SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

PALBOCICLIB PFIZER 75 mg Capsules

PALBOCICLIB PFIZER 100 mg Capsules

PALBOCICLIB PFIZER 125 mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PALBOCICLIB PFIZER 75 mg: each capsule contains 75 mg palbociclib.

PALBOCICLIB PFIZER 100 mg: each capsule contains 100 mg palbociclib.

PALBOCICLIB PFIZER 125 mg: each capsule contains 125 mg palbociclib.

Excipient with known effect

Contains sugar (lactose monohydrate)

PALBOCICLIB PFIZER 75 mg: each capsule contains 55,78 mg lactose monohydrate.

PALBOCICLIB PFIZER 100 mg: each capsule contains 74,37 mg lactose monohydrate.

PALBOCICLIB PFIZER 125 mg: each capsule contains 92,96 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules

PALBOCICLIB PFIZER 75 mg: opaque, hard capsule with a light orange body/ light orange cap capsule imprinted with “PBC 75” on the body and “Pfizer” on the cap, in white ink. The capsule contains off-white to yellow powder.

PALBOCICLIB PFIZER 100 mg: opaque, hard capsule with a light orange body/caramel cap capsule imprinted

with “PBC 100” on the body and “Pfizer” on the cap, in white ink. The capsule contains off-white to yellow powder.

PALBOCICLIB PFIZER 125 mg: opaque, hard capsule with a caramel body/caramel cap capsule imprinted with “PBC 125” on the body and “Pfizer” on the cap, in white ink. The capsule contains off-white to yellow powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

- with letrozole as initial endocrine-based therapy in postmenopausal women
- with fulvestrant in women with disease progression who have received prior endocrine therapy

4.2 Posology and method of administration

Treatment with PALBOCICLIB PFIZER should be conducted by a medical practitioner experienced in the use of anticancer therapies.

Posology

The recommended starting dose of PALBOCICLIB PFIZER is a 125 mg capsule taken orally once daily with food 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 PFIZER, 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 PFIZER, 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.

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. PALBOCICLIB PFIZER capsules should be swallowed whole (do not chew, crush or open them prior to swallowing). No capsule should be ingested if it is broken, cracked, or otherwise not intact.

Prior to the start of, and throughout treatment with the combination PALBOCICLIB PFIZER plus fulvestrant, pre/perimenopausal women should be treated with luteinizing hormone-releasing hormone (LHRH) agonists according to local clinical practice.

Dose modifications

Dose modification of PALBOCICLIB PFIZER 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 3, 4 and 5 (see sections 4.4 and 4.8).

Table 1. PALBOCICLIB PFIZER 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*
* If further dose reduction below 75 mg/day is required, discontinue the treatment.	

Table 2. PALBOCICLIB PFIZER Dose modification and management – haematologic toxicities[a]

Monitor complete blood counts prior to the start of PALBOCICLIB PFIZER 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.

CTCAE Grade	**Dose Modifications**
Grade 1 or 2	No dose adjustment is required.
Grade 3[a]	Day 1 of cycle: Withhold PALBOCICLIB PFIZER, 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 PALBOCICLIB PFIZER 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] (< 1 000 to 500/mm^3) + fever ≥ 38,5ºC and/or infection	At any time: Withhold PALBOCICLIB PFIZER until recovery to Grade ≤ 2. Resume at the *next lower dose.*
Grade 4[a]	At any time: Withhold PALBOCICLIB PFIZER until recovery to Grade ≤ 2. Resume at the *next lower dose.*

Grading according to CTCAE 4,0 (Grade 1: ANC < LLN – 1 500/mm^3; Grade 2: ANC 1 000 - <1 500/mm^3; Grade 3: ANC 500 - < 1 000/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 haematologic adverse reactions except lymphopenia (unless associated with clinical events, e.g. opportunistic infections).

[b] ANC: Grade 1: ANC < LLN – 1 500/mm^3; Grade 2: ANC 1 000 - < 1 500/mm^3; Grade 3: ANC 500 - < 1 000/mm^3; Grade 4: ANC < 500/mm^3.

Table 3. PALBOCICLIB PFIZER Dose modification and management – non-haematologic toxicities

CTCAE Grade	**Dose modifications**
Grade 1 or 2	No dose adjustment is required.
Grade ≥ 3 non-haematologic	Withhold until symptoms resolve

toxicity (if persisting despite medical treatment)	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).

Permanently discontinue PALBOCICLIB PFIZER in patients with severe interstitial lung disease (ILD) or pneumonitis (see section 4.4).

Special populations

Elderly population

No dose adjustment is necessary in patients ≥ 65 years of age (see section 5.2).

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 PALBOCICLIB PFIZER is 75 mg once daily for 21 consecutive days followed by 7 days off treatment (Schedule 3/1) to comprise a complete cycle of 28 days (see section 4.1 and section 5.2).

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 haemodialysis to provide any dosing recommendation in this patient population.

Paediatric population

The safety and efficacy of PALBOCICLIB PFIZER in children and adolescents ≤ 18 years of age have not been established.

4.3 Contraindications

- Hypersensitivity to palbociclib or any of the excipients of PALBOCICLIB PFIZER (listed in section 6.1).

4.4 Special warnings and precautions for use

Neutropenia

Decreased neutrophil counts have been observed in clinical studies with PALBOCICLIB PFIZER. In patients receiving PALBOCICLIB PFIZER in combination with letrozole (Study 1 and 2) or fulvestrant (Study 3), Grade 3 and Grade 4 decreased neutrophil counts were reported in 56,1 % and 10,6 % of patients, respectively.

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.

Monitor complete blood count prior to starting PALBOCICLIB PFIZER 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.

Treatment interruption, dose reduction or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia (see section 4.2).

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 PALBOCICLIB PFIZER when taken in combination with endocrine therapy.

Across clinical trials, 1,4 % of PALBOCICLIB PFIZER-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), with fatalities reported.

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

Infections

Since PALBOCICLIB PFIZER has myelosuppressive properties, it may predispose to infections.

Infections of any grade have been reported at a higher rate in patients treated with PALBOCICLIB PFIZER plus letrozole or fulvestrant (54,8 %) compared to patients treated in the respective comparator arms (36,9 %). Grades 3 and 4 infections occurred in 4,4 % and 0,7 %, respectively, in patients treated with PALBOCICLIB PFIZER 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).

Healthcare providers should inform patients to promptly report any episodes of fever.

Venous thromboembolism

Venous thromboembolic events were reported in patients treated with PALBOCICLIB PFIZER (see section 4.8).

Patients should be monitored for signs and symptoms of deep vein thrombosis and pulmonary embolism and treated as medically appropriate.

Excipients with known effect

PALBOCICLIB PFIZER contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take PALBOCICLIB PFIZER. PALBOCICLIB PFIZER may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction

PALBOCICLIB PFIZER is primarily metabolised by CYP3A and sulphotransferase (SULT) enzyme SULT2A1. *In vivo*, PALBOCICLIB PFIZER is a time-dependent inhibitor of CYP3A.

Medicines that may increase PALBOCICLIB PFIZER plasma concentrations

Effect of CYP3A inhibitors

Data from a drug-drug interaction (DDI) study in healthy subjects indicate that co-administration of multiple 200 mg doses of itraconazole with a single 125 mg dose of PALBOCICLIB PFIZER increased PALBOCICLIB PFIZER total exposure area under the plasma concentration-time curve from zero to infinity ($AUC_{0\text{-}inf}$) and the maximum observed plasma concentration (C_{max}) by approximately 87 % and 34 %, respectively, relative to a single 125 mg dose of PALBOCICLIB PFIZER 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.

Medicines that may decrease PALBOCICLIB PFIZER plasma concentrations

Effect of CYP3A inducers

Data from a DDI study in healthy subjects indicate that co-administration of multiple 600 mg doses of rifampicin, a strong CYP3A inducer, with a single 125 mg dose of PALBOCICLIB PFIZER decreased PALBOCICLIB PFIZER $AUC_{0\text{-}inf}$ and C_{max} by 85 % and 70 %, respectively, relative to a single 125 mg dose of PALBOCICLIB PFIZER given alone. Data from a DDI study in healthy subjects indicate that co-administration of multiple 400 mg daily doses of modafinil, a moderate CYP3A inducer, with a single 125 mg dose of PALBOCICLIB PFIZER decreased palbociclib $AUC_{0\text{-}inf}$ and C_{max} by 32 % and 11 %, respectively, relative to a single 125 mg dose of PALBOCICLIB PFIZER given alone.

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

Co-administration 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 PALBOCICLIB PFIZER when unavoidable. No dosing adjustments are required.

Effect of acid reducing medicines

Data from a DDI study in healthy subjects indicated that co-administration of a single 125 mg dose of PALBOCICLIB PFIZER with multiple doses of the PPI rabeprazole under fed conditions decreased PALBOCICLIB PFIZER C_{max} by 41 % but had limited impact on $AUC_{0\text{-}inf}$ (13 % decrease) compared with a single 125 mg dose of PALBOCICLIB PFIZER administered alone.

Given the reduced effect on gastric pH of H2-receptor antagonists and local antacids compared to PPIs, under fed conditions there is no clinically relevant effect of PPIs, H2-receptor antagonists, or local antacids on PALBOCICLIB PFIZER exposure.

Data from another DDI study in healthy subjects indicated that co-administration of a single dose of

PALBOCICLIB PFIZER with multiple doses of the PPI rabeprazole under fasted conditions decreased PALBOCICLIB PFIZER $AUC_{0\text{-}inf}$ and C_{max} by 62 % and 80 %, respectively, when compared with a single dose of PALBOCICLIB PFIZER administered alone.

Therefore, PALBOCICLIB PFIZER should be taken with food (see section 4.2).

Effects of PALBOCICLIB PFIZER on other medicines

PALBOCICLIB PFIZER, 125 mg daily dosing, is a weak time-dependent inhibitor of CYP3A at steady state in humans. In a DDI study in healthy subjects, co-administration of midazolam with multiple doses of PALBOCICLIB PFIZER increased the midazolam $AUC_{0\text{-}inf}$ and C_{max} values by 61 % and 37 %, respectively, as compared with administration of midazolam alone.

In vitro, PALBOCICLIB PFIZER 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 PFIZER and letrozole when the two medicines were co-administered.

Fulvestrant

Data from a clinical study in patients with breast cancer showed that there was no clinically relevant interaction between PALBOCICLIB PFIZER and fulvestrant when the 2 medicines were co-administered.

Goserelin

Data from a clinical study in patients with breast cancer showed that there was no clinically relevant interaction between PALBOCICLIB PFIZER and goserelin when the 2 medicines 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 PFIZER was co-administered with multiple doses of tamoxifen and when PALBOCICLIB PFIZER was given alone.

In vitro studies with transporters

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

Based on *in vitro* data, PALBOCICLIB PFIZER may inhibit the uptake transporter organic cationic transporter OCT1 and then may increase the exposure of medicine substrates of this transporter (e.g., metformin).

Drug-drug interaction between PALBOCICLIB PFIZER and statins

Concomitant use of PALBOCICLIB PFIZER with statins which are substrates of CYP3A4 and/or BCRP may increase the risk of rhabdomyolysis due to increased statin plasma concentration. Cases of rhabdomyolysis including fatal cases have been reported following coadministration of PALBOCICLIB PFIZER with simvastatin or atorvastatin.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well-controlled studies using PALBOCICLIB PFIZER in pregnant women. Based on findings in animals and mechanism of action, PALBOCICLIB PFIZER can cause foetal harm when administered to a pregnant woman. In animal studies, PALBOCICLIB PFIZER was teratogenic and foetotoxic at maternally toxic doses.

PALBOCICLIB PFIZER is not recommended during pregnancy and in women of childbearing potential not using contraception (see section 5.3).

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

Breastfeeding

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

Fertility

There were no effects on oestrous 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 nonclinical safety findings in male reproductive tissues, male fertility may be compromised by treatment with PALBOCICLIB PFIZER. Men should consider sperm preservation prior to beginning therapy with PALBOCICLIB PFIZER (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects of PALBOCICLIB PFIZER on the ability to drive or operate machinery have been conducted. However, patients experiencing fatigue and dizziness while taking PALBOCICLIB PFIZER should exercise caution when driving or operating machinery.

4.8 Undesirable effects

Summary of the safety profile

The overall safety profile of PALBOCICLIB PFIZER is based on pooled data from 872 patients who received palbociclib in combination with endocrine therapy (N = 527 in combination with letrozole and N = 345 in combination with fulvestrant) in randomised clinical studies in HR-positive, HER2-negative advanced or metastatic breast cancer.

Table 4 presents the adverse drug reactions for palbociclib from the pooled dataset of 3 randomised studies within each system organ class by decreasing medical seriousness.

Table 4. Side effects by SOC and CIOMS frequency category (Very common ≥ 1/10, Common ≥ 1/1 00 to <1/10) uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), not known (cannot be estimated from the available data).

Infections and Infestations	Very common	Infections
Blood and lymphatic system disorders	Very common	Neutropenia (neutropenia, decreased neutrophil count), leukopenia (leukopenia, decreased white blood cell count), anaemia (anaemia, decreased haemoglobin, decreased haematocrit), thrombocytopenia (thrombocytopenia, decreased platelet count)
	Common	Febrile neutropenia

Metabolism and nutrition disorders	Very common	Decreased appetite
Nervous system disorders	Common	Dysgeusia
Eye disorders	Common	Blurred vision, increased lacrimation, dry eye
Respiratory, thoracic and mediastinal disorders	Common	Epistaxis
Gastrointestinal disorders	Very common	Stomatitis (aphthous stomatitis, cheilitis, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral pain, oropharyngeal discomfort, oropharyngeal pain, stomatitis), nausea, diarrhoea, vomiting
Skin and subcutaneous tissue disorders	Very common	Rash (rash, maculo-papular rash, pruritic rash, erythematous rash, papular rash, dermatitis, acneiform dermatitis, toxic skin eruption), alopecia

	Common	Dry skin
General disorders and administration site conditions	Very common	Fatigue, asthenia, pyrexia
Investigations	Common	Increased alanine aminotransferase, increased aspartate aminotransferase, increased blood creatinine

The most common (≥ 20 %) adverse drug reactions of any grade reported in patients receiving palbociclib in randomised clinical trials were neutropenia, infections, leukopenia, fatigue, nausea, stomatitis, anaemia, alopecia, and diarrhoea.

Dose reductions due to any adverse reaction occurred in 34,4 % of patients receiving PALBOCICLIB PFIZER in any combination in randomised clinical studies, Study 1, Study 2, and Study 3.

Permanent discontinuation associated with an adverse drug reaction occurred in 4,1 % of patients receiving PALBOCICLIB PFIZER in any combination in randomised clinical trials Study 1, Study 2, and Study 3.

The most frequently (≥ 1 %) reported serious adverse drug reactions in patients receiving palbociclib plus letrozole (Study 1 and Study 2) were infections (4,6 %) and febrile neutropenia (1,3 %).

The most frequently (≥ 1 %) reported serious adverse drug reactions in patients receiving palbociclib plus fulvestrant (Study 3) were infections (4,1 %), pyrexia (1,4 %), and neutropenia (1,2 %).

Post-marketing adverse events

System organ class	**Side effect**
Vascular disorders	Venous thromboembolism[j]
Respiratory, thoracic and mediastinal disorders	ILD/pneumonitis[h]
Skin and subcutaneous tissue disorders	Palmar-plantar erythrodysaesthesia syndrome, Cutaneous lupus erythematosus, Erythema multiforme

[h] ILD/Pneumonitis includes any reported Preferred Terms that are part of the Standardized MedDRA Query Interstitial Lung Disease (narrow).

[j] Venous thromboembolism includes the following PTs: pulmonary embolism, embolism, deep vein thrombosis, peripheral embolism, thrombosis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine.

Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Report any suspected adverse drug reactions associated with the use of the medicine directly to Pfizer via ZAF.AEReporting@pfizer.com.

4.9 Overdose

There is no known antidote for PALBOCICLIB PFIZER. The treatment of PALBOCICLIB PFIZER overdose should consist of general supportive measures.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic medicines, protein kinase inhibitors, ATC code: L01EF01.

Palbociclib is taken orally and is a highly selective, reversible, small molecule inhibitor of cyclin-dependent kinases (CDK) 4 and 6. Cyclin D1 and CDK4/6 are downstream of multiple signalling pathways which lead to cellular proliferation. 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 oestrogen receptor (ER)-positive breast cancers. Mechanistic analyses revealed that the combination of palbociclib with anti-oestrogen medicines enhanced the re-activation of retinoblastoma (Rb) through inhibition of Rb phosphorylation resulting in reduced E2F signalling and growth arrest. The enhanced growth arrest of the ER-positive breast cancer cell lines treated with palbociclib and anti-oestrogen medicines is accompanied by increased cell senescence resulting in a sustained cell cycle arrest following drug removal and increased cell size associated with a senescent phenotype. *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 signalling and dose-dependent tumour growth. This supports the contribution of senescence-associated growth arrest as a mechanism associated with the anti-tumour efficacy of combined palbociclib/ER antagonist in ER-positive breast cancer models.

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).

Clinical efficacy and safety

Summary of clinical studies

Study 1: Randomised Phase1/2 study of palbociclib in combination with letrozole (PALOMA-1).

The efficacy of palbociclib was evaluated in a randomised, open-label, multicentre study of palbociclib plus letrozole versus letrozole alone conducted in postmenopausal women with ER-positive, HER2-negative advanced breast cancer who did not receive previous systemic treatment for their advanced disease (PALOMA-1).

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 randomised 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.

Randomisation 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 Tumours (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 favour of palbociclib plus letrozole, with a stratified log-rank test 1-sided p-value of 0,0004.

Study 2 - Randomised Phase 3 Study of palbociclib in combination with letrozole (PALOMA-2)

The efficacy of palbociclib in combination with letrozole versus letrozole plus placebo was evaluated in an international, randomised, double-blind, placebo-controlled, parallel-group, multicentre study conducted in women with ER-positive, HER2-negative 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 randomised 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 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 and 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 and 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 estimated HR was 0,576 (95 % CI: 0,463; 0,718) in favour 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 an 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.

Efficacy data from the PALOMA-2 study are summarised in Table 5 and the Kaplan-Meier curve for PFS is shown in Figure 1.

Table 5. Efficacy results from PALOMA 2 Study (intent-to-treat population)

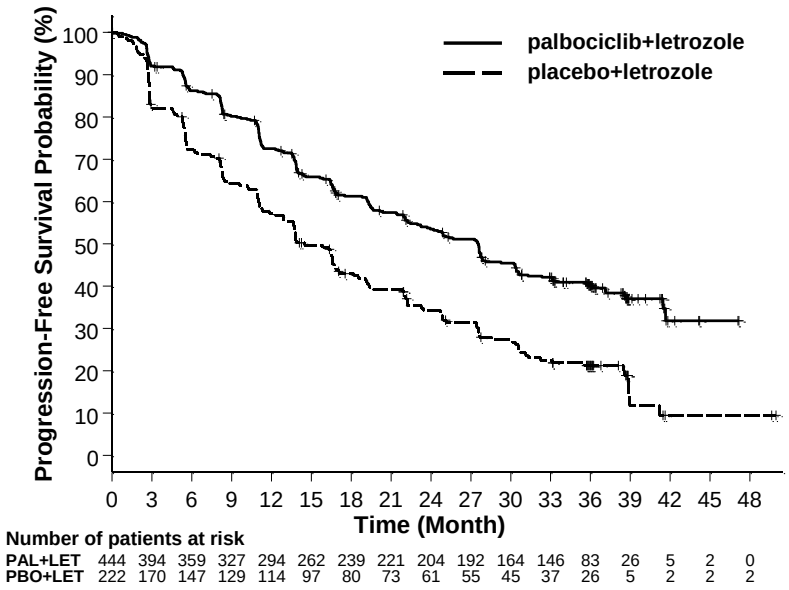
	Primary analysis (26 February 2016 cutoff)		**Updated analysis (31 May 2017 cutoff)**	
	PALBOCICLIB PFIZER plus letrozole (N=444)	**Placebo plus letrozole (N=222)**	**PALBOCICLIB PFIZER plus letrozole (N=444)**	**Placebo plus letrozole (N=222)**
Median progression-free survival [months (95 % CI)]				
Investigator assessment	24,8 (22,1, NE)	14,5 (12,9; 17,1)	27,6 (22,4; 30,3)	14,5 (12,3; 17,1)
HR (95 % CI) and 1-sided p value	0,576 (0,463; 0,718), p < 0,000001		0,563 (0,461; 0,687), p< 0,000001	
Independent radiographic review	30,5 (27,4, NE)	19,3 (16,4; 30,6)	35,7 (27,7; 38,9)	19,5 (16,6; 26,6)
HR (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	

Secondary efficacy endpoints (investigator assessment)				
ORR [% (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)
ORR (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 (measurable disease) [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)
CBRR [% (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; ORR = objective response rate; CBRR = clinical benefit response rate; DOR = duration of response.

*Secondary endpoints results are based on confirmed and unconfirmed responses according to RECIST 1.1.

Figure 1. Kaplan-Meier plot of progression-free survival (investigator assessment, intent to treat population) – PALOMA-2 Study (31 May 2017)



PAL = palbociclib; LET = letrozole; PBO = placebo.

A series of pre-specified 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 analysis.

Based on the 31-May-2017 data cutoff date, this reduction in risk continued to be observed in the following subgroups: (1) patients with either visceral metastases (HR of 0,62 [95 % CI: 0,47 ; 0,81], median progression-free survival [mPFS] 19,3 months versus 12,3 months) or without visceral metastases (HR of 0,50 [95 % CI: 0,37 ; 0,67], mPFS 35,9 months versus 17,0 months) and (2) patients with either bone only disease (HR of 0,41 [95 % CI: 0,26 ; 0,63], mPFS 36,2 months versus 11,2 months) or without bone-only disease (HR of 0,62 [95 % CI: 0,50 ; 0,78], mPFS 24,2 months versus 14,5 months), Similarly, a reduction in the risk of disease progression or death in the palbociclib plus letrozole arm was observed in 512 patients whose tumour tested positive for Rb protein expression by immunohistochemistry (IHC) (HR of 0,543 [95 % CI: 0,433 ; 0,681], mPFS

27,4 months versus 13,7 months), For the 51 patients IHC negative for Rb expression, the difference between treatment arms was not statistically significant (HR of 0,868 [95 % CI: 0,424 ; 1,777], mPFS 23,2 versus 18,5 months) for the palbociclib plus letrozole arm versus the placebo plus letrozole arm, respectively.

Additional efficacy measures (OR and time to response [TTR]) assessed in the sub-groups of patients with or without visceral disease based on the 31-May-2017 updated cutoff date are displayed in Table 6.

Table 6. Efficacy results in patients with visceral or non-visceral disease from PALOMA–2 study (intent-to-treat population; 31-May-2017 cutoff date)

	Visceral disease		**Non-visceral disease**	
	PALBOCICLIB PFIZER plus letrozole (N=214)	**Placebo plus letrozole (N=110)**	**PALBOCICLIB PFIZER plus letrozole (N=230)**	**Placebo plus letrozole (N=112)**
OR [% (95 % CI)]	59,8 (52,9; 66,4)	46,4 (36,8; 56,1)	36,1 (29,9; 42,7)	31,3 (22,8; 40,7)
TTR, Median [months (range)]	5,4 (2,0; 30,4)	5,3 (2,6; 27,9)	3,0 (2,1; 27,8)	5,5 (2,6; 22,2)

N=number of patients; CI=confidence interval; OR=objective response based on confirmed and unconfirmed responses according to RECIST 1.1;

TTR=time to first tumour response.

At the time of the updated analyses, the median time from randomisation to second subsequent therapy was 38,8 months in the palbociclib + letrozole arm and 28,8 months in the placebo + letrozole arm, HR 0,73 (95 % CI: 0,58 ; 0,91).

The results from the final OS analysis from the PALOMA-2 study are presented in Table 7. 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 7. PALOMA-2 (intent-to-treat population) – Final overall survival results

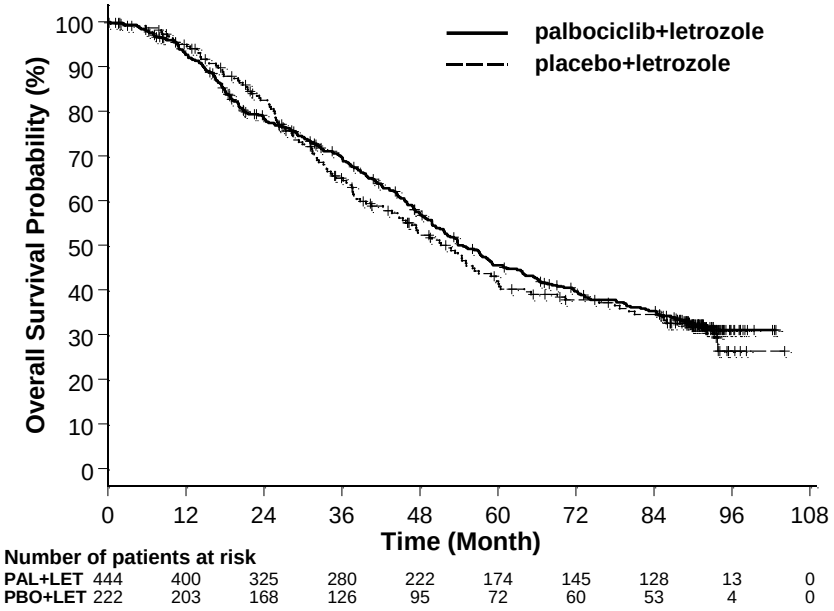
Final Overall Survival (OS) **(15 November 2021 Cutoff)**		
	PALBOCICLIB PFIZER **plus letrozole** **(N=444)**	**Placebo** **plus letrozole** **(N=222)**
Number of events (%)	273 (61,5)	132 (59,5)
Number of subjects remaining in follow-up (%)	112 (25,2)	43 (19,4)
Median OS (months [95 % CI])	53,9 (49,8; 60,8)	51,2 (43,7; 58,9)
Hazard ratio (95 % CI) and p-value†	0,956 (0,777; 1,177), p=0,6755†*	

CI=confidence interval.

* Not statistically significant.

† 2-sided p-value from the log-rank test stratified by disease site (visceral vs. non-visceral) per randomisation.

Figure 2. Kaplan-Meier plot of overall survival (intent-to-treat population) - PALOMA 2



PAL=palbociclib; LET=letrozole; PBO=placebo.

Study 3: Randomised, Phase 3 study of palbociclib in combination with fulvestrant

The efficacy of palbociclib in combination with fulvestrant versus placebo plus fulvestrant was evaluated in an international, randomised, double-blind, parallel-group, multicentre study conducted in women with HR-positive, HER2-negative advanced breast cancer, regardless of their menopausal status, whose disease progressed after prior endocrine therapy in the (neo)adjuvant or metastatic setting.

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 randomised 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. A more mature update of efficacy data is reported in Table 8.

After a median follow-up time of 45 months, the final OS analysis was performed based on 310 events (60 % of randomised patients). A 6,9-month difference in median OS in the palbociclib plus fulvestrant arm compared with the placebo plus fulvestrant arm was observed; this result was not statistically significant at the prespecified significance level of 0,0235 (1-sided). In the placebo plus fulvestrant arm, 15,5 % of randomised patients received palbociclib and other CDK inhibitors as post progression subsequent treatments.

The results from the investigator-assessed PFS and final OS data from PALOMA-3 study are presented in

Table 8. The relevant Kaplan-Meier plots are shown in Figures 3 and 4, respectively.

Table 8. Efficacy results – Study 3 (investigator assessment, intent-to-treat population)

	Updated analysis (23-Oct-2015 Cutoff)	
	PALBOCICLIB PFIZER plus Fulvestrant (N=347)	**Placebo plus Fulvestrant (N=174)**
Progression-free survival (PFS)		
Median PFS [months (95 % CI)]	11,2 (9,5; 12,9)	4,6 (3,5; 5,6)
Hazard ratio [(95 % CI) and p-value]	0,497 (0,398; 0,620), p < 0,000001	
Secondary efficacy endpoints		
ORR [% (95 % CI)]	26,2 (21,7; 31,2)	13,8 (9,0; 19,8)
ORR mea-surable disease [% (95 % CI)]	33,7 (28,1; 39,7)	17,4 (11,5; 24,8)
DOR [months (95 % CI)]	9,2 (7,2; 10,4)	7,4 (3,9; NE)
CBRR [% (95 % CI)]	68,0 (62,8; 72,9)	39,7 (32,3; 47,3)

Final overall survival (OS) **(13 April 2018 cutoff)**		
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†*	

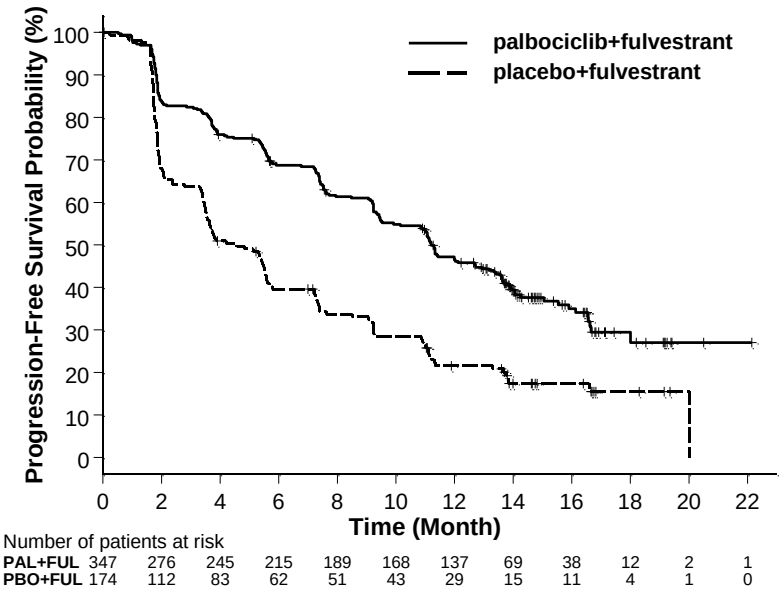
CBRR = clinical benefit response rate; CI = confidence interval; DOR = duration of response; N = number of patients; NE = not estimable; PFS = progression-free survival; ORR = objective response rate.

Secondary endpoint results are based on confirmed and unconfirmed responses according to RECIST 1.1.

* 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 randomisation.

Figure 3. Kaplan-Meier Plot of Progression-Free Survival (investigator assessment, intent-to-treat population) – Study 3 (23 October 2015 cutoff)

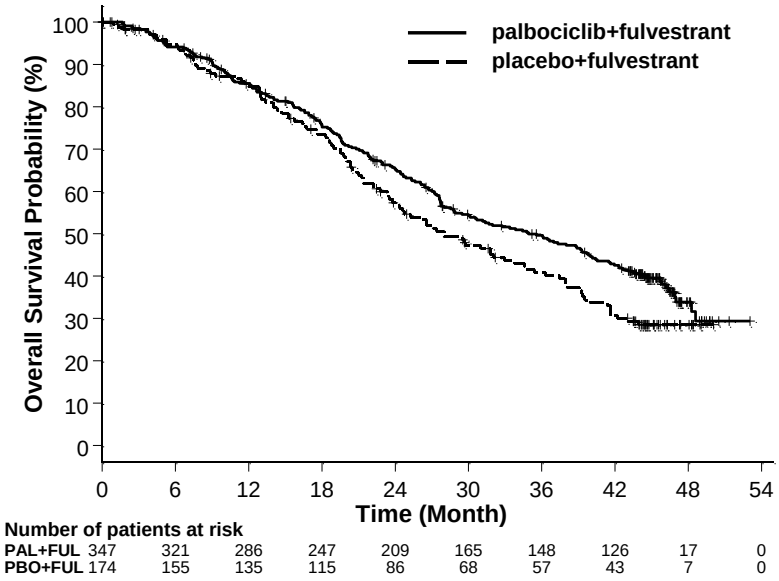


CI=confidence interval; FUL=fulvestrant; N=number of patients; NE=not estimable; PA=palbociclib; PBO

=placebo; PFS=progression-free survival.

A reduction in the risk of disease progression or death in the palbociclib plus fulvestrant arm was observed in all individual patient subgroups defined by stratification factors and baseline characteristics. This was evident for pre/perimenopausal women (HR of 0,46 [95 % CI: 0,28; 0,75]) and postmenopausal women (HR of 0,52 [95 % CI: 0,40; 0,66]) and patients with visceral site of metastatic disease (HR of 0,50 [95 % CI: 0,38; 0,65]) and non-visceral site of metastatic disease (HR of 0,48 [95 % CI: 0,33; 0,71]). Benefit was also observed regardless of lines of prior therapy in the metastatic setting, whether 0 (HR of 0,59 [95 % CI: 0,37 ; 0,93]), 1 (HR of 0,46 [95 % CI: 0,32; 0,64]), 2 (HR of 0,48 [95 % CI: 0,30 ; 0,76]), or ≥ 3 lines (HR of 0,59 [95 % CI: 0,28 ; 1,22]).

Figure 4. Kaplan-Meier plot of overall survival (intent-to-treat population) – PALOMA-3 study (13 April 2018 cutoff)



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

Additional efficacy measures (OR and TTR) assessed in the sub-groups of patients with or without visceral disease are displayed in Table 9.

Table 9. Efficacy results in visceral and non-visceral disease from PALOMA–3 study (intent-to-treat

population)

	Visceral disease		**Non-visceral disease**	
	PALBOCICLIB PFIZER plus fulvestrant (N=206)	**Placebo plus fulvestrant (N=105)**	**PALBOCICLIB PFIZER plus fulvestrant (N=141)**	**Placebo plus fulvestrant (N=69)**
OR [%, (95 % CI)]	35,0 (28,5; 41,9)	13,3 (7,5; 21,4)	13,5 (8,3; 20,2)	14,5 (7,2; 25,0)
TTR, Median [months (range)]	3,8 (3,5; 16,7)	5,4 (3,5; 16,7)	3,7 (1,9; 13,7)	3,6 (3,4; 3,7)

N=number of patients; CI=confidence interval; OR=objective response based on confirmed and unconfirmed responses according to RECIST 1.1; TTR=time to first tumour response.

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 post baseline visit.

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]; $p < 0,001$).

5.2 Pharmacokinetic properties

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

Absorption

The mean time to C_{max} (T_{max}) of palbociclib is generally between 4 to 8 hours following oral administration.

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

Palbociclib absorption and exposure were very low in approximately 13 % of the population under the fasted condition.

Food intake increased the palbociclib exposure in this small subset of the population but did not alter palbociclib exposure in the rest of the population to a clinically relevant extent. Therefore, food intake reduced the inter-subject variability of palbociclib exposure, which supports administration of palbociclib with food.

Compared to palbociclib given under overnight fasted conditions, the $AUC_{0\text{-}inf}$ and C_{max} of palbociclib increased by 21 % and 38 % when given with high-fat food, by
12 % and 27 % when given with low-fat food, and by 13 % and 24 % when moderate-fat food was given 1 hour before and 2 hours after palbociclib dosing. In addition, food intake significantly reduced the inter-subject and

intrasubject variability of palbociclib exposure. Based on these results, palbociclib should be taken with food (see section 4.2).

Gastric pH elevating medication effect

In a healthy subject study, co-administration of a single 125 mg dose of palbociclib with multiple doses of the proton pump inhibitor (PPI) rabeprazole under fed conditions decreased palbociclib C_{max} by 41 % but had limited impact on AUC_{inf} (13 % decrease), when compared to a single 125 mg dose of palbociclib administered alone.

Given the reduced effect on gastric pH of H2-receptor antagonists and local antacids compared to PPIs, the effect of these classes of acid-reducing medicines on palbociclib exposure under fed conditions is expected to be minimal. Under fed conditions there is no clinically relevant effect of PPIs, H2-receptor antagonists, or local antacids on palbociclib exposure. In another healthy subject study, co-administration of a single 125 mg dose of palbociclib with multiple doses of the PPI rabeprazole under fasted conditions decreased palbociclib $AUC_{0\text{-}inf}$ and C_{max} by 62 % and 80 %, respectively, when compared with a single dose of palbociclib 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 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 sulphonation, 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 faeces, the sulphamic 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 sulphotransferase (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; faeces (74,1 % of dose) was the major route of excretion, with 17,5 % of the dose recovered in urine.

Excretion of unchanged palbociclib in faeces and urine was 2,3 % and 6,9 % of the administered dose, respectively.

Age, sex, 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.

Special populations

Elderly population

Of 444 patients who received palbociclib in Study 2, 181 patients (41 %) were ≥ 65 years of age. Of 347 patients who received palbociclib in Study 3, 86 patients (24,8 %) were ≥ 65 years of age.

No overall differences in safety or effectiveness of palbociclib were observed between these patients and younger patients.

Hepatic impairment

Data from a pharmacokinetic trial in subjects with varying degrees of hepatic impairment indicate that palbociclib unbound $AUC_{0\text{-}inf}$ decreased 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 (Child-Pugh class C) hepatic impairment, respectively, relative to subjects with normal hepatic function. Palbociclib unbound C_{max} 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, where 40 patients had mild hepatic impairment based on National Cancer Institute (NCI) classification (total bilirubin ≤ ULN and AST > ULN, or total bilirubin >1,0 to 1,5 × ULN and any AST), mild hepatic impairment had no effect on the exposure of palbociclib, further supporting the findings from the dedicated hepatic impairment study.

Renal impairment

Data from a pharmacokinetic trial in subjects with varying degrees of renal impairment indicate that palbociclib $AUC_{0\text{-}inf}$ 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 renal function. Peak palbociclib exposure (C_{max}) 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 where 73 patients had mild renal impairment and 29 patients had moderate renal impairment, mild and moderate renal impairment had no effect on the exposure of palbociclib. The pharmacokinetics of palbociclib have not been studied in patients requiring haemodialysis.

Paediatric population

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

5.3 Pre-clinical safety data

The primary target organ findings following single and/or repeat dosing included haematolymphopoietic 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 haematolymphopoietic, male reproductive systems, and incisor teeth were established, whereas the bone effect was not reversed following a 12-week non-dosing 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 tumours 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 foetotoxic 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 foetal 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 foetal exposure and cross-placenta transfer have not been examined.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicon dioxide

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Sodium starch glycolate

Hard gelatin capsule shells

The light orange, light orange/caramel, and caramel opaque capsule shells contain:

Gelatin

Red iron oxide

Titanium dioxide

Yellow iron oxide

The printing ink contains:

Ammonium hydroxide

Isopropyl alcohol

N-butyl alcohol

Propylene glycol

Shellac

Simethicone

Titanium dioxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Blisters: 36 months.

Bottles: 48 months.

6.4 Special precautions for storage

Store at or below 30 °C.

Store in the original container until required for administration.

6.5 Nature and content of container

PALBOCICLIB PFIZER is packed in high-density polyethylene bottles with polypropylene closures and heat induction seal liners, in a pack size of 21 capsules or in polychlorotrifluoroethylene/aluminium foil blister system as a unit dose of 1 capsule per cell.

6.6 Special precautions for disposal

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd

Building 2, 1st Floor

Maxwell Office Park

Magwa Crescent

Waterfall City

Midrand

Gauteng

1685

South Africa

Tel: +27(0)11 320 6000 / 0860 734 937 (toll free South Africa)

8. REGISTRATION NUMBERS

PALBOCICLIB PFIZER 75 mg: 52/26/0041

PALBOCICLIB PFIZER 100 mg: 52/26/0042

PALBOCICLIB PFIZER 125 mg: 52/26/0043

9. DATE OF FIRST AUTHORISATION

10 November 2020

10. DATE OF REVISION OF THE TEXT

28 May 2026

Manufacturer: Pfizer Manufacturing Deutschland GmbH, Freiburg Im Breisgau, Germany

NAMIBIA: NS2

PALBOCICLIB PFIZER 75 mg: 18/26/0047

PALBOCICLIB PFIZER 100 mg: 18/26/0048

PALBOCICLIB PFIZER 125 mg: 18/26/0049

ZIMBABWE: PP

PALBOCICLIB PFIZER 75 mg: 2017/9.7/5505

PALBOCICLIB PFIZER 100 mg: 2017/9.7/5506

PALBOCICLIB PFIZER 125 mg: 2017/9.7/5507