FASLODEX®
(Fulvestrant)

1. NAME OF THE MEDICINAL PRODUCT

FASLODEX 250 mg
Fulvestrant
Solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One pre-filled syringe contains 250 mg fulvestrant in 5 ml solution.
For a full list of excipients, see "List of excipients".

3. PHARMACEUTICAL FORM

Solution for injection.
Clear, colourless to yellow, viscous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

FASLODEX is indicated for the treatment of estrogen receptor positive, locally advanced or metastatic breast cancer in postmenopausal women not previously treated with endocrine therapy, or with disease relapse on or after adjuvant antiestrogen therapy, or disease progression on antiestrogen therapy.

Combination therapy with palbociclib

FASLODEX is indicated in combination with palbociclib for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in women with disease progression following endocrine therapy.

Combination therapy with abemaciclib

FASLODEX is indicated in combination with abemaciclib for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in women with disease progression after endocrine therapy.

Combination therapy with ribociclib

FASLODEX is indicated in combination with ribociclib for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in postmenopausal women as initial endocrine based therapy or following disease progression on endocrine therapy.

4.2 Posology and method of administration

Posology

Adult females (including the elderly)

The recommended dose is 500 mg at intervals of one month, with an additional 500 mg dose given two weeks after the initial dose.

Combination therapy with palbociclib

When FASLODEX is used in combination with palbociclib, refer to monotherapy recommended dose instruction for FASLODEX. Refer to the prescribing information for palbociclib for Posology and method of administration.

Prior to the start of treatment with the combination of FASLODEX plus palbociclib, and throughout its duration, pre/perimenopausal women should be treated with LHRH agonists according to local clinical practice.

Combination therapy with abemaciclib

When FASLODEX is used in combination with abemaciclib, refer to monotherapy recommended dose instruction for FASLODEX. Refer to the prescribing information for abemaciclib for Posology and method of administration.

Prior to the start of treatment with the combination of FASLODEX plus abemaciclib, and throughout its duration, pre/perimenopausal women should be treated with LHRH agonists according to local clinical practice.

Combination therapy with ribociclib

When FASLODEX is used in combination with ribociclib, refer to monotherapy recommended dose instruction for FASLODEX. Refer to the prescribing information for ribociclib for Posology and method of administration.

Special population

Paediatric patient:

FASLODEX is not recommended for use in children or adolescents, as safety and efficacy have not been established in this age group.

Renal impairment:

No dose adjustments are recommended for patients with mild to moderate renal impairment (creatinine clearance ≥ 30 ml/min). Safety and efficacy have not been evaluated in patients with severe renal impairment (creatinine clearance < 30 ml/min) and, therefore, caution is recommended in these patients (see Special warnings and precautions for use).

Hepatic impairment:

No dose adjustments are recommended for patients with mild to moderate hepatic impairment. However, as fulvestrant exposure may be increased, FASLODEX should be used with caution

in these patients. There are no data in patients with severe hepatic impairment (see Contraindications, Special warnings and precautions for use and Pharmacokinetic properties).

Method of administration

FASLODEX should be administered as two consecutive 5 ml injections by slow intramuscular injection (1-2 minutes/injection), one in each buttock (gluteal area).

Caution should be taken if injecting FASLODEX at the dorsogluteal site due to the proximity of the underlying sciatic nerve.

For detailed instructions for administration, see "Instructions for administration and Special precautions for disposal".

4.3 Contraindications

Hypersensitivity to the active substance, or to any of the other excipients.

Pregnancy and lactation (see Pregnancy and lactation).

Severe hepatic impairment (see Special warnings and precautions for use and Pharmacokinetic Properties).

Combination therapy with palbociclib

See palbociclib local Prescribing Information for Contraindications.

Combination therapy with abemaciclib

See abemaciclib local Prescribing Information for Contraindications.

Combination therapy with ribociclib

See ribociclib local Prescribing Information for Contraindications.

4.4 Special warnings and precautions for use

FASLODEX should be used with caution in patients with mild to moderate hepatic impairment (see Posology and method of administration, Contraindications, and Pharmacokinetic properties).

FASLODEX should be used with caution in patients with severe renal impairment (creatinine clearance less than 30 ml/min) (see Pharmacokinetic properties).

Due to the intramuscular route of administration, FASLODEX should be used with caution if treating patients with bleeding diatheses, thrombocytopenia or those taking anticoagulant treatment.

Injection site related events including sciatica, neuralgia, neuropathic pain, and peripheral neuropathy have been reported with FASLODEX injection. Caution should be taken while administering FASLODEX at the dorsogluteal injection site due to the proximity of the underlying sciatic nerve (see Posology and method of administration and Undesirable effects).

Thromboembolic events are commonly observed in women with advanced breast cancer and have been observed in clinical studies with FASLODEX (see Undesirable effects). This should be taken into consideration when prescribing FASLODEX to patients at risk.

There are no long-term data on the effect of fulvestrant on bone. Due to the mechanism of action of fulvestrant, there is a potential risk of osteoporosis.

FASLODEX can interfere with oestradiol measurement by immunoassay, resulting in falsely elevated oestradiol levels.

Combination therapy with palbociclib

See palbociclib local Prescribing Information for Special warnings and precautions for use.

Combination therapy with abemaciclib

See abemaciclib local Prescribing Information for Special warnings and precautions for use.

Combination therapy with ribociclib

See ribociclib local Prescribing Information for Special warnings and precautions for use.

4.5 Interactions with other medicinal products and other forms of interaction

A clinical interaction study with midazolam (substrate of CYP 3A4) demonstrated that fulvestrant does not inhibit CYP 3A4. Clinical interaction studies with rifampicin (inducer of CYP 3A4) and ketoconazole (inhibitor of CYP 3A4) showed no clinically relevant change in fulvestrant clearance. Dose adjustment is therefore not necessary in patients who are receiving fulvestrant and CYP 3A4 inhibitors or inducers concomitantly.

Due to the structural similarity of fulvestrant and oestradiol, fulvestrant may interfere with antibody-based oestradiol assays and may result in falsely increased levels of oestradiol.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Patients of childbearing potential should use effective contraception during treatment with FASLODEX and for 2 years after the last dose.

Pregnancy

FASLODEX is contraindicated in pregnancy (see Contraindications). Fulvestrant has been shown to cross the placenta after single intramuscular doses in rat and rabbit. Studies in animals have shown reproductive toxicity including an increased incidence of foetal abnormalities and deaths (see Preclinical safety data). If pregnancy occurs while taking FASLODEX, the patient must be informed of the potential hazard to the foetus and potential risk for loss of pregnancy.

Breast-feeding

Breast-feeding must be discontinued during treatment with FASLODEX. Fulvestrant is excreted in milk in lactating rats. It is not known whether fulvestrant is excreted in human milk.

Considering the potential for serious adverse reactions due to fulvestrant in breast-fed infants, use during lactation is contraindicated (see Contraindications).

Fertility

The effects of FASLODEX on fertility in humans has not been studied.

4.7 Effects on ability to drive and use machines

FASLODEX has no or negligible influence on the ability to drive or use machines. However, since asthenia has been reported very commonly with FASLODEX, caution should be observed by those patients who experience this adverse reaction when driving or operating machinery.

4.8 Undesirable effects

Monotherapy

This section provides information based on all adverse reactions from clinical studies, post-marketing studies or spontaneous reports. The most frequently reported adverse reactions are injection site reactions, asthenia, nausea, and increased hepatic enzymes (ALT, AST, ALP).

The following frequency categories for adverse drug reactions (ADRs) were calculated based on the FASLODEX 500 mg treatment group in pooled safety analyses of studies that compared FASLODEX 500 mg with FASLODEX 250 mg [CONFIRM (Study D6997C00002), FINDER 1 (Study D6997C00004), FINDER 2 (Study D6997C00006), and NEWEST (Study D6997C00003) studies], or from FALCON (Study D699BC00001) alone that compared FASLODEX 500 mg with anastrozole 1 mg. Where frequencies differ between the pooled safety analysis and FALCON, the highest frequency is presented. The frequencies in the following table were based on all reported events, regardless of the investigator assessment of causality.

Adverse reactions listed below are classified according to frequency and System Organ Class (SOC). Frequency groupings are defined according to the following convention: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100). Within each frequency grouping adverse reactions are reported in order of decreasing seriousness.

Table 1 Adverse Drug Reactions

SOC	Very Common ≥10%	Common ≥1 - <10%	Uncommon ≥ 0.1% - < 1%
Nervous system disorders		Headache	
Gastrointestinal disorders	Nausea	Vomiting, diarrhoea	
Infections and infestations		Urinary tract infections	
Skin and subcutaneous tissue disorders	Rash[e]		

Musculoskeletal and connective tissue disorders	Joint and musculoskeletal pain[d]	Back pain[a]	
Metabolism and nutrition disorders		Anorexia	
Vascular disorders	Hot flushes[e]	Venous thromboembolism[a]	
General disorders and administration site conditions	Asthenia[a], injection site reactions[b]	Neuropathy peripheral[e], sciatica[e]	Injection site haemorrhage[f], injection site haematoma[f], neuralgia[c,f]
Immune system disorders	Hypersensitivity reactions[e]		
Hepatobiliary disorders	Elevated hepatic enzymes (ALT, AST, ALP)[a]	Elevated bilirubin[a]	Hepatic failure[c,f], hepatitis[f], elevated gamma-GT[f]
Reproductive system and breast disorders		Vaginal haemorrhage[e]	Vaginal moniliasis[f], Leukorrhea[f]
Blood and lymphatic system		Reduced platelet count[e]	

[a] Includes adverse drug reactions for which the exact contribution of FASLODEX cannot be assessed due to the underlying disease.
[b] The term injection site reactions does not include the terms injection site haemorrhage, injection site haematoma, sciatica, neuralgia and neuropathy peripheral.
[c] The event was not observed in major clinical studies (CONFIRM, FINDER1, FINDER2, NEWEST). The frequency has been calculated using the upper limit of the 95% confidence interval for the point estimate. This is calculated as 3/560 (where 560 is the number of patients in the major clinical studies), which equates to a frequency category of 'uncommon'.
[d] Includes: arthralgia, and less frequently musculoskeletal pain, myalgia and pain in extremity.
[e] Frequency category differs between pooled safety dataset and FALCON.
[f] ADR was not observed in FALCON.

Description of selected adverse reactions

The descriptions included below are based on the safety analysis set of 228 patients who received at least one (1) dose of fulvestrant and 232 patients who received at least one (1) dose of anastrozole, respectively in the Phase 3 FALCON study.

Joint and musculoskeletal pain

In the FALCON study, the number of patients who reported an adverse reaction of joint and musculoskeletal pain was 65 (31.2%) and 48 (24.1%) for fulvestrant and anastrozole arms, respectively. Of the 65 patients in the FASLODEX arm, 40% (26/65) of patients reported joint and musculoskeletal pain within the first month of treatment, and 66.2% (43/65) of patients within the first 3 months of treatment. No patients reported events that were CTCAE Grade ≥3

or that required a dose reduction, dose interruption, or discontinued treatment due to these adverse reactions.

Combination therapy with palbociclib

See palbociclib local Prescribing Information for Undesirable effects.

Combination therapy with abemaciclib

See abemaciclib local Prescribing Information for Undesirable effects.

Combination therapy with ribociclib

See ribociclib local Prescribing Information for Undesirable effects.

4.9 Overdose

There are isolated reports of overdose with FASLODEX in humans. If overdose occurs, symptomatic supportive treatment is recommended. Animal studies suggest that no effects other than those related directly or indirectly to antiestrogenic activity were evident with higher doses of fulvestrant.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Endocrine therapy, antiestrogen, ATC code: L02BA03.

Mechanism of action and pharmacodynamic effects

Fulvestrant is a competitive estrogen receptor (ER) antagonist with an affinity comparable to estradiol. Fulvestrant blocks the trophic actions of estrogens without any partial agonist (estrogen-like) activity. The mechanism of action is associated with down-regulation of estrogen receptor (ER) protein levels. Clinical studies in postmenopausal women with primary breast cancer have shown that fulvestrant significantly downregulates ER protein in ER positive tumours compared with placebo. There was also a significant decrease in progesterone receptor expression consistent with a lack of intrinsic estrogen agonist effects. It has also been shown that fulvestrant 500 mg downregulates ER and the proliferation marker Ki67, to a greater degree than fulvestrant 250 mg in breast tumours in postmenopausal neoadjuvant setting.

Clinical safety and efficacy in advanced breast cancer

Fulvestrant Monotherapy

A Phase 3 clinical study was completed in 736 postmenopausal women with advanced breast cancer who had disease recurrence on or after adjuvant endocrine therapy or progression following endocrine therapy for advanced disease. The study included 423 patients whose disease had recurred or progressed during antiestrogen therapy (AE subgroup) and 313 patients whose disease had recurred or progressed during aromatase inhibitor therapy (AI subgroup). This study compared the efficacy and safety of FASLODEX 500 mg (n=362) with FASLODEX 250 mg (n=374). Progression-free survival (PFS) was the primary endpoint; key secondary efficacy endpoints included objective response rate (ORR), clinical benefit rate (CBR) and overall survival (OS). Efficacy results for the CONFIRM study are summarized in Table 2.

Table 2 Summary of results of the primary efficacy endpoint (PFS) and key secondary efficacy endpoints in the CONFIRM study

Variable	Type of estimate; treatment comparison	FASLODEX 500 mg (N=362)	FASLODEX 250 mg (N=374)	Comparison between groups (FASLODEX 500 mg/FASLODEX 250 mg)		
				Hazard ratio	95% CI	p-value
PFS	**K-M median in months; hazard ratio**					
All Patients		6.5	5.5	0.80	0.68, 0.94	0.006
-AE subgroup (n=423)		8.6	5.8	0.76	0.62, 0.94	0.013
-AI subgroup (n=313)[a]		5.4	4.1	0.85	0.67, 1.08	0.195
OS[b]	**K-M median in months; hazard ratio**					
All Patients		26.4	22.3	0.81	0.69, 0.96	0.016[c]
-AE subgroup (n=423)		30.6	23.9	0.79	0.63, 0.99	0.038[c]
-AI subgroup (n=313)[a]		24.1	20.8	0.86	0.67, 1.11	0.241[c]
Variable	**Type of estimate; treatment comparison**	**FASLODEX 500 mg (N=362)**	**FASLODEX 250 mg (N=374)**	**Comparison between groups (FASLODEX 500 mg/FASLODEX 250 mg)**		
				Absolute difference in %	**95% CI**	
ORR[d]	**% of patients with OR; absolute difference in %**					
All Patients		13.8	14.6	-0.8	-5.8, 6.3	
-AE subgroup (n=296)		18.1	19.1	-1.0	-8.2, 9.3	
-AI subgroup (n=205)[a]		7.3	8.3	-1.0	-5.5, 9.8	
CBR[e]	**% of patients with CB; absolute difference in %**					
All Patients		45.6	39.6	6.0	-1.1, 13.3	

-AE subgroup (n=423)	52.4	45.1	7.3	-2.2, 16.6	
-AI subgroup (n=313)[a]	36.2	32.3	3.9	-6.1, 15.2	

[a] FASLODEX is indicated in patients whose disease had recurred or progressed on an anti-estrogen therapy. The results in the AI subgroup are inconclusive.
[b] OS is presented for the final survival analyses at 75% maturity.
[c] Nominal p-value with no adjustments made for multiplicity between the initial overall survival analyses at 50% maturity and the updated survival analyses at 75% maturity.
[d] ORR was assessed in patients who were evaluable for response at baseline (ie, those with measurable disease at baseline: 240 patients in the FASLODEX 500 mg group and 261 patients in the FASLODEX 250 mg group).
[e] Patients with a best objective response of complete response, partial response or stable disease ≥24 weeks.

PFS: Progression-free survival; ORR: Objective response rate; OR: Objective response; CBR: Clinical benefit rate; CB: Clinical benefit; OS: Overall survival; K-M: Kaplan-Meier; CI: Confidence interval; AI: Aromatase inhibitor; AE: Anti-estrogen.

A Phase 3, randomised, double-blind, double-dummy, multicentre study of FASLODEX 500 mg versus anastrozole 1 mg was conducted in postmenopausal women with ER-positive and/or PgR-positive locally advanced or metastatic breast cancer who had not previously been treated with any hormonal therapy. A total of 462 patients were randomised 1:1 sequentially to receive either fulvestrant 500 mg or anastrozole 1 mg.

Randomisation was stratified by disease setting (locally advanced or metastatic), prior chemotherapy for advanced disease, and measurable disease.

The primary efficacy endpoint of the study was investigator assessed progression-free survival (PFS) evaluated according to RECIST 1.1 (Response Evaluation Criteria in Solid Tumours). Key secondary efficacy endpoints included overall survival (OS), and objective response rate (ORR).

Patients enrolled in this study had a median age of 63 years (range 36-90). The majority of patients (87.0%) had metastatic disease at baseline. Fifty-five percent (55.0%) of patients had visceral metastasis at baseline. A total of 17.1% of patients received a prior chemotherapy regimen for advanced disease; 84.2% of patients had measurable disease.

Consistent results were observed across the majority of pre-specified patient subgroups. For the subgroup of patients with disease limited to non-visceral metastasis (n=208), the HR was 0.592 (95% CI: 0.419, 0.837) for the FASLODEX arm compared to the anastrozole arm. For the subgroup of patients with visceral metastasis (n=254), the HR was 0.993 (95% CI: 0.740, 1.331) for the FASLODEX arm compared to the anastrozole arm. The efficacy results of the FALCON study are presented in Table 3 and Figure 1.

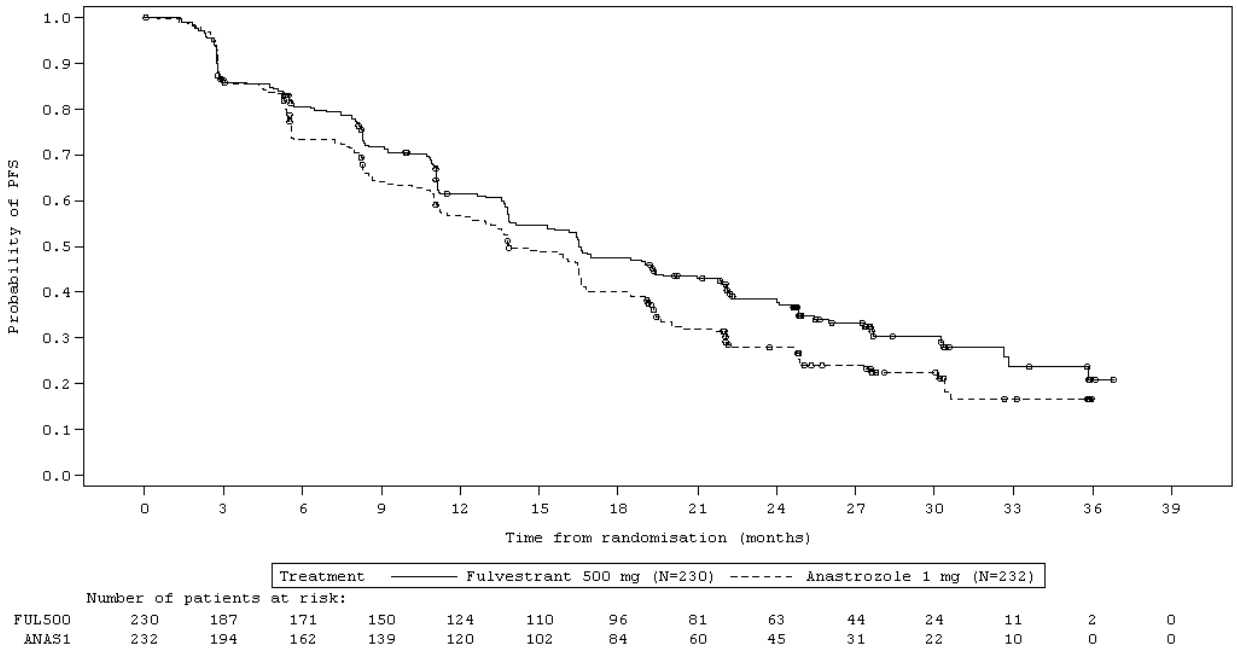
Table 3 Summary of results of the primary efficacy endpoint (PFS) and key secondary efficacy endpoints (Investigator Assessment, Intent-To-Treat Population) – FALCON study

	FASLODEX 500 mg (N=230)	**Anastrozole 1 mg (N=232)**

Progression-Free Survival		
Number of PFS Events (%)	143 (62.2%)	166 (71.6%)
PFS Hazard Ratio (95% CI) and p-value	HR 0.797 (0.637 - 0.999) p = 0.0486	
PFS Median [months (95% CI)]	16.6 (13.8, 21.0)	13.8 (12.0, 16.6)
Number of OS Events*	67 (29.1%)	75 (32.3%)
OS Hazard Ratio (95% CI) and p-value	HR 0.875 (0.629 – 1.217) p = 0.4277	
ORR**	89 (46.1%)	88 (44.9%)
ORR Odds Ratio (95% CI) and p-value	OR 1.074 (0.716 – 1.614) p = 0.7290	
Median DoR (months)	20.0	13.2
CBR	180 (78.3%)	172 (74.1%)
CBR Odds Ratio (95% CI) and p-value	OR 1.253 (0.815 – 1.932) p = 0.3045	

* (31% maturity)-not final OS analysis
** for patients with measurable disease

Figure 1 Kaplan-Meier Plot of Progression-Free Survival (Investigator Assessment Intent-To-Treat Population) ─ FALCON Study



Two Phase 3 clinical studies were completed in a total of 851 postmenopausal women with advanced breast cancer who had disease recurrence on or after adjuvant endocrine therapy or progression following endocrine therapy for advanced disease. Seventy seven percent (77%) of the study population had estrogen receptor positive breast cancer. These studies compared the

safety and efficacy of monthly administration of FASLODEX 250 mg verses the daily administration of 1 mg anastrozole (aromatise inhibitor). Overall, FASLODEX at the 250 mg monthly dose was at least as effective as anastrozole in terms of progression-free survival, objective response, and time to death. There were no statistically significant differences in any of these endpoints between the two treatment groups. Progression-free survival was the primary endpoint. Combined analysis of both studies showed that 83% of patients who received FASLODEX progressed, compared with 85% of patients who received anastrozole. Combined analysis of both studies showed the hazard ratio of FASLODEX 250 mg to anastrozole for progression-free survival was 0.95 (95% CI 0.82 to 1.10). The objective response rate for FASLODEX 250 mg was 19.2% compared with 16.5% for anastrozole. The median time to death was 27.4 months for patients treated with FASLODEX and 27.6 months for patients treated with anastrozole. The hazard ratio of FASLODEX 250 mg to anastrozole for time to death was 1.01 (95% CI 0.86 to 1.19).

Combination therapy with palbociclib

PALOMA-3 was a randomized, double-blind, parallel group, multicenter study of FASLODEX 500 mg plus palbociclib 125 mg versus FASLODEX 500 mg plus placebo conducted in women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced breast cancer not amenable to resection or radiation therapy with curative intent or metastatic 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/peri- and postmenopausal women who had progressed on or within 12 months from completion of adjuvant endocrine therapy or on or within 1 month from prior endocrine therapy for advanced disease, were randomized 2:1 to FASLODEX plus palbociclib or FASLODEX plus placebo and stratified by documented sensitivity to prior hormonal therapy, menopausal status at study entry (pre/peri- versus postmenopausal), and presence of visceral metastases. Pre/perimenopausal women received the LHRH agonist goserelin. Patients with advanced/metastatic, 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 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 prognostic characteristics between the FASLODEX plus palbociclib arm and the FASLODEX plus placebo arm. The median age of patients enrolled in this study was 57 years (range 29, 88). In each treatment arm the majority of patients were White, had documented sensitivity to prior hormonal therapy, and were postmenopausal.

Approximately 20% of patients were pre/perimenopausal. All patients had received prior systemic therapy and most patients in each treatment arm had received a previous chemotherapy regimen for their primary diagnosis. More than half (62%) had an ECOG PS of 0, 60% had

visceral metastases, and 60% had received more than 1 prior hormonal regimen for their primary diagnosis.

The primary endpoint of the study was investigator-assessed PFS evaluated according to RECIST 1.1. Supportive PFS analyses were based on an Independent Central Radiologic Review. Secondary endpoints included overall survival (OS), OR, clinical benefit response (CBR), safety and time to deterioration (TTD) in pain endpoint.

The study met its primary endpoint of prolonging investigator-assessed PFS at the interim analysis conducted on 82% of the planned PFS events; the results crossed the pre-specified 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 4.

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 PALOMA3 study are presented in Table 4. The relevant Kaplan-Meier plots are shown in Figures 2 and 3, respectively.

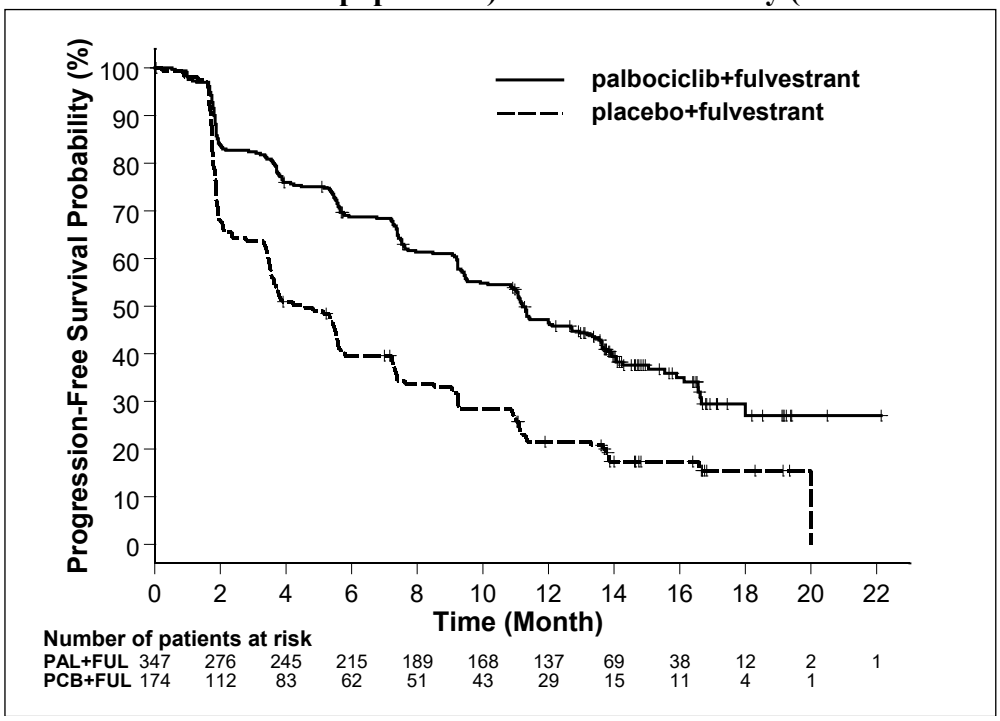
Table 4 Efficacy results – PALOMA-3 study (Investigator assessment, intent-to-treat population)

	Updated Analysis (23 October 2015 cutoff)	
	FASLODEX plus palbociclib (N=347)	**FASLODEX plus placebo (N=174)**
Progression-Free Survival		
Median [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 end-points*		
OR [% (95% CI)]	21.0 (16.9, 25.7)	8.6 (4.9, 13.8)
OR (measurable disease) [% (95% CI)]	27.3 (22.1, 33.1)	10.9 (6.2, 17.3)
DOR (measurable disease) [months (95% CI)]	10.4 (8.3, NE)	9.0 (5.6, NE)
CBR [% (95% CI)]	66.3 (61.0, 71.2)	39.7 (32.3, 47.3)

Final overall survival (OS) (13 April 2018 cutoff)		
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=0.0857†*	

* Response endpoints based on confirmed responses
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 endpoint results are based on confirmed and unconfirmed responses according to RECIST 1.1.
*Not statistically significant at the pre-specified 2-sided alpha level of 0.047.
† 2-sided p-value from the log-rank test stratified by the presence of visceral metastases and sensitivity to prior endocrine therapy per randomisation.

Figure 2 Kaplan-Meier plot of progression-free survival (investigator assessment, intent-to-treat population) – PALOMA-3 study (23 October 2015 cutoff)

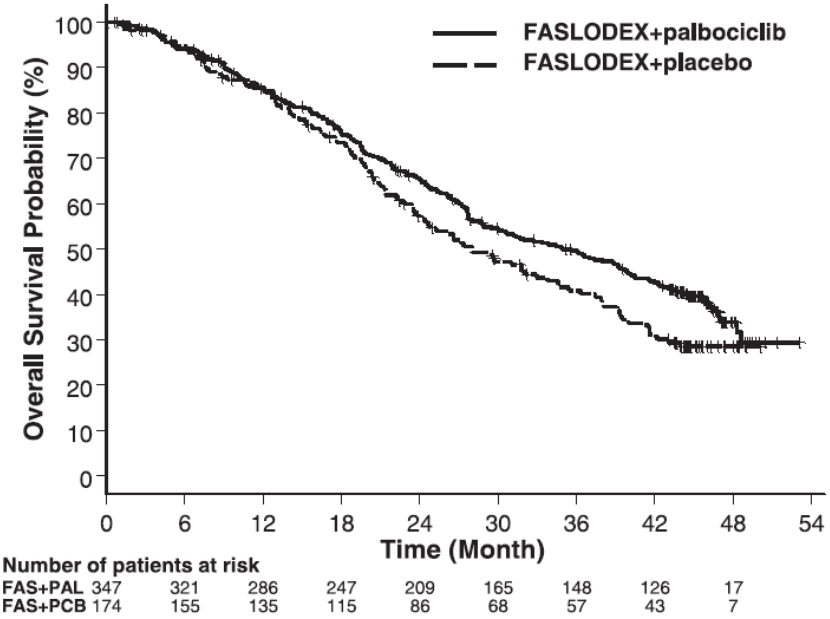


FUL=fulvestrant; PAL=palbociclib; PCB=placebo

A reduction in the risk of disease progression or death in the FASLODEX plus palbociclib 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 3 Kaplan-Meier plot of overall survival (intent-to-treat population) – PALOMA3 study (13 April 2018 cutoff)



FAS=FASLODEX; PAL=palbociclib; PCB=placebo.

Patient-reported symptoms were assessed using the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30 and its Breast Cancer Module (EORTC QLQ-BR23). A total of 335 patients in the FASLODEX plus palbociclib arm and 166 patients in the FASLODEX plus placebo arm completed the questionnaire at baseline and at least 1 post-baseline visit.

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

Combination therapy with abemaciclib

MONARCH 2 was a randomized, placebo-controlled, multicenter study conducted in women with HR-positive, HER2-negative metastatic breast cancer with disease progression following endocrine therapy treated with FASLODEX plus abemaciclib versus FASLODEX plus placebo. Randomization was stratified by disease site (visceral, bone only, or other) and by sensitivity to prior endocrine therapy (primary or secondary resistance). A total of 669 patients received intramuscular injection of FASLODEX 500 mg on Days 1 and 15 of cycle 1 and then on Day 1 of cycle 2 and beyond (28-day cycles), plus abemaciclib or placebo orally twice daily. Pre/perimenopausal women were enrolled in the study and received the gonadotropin-releasing

hormone agonist goserelin for at least 4 weeks prior to and for the duration of MONARCH 2. Patients remained on continuous treatment until development of progressive disease or unmanageable toxicity.

Patient median age was 60 years (range, 32-91 years), and 37% of patients were older than 65. The majority were White (56%), and 99% of patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Twenty percent (20%) of patients had de novo metastatic disease, 27% had bone only disease, and 56% had visceral disease. Twenty-five percent (25%) of patients had primary endocrine therapy resistance. Seventeen percent (17%) of patients were pre- or perimenopausal.

The efficacy results from the MONARCH 2 study are summarized in Table 5, Figures 4 and 5. PFS assessment based on a blinded independent radiologic review was consistent with the investigator assessment. Consistent results were observed across patient stratification subgroups of disease site and endocrine therapy resistance for PFS and OS.

Table 5 Efficacy Results in MONARCH 2 (Intent-to-Treat Population)

	FASLODEX plus Abemaciclib	**FASLODEX plus Placebo**
Progression-Free Survival (Investigator Assessment)	**N=446**	**N=223**
Number of patients with an event (n, %)	222 (49.8)	157 (70.4)
Median (months, 95% CI)	16.4 (14.4, 19.3)	9.3 (7.4, 12.7)
Hazard ratio (95% CI)[1]	0.553 (0.449, 0.681)	
p-value[1]	p<0.0001	
Overall Survival[2]		
Number of deaths (n, %)	211 (47.3)	127 (57.0)
Median OS in months (95% CI)	46.7 (39.2, 52.2)	37.3 (34.4, 43.2)
Hazard ratio (95% CI)[1]	0.757 (0.606, 0.945)	
p-value[1]	p=0.0137	
Objective Response for Patients with Measurable Disease	**N=318**	**N=164**
Objective response rate[3] (n, %)	153 (48.1)	35 (21.3)
95% CI	42.6, 53.6	15.1, 27.6

Abbreviations: CI=confidence interval, OS=overall survival.

[1] Stratified by disease site (visceral metastases vs. bone-only metastases vs. other) and endocrine therapy resistance (primary resistance vs. secondary resistance)

[2] Data from a pre-specified interim analysis (77% of the number of events needed for the planned final analysis) with the p-value compared with the allocated alpha of 0.021.

[3] Complete response + partial response.

Figure 4 Kaplan-Meier Curves of Progression-Free Survival: FASLODEX Plus Abemaciclib versus FASLODEX plus Placebo (MONARCH 2)

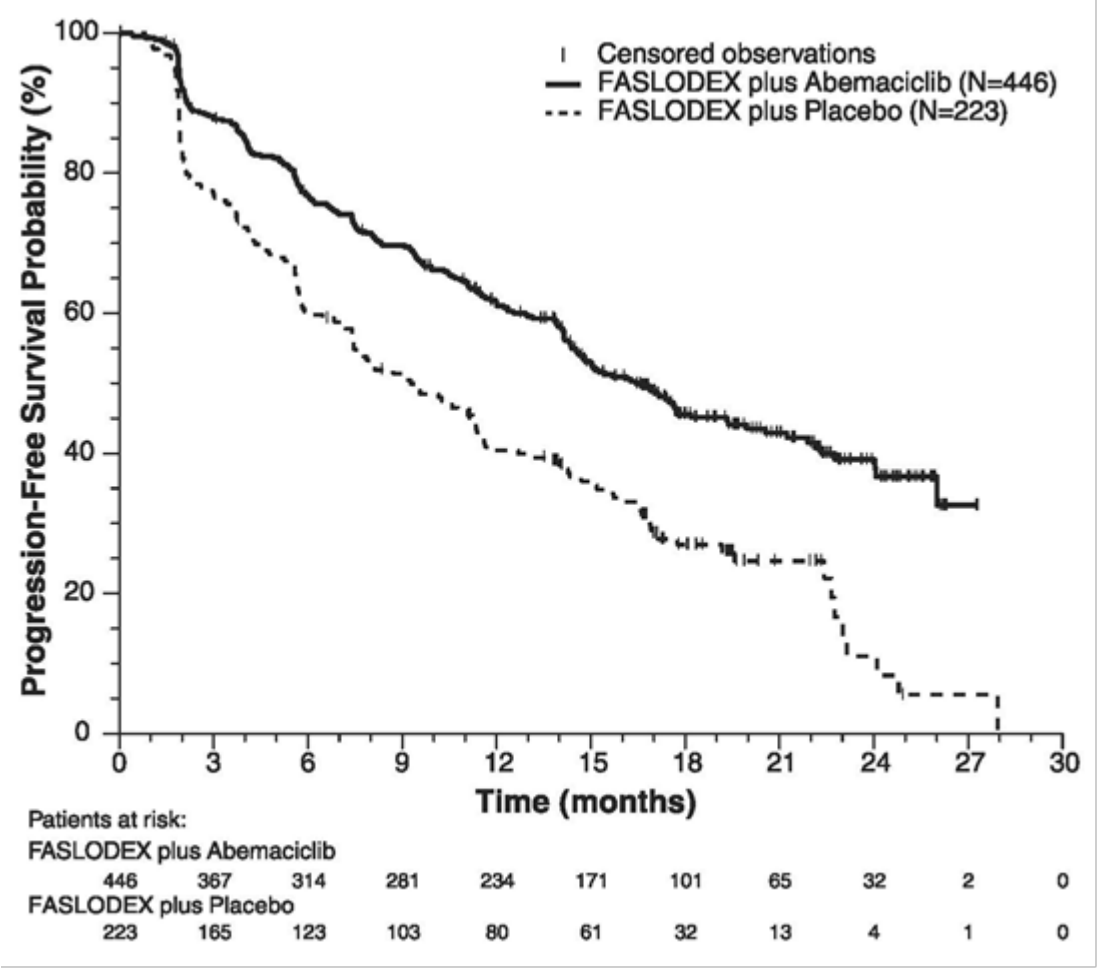
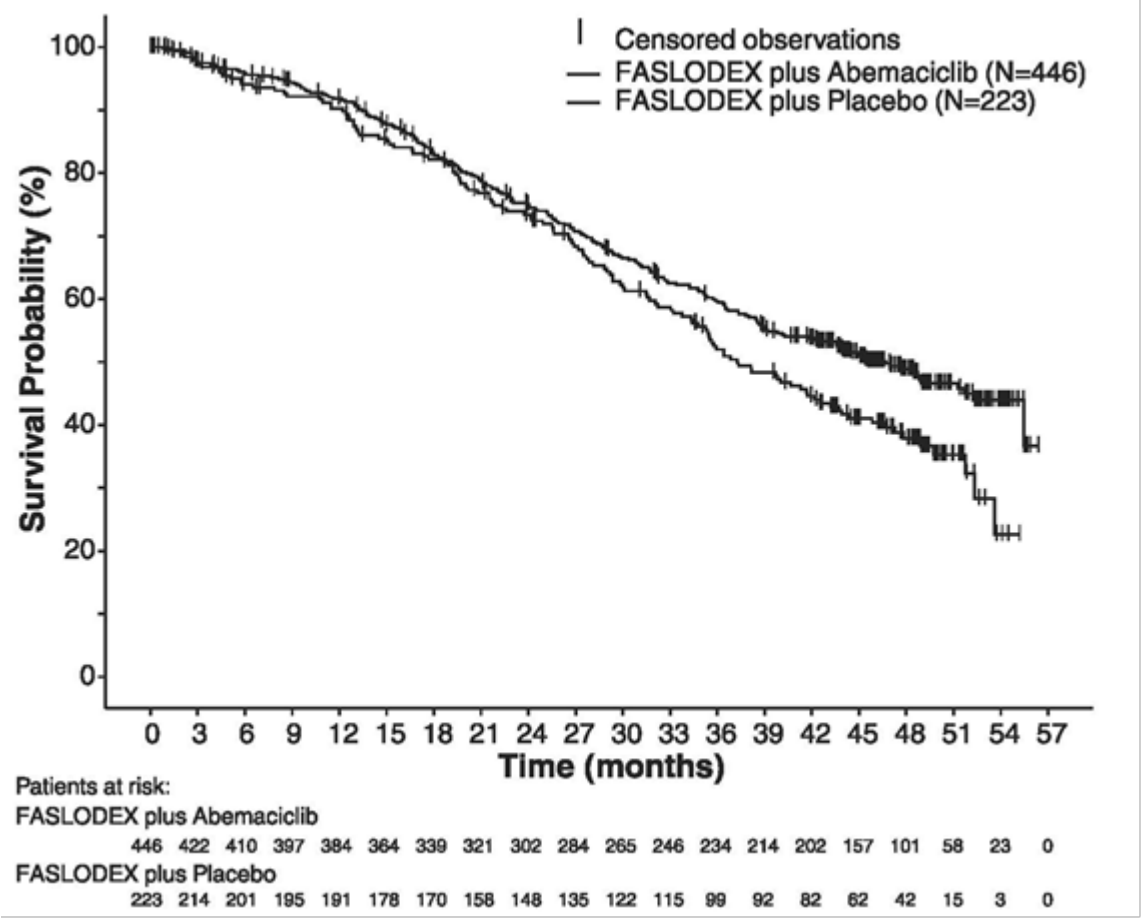


Figure 5 Kaplan-Meier Curves of Overall Survival: FASLODEX plus Abemaciclib versus FASLODEX plus Placebo (MONARCH 2)



Combination therapy with ribociclib

MONALEESA-3 was a randomized double-blind, placebo-controlled study of FASLODEX plus ribociclib versus FASLODEX plus placebo conducted in postmenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer who have received no or only one line of prior endocrine treatment.

A total of 726 patients were randomized in a 2:1 ratio to receive FASLODEX plus ribociclib or FASLODEX plus placebo and stratified according to the presence of liver and/or lung metastases and prior endocrine therapy for advanced or metastatic disease. Fulvestrant 500 mg was administered intramuscularly on Days 1, 15, 29, and once monthly thereafter, with either ribociclib 600 mg or placebo given orally once daily for 21 consecutive days followed by 7 days off until disease progression or unacceptable toxicity. The major efficacy outcome measure for the study was investigator-assessed progression-free survival (PFS) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Patients enrolled in this study had a median age of 63 years (range 31 to 89). Of the patients enrolled, 47% were 65 years and older, including 14% age 75 years and older. The patients enrolled were primarily Caucasian (85%), Asian (9%), and Black (0.7%). Nearly all patients (99.7%) had an ECOG performance status of 0 or 1. First and second line patients were enrolled in this study (of which 19% had de novo metastatic disease). Forty-three percent (43%) of

patients had received chemotherapy in the adjuvant vs. 13% in the neoadjuvant setting and 59% had received endocrine therapy in the adjuvant vs. 1% in the neoadjuvant setting prior to study entry. Twenty-one percent (21%) of patients had bone only disease and 61% had visceral disease. Demographics and baseline disease characteristics were balanced and comparable between study arms.

The efficacy results from MONALEESA-3 are summarized in Table 6, Figures 6 and 7. Consistent results were observed in stratification factor subgroups of disease site and prior endocrine treatment for advanced disease.

Table 6 Efficacy Results – MONALEESA-3 (Investigator Assessment, Intent-to-Treat Population)

	FASLODEX plus Ribociclib	**FASLODEX plus Placebo**
Progression-free survival*	**N=484**	**N=242**
Events (n, %)	210 (43.4%)	151 (62.4%)
Median (months, 95% CI)	20.5 (18.5, 23.5)	12.8 (10.9, 16.3)
Hazard Ratio (95% CI)	0.593 (0.480 to 0.732)	
p-value[1]	p<0.0001	
Overall Survival	**N=484**	**N=242**
Events (n, %)	167 (34.5%)	108 (44.6%)
Median (months, 95% CI)	NR (42.5, NR)	40.0 (37.0, NR)
Hazard Ratio (95% CI)	0.724 (0.568, 0.924)	
p-value[1]	0.00455	
Overall Response Rate[2*]	**N=379**	**N=181**
Patients with measurable disease (95% CI)	40.9 (35.9, 45.8)	28.7 (22.1, 35.3)

Abbreviation: NR, not reached

[1] p-value is obtained from the one-sided log-rank

[2] Based on confirmed responses

[*] Investigator Assessment

Figure 6 Kaplan-Meier Progression Free Survival Curves – MONALEESA-3 (Intent-To-Treat Population, Investigator assessment)

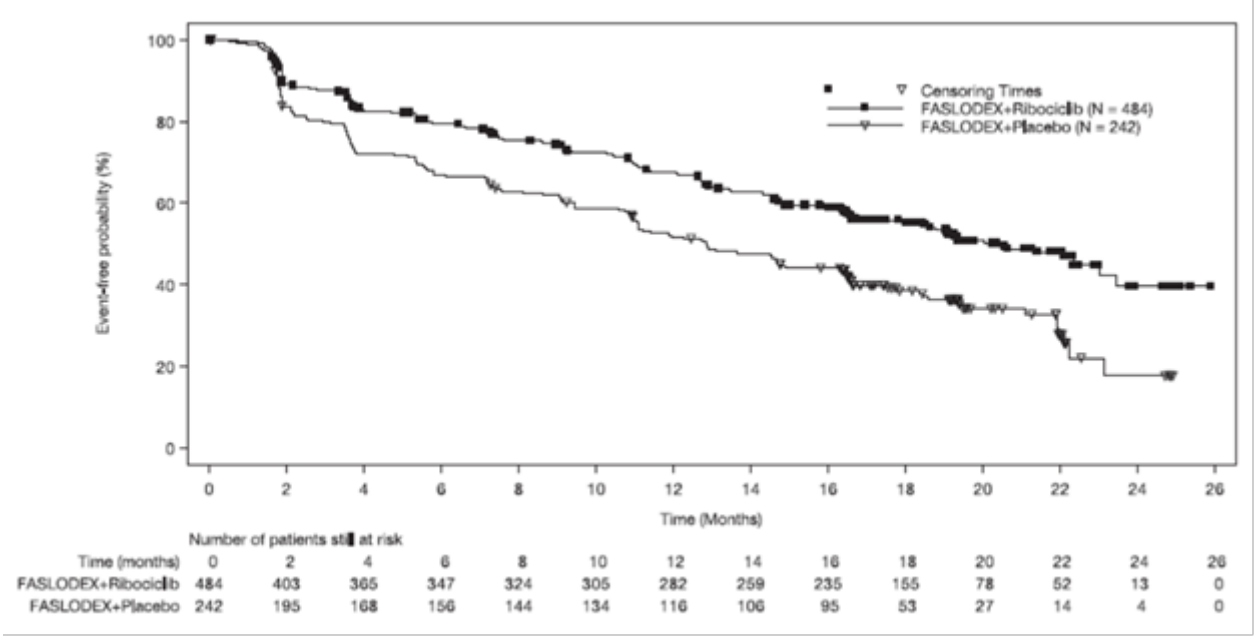
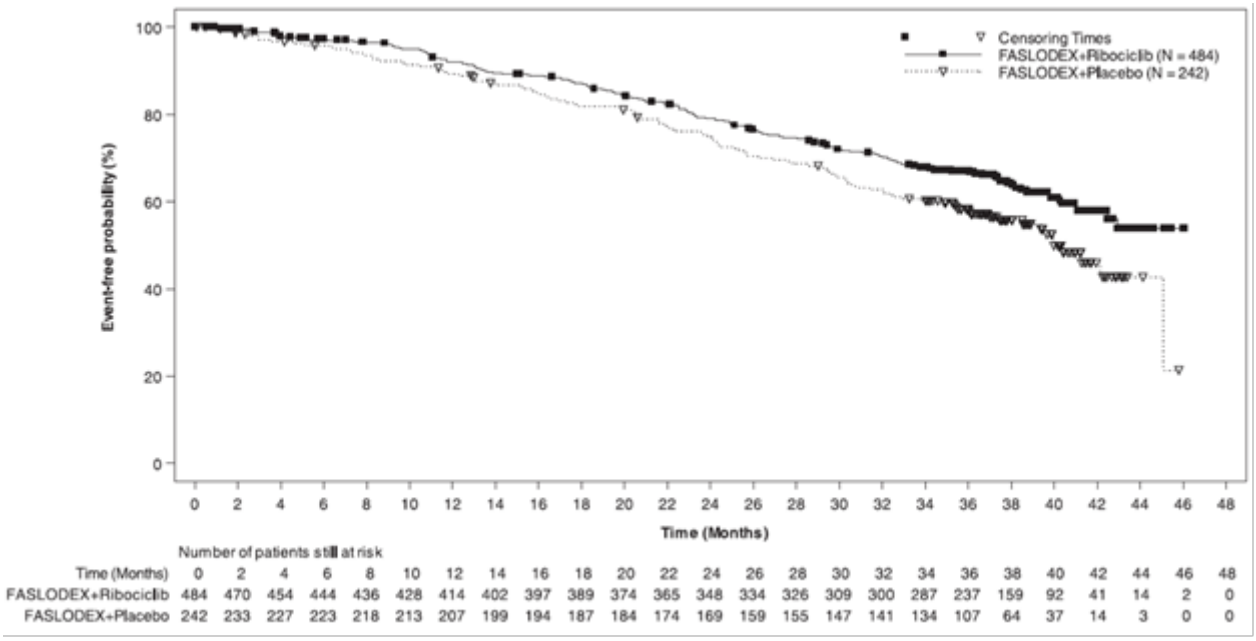


Figure 7 Kaplan-Meier plot of Overall Survival – MONALEESA-3 (Intent -to-Treat Population)



Effects on the postmenopausal endometrium

Preclinical data do not suggest a stimulatory effect of fulvestrant on the postmenopausal endometrium (see Preclinical safety data). A 2-week study in healthy postmenopausal volunteers treated with 20 µg per day of ethinylestradiol showed that pre-treatment with FASLODEX 250 mg resulted in significantly reduced stimulation of the postmenopausal

endometrium, compared to pre-treatment with placebo, as judged by ultrasound measurement of endometrium thickness.

Neoadjuvant treatment for up to 16 weeks in breast cancer patients treated with either FASLODEX 500 mg or FASLODEX 250 mg did not result in clinically significant changes in endometrial thickness, indicating a lack of agonist effect. There is no evidence of adverse endometrial effects in the breast cancer patients studied. No data are available regarding endometrial morphology.

In two short-term studies (1 and 12 weeks) in premenopausal patients with benign gynaecologic disease, no significant differences in endometrial thickness were observed by ultrasound measurement between fulvestrant and placebo groups.

Effects on bone

There are no long-term data on the effect of fulvestrant on bone. Neoadjuvant treatment for up to 16 weeks in breast cancer patients with either FASLODEX 500 mg or FASLODEX 250 mg did not result in clinically significant changes in serum bone-turnover markers.

5.2 Pharmacokinetic properties

Absorption:

After administration of FASLODEX long-acting intramuscular injection, fulvestrant is slowly absorbed and maximum plasma concentrations (C_{max}) are reached after about 5 days. Administration of FASLODEX 500 mg regimen achieves exposure levels at, or close to, steady state within the first month of dosing (mean [CV]: AUC 475 [33.4%] ng.days/ml, C_{max} 25.1 [35.3%] ng/ml, C_{min} 16.3 [25.9%] ng/ml, respectively). At steady state, fulvestrant plasma concentrations are maintained within a relatively narrow range with up to an approximately 3-fold difference between maximum and trough concentrations. After intramuscular administration, the exposure is approximately dose proportional in the dose range 50 to 500 mg.

Distribution:

Fulvestrant is subject to extensive and rapid distribution. The large apparent volume of distribution at steady state (Vd_{ss}) of approximately 3 to 5 l/kg suggests that distribution is largely extravascular. Fulvestrant is highly (99%) bound to plasma proteins. Very low density lipoprotein (VLDL), low density lipoprotein (LDL), and high density lipoprotein (HDL) fractions are the major binding components. No interaction studies were conducted on competitive protein binding. The role of sex hormone-binding globulin (SHBG) has not been determined.

Metabolism:

The metabolism of fulvestrant has not been fully evaluated, but involves combinations of a number of possible biotransformation pathways analogous to those of endogenous steroids. Identified metabolites (includes 17-ketone, sulphone, 3-sulphate, 3- and 17-glucuronide metabolites) are either less active or exhibit similar activity to fulvestrant in antiestrogen models. Studies using human liver preparations and recombinant human enzymes indicate that CYP 3A4 is the only P450 isoenzyme involved in the oxidation of fulvestrant, however, non-

P450 routes appear to be more predominant *in vivo*. *In vitro* data suggest that fulvestrant does not inhibit CYP450 isoenzymes.

Elimination:

Fulvestrant is eliminated mainly in metabolised form. The major route of excretion is via the faeces, with less than 1% being excreted in the urine. Fulvestrant has a high clearance, 11±1.7 ml/min/kg, suggesting a high hepatic extraction ratio. The terminal half-life ($t_{1/2}$) after intramuscular administration is governed by the absorption rate and was estimated to be 50 days.

Special populations:

In a population pharmacokinetic analysis of data from Phase 3 studies, no difference in fulvestrant's pharmacokinetic profile was detected with regard to age (range 33 to 89 years), weight (40-127 kg) or race.

Renal impairment

Mild to moderate impairment of renal function did not influence the pharmacokinetics of fulvestrant to any clinically relevant extent.

Hepatic impairment

The pharmacokinetics of fulvestrant has been evaluated in a single-dose clinical study conducted in women with mild to moderate hepatic impairment (Child-Pugh class A and B). A high dose of a shorter duration intramuscular injection formulation was used. There was up to about 2.5-fold increase in AUC in women with hepatic impairment compared to healthy women. In patients administered FASLODEX, an increase in exposure of this magnitude is expected to be well tolerated. Women with severe hepatic impairment (Child-Pugh class C) were not evaluated.

5.3 Preclinical safety data

The acute toxicity of fulvestrant is low.

FASLODEX and other formulations of fulvestrant were well tolerated in animal species used in multiple dose studies. Local reactions, including myositis and granulomata at the injection site were attributed to the vehicle but the severity of myositis in rabbits increased with fulvestrant, compared to the saline control. In toxicity studies with multiple intramuscular doses of fulvestrant in rats and dogs, the antiestrogenic activity of fulvestrant was responsible for most of the effects seen, particularly in the female reproductive system, but also in other organs sensitive to hormones in both sexes. Arteritis involving a range of different tissues was seen in some dogs after chronic (12 months) dosing.

In dog studies following oral and intravenous administration, effects on the cardiovascular system (slight elevations of the S-T segment of the ECG [oral], and sinus arrest in one dog [intravenous]) were seen. These occurred at exposure levels higher than in patients (C_{max} >15 times) and are likely to be of limited significance for human safety at the clinical dose.

Fulvestrant showed no genotoxic potential.

Fulvestrant showed effects upon reproduction and embryo/foetal development consistent with its antiestrogenic activity, at doses similar to the clinical dose. In rats a reversible reduction in female fertility and embryonic survival, dystocia and an increased incidence of foetal abnormalities including tarsal flexure were observed. Rabbits given fulvestrant failed to maintain pregnancy. Increases in placental weight and post-implantation loss of foetuses were seen. There was an increased incidence of foetal variations in rabbits (backwards displacement of the pelvic girdle and 27 pre-sacral vertebrae).

A two-year oncogenicity study in rats (intramuscular administration of FASLODEX) showed increased incidence of ovarian benign granulosa cell tumours in female rats at the high dose, 10 mg/rat/15 days and an increased incidence of testicular Leydig cell tumours in males. In a two-year mouse oncogenicity study (daily oral administration) there was an increased incidence of ovarian sex cord stromal tumours (both benign and malignant) at doses of 150 and 500 mg/kg/day. At the no-effect level for these findings, systemic exposure levels (AUC) were, in rats, approximately 1.5–fold the expected human exposure levels in females and 0.8-fold in males, and in mice, approximately 0.8-fold the expected human exposure levels in both males and females. Induction of such tumours is consistent with pharmacology-related endocrine feedback alterations in gonadotropin levels caused by antiestrogens in cycling animals. Therefore these findings are not considered to be relevant to the use of fulvestrant in postmenopausal women with advanced breast cancer.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol 96%
Benzyl alcohol
Benzyl benzoate
Castor oil

6.2 Incompatibilities

In the absence of incompatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Please refer to expiry date on label/outer carton.

6.4 Special precautions for storage

Store at 2°C-8°C (in a refrigerator).

Store the pre-filled syringe in the original package in order to protect from light.

6.5 Pack size

Please refer to outer carton for pack size.

6.6 Instructions for administration and Special precautions for disposal and other handling

Administer the injection according to the local guidelines for performing large volume intramuscular injections.

NOTE: Due to the proximity of the underlying sciatic nerve, caution should be taken if administering FASLODEX at the dorsogluteal injection site (see Special warnings and precautions for use).

Warning - Do not autoclave safety needle (BD SafetyGlide™ Shielding Hypodermic Needle) before use. Hands must remain behind the needle at all times during use and disposal.

For each syringe:

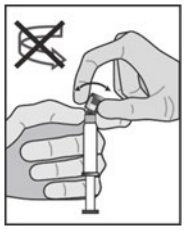
Remove glass syringe barrel from tray and check that it is not damaged.

Peel open the safety needle (SafetyGlide™) outer packaging.

Parenteral solutions must be inspected visually for particulate matter and discolouration prior to administration.

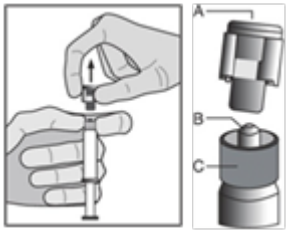
Hold the syringe upright on the ribbed part (C). With the other hand, take hold of the cap (A) and carefully tilt back and forth until the cap disconnects and can be pulled off, do not twist (see Figure 1).

Figure 1



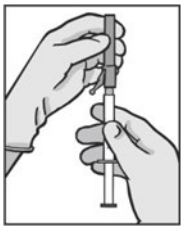
Remove the cap (A) in a straight upward direction. To maintain sterility do not touch the syringe tip (B) (see Figure 2).

Figure 2



Attach the safety needle to the syringe tip (Luer-Lok) and twist until firmly seated (see Figure 3).

Figure 3



Check that the needle is locked to the Luer connector before moving out of the vertical plane.

Pull shield straight off needle to avoid damaging needle point.

Transport filled syringe to point of administration.

Remove needle sheath.

Expel excess gas from the syringe.
Administer intramuscularly slowly (1-2 minutes/injection) into the buttock (gluteal area). For user convenience, the needle bevel-up position is oriented to the lever arm (see Figure 4).

Figure 4

After injection, immediately apply a single-finger stroke to the activation assisted lever arm to activate the shielding mechanism (see Figure 5).

Figure 5

NOTE: Activate away from self and others. Listen for click and visually confirm needle tip is fully covered.

Disposal

Pre-filled syringes are for single use **only**.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Product Owner

AstraZeneca UK Limited
1 Francis Crick Avenue
Cambridge Biomedical Campus
Cambridge, CB2 0AA
United Kingdom

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