirable effects).

Physicians should inform patients to promptly report any episodes of fever.

Pre/perimenopausal women

Ovarian ablation or suppression with an LHRH agonist is mandatory when pre/perimenopausal women are administered IBRANCE in combination with an aromatase inhibitor, due to the mechanism of action of aromatase inhibitors. Palbociclib in combination with fulvestrant in pre/perimenopausal women has only been studied in combination with an LHRH agonist.

Critical visceral disease

The efficacy and safety of palbociclib have not been studied in patients with critical visceral disease (see Section 5.1 Pharmacodynamic properties).

Embryo-fetal toxicity

Based on findings from animal studies and its mechanism of action, IBRANCE can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of palbociclib to pregnant rats and rabbits during organogenesis resulted in embryo-fetal toxicity at maternal exposures that were ≥4 times the human clinical exposure based on area under the curve (AUC). Advise pregnant women of the potential to use effective contraception during treatment with IBRANCE and for at least 3 weeks after the last dose.

Hepatic impairment

Administer IBRANCE with caution to patients with moderate or severe hepatic impairment, with close monitoring of signs of toxicity (see Sections 4.2 Posology and method of administration and 5.2 Pharmacokinetic properties).

Renal impairment

Administer IBRANCE with cautions to patients with moderate or severe renal impairment, with close monitoring of signs of toxicity (see Sections 4.2 Posology and method of administration and 5.2 Pharmacokinetic properties).

Concomitant treatment with inhibitors or inducers of CYP3A4

Strong inhibitors of CYP3A4 may lead to increased toxicity (see Sections 4.5 Interaction with other medicinal products and other forms of interaction). Concomitant use of strong CYP3A inhibitors during treatment with palbociclib should be avoided. Coadministration should only be considered after careful evaluation of the potential benefits and risks. If coadministration with a strong CYP3A inhibitor is unavoidable, reduce the IBRANCE dose to 75 mg once daily. When the strong inhibitor is discontinued, increase the IBRANCE dose (after 3-5 half-lives of the inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor (see Section 4.5 Interaction with other medicinal products and other forms of interaction).

Coadministration of CYP3A inducers may lead to decreased palbociclib exposure and consequently a risk for lack of efficacy. Therefore, concomitant use of palbociclib with strong CYP3A4 inducers should be avoided. No dose adjustments are required for coadministration of palbociclib with moderate CYP3A inducers (see Section 4.5 Interaction with other medicinal products and other forms of interaction).

Women of childbearing potential or their partners

Women of childbearing potential or their male partners must use a highly effective method of contraception while taking IBRANCE (see Section 4.6. Fertility, pregnancy and lactation).

4.5. Interaction with other medicinal products and other forms of interaction

Palbociclib is primarily metabolized by CYP3A and sulfotransferase (SULT) enzyme SULT2A1. *In vivo*, palbociclib is a time-dependent inhibitor of CYP3A.

Agents that may increase palbociclib plasma concentrations

Effect of CYP3A inhibitors

Data from a drug-drug interaction (DDI) study in healthy subjects indicate that coadministration of multiple 200 mg doses of itraconazole with a single 125 mg dose of IBRANCE increased palbociclib total exposure area under the plasma concentration-time curve from time zero to infinity (AUC_{inf}) and the maximum observed plasma concentration (C_{max}) by approximately 87% and 34%, respectively, relative to a single 125 mg dose of IBRANCE given alone. The concomitant use of strong CYP3A inhibitors including, but not limited to: amprenavir, atazanavir, boceprevir, clarithromycin, conivaptan, delavirdine, diltiazem, erythromycin, fosamprenavir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, miconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole, and grapefruit or grapefruit juice, should be avoided.

Agents that may decrease palbociclib plasma concentrations

Effect of CYP3A inducers

Data from a DDI study in healthy subjects indicate that coadministration of multiple 600 mg doses of rifampin, a strong CYP3A inducer, with a single 125 mg dose of IBRANCE decreased palbociclib AUC_{inf} and C_{max} by 85% and 70%, respectively, relative to a single 125 mg dose of IBRANCE given alone. Data from a DDI study in healthy subjects indicate that coadministration of multiple 400 mg daily doses of modafinil, a moderate CYP3A inducer, with a single 125 mg IBRANCE dose decreased palbociclib AUC_{inf} and C_{max} by 32% and 11%, respectively, relative to a single 125 mg dose of IBRANCE given alone.

The concomitant use of strong CYP3A inducers including, but not limited to: carbamazepine, enzalutamide, felbamate, nevirapine, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifapentine, and St. John's wort, should be avoided.

Coadministration of a moderate CYP3A inducer (modafinil) decreased the plasma exposure of palbociclib in healthy subjects by 32%. Moderate CYP3A inducers (e.g., bosentan, efavirenz, etravirine, modafinil, and nafcillin) can be used concurrently with IBRANCE when unavoidable. No dosing adjustments are required.

Effect of acid reducing agents

Coadministration of multiple doses of the PPI rabeprazole with a single 125 mg IBRANCE tablet under fasted conditions had no effect on the rate and extent of absorption of palbociclib when compared to a single 125 mg IBRANCE tablet administered alone (see Section 4.2 Posology and method of administration).

Effects of IBRANCE on other drugs

Palbociclib is a weak time-dependent inhibitor of CYP3A following daily 125 mg dosing at steady state in humans. In a DDI study in healthy subjects, coadministration of midazolam with multiple doses of palbociclib increased the midazolam AUC_{inf} and C_{max} values by 61% and 37%, respectively, as compared with administration of midazolam alone.

Coadministration of midazolam with multiple doses of IBRANCE increased the midazolam plasma exposure by 61% in healthy subjects, compared to administration of midazolam alone. The dose of the sensitive CYP3A substrate with a narrow therapeutic index (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus) may need to be reduced, as IBRANCE may increase its exposure.

In vitro, palbociclib is not an inhibitor of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, and 2D6, and is not an inducer of CYP1A2, 2B6, 2C8, and 3A4 at clinically relevant concentrations.

Letrozole: Data from a clinical study in patients with breast cancer showed that there was no drug interaction between palbociclib and letrozole when the 2 drugs were co-administered.

Fulvestrant: Data from a clinical study in patients with breast cancer showed that there was no clinically relevant drug interaction between palbociclib and fulvestrant when the 2 drugs were co-administered.

Goserelin: Data from a clinical study in patients with breast cancer showed that there was no clinically relevant drug interaction between palbociclib and goserelin when the 2 drugs were co-administered.

Tamoxifen: Data from a DDI study in healthy male subjects indicated that palbociclib exposures were comparable when a single dose of palbociclib was co-administered with multiple doses of tamoxifen and when palbociclib was given alone.

Drug-drug interaction between palbociclib and oral contraceptives

DDI studies of palbociclib with oral contraceptives have not been conducted (see Section 4.6 Fertility, pregnancy and lactation).

In vitro studies with transporters

Based on *in vitro* data, palbociclib is predicted to inhibit intestinal P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) mediated transport. Therefore, administration of palbociclib with medicinal products that are substrates of palbociclib with medicinal products that are substrates of P-gp (e.g., digoxin, dabigatran, colchicine) or BCRP (e.g., pravastatin, rosuvastatin, sulfasalazine) may increase their therapeutic effect and adverse reactions.

Based on *in vitro* data, palbociclib may inhibit the uptake transporter organic cationic transporter OCTI and then may increase the exposure of medical product substrates of this transporter (e.g., metformin).

4.6. Fertility, pregnancy and lactation

Fertility

There were no effects on estrous cycle (female rats) or mating and fertility in rats in nonclinical studies. However, no clinical data have been obtained on fertility in human females. Based on male reproductive organ findings (seminiferous tubule degeneration in testis, epididymal hypospermia, lower sperm motility and density, and decreased prostate secretion) in nonclinical safety studies, male fertility may be compromised by treatment with palbociclib (see Section 5.3 Preclinical safety data).

Women of childbearing potential/pregnancy

There are no adequate and well-controlled studies using IBRANCE in pregnant women. Based on findings in animals and mechanism of action, palbociclib can cause fetal harm when administered to a pregnant woman. In animal studies, palbociclib was fetotoxic at maternally-toxic doses. IBRANCE is not recommended during pregnancy and in women of childbearing potential not using contraception.

Females of childbearing potential who are receiving this medicinal product, or their male partners should use adequate contraceptive methods during therapy and for at least 21 days or 97 days after completing therapy for females and males, respectively.

Lactation

No studies have been conducted in humans to assess the effect of IBRANCE on milk production, its presence in breast milk, or its effects on the breastfed child. It is unknown whether palbociclib is excreted in human milk. Patients receiving palbociclib should not breastfeed.

4.7. Effects on ability to drive and use machines

IBRANCE has minor influence on the ability to drive and use machines. However, patients experiencing fatigue while taking IBRANCE should exercise caution when driving or operating machinery.

4.8. Undesirable effects

The following clinically significant adverse reactions are described and elsewhere in the labeling:

- Neutropenia (see Section 4.4 Special warnings and precautions for use)
- ILD/Pneumonitis (see Section 4.4 Special warnings and precautions for use)

Clinical Studies Experience

- Because clinical trials are conducted under varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other trials and may not reflect the rates observed in clinical practice.

Study 1: IBRANCE plus Letrozole

Patients with estrogen receptor (ER)-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy.

The safety of IBRANCE (125 mg/day) plus letrozole (2.5 mg/day) versus placebo plus letrozole was evaluated in Study 1 (PALOMA-2). The data described below reflect exposure to IBRANCE in 444 out of 666 patients with ER-positive, HER2-negative advanced breast cancer who received at least 1 dose of IBRANCE plus letrozole in Study 1. The median duration of treatment for IBRANCE plus letrozole was 19.8 months while the median duration of treatment for placebo plus letrozole arm was 13.8 months.

Dose reductions due to an adverse reaction of any grade occurred in 36% of patients receiving IBRANCE plus letrozole. No dose reduction was allowed for letrozole in Study 1.

Permanent discontinuation associated with an adverse reaction occurred in 43 of 444 (9.7%) patients receiving IBRANCE plus letrozole and in 13 of 222 (5.9%) patients receiving placebo plus letrozole. Adverse reactions leading to permanent discontinuation for patients receiving IBRANCE plus letrozole included neutropenia (1.1%) and alanine aminotransferase increase (0.7%).

The most common adverse reactions (>10%) of any grade reported in patients in the IBRANCE plus letrozole arm by descending frequency were neutropenia, infections, leukopenia, fatigue, nausea, alopecia, stomatitis, diarrhea, anemia, rash, asthenia, thrombocytopenia, vomiting, decreased appetite, dry skin, pyrexia, and dysgeusia.

The most frequently reported Grade ≥3 adverse reactions (≥5%) in patients receiving IBRANCE plus letrozole by descending frequency were neutropenia, leukopenia, infections, and anemia.

Adverse reactions (>10%) reported in patients who received IBRANCE plus letrozole or placebo plus letrozole in Study 1 are listed in Table 4.

Table 4. Adverse Reactions (>10%) in Study 1

	IBRANCE plus Letrozole (N=444)			Placebo plus Letrozole (N=222)		
Adverse Reaction	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
Infections and infestations						
Infections[a]	60[b]	6	1	42	3	0
Blood and lymphatic system disorders						
Neutropenia	80	56	10	6	1	1
Leukopenia	39	24	1	2	0	0
Anemia	24	5	<1	9	2	0
Thrombocytopenia	16	1	<1	1	0	0
Metabolism and nutrition disorders						
Decreased appetite	15	1	0	9	0	0
Nervous system disorders						
Dysgeusia	10	0	0	5	0	0
Gastrointestinal disorders						
Stomatitis[c]	30	1	0	14	0	0
Nausea	35	<1	0	26	2	0
Diarrhea	26	1	0	19	1	0
Vomiting	16	1	0	17	1	0
Skin and subcutaneous tissue disorders						
Alopecia	33[d]	N/A	N/A	16[e]	N/A	N/A
Rash[f]	18	1	0	12	1	0
Dry skin	12	0	0	6	0	0
General disorders and administration site conditions						
Fatigue	37	2	0	28	1	0
Asthenia	17	2	0	12	0	0
Pyrexia	12	0	0	9	0	0

Grading according to CTCAE 4.0.
CTCAE=Common Terminology Criteria for Adverse Events; N=number of patients; N/A=not applicable.

[a] Infections includes all reported preferred terms (PTs) that are part of the System Organ Class Infections and infestations.

[b] Most common infections (≥1%) include: nasopharyngitis, upper respiratory tract infection, urinary tract infection, oral herpes, sinusitis, rhinitis, bronchitis, influenza, pneumonia, gastroenteritis, conjunctivitis, herpes zoster, pharyngitis, cellulitis, cystitis, lower respiratory tract infection, tooth infection, gingivitis, skin infection, gastroenteritis viral, respiratory tract infection, respiratory tract infection viral, and folliculitis.

[c] Stomatitis includes: aphthous stomatitis, cheilitis, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral pain, oral discomfort, oropharyngeal pain, and stomatitis.

[d] Grade 1 events – 30%; Grade 2 events – 3%.

[e] Grade 1 events – 15%; Grade 2 events – 1%.

[f] Rash includes the following PTs: rash, rash maculo-papular, rash pruritic, rash erythematous, rash papular, dermatitis, dermatitis acneiform, and toxic skin eruption.

Additional adverse reactions occurring at an overall incidence of <10.0% of patients receiving IBRANCE plus letrozole in Study 1 included alanine aminotransferase increased (9.9%), aspartate aminotransferase increased (9.7%), epistaxis (9.2%),

lacrimation increased (5.6%), dry eye (4.1%), vision blurred (3.6%), and febrile neutropenia (2.5%).

Table 5. Laboratory Abnormalities in Study 1

	IBRANCE plus Letrozole (N=444)			**Placebo plus Letrozole (N=222)**		
Laboratory Abnormality	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
WBC decreased	97	35	1	25	1	0
Neutrophils decreased	95	56	12	20	1	1
Anemia	78	6	0	42	2	0
Platelets decreased	63	1	1	14	0	0
Aspartate aminotransferase increased	52	3	0	34	1	0
Alanine aminotransferase increased	43	2	<1	30	0	0

N=number of patients; WBC=white blood cells.

Study 2: IBRANCE plus Fulvestrant

Patients with HR-positive, HER2-negative advanced or metastatic breast cancer who have had disease progression on or after prior adjuvant or metastatic endocrine therapy.

The safety of IBRANCE (125 mg/day) plus fulvestrant (500 mg) versus placebo plus fulvestrant was evaluated in Study 2 (PALOMA-3). The data described below reflect exposure to IBRANCE in 345 out of 517 patients with HR-positive, HER2-negative advanced or metastatic breast cancer who received at least 1 dose of IBRANCE plus fulvestrant in Study 2. The median duration of treatment for IBRANCE plus fulvestrant was 10.8 months while the median duration of treatment for placebo plus fulvestrant arm was 4.8 months.

Dose reductions due to an adverse reaction of any grade occurred in 36% of patients receiving IBRANCE plus fulvestrant. No dose reduction was allowed for fulvestrant in Study 2.

Permanent discontinuation associated with an adverse reaction occurred in 19 of 345 (6%) patients receiving IBRANCE plus fulvestrant, and in 6 of 172 (3%) patients receiving placebo plus fulvestrant. Adverse reactions leading to discontinuation for those patients receiving IBRANCE plus fulvestrant included fatigue (0.6%), infections (0.6%), and thrombocytopenia (0.6%).

The most common adverse reactions (≥10%) of any grade reported in patients in the IBRANCE plus fulvestrant arm by descending frequency were neutropenia, leukopenia, infections, fatigue, nausea, anemia, stomatitis, diarrhea, thrombocytopenia, vomiting, alopecia, rash, decreased appetite, and pyrexia.

The most frequently reported Grade ≥3 adverse reactions (≥5%) in patients receiving IBRANCE plus fulvestrant in descending frequency were neutropenia and leukopenia.

Adverse reactions (≥10%) reported in patients who received IBRANCE plus fulvestrant or placebo plus fulvestrant in Study 2 are listed in Table 6.

Table 6. Adverse Reactions (≥10%) in Study 2

Adverse Reaction	IBRANCE plus Fulvestrant (N=345)			Placebo plus Fulvestrant (N=172)		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Infections and infestations						
Infections[a]	47[b]	3	1	31	3	0
Blood and lymphatic system disorders						
Neutropenia	83	55	11	4	1	0
Leukopenia	53	30	1	5	1	1
Anemia	30	4	0	13	2	0
Thrombocytopenia	23	2	1	0	0	0
Metabolism and nutrition disorders						
Decreased appetite	16	1	0	8	1	0
Gastrointestinal disorders						
Nausea	34	0	0	28	1	0
Stomatitis[c]	28	1	0	13	0	0
Diarrhea	24	0	0	19	1	0
Vomiting	19	1	0	15	1	0
Skin and subcutaneous tissue disorders						
Alopecia	18[d]	N/A	N/A	6[e]	N/A	N/A
Rash[f]	17	1	0	6	0	0
General disorders and administration site conditions						
Fatigue	41	2	0	29	1	0
Pyrexia	13	<1	0	5	0	0

Grading according to CTCAE 4.0.
CTCAE=Common Terminology Criteria for Adverse Events; N=number of patients; N/A=not applicable.
[a] Infections includes all reported preferred terms (PTs) that are part of the System Organ Class Infections and infestations.
[b] Most common infections (≥1%) include: nasopharyngitis, upper respiratory infection, urinary tract infection, bronchitis, rhinitis, influenza, conjunctivitis, sinusitis, pneumonia, cystitis, oral herpes, respiratory tract infection, gastroenteritis, tooth infection, pharyngitis, eye infection, herpes simplex, and paronychia.
[c] Stomatitis includes: aphthous stomatitis, cheilitis, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral pain, oropharyngeal discomfort, oropharyngeal pain, stomatitis.
[d] Grade 1 events – 17%; Grade 2 events – 1%.
[e] Grade 1 events – 6%.
[f] Rash includes: rash, rash maculo-papular, rash pruritic, rash erythematous, rash papular, dermatitis, dermatitis acneiform, toxic skin eruption.

Additional adverse reactions occurring at an overall incidence of <10.0% of patients receiving IBRANCE plus fulvestrant in Study 2 included asthenia (7.5%), aspartate aminotransferase increased (7.5%), dysgeusia (6.7%), epistaxis (6.7%), lacrimation increased (6.4%), dry skin (6.1%), alanine aminotransferase increased (5.8%), vision blurred (5.8%), dry eye (3.8%), and febrile neutropenia (0.9%).

Table 7. Laboratory Abnormalities in Study 2

Laboratory Abnormality	IBRANCE plus Fulvestrant (N=345)			Placebo plus Fulvestrant (N=172)		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %

WBC decreased	99	45	1	26	0	1
Neutrophils decreased	96	56	11	14	0	1
Anemia	78	3	0	40	2	0
Platelets decreased	62	2	1	10	0	0
Aspartate aminotransferase increased	43	4	0	48	4	0
Alanine aminotransferase increased	36	2	0	34	0	0

N=number of patients; WBC=white blood cells.

Description of selected adverse reactions

Overall, neutropenia of any grade was reported in patients receiving IBRANCE regardless of the combination, with Grade 3 and Grade 4 neutropenia.

The median time to first episode of any grade neutropenia was 15 days (12-700 days) and the median duration of Grade >3 neutropenia was 7 days across 3 randomised clinical studies.

Febrile neutropenia has been reported in 2.1% of patients receiving palbociclib in combination with letrozole.

The most common adverse reactions (≥20%) of any grade reported in patients in the IBRANCE plus letrozole arm by descending frequency were neutropenia, infections, leukopenia, nausea, fatigue, alopecia, stomatitis, anaemia and diarrhoea.

Dose reductions due to an adverse event of any grade occurred in 36.2% of patients receiving IBRANCE plus letrozole in PALOMA-1 and PALOMA-2. No dose reductions were allowed for the comparator arm. Permanent treatment discontinuation associated with an adverse event occurred in 10.6% patients receiving IBRANCE plus letrozole in PALOMA-1 and PALOMA-2 and in 5.0% of patients in the comparator arm.

In PALOMA-2 patients receiving IBRANCE plus letrozole, the starting dose of IBRANCE was 125 mg once daily. Dose reductions to 100 mg occurred in 36% of patients and dose reductions to 75 mg occurred in 14% of patients due to adverse events.

Neutropenia of any grade was reported in 78.9% of patients receiving IBRANCE plus letrozole in PALOMA-1 and PALOMA-2, with Grade 3 neutropenia reported in 55.2% of patients and Grade 4 neutropenia reported in 9.7% of patients (see Section 4.4 Special warnings and precautions for use). The most frequently reported Grade >3 adverse reactions (≥5%) in patients receiving IBRANCE plus letrozole by descending frequency were neutropenia, leukopenia, infections and anaemia.

The most frequently (≥1%) reported serious adverse drug reactions in patients receiving palbociclib plus letrozole (PALOMA-1 and PALOMA-2) were infections (4.6%) and febrile neutropenia (1.3%).

Cataract was reported in 3.2% of patients receiving IBRANCE plus letrozole and in 0.5% of patients receiving placebo plus letrozole in PALOMA-2.

Post-marketing experience
The following adverse reactions have been identified during post-approval use of IBRANCE. 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.

Respiratory disorders: Interstitial lung disease (ILD)/non-infectious pneumonitis.

Skin and subcutaneous tissue disorders: Palmar-plantar erythrodysesthesia syndrome (PPES)

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9. Overdose
In the event of a palbociclib overdose, both gastrointestinal (e.g., nausea, vomiting) and haematological (e.g., neutropenia) toxicity may occur. There is no known antidote for palbociclib. The treatment of IBRANCE overdose should consist of general supportive measures.

5. PHARMACOLOGICAL PROPERTIES
5.1. Pharmacodynamic properties

Mechanism of action

Palbociclib is a highly selective, reversible inhibitor of cyclin-dependent kinases (CDK) 4 and 6. Cyclin D1 and CDK4/6 are downstream of multiple signaling pathways which lead to cellular proliferation.

Pharmacodynamic effects

Through inhibition of CDK4/6, palbociclib reduced cellular proliferation by blocking progression of the cell from G1 into S phase of the cell cycle. Testing of palbociclib in a panel of molecularly profiled breast cancer cell lines revealed high efficacy against luminal breast cancers, particularly estrogen receptor (ER)-positive breast cancers. In the cell lines tested, the loss of retinoblastoma (Rb) was associated with loss of palbociclib activity. Available clinical data are reported in the clinical efficacy and safety section (see Section 5.1 Pharmacodynamic properties). Mechanistic analyses revealed that the combination of palbociclib with anti-estrogen agents enhanced the re-activation of retinoblastoma (Rb) through inhibition of Rb phosphorylation resulting in reduced E2F signaling and growth arrest. *In vivo* studies using a patient-derived ER-positive breast cancer xenograft model (HBCx-34)

demonstrated that the combination of palbociclib and letrozole further enhanced inhibition of Rb phosphorylation, downstream signaling, and dose-dependent tumor growth. Studies are ongoing investigating the importance of Rb expression for the activity of palbociclib in fresh tumour samples.

Cardiac electrophysiology

The effect of palbociclib on the QT interval corrected for heart rate (QTc) interval was evaluated using time matched electrocardiogram (ECG) evaluating the change from baseline and corresponding pharmacokinetic data in 77 patients with advanced breast cancer. Palbociclib did not prolong the QTc to any clinically relevant extent at the recommended dose of 125 mg daily (Schedule 3/1).

Clinical trial efficacy

Study 1:

The efficacy of palbociclib was evaluated in a randomized, open-label, multicenter study of palbociclib plus letrozole versus letrozole alone conducted in postmenopausal women with ER-positive, HER2-negative locally advanced or metastatic breast cancer.

The study was comprised of a limited Phase 1 portion (N = 12), designed to confirm the safety and tolerability of the combination palbociclib plus letrozole, followed by a randomized Phase 2 portion (N = 165), designed to evaluate the efficacy and safety of palbociclib in combination with letrozole compared with letrozole alone in the first-line treatment of postmenopausal women with ER-positive, HER2-negative advanced breast cancer.

Randomization was stratified by disease site (visceral versus bone only versus other) and by disease-free interval (>12 months from the end of adjuvant treatment to disease recurrence versus ≤12 months from the end of adjuvant treatment to disease recurrence or *de novo* advanced disease).

The patient demographic and baseline characteristics were generally balanced between the study arms in terms of age, race, disease sites, stage, and prior therapies.

The primary endpoint of the study was investigator-assessed progression-free survival (PFS) evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0.

The median PFS (mPFS) for patients in the palbociclib plus letrozole arm was 20.2 months (95% confidence interval [CI]: 13.8, 27.5) and 10.2 months (95% CI: 5.7, 12.6) for patients in the letrozole-alone arm. The observed hazard ratio (HR) was 0.488 (95% CI: 0.319, 0.748) in favor of palbociclib plus letrozole, with a stratified log-rank test 1-sided p-value of 0.0004.

At the final overall survival (OS) analysis, the observed HR was 0.897 (95% CI: 0.623, 1.294) with a stratified 1-sided p-value of 0.2812. The median OS in the palbociclib plus letrozole arm was 37.5 months (95% CI: 31.4, 47.8) and in the letrozole alone arm was 34.5 months (95% CI: 27.4, 42.6).

The estimated survival probabilities at 12, 24, and 36 months between the 2 treatment arms were 89.0% versus 87.0%, 77.9% versus 71.1%, and 50.8% versus 47.4%, in favor of palbociclib plus letrozole, respectively.

Study 2:

The efficacy of palbociclib in combination with letrozole versus letrozole plus placebo was evaluated in an international, randomized, double-blind, placebo-controlled, parallel-group, multicenter study conducted in women with ER-positive, HER2-negative locally advanced or metastatic breast cancer (PALOMA-2) who had not received prior systemic treatment for their advanced disease.

A total of 666 postmenopausal women were randomized 2:1 to either the palbociclib plus letrozole arm or to the placebo plus letrozole arm and were stratified by site of disease (visceral, non-visceral), disease-free interval from the end of (neo)adjuvant treatment to disease recurrence (*de novo* metastatic, ≤12 months from the end of adjuvant treatment to disease recurrence, >12 months from the end of adjuvant treatment to disease recurrence), and by the type of prior (neo)adjuvant anticancer therapies (prior hormonal therapy, no prior hormonal therapy). Patients with advanced symptomatic, visceral spread, that were at risk of life-threatening complications in the short term (including patients with massive uncontrolled effusions [pleural, pericardial, peritoneal], pulmonary lymphangitis, and over 50% liver involvement), were not eligible for enrolment into the study.

Patients continued to receive their assigned treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurred first. Crossover between treatment arms was not allowed.

Patients were well matched for baseline demographics and disease characteristics between the palbociclib plus letrozole arm and the placebo plus letrozole arm. The median age of patients enrolled in this study was 62 years (range 28-89); 48.3% of patients had received chemotherapy and 56.3% had received antihormonal therapy in the (neo)adjuvant setting prior to their diagnosis of advanced breast cancer, while 37.2% of patients had received no prior systemic therapy in the (neo)adjuvant setting. Most patients (97.4%) had metastatic disease at baseline; 22.7% of patients had bone only disease and 49.2% of patients had visceral disease.

The primary endpoint of the study was PFS evaluated according to RECIST version 1.1 as assessed by investigator. Secondary efficacy endpoints included objective response (OR), duration of response (DOR), clinical benefit response (CBR), overall

survival (OS), safety, EQ-5D scores and health-related quality of life (QoL) assessed using the FACT-B questionnaire.

At the data cutoff date of 26 February 2016, the study met its primary objective of improving PFS. The observed HR was 0.576 (95% CI: 0.463, 0.718) in favor of palbociclib plus letrozole, with a stratified log-rank test 1-sided p-value of <0.000001. An updated analysis of the primary and secondary endpoints was performed after additional 15 months of follow up (data cutoff date: 31 May 2017). A total of 405 PFS events were observed; 245 events (55.2%) in the palbociclib plus letrozole arm and 160 (72.1%) in the comparator arm respectively.

Table 8 shows the efficacy results based on the primary and the updated analyses from the PALOMA-2 study, as assessed by the investigator and by the independent review.

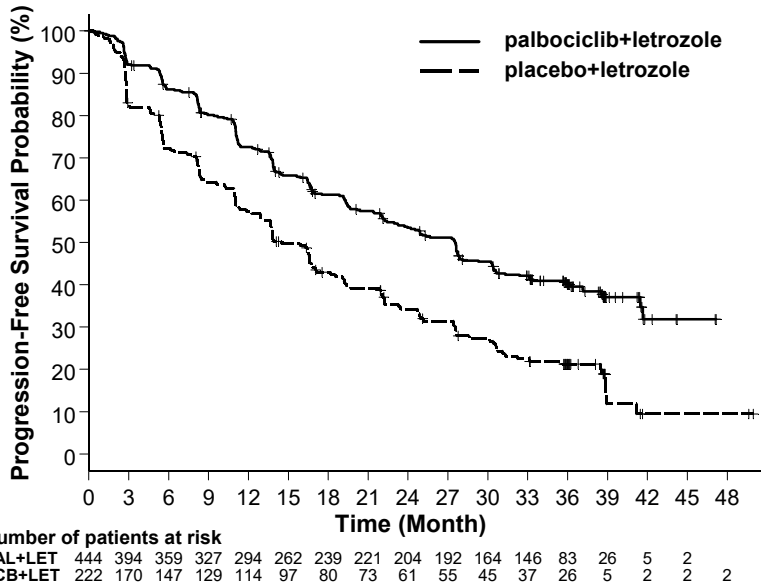
Table 8. PALOMA-2 (Intent-to-Treat Population) - Efficacy Results Based on Primary and Updated Cutoff Dates

	Primary Analysis (26 February 2016 Cutoff)		**Updated Analysis (31 May 2017 Cutoff)**	
	IBRANCE plus Letrozole (N = 444)	**Placebo plus Letrozole (N = 222)**	**IBRANCE plus Letrozole (N = 444)**	**Placebo plus Letrozole (N = 222)**
Progression-free Survival by Investigator Assessment				
Number of events (%)	194 (43.7)	137 (61.7)	245 (55.2)	160 (72.1)
Median PFS [months (95% CI)]	24.8 (22.1, NE)	14.5 (12.9, 17.1)	27.6 (22.4 30.3)	14.5 (12.3, 17.1)
Hazard ratio [(95% CI) and p-value]	0.576 (0.463, 0.718), p<0.000001		0.563 (0.461, 0.687), p<0.000001	
Progression-free Survival by Independent Assessment				
Number of events (%)	152 (34.2)	96 (43.2)	193 (43.5)	118 (53.2)
Median PFS [months (95% CI)] and p-value	30.5 (27.4, NE)	19.3 (16.4, 30.6)	35.7 (27.7, 38.9)	19.5 (16.6, 26.6)
Hazard ratio (95% CI) and 1-sided p-value	0.653 (0.505, 0.844), p=0.000532		0.611 (0.485, 0.769), p=0.000012	
OR* [% (95% CI)]	46.4 (41.7, 51.2)	38.3 (31.9, 45.0)	47.5 (42.8, 52.3)	38.7 (32.3, 45.5)
OR* measurable disease [% (95% CI)]	60.7 (55.2, 65.9)	49.1 (41.4, 56.9)	62.4 (57.0, 67.6)	49.7 (42.0, 57.4)
DOR* [months (95% CI)]	20.1 (19.3, 28.0)	16.7 (13.8, 22.5)	25.3 (22.1, 34.5)	16.8 (14.2, 25.3)
CBR* [% (95% CI)]	85.8 (82.2, 88.9)	71.2 (64.7, 77.0)	85.6 (82.0, 88.7)	71.2 (64.7, 77.0)

N=number of patients; CI=confidence interval; NE=not estimable; OR=objective response; CBR=clinical benefit response; DOR=duration of response; PFS=progression-free-survival.
Secondary endpoints results are based on confirmed and unconfirmed responses according to RECIST 1.1.

The Kaplan-Meier curves for PFS based on the updated cutoff date of 31 May 2017 are displayed in Figure 1 below.

Figure 1. Kaplan-Meier Plot of Progression-free Survival (Investigator Assessment, Intent-to-Treat Population) – PALOMA-2 Study (31 May 2017)



Abbreviations: LET=letrozole; PAL=palbociclib; PCB=placebo.

A series of prespecified subgroup PFS analyses was performed based on baseline demographic and disease characteristics to investigate the internal consistency of treatment effect. A reduction in the risk of disease progression or death in the palbociclib plus letrozole arm was observed in all individual patient subgroups defined by stratification factors and baseline characteristics in the primary and in the updated analyses.

At the time of the updated analyses, the times to initiation of the first and the second subsequent anticancer therapies were also assessed. Similarly, the time to initiation of subsequent chemotherapy was also evaluated. The results from these analyses are shown in Table 9.

Table 9. PALOMA-2 Study: Time to Initiation of Subsequent Anticancer Therapies (31-May-2017 Cutoff Date)

	IBRANCE plus letrozole (N=444)	**Placebo plus letrozole (N=222)**
Median (95% CI) time to first subsequent therapy	28.0 (23.6, 29.6)	17.7 (14.3, 21.5)
Median (95% CI) time to second subsequent therapy	38.8 (34.4, NE)	28.8 (25.7, 33.5)
Median (95% CI) time to first chemotherapy	40.4 (34.7, 47.3)	29.9 (25.6, 35.1)
N=number of patients; CI=confidence interval		

Patients with advanced, symptomatic visceral spread at risk of life-threatening complications in the short term were not included in PALOMA-2. Objective Response Rate (ORR) was higher in patients with visceral disease treated with palbociclib plus letrozole compared to placebo plus letrozole (58.9% [95% CI: 52.0, 65.5], versus 45.5% [95% CI: 35.9, 55.2], respectively), while in patients with non visceral metastases (n= 342, of whom 151 had bone only disease) ORR was comparable between treatment groups (34.8% [95% CI: 28.6, 41.3], versus 31.3% [95% CI: 22.8, 40.7]) The overall survival (OS) data were not mature at the time of the final PFS analysis (20% of patients had died). Patients will continue to be followed for the final analysis.

An analysis of time-to-deterioration composite endpoint (TTD) in Functional Assessment of Cancer Therapy-Breast (FACT-B), defined as the time between baseline and first occurrence of decrease of ≥7 points in FACT-B scores, was carried out based on survival analysis methods using a Cox proportional hazards model and log-rank test. No statistically significant difference was observed in TTD in FACT-B total scores between the palbociclib plus letrozole arm and the placebo plus letrozole arm (HR of 1.042 [95% CI: 0.838, 1.295]; 1-sided p-value=0.663).

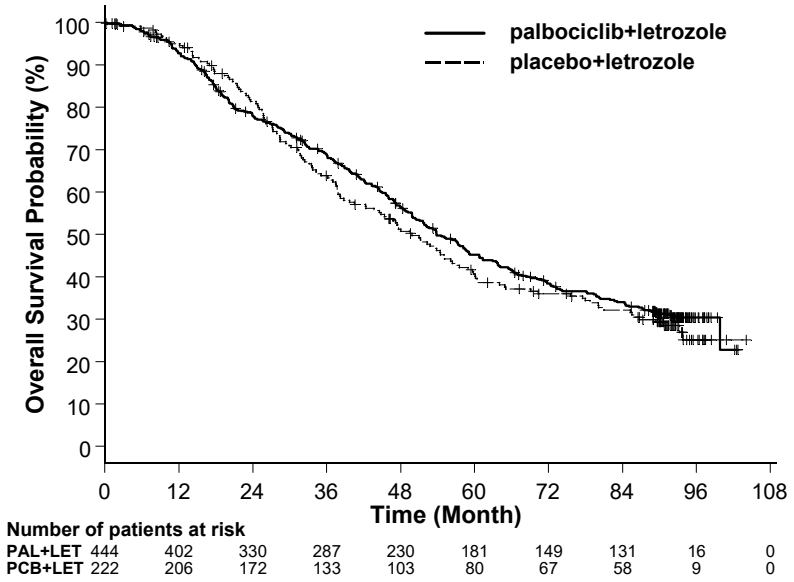
The results from the final OS analysis from the PALOMA-2 study are presented in Table 10. After a median follow-up time of 90 months, the final OS results were not statistically significant. The Kaplan-Meier plot of OS is shown in Figure 2.

Table 10. PALOMA-2 (Intent-to-Treat Population) – Final Overall Survival Results

Final Overall Survival (OS) (15 November 2021 Cutoff)		
	IBRANCE plus letrozole (N = 444)	**Placebo plus letrozole (N = 222)**
Number of OS events (%)	287 (64.6)	148 (66.7)
Number of subjects remaining in follow-up (%)	116 (26.1)	48 (21.6)
Median OS (months, 95% CI)	53.8 (49.8, 59.2)	49.8 (42.3, 56.4)
Hazard ratio (95% CI) and p-value[†]	0.921 (0.755, 1.124), p=0.2087[†*]	

CI=confidence interval.
[*] Not statistically significant.
[†] 1-sided p-value from the log-rank test stratified by disease site (visceral vs. non-visceral) per randomization.

Figure 2. Kaplan-Meier Plot of Overall Survival (Intent-to-Treat Population) – PALOMA-2



Study 3: Randomized, Phase 3 study of IBRANCE in combination with fulvestrant (PALOMA-3)

The efficacy of palbociclib in combination with fulvestrant versus placebo plus fulvestrant was evaluated in an international, randomized, double-blind, parallel-group, multicenter study conducted in women with HR-positive, HER2-negative advanced breast cancer, regardless of their menopausal status, whose disease progressed after prior endocrine therapy.

A total of 521 pre/postmenopausal women whose disease had progressed during or within 12 months after completion of adjuvant endocrine therapy or during or within 1 month after prior endocrine therapy for advanced disease were randomized 2:1 to the palbociclib plus fulvestrant arm or the placebo plus fulvestrant arm and stratified by documented sensitivity to prior hormonal therapy, menopausal status at study entry (pre/peri versus postmenopausal), and presence of visceral metastases.

Crossover between treatment arms was not allowed.

Patients were balanced for baseline demographics and prognostic characteristics between the palbociclib plus fulvestrant arm and the placebo plus fulvestrant arm. The majority of patients in each treatment arm were White, <65 years of age, had documented sensitivity to prior hormonal therapy, and were postmenopausal. All patients had received prior systemic therapy and most patients in each treatment arm had received a previous chemotherapy regimen. More than a half had an Eastern

Cooperative Oncology Group (ECOG) performance status of 0, had visceral metastases, and had received more than 1 prior hormonal regimen for the primary diagnosis.

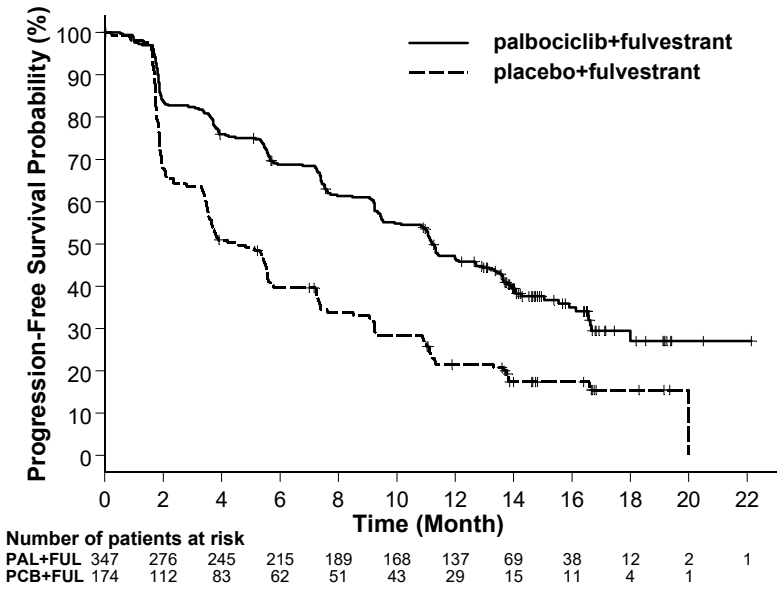
The primary endpoint of the study was investigator-assessed PFS evaluated according to RECIST version 1.1. Supportive PFS analyses were based on an Independent Central Radiology Review. Secondary endpoints included OR, DOR, CBR, OS, safety, change in QoL, and TTD. Patient-reported outcomes including Global QoL and pain were measured using the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ-C30) and the Breast Cancer Module (BR23) questionnaire.

The study met its primary endpoint of prolonging investigator-assessed PFS at the interim analysis conducted on 82% of the planned PFS events at final analysis; the results crossed the prespecified Haybittle-Peto efficacy boundary (α=0.00135), demonstrating a statistically significant prolongation in PFS and a clinically meaningful treatment effect.

The estimated HR from the stratified analysis was 0.422 (95% CI: 0.318, 0.560; 1-sided $p<0.000001$) in favor of palbociclib plus fulvestrant.

The mPFS was 9.2 months (95% CI: 7.5, NE) in the palbociclib plus fulvestrant arm and 3.8 months (95% CI: 3.5, 5.5) in the placebo plus fulvestrant arm.

Figure 3. Kaplan-Meier Plot of Progression-Free Survival (Investigator Assessment, Intent-to-Treat Population) – PALOMA-3 (23 October 2015 Cutoff)



CI=confidence interval; FUL=fulvestrant; N=number of patients; NE=not estimable; PAL=palbociclib; PCB=placebo; PFS=progression-free survival.

Table 11. Efficacy Results – Study 3 (Investigator Assessment, Intent-to-Treat Population)

	Final Analysis (05-Dec-2014 Cutoff)		Updated Analysis (23-Oct-2015 Cutoff)	
	IBRANCE plus Fulvestrant (N = 347)	**Placebo plus Fulvestrant (N = 174)**	**IBRANCE plus Fulvestrant (N = 347)**	**Placebo plus Fulvestrant (N = 174)**
Progression-Free Survival				
Median PFS [months (95% CI)]	9.2 (7.5, NE)	3.8 (3.5, 5.5)	11.2 (9.5, 12.9)	4.6 (3.5, 5.6)
Hazard ratio [(95% CI) and p-value]	0.422 (0.318, 0.560), p<0.000001		0.497 (0.398, 0.620), p<0.000001	
ORR [% (95% CI)]	20.2 (16.1, 24.1)	11.5 (7.2, 17.2)	26.2 (21.7, 31.2)	13.8 (9.0, 19.8)
ORR measurable disease [% (95% CI)]	26.1 (21.0, 31.8)	14.5 (9.1, 21.5)	33.7 (28.1, 39.7)	17.4 (11.5, 24.8)
DOR [months (95% CI)]	9.3 (4.0, NE)	5.7 (3.7, 5.7)	9.2 (7.2, 10.4)	7.4 (3.9, NE)
CBRR [% (95% CI)]	41.5 (36.3, 46.9)	21.8 (15.9, 28.7)	68.0 (62.8, 72.9)	39.7 (32.3, 47.3)

CBRR=clinical benefit response rate; CI=confidence interval; DOR=duration of response; N=number of patients; NE=not estimable; PFS=progression-free survival; ORR=objective response rate.

Prolongation of PFS in the palbociclib plus fulvestrant arm was also demonstrated in individual patient subgroups supporting internal consistency of PFS benefit findings within the study, and was supported by a random sample Blinded Independent Central

Review (BICR) audit analysis conducted on 40.5% (N=211) of 521 randomized patients.

Pre/perimenopausal women were enrolled in the study and received the LHRH agonist goserelin for at least 4 weeks prior and for duration of Study 2.

The palbociclib plus fulvestrant arm demonstrated similar clinical benefit in the pre/perimenopausal patient population (HR = 0.435 [95% CI: 0.228, 0.831]) and postmenopausal population (HR= 0.409 [95% CI: 0.298, 0.560]). Similarly, the mPFS for the palbociclib plus fulvestrant arm was 9.5 months (95% CI: 7.2, NE) in the pre/perimenopausal setting versus 9.2 months (95% CI: 7.5, NE) in the postmenopausal setting; while the mPFS in the placebo plus fulvestrant arm was 5.6 months (95% CI: 1.8, NE) in the pre/perimenopausal setting versus 3.7 months (95% CI: 3.5, 5.5) in the postmenopausal setting.

Patient-reported symptoms were assessed using the EORTC QLQ-C30 and EORTC QLQ-BR23. A total of 335 patients in the palbociclib plus fulvestrant arm and 166 patients in the placebo plus fulvestrant arm completed the questionnaire at baseline and at least 1 postbaseline visit.

Results of the Global Health Status/QoL comparison between the palbociclib plus fulvestrant arm versus the fulvestrant plus placebo arm showed a statistically significant difference favoring the palbociclib plus fulvestrant arm compared to the placebo plus fulvestrant arm (-0.9 [95% CI: -2.5, 0.7] versus -4.0 [95% CI: -6.3, -1.7], respectively; 2-sided p=0.0313). In addition, a comparison in emotional functioning also showed a statistically significant difference favoring the palbociclib plus fulvestrant arm compared to the placebo plus fulvestrant arm (2.7 [95% CI: 1.1, 4.3] versus-1.9 [95% CI: -4.2, 0.5], respectively; 2-sided p=0.0016) (data unadjusted for multiple comparisons).

Time to Deterioration (TTD) was prespecified as time between baseline and first occurrence of ≥10-point increase from baseline in pain symptom scores. Addition of palbociclib to fulvestrant resulted in a symptom benefit by significantly delaying TTD in pain symptom scores compared with placebo plus fulvestrant (median 8.0 months versus 2.8 months; HR of 0.64 [95% CI: 0.49, 0.85]; p<0.001).

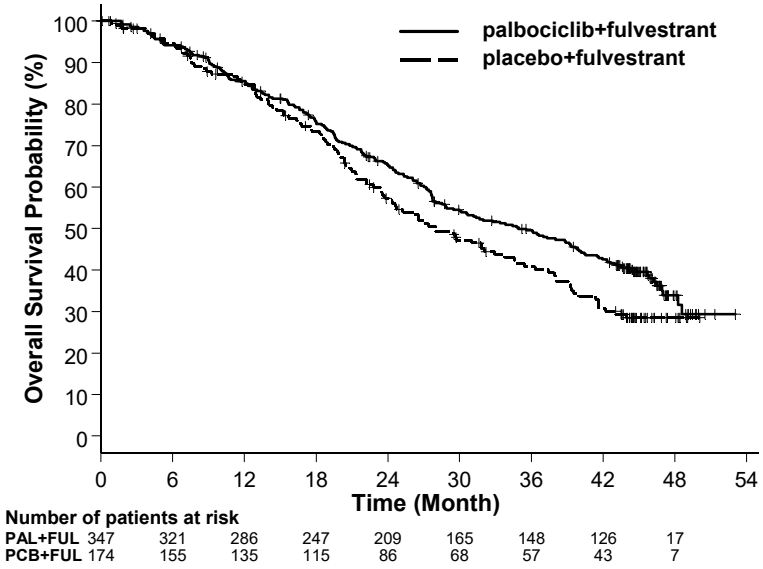
After a median follow-up time of 45 months, the final OS analysis was performed based on 310 events (59.5% of randomized patients). A clinically meaningful 6.9-month improvement in median OS in the palbociclib plus fulvestrant arm compared with the placebo plus fulvestrant arm was observed, although this result was not statistically significant at the prespecified significance level of 0.0235. A higher proportion of patients in the placebo plus fulvestrant arm received post-progression systemic treatments overall in comparison with the patients in the palbociclib plus fulvestrant arm (80.5% versus 71.8%) respectively. Also, in placebo plus fulvestrant arm, 15.5% of randomized patients received palbociclib and other CDK inhibitors as post progression subsequent treatments. The results from the final OS data from PALOMA-3 Study are presented in Table 12. The relevant Kaplan-Meier plots are shown in Figures 3 and 4.

Table 12. Efficacy Results – Study 3 (Investigator Assessment, Intent-to-Treat Population)

Final Overall Survival (OS) (13 April 2018 Cutoff)		
	IBRANCE plus Fulvestrant (N=347)	**Placebo plus Fulvestrant (N=174)**
Number of events (%)	201 (57.9)	109 (62.6)
Median (months [95% CI])	34.9 (28.8, 40.0)	28.0 (23.6, 34.6)
Hazard ratio (95% CI) and p-value[†]	0.814 (0.644, 1.029) p=0.0429[†*]	

CI=confidence interval.
[*] Not statistically significant.
[†] 1-sided p-value from the log-rank test stratified by the presence of visceral metastases and sensitivity to prior endocrine therapy per randomization.

Figure 4. Kaplan-Meier Plot of Overall Survival (Intent-to-Treat Population) – PALOMA-3



FUL=fulvestrant; PAL=palbociclib; PCB=placebo.

A positive treatment effect of palbociclib plus fulvestrant versus placebo plus fulvestrant on OS was observed in the majority of the prespecified subgroups. Due to the low event number and smaller sample size in some of the prespecified subgroups, the magnitude of estimated effect of palbociclib added to fulvestrant could not always be determined. The OS results from patients subgroups defined by stratification factors at randomization are reported in Table 13 below.

Table 13. Overall Survival in Patients Subgroups Defined by Stratification Factors

	PAL + FUL	PCB + FUL	HR (95% CI)	p-value*
ITT Sub-group	**ne/N**	**ne/N**		
Menopausal Status at Study Entry				
Postmenopausal	161/275	91/138	0.73 (0.57, 0.95)	p=0.009
Peri/premenopausal	40/72	18/36	1.07 (0.61, 1.86)	p=0.41
Documented Sensitivity to Prior Hormonal Therapy				
Yes	150/274	84/136	0.72 (0.55, 0.94)	p=0.008
No	51/73	25/38	1.14 (0.70, 1.84)	p=0.297
Site of Metastatic Disease				
Visceral	138/206	72/105	0.85 (0.64, 1.13)	p=0.132
Non-visceral	63/141	37/69	0.69 (0.46, 1.04)	p=0.036

CI=confidence interval; FUL=fulvestrant; HR=Hazard Ratio; ITT=Intent-to-Treat; ne=number of events; N=number of patients; PAL=palbociclib; PCB=placebo.
* One sided p-value. No multiplicity adjustments were made for the subgroup analyses.

The estimated survival probabilities for palbociclib plus fulvestrant versus placebo plus fulvestrant were respectively: 65.3% (95% CI: 59.9, 70.2) vs. 57.3% (95% CI: 49.2, 64.6) at 2 years and 49.6% (95% CI: 44.0, 54.9) vs. 40.8% (95% CI: 32.9, 48.5) at 3 years.

5.2. Pharmacokinetic properties

The pharmacokinetics of palbociclib were characterized in patients with solid tumors including advanced breast cancer and in healthy subjects.

Absorption

The T_{max} of palbociclib is generally observed between 4 to 12 hours following oral administration of IBRANCE tablets. The mean absolute bioavailability of palbociclib after an oral 125 mg dose is 46%. In the dosing range of 25 mg to 225 mg, the AUC and C_{max} increase proportionally with dose in general. Steady state was achieved within 8 days following repeated once daily dosing. With repeated once daily administration, palbociclib accumulates with a median accumulation ratio of 2.4 (range 1.5-4.2).

Food effect: The AUC_{inf} and C_{max} of palbociclib increased by 22% and 26%, respectively, when IBRANCE tablets were given with a high-fat, high-calorie meal (approximately 800 to 1000 calories with 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively), and by 9% and 10%, respectively, when IBRANCE tablets were given with a moderate fat, standard-calorie meal (approximately 500 to 700 calories with 75 to 105, 250 to 350, and 175 to 245 calories from protein, carbohydrate, and fat, respectively), compared to IBRANCE

tablets given under overnight fasted conditions. Based on these results, IBRANCE tablets may be taken with or without food.

Gastric pH elevating medication effect: Coadministration of multiple doses of the PPI rabeprazole with a single 125 mg IBRANCE tablet under fasted conditions had no effect on the rate and extent of absorption of palbociclib when compared to a single 125 mg IBRANCE tablet administered alone.

Distribution

Binding of palbociclib to human plasma proteins *in vitro* was ~85%, with no concentration dependence over the concentration range of 500 ng/mL to 5000 ng/mL. The mean fraction unbound (f_u) of palbociclib in human plasma *in vivo* increased incrementally with worsening hepatic function. There was no obvious trend in the mean palbociclib f_u in human plasma *in vivo* with worsening renal function. The geometric mean apparent volume of distribution (V_z/F) was 2583 (26%) L.

Metabolism

In vitro and *in vivo* studies indicate that palbociclib undergoes extensive hepatic metabolism in humans. Following oral administration of a single 125 mg dose of [^{14}C] palbociclib to humans, the major primary metabolic pathways for palbociclib involved oxidation and sulfonation, with acylation and glucuronidation contributing as minor pathways. Palbociclib was the major circulating drug-derived entity in plasma. The major circulating metabolite was a glucuronide conjugate of palbociclib, although it only represented 1.5% of the administered dose in the excreta. The majority of the material was excreted as metabolites. In feces, the sulfamic acid conjugate of palbociclib was the major drug-related component, accounting for 25.8% of the administered dose. *In vitro* studies with human hepatocytes, liver cytosolic and S9 fractions, and recombinant sulfotransferase (SULT) enzymes indicated that CYP3A and SULT2A1 are mainly involved in the metabolism of palbociclib.

Elimination

The geometric mean apparent oral clearance (CL/F) of palbociclib was 63.08 L/h, and the mean plasma elimination half-life was 28.8 hours in patients with advanced breast cancer. In 6 healthy male subjects given a single oral dose of [^{14}C] palbociclib, a median of 91.6% of the total administered radioactive dose was recovered in 15 days; feces (74.1% of dose) was the major route of excretion, with 17.5% of the dose recovered in urine. Excretion of unchanged palbociclib in feces and urine was 2.3% and 6.9% of the administered dose, respectively.

Age, gender, and body weight

Based on a population pharmacokinetic analysis in 183 patients with cancer (50 male and 133 female patients, age ranging from 22 to 89 years, and body weight ranging from 37.9 to 123 kg), gender had no effect on the exposure of palbociclib, and age and body weight had no clinically important effect on the exposure of palbociclib.

Pediatric population

Pharmacokinetics of palbociclib have not been evaluated in patients ≤18 years of age.

Elderly population

Of 444 patients who received IBRANCE in Study A5481008 (PALOMA-2), 181 patients (41%) were ≥65 years of age with 133 (30%) patients between the age of 65 and 74, and 48 (11%) patients ≥75 years of age. Of 347 patients who received IBRANCE in Study A5481023 (PALOMA-3), 86 patients (25%) were ≥65 years of age with 59 (17%) patients between the age of 65 and 74, and 27 (8%) patients ≥75 years of age. No overall differences in safety were observed across all age groups and elderly age groups. Neutropenia was the most common adverse event with palbociclib across all age groups; however, the incidence of febrile neutropenia was low in all age groups.

Hepatic impairment

Data from a pharmacokinetic trial in subjects with varying degrees of hepatic function indicate that palbociclib unbound exposure (unbound AUC_{inf}) decreased by 17% in subjects with mild hepatic impairment (Child-Pugh class A), and increased by 34% and 77% in subjects with moderate (Child-Pugh class B) and severe hepatic impairment (Child-Pugh class C), respectively, relative to subjects with normal hepatic function. Peak palbociclib unbound exposure (unbound C_{max}) was increased by 7%, 38% and 72% for mild, moderate and severe hepatic impairment, respectively, relative to subjects with normal hepatic function. In addition, based on a population pharmacokinetic analysis that included 183 patients with advanced cancer where 40 patients had mild hepatic impairment based on National Cancer institute (NCI) classification (total bilirubin ≤Upper Limit of Normal (ULN) and Aspartate Aminotransferase (AST) >ULN, or total bilirubin >1.0 to 1.5 × ULN and any AST), mild hepatic impairment had no effect on the pharmacokinetics (PK) of palbociclib.

Renal impairment

Data from a pharmacokinetic trial in subjects with varying degrees of renal function indicate that total palbociclib exposure (AUC_{inf}) was increased by 39%, 42%, and 31% with mild (60 mL/min≤CrCl<90 mL/min), moderate (30 mL/min≤CrCl<60 mL/min), and severe (CrCl <30 mL/min) renal impairment, respectively, relative to subjects with normal (CrCl ≥90 mL/min) renal function. Peak palbociclib exposure (C_{max}) was increased by 17%, 12%, and 15% for mild, moderate, and severe renal impairment, respectively, relative to subjects with normal renal

function. In addition, based on a population pharmacokinetic analysis that included 183 patients with advanced cancer where 73 patients had mild renal impairment and 29 patients had moderate renal impairment, mild and moderate renal impairment had no effect on the PK of palbociclib. The pharmacokinetics of palbociclib have not been studied in patients requiring hemodialysis.

Asian race

In a pharmacokinetic study in healthy volunteers, palbociclib AUC_{inf} and C_{max} values were 30% and 35% higher, respectively, in Japanese subjects compared with non-Asian subjects after a single oral dose. However, this finding was not reproduced consistently in subsequent studies in Japanese or Asian breast cancer patients after multiple dosing. Based on an analysis of the cumulative pharmacokinetic, safety, and efficacy data across Asian and non-Asian populations, no dose adjustment based on Asian race is considered necessary.

Cardiac electrophysiology

The effect of palbociclib on the QT interval corrected for heart rate (QTc) was evaluated using time-matched electrocardiograms (ECGs) evaluating the change from baseline and corresponding pharmacokinetic data in 77 patients with breast cancer. Palbociclib did not prolong QTc to any clinically relevant extent at the recommended dose of 125 mg daily (Schedule 3/1).

5.3. Preclinical safety data

The primary target organ findings following single and/or repeat dosing included hematolymphopoietic and male reproductive organ effects in rats and dogs, and effects on bone and actively growing incisors in rats only. These systemic toxicities were generally observed at clinically relevant exposures based on AUC. Partial to full reversal of effects on the hematolymphopoietic, male reproductive systems, and incisor teeth were established, whereas the bone effect was not reversed following a 12-week nondosing period. In addition, cardiovascular effects (QTc prolongation, decreased heart rate, and increased RR interval and systolic blood pressure) were identified in telemetered dogs at ≥4 times human clinical exposure based on C_{max}.

Carcinogenicity

Palbociclib was assessed for carcinogenicity in a 6-month transgenic mouse study and in a 2-year rat study. Palbociclib was negative for carcinogenicity in transgenic mice at doses up to 60 mg/kg/day (No Observed Effect Level [NOEL] approximately 11 times human clinical exposure based on AUC). Palbociclib-related neoplastic finding in rats included an increased incidence of microglial cell tumors in the central nervous system of males at 30 mg/kg/day; there were no neoplastic findings in female rats at any dose up to 200 mg/kg/day. The NOEL for palbociclib-related carcinogenicity effects was 10 mg/kg/day (approximately 2 times the human clinical exposure based on AUC) and 200 mg/kg/day (approximately 4 times the human clinical exposure based on AUC) in males and females, respectively. The relevance of the male rat

neoplastic finding to humans is unknown.

Genotoxicity

Palbociclib was not mutagenic in a bacterial reverse mutation (Ames) assay and did not induce structural chromosomal aberrations in the *in vitro* human lymphocyte chromosome aberration assay.

Palbociclib induced micronuclei via an aneugenic mechanism in Chinese Hamster Ovary cells *in vitro* and in the bone marrow of male rats at doses ≥100 mg/kg/day. The no-observed effect level for aneugenicity was approximately 7 times human clinical exposure based on AUC.

Impairment of fertility

Palbociclib did not affect mating or fertility in female rats at any dose tested up to 300 mg/kg/day (approximately 3 times human clinical exposure based on AUC) and no adverse effects were observed in female reproductive tissues in repeat-dose toxicity studies up to 300 mg/kg/day in the rat and 3 mg/kg/day in the dog (approximately 5 and 3 times human clinical exposure based on AUC, respectively).

Palbociclib is considered to have the potential to impair reproductive function and fertility in male humans based on nonclinical findings in rats and dogs. Palbociclib-related findings in the testis, epididymis, prostate, and seminal vesicle included decreased organ weight, atrophy or degeneration, hypospermia, intratubular cellular debris, lower sperm motility and density, and decreased secretion. These findings were observed in rats and/or dogs at exposures ≥9 times or subtherapeutic compared to human clinical exposure based on AUC. Partial reversibility of male reproductive organ effects was observed in the rat and dog following a 4- and 12-week non-dosing period, respectively. Despite these male reproductive organ findings, there were no effects on mating or fertility in male rats at projected exposure levels 13 times human clinical exposure based on AUC.

Developmental toxicity

Palbociclib was fetotoxic in pregnant animals. An increased incidence of a skeletal variation (increased incidence of a rib present at the seventh cervical vertebra) at ≥100 mg/kg/day was observed in rats. Reduced fetal body weights were observed at a maternally toxic dose of 300 mg/kg/day in rats (3 times human clinical exposure based on AUC), and an increased incidence of skeletal variations, including small phalanges in the forelimb was observed at a maternally toxic dose of 20 mg/kg/day in rabbits (4 times human clinical exposure based on AUC). Actual fetal exposure and cross-placenta transfer have not been examined.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Tablet core
Microcrystalline cellulose, colloidal silicon dioxide, crospovidone, magnesium stearate, and succinic acid.

Film coating
Hypromellose, titanium dioxide, triacetin, indigo carmine aluminum lake, iron oxide red (75 mg and 125 mg tablets only), and iron oxide yellow (100 mg tablets only).

6.2. Shelf life

36 months.

6.3. Special precautions for storage

Store below 30°C.

6.4. Special precautions for disposal and other handling

Store in the original blister package in order to protect from moisture.

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

7. MARKETING AUTHORISATION HOLDER NAME AND ADDRESS

Manufactured by:
Pfizer Manufacturing Deutschland GmbH
Betriebsstätte Freiburg
Germany

Imported by:
PT. Pfizer Indonesia
Jakarta, Indonesia

8. MARKETING AUTHORISATION NUMBER

Ibrance 75 mg Film-coated tablet; Box of 1 blister @ 7 film-coated tablets; No. Reg. DKI2158501617A1
Ibrance 100 mg Film-coated tablet; Box of 1 blister @ 7 film-coated tablets; No. Reg. DKI2158501617B1
Ibrance 125 mg Film-coated tablet; Box of 1 blister @ 7 film-coated tablets; No. Reg. DKI2158501617C1

HARUS DENGAN RESEP DOKTER

9. DATE OF REVISION OF THE TEXT

03/2023

CDS version 16.0