SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Faslodex® 250 mg/5 ml solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One pre-filled syringe contains 250 mg fulvestrant in 5 ml solution.
Excipients with known effect (per 5 ml)
Ethanol (96%. 500mg)
Benzyl alcohol (500 mg)
Benzyl benzoate (750 mg)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Monotherapy
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 endocrine therapy; or
- disease progression on endocrine therapy

Combination Therapy
FASLODEX is indicated for the treatment of:

- HR-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in men and postmenopausal women in combination with ribociclib as initial endocrine based therapy or following disease progression on endocrine therapy.
- HR-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with palbociclib or abemaciclib in women with disease progression after endocrine therapy.

4.2 Posology and method of administration

Monotherapy

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, abemaciclib, or ribociclib, the recommended dose of FASLODEX is 500 mg to be administered intramuscularly into the buttocks (gluteal area) slowly (1-2 minutes per injection) as two 5 mL injections, one in each buttock, on Days 1, 15, 29 and once monthly thereafter.

When FASLODEX is used in combination with Palbociclib, the recommended dose of palbociclib is a 125 mg capsule taken orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days. Palbociclib should be taken with food. Refer to the Full Prescribing Information of palbociclib.

When FASLODEX is used in combination with abemaciclib, the recommended dose of abemaciclib is 150 mg orally, twice daily. Abemaciclib may be taken with or without food. Refer to the Full Prescribing Information for abemaciclib.

When FASLODEX is used in combination with ribociclib, the recommended dose of ribociclib is 600 mg taken orally, once daily for 21 consecutive days followed by 7 days off treatment resulting in a complete cycle of 28 days. Ribociclib can be taken with or without food. Refer to the Full Prescribing Information for ribociclib.

Pre/perimenopausal women treated with the combination of FASLODEX plus palbociclib, abemaciclib, or ribociclib, should be treated with luteinizing hormone-releasing hormone (LHRH) agonists according to current clinical practice standards [*see* Pharmacodynamic properties 5.1].

Special populations:

Renal impairment:

No dose adjustments are recommended for patients with mild to moderate renal impairment (creatinine clearance $\geq$ 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 section 4.4).

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 sections 4.3, 4.4 and 5.2).

Paediatric population

The safety and efficacy of Faslodex in children from birth to 18 years of age have not been established. Currently available data are described in sections 5.1 and 5.2, but no recommendation on a posology can be made.

Combination Therapy with Palbociclib, Abemaciclib, or Ribociclib

When FASLODEX is used in combination with palbociclib, abemaciclib, or ribociclib, refer to monotherapy instructions for FASLODEX.

Refer to the full prescribing information of co-administered palbociclib, abemaciclib, or ribociclib for dose modification, guidelines in the event of toxicities, for use with concomitant medications and other relevant safety information.

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 section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients (listed in section 6.1)
- Pregnancy and lactation (see section 4.6).
- Severe hepatic impairment (see sections 4.4 and 5.2).

4.4 Special warnings and precautions for use

Faslodex should be used with caution in patients with mild to moderate, hepatic impairment (see sections 4.2, 4.3 and 5.2).

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

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.

Thromboembolic events are commonly observed in women with advanced breast cancer and have been observed in clinical studies with Faslodex (see section 4.8). This should be taken into consideration when prescribing Faslodex to patients at risk.

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 sections 4.2 and 4.8).
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.

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

The falsely elevated estradiol levels could lead the clinician to incorrect medical decisions and unnecessary procedures. If this situation has occurred, reassessing the status of the patient by other means or using an alternate method for estradiol measurement should be considered.
The results should always be assessed in correlation with the clinical evaluation. The laboratory performing the Estradiol immunoassay should be informed that the patient is taking Faslodex.

Ethanol
Faslodex contains 10% w/v ethanol (alcohol) as an excipient, i.e. up to 500 mg per injection, equivalent to 10 ml beer or 4 ml wine. This may be harmful for those suffering from alcoholism and should be taken into account in high risk groups such as patients with liver disease and epilepsy.

Benzyl alcohol
Faslodex contains benzyl alcohol as an excipient which may cause allergic reactions.

Paediatric population
Faslodex is not recommended for use in children and adolescents as safety and efficacy have not been established in this group of patients (see section 5.1).

4.5 Interaction with other medicinal products and other forms of interaction

A clinical interaction study with midazolam (substrate of CYP3A4) demonstrated that fulvestrant does not inhibit CYP3A4.
Clinical interaction studies with rifampicin (inducer of CYP3A4) and ketoconazole (inhibitor of CYP3A4) showed no clinically relevant change in fulvestrant clearance. Dose adjustment is therefore not necessary in patients who are receiving fulvestrant and CYP3A4 inhibitors or inducers concomitantly.

Fulvestrant has a similar chemical structure to estradiol. 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. The falsely elevated estradiol levels could lead the clinician to incorrect medical decisions and unnecessary procedures. If this situation has occurred, reassessing

the status of the patient by other means or using an alternate method for estradiol measurement should be considered.
The results should always be assessed in correlation with the clinical evaluation.
The laboratory performing the Estradiol immunoassay should be informed that the patient is taking Faslodex.

4.6 Fertility, Pregnancy and lactation

Women of childbearing potential

Patients of child-bearing potential should use effective contraception during treatment with Faslodex and for 2 years after the last dose.

Pregnancy

Faslodex is contraindicated in pregnancy (see section 4.3). 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 section 5.3). 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 section 4.3).

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

Summary of the safety profile

Monotherapy

This section provides information based on all adverse reactions from clinical studies, post-marketing studies or spontaneous reports. In the pooled dataset of fulvestrant monotherapy, the most frequently

reported adverse reactions were injection site reactions, asthenia, nausea, and increased hepatic enzymes (ALT, AST, ALP).

In table 1, 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 Table 1 were based on all reported adverse drug reactions, regardless of the investigator assessment of causality. The median duration of fulvestrant 500 mg treatment across the pooled dataset (including the studies mentioned above plus FALCON) was 6.5 months.

Tabulated list of adverse reactions

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 reported in patients treated with Faslodex monotherapy

Adverse reactions by system organ class and frequency		
Infections and infestations	Common	Urinary tract infections
Blood and lymphatic system disorders	Common	Reduced platelet count[e]
Immune system disorders	Very Common	Hypersensitivity reactions[e]
	Uncommon	Anaphylactic reactions
Metabolism and nutrition disorders	Common	Anorexia[a]
Nervous system disorders	Common	Headache
Vascular disorders	Very Common	Hot flushes[e]
	Common	Venous thromboembolism[a]
Gastrointestinal disorders	Very common	Nausea
	Common	Vomiting, diarrhoea
Hepatobiliary disorders	Very common	Elevated Hepatic Enzymes (ALT, AST, ALP) [a]
	Common	Elevated bilirubin[a]
	Uncommon	Hepatic failure[c,f], hepatitis[f], elevated gamma-GT[f]
Skin and subcutaneous tissue disorders	Very common	Rash[e]

Musculoskeletal and connective tissue disorders	Very common	Joint and musculoskeletal pain[d]
	Common	Back pain[a]
Reproductive system and breast disorders	Common	Vaginal haemorrhage[e]
	Uncommon	Vaginal Moniliasis[f], Leukorrhoea[f]
General disorders and administration site conditions	Very common	Asthenia[a], Injection site reactions[b]
	Common	Neuropathy peripheral[e], sciatica[e]
	Uncommon	Injection site haemorrhage[f], injection site haematoma[f], neuralgia[c,f]

[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, FINDER 1, FINDER 2, 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

Combination Therapy with Palbociclib (PALOMA-3)

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

No dose reduction was allowed for FASLODEX in PALOMA-3. Dose reductions of palbociclib due to an adverse reaction of any grade occurred in 36% of patients receiving FASLODEX plus palbociclib.

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

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

The most frequently reported Grade ≥3 adverse reactions (≥5%) in patients receiving FASLODEX plus palbociclib in descending frequency were neutropenia (1%), and leukopenia.
Adverse reactions (≥10%) reported in patients who received FASLODEX plus palbociclib or FASLODEX plus placebo in PALOMA-3 are listed in Table 2, and laboratory abnormalities are listed in Table 3.

Table 2: Adverse Reaction (≥10%) in PALOMA-3

Adverse Reactions	FASLODEX plus palbociclib (N=345)			FASLODEX plus placebo (N=172)		
	All Grades %	Grade 3 %	Grade4 %	All Grades %	Grade 3 %	Grade 4 %
Infections and infestations						
Infections[1]	47[2]	3	1	31	3	0
Blood and lymphatic system						

disorders						
Neutropenia	83	55	11	4	1	0
Leukopenia	53	30	1	5	1	1
Anemia	30	4	0	13	2	0
Thrombocytopenia	23	2	1	0	0	0
Metabolism and nutrition disorders						
Decreased appetite	16	1	0	8	1	0
Gastrointestinal disorders						
Nausea	34	0	0	28	1	0
Stomatitis[3]	28	1	0	13	0	0
Diarrhea	24	0	0	19	1	0
Vomiting	19	1	0	15	1	0
Skin and subcutaneous tissue disorders						
Alopecia	18[4]	N/A	N/A	6[5]	N/A	N/A
Rash[6]	17	1	0	6	0	0
General disorders and administration site conditions						
Fatigue	41	2	0	29	1	0
Pyrexia	13	<1	0	5	0	0

Grading according to CTCAE 4.0.

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

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

2. Most common infections (≥1%) include: nasopharyngitis, upper respiratory infection, urinary tract infection, influenza, bronchitis, rhinitis, conjunctivitis, pneumonia, sinusitis, cystitis, oral herpes, respiratory tract infection, gastroenteritis, tooth infection, pharyngitis, eye infection, herpes simplex, paronychia.

3. Stomatitis includes: aphthous stomatitis, cheilitis, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral pain, oropharyngeal discomfort, oropharyngeal pain, stomatitis.

4. Grade 1 events – 17%; Grade 2 events – 1%.

5. Grade 1 events – 6%.

6. Rash includes: rash, rash maculo-papular, rash pruritic, rash erythematous, rash papular, dermatitis, dermatitis acneiform, toxic skin eruption.

Additional adverse reactions occurring at an overall incidence of <10.0% of patients receiving FASLODEX plus palbociclib in PALOMA-3 included asthenia (7.5%), aspartate aminotransferase increased (7.5%), dysgeusia (6.7%), epistaxis (6.7%), lacrimation increased (6.4%), dry skin (6.1%), alanine aminotransferase increased (5.8%), vision blurred (5.8%), dry eye (3.8%), and febrile neutropenia (0.9%).

Table 3: Laboratory Abnormalities in PALOMA-3

Laboratory Parameters	FASLODEX plus palbociclib (N=345)			FASLODEX plus placebo (N=172)		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
WBC decreased	99	45	1	26	0	1
Neutrophils decreased	96	56	11	14	0	1
Anemia	78	3	0	40	2	0
Platelets decreased	62	2	1	10	0	0
Aspartate aminotransferase increased	43	4	0	48	4	0
Alanine aminotransferase increased	36	2	0	34	0	0

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

Combination Therapy with Abemaciclib (MONARCH 2)

The safety of FASLODEX (500 mg) plus abemaciclib (150 mg twice daily) versus FASLODEX plus placebo was evaluated in MONARCH 2. The data described below reflect exposure to FASLODEX in 664 patients with HR-positive, HER2-negative advanced breast cancer who received at least one dose of FASLODEX plus abemaciclib or placebo in MONARCH 2.

Median duration of treatment was 12 months for patients receiving FASLODEX plus abemaciclib and 8 months for patients receiving FASLODEX plus placebo.

Dose reductions due to an adverse reaction occurred in 43% of patients receiving FASLODEX plus abemaciclib. Adverse reactions leading to dose reductions ≥5% of patients were diarrhea and neutropenia. Abemaciclib dose reduction due to diarrhea of any grade occurred in 19% of patients receiving FASLODEX plus abemaciclib compared to 0.4% of patients receiving FASLODEX plus placebo. Abemaciclib dose reductions due to neutropenia of any grade occurred in 10% of patients receiving FASLODEX plus abemaciclib compared to no patients receiving FASLODEX plus placebo.

Permanent study treatment discontinuation due to an adverse event was reported in 9% of patients receiving FASLODEX plus abemaciclib and in 3% of patients receiving FASLODEX plus placebo. Adverse reactions leading to permanent discontinuation for patients receiving FASLODEX plus abemaciclib were infection (2%), diarrhea (1%), hepatotoxicity (1%), fatigue (0.7%), nausea (0.2%), abdominal pain (0.2%), acute kidney injury (0.2%), and cerebral infarction (0.2%).

Deaths during treatment or during the 30-day follow up, regardless of causality, were reported in 18 cases (4%) of FASLODEX plus abemaciclib treated patients versus 10 cases (5%) of FASLODEX plus placebo treated patients. Causes of death for patients receiving FASLODEX plus abemaciclib included: 7 (2%) patient deaths due to underlying disease, 4 (0.9%) due to sepsis, 2 (0.5%) due to pneumonitis, 2 (0.5%) due to hepatotoxicity, and one (0.2%) due to cerebral infarction.

The most common adverse reactions reported (≥20%) in the FASLODEX plus abemaciclib arm were diarrhea, fatigue, neutropenia, nausea, infections, abdominal pain, anemia, leukopenia, decreased appetite, vomiting, and headache (Table 4). The most frequently reported (≥5%) Grade 3 or 4 adverse reactions were neutropenia, diarrhea, leukopenia, anemia, and infections.

Table 4: Adverse Reactions ≥10% of Patients Receiving FASLODEX Plus Abemaciclib and ≥2% Higher Than FASLODEX Plus Placebo in MONARCH 2

Adverse Reactions	FASLODEX plus Abemaciclib N=441			FASLODEX plus Placebo N=223		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Gastrointestinal Disorders						
Diarrhea	86	13	0	25	<1	0
Nausea	45	3	0	23	1	0
Abdominal pain[1]	35	2	0	16	1	0
Vomiting	26	<1	0	10	2	0
Stomatitis	15	<1	0	10	0	0
Infections and Infestations						
Infections[2]	43	5	<1	25	3	<1

Blood and Lymphatic System Disorders						
Neutropenia[3]	46	24	3	4	1	<1
Anemia[4]	29	7	<1	4	1	0
Leukopenia[5]	28	9	<1	2	0	0
Thrombocytopenia[6]	16	2	1	3	0	<1
General Disorders and Administration Site Conditions						
Fatigue[7]	46	3	0	32	<1	0
Edema peripheral	12	0	0	7	0	0
Pyrexia	11	<1	<1	6	<1	0
Metabolism and Nutrition Disorders						
Decreased appetite	27	1	0	12	<1	0
Respiratory, Thoracic, and Mediastinal Disorders						
Cough	13	0	0	11	0	0
Skin and Subcutaneous Tissue Disorders						
Alopecia	16	0	0	2	0	0
Pruritus	13	0	0	6	0	0
Rash	11	1	0	4	0	0
Nervous System Disorders						
Headache	20	1	0	15	<1	0
Dysgeusia	18	0	0	3	0	0
Dizziness	12	1	0	6	0	0
Investigations						
Alanine aminotransferase increased	13	4	<1	5	2	0
Aspartate aminotransferase increased	12	2	0	7	3	0
Creatinine increased	12	<1	0	<1	0	0
Weight decreased	10	<1	0	2	<1	0

1. Includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, abdominal tenderness.
2. Includes upper respiratory tract infection, urinary tract infection, lung infection, pharyngitis, conjunctivitis, sinusitis, vaginal infection, sepsis.

3. Includes neutropenia, neutrophil count decreased.
4. Includes anemia, hematocrit decreased, hemoglobin decreased, red blood cell count decreased.
5. Includes leukopenia, white blood cell count decreased.
6. Includes platelet count decreased, thrombocytopenia.
7. Includes asthenia, fatigue.

Additional adverse reactions in MONARCH 2 include venous thromboembolic events (deep vein thrombosis, pulmonary embolism, cerebral venous sinus thrombosis, subclavian vein thrombosis, axillary vein thrombosis, and DVT inferior vena cava), which were reported in 5% of patients treated with FASLODEX plus abemaciclib as compared to 0.9% of patients treated with FASLODEX plus placebo.

Table 5: Laboratory Abnormalities ≥10% in Patients Receiving FASLODEX Plus Abemaciclib and ≥2% Higher Than FASLODEX Plus Placebo in MONARCH 2

Laboratory Parameters	Fulvestrant plus Abemaciclib N=441			Fulvestrant plus Placebo N=223		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Creatinine increased	98	1	0	74	0	0
White blood cell decreased	90	23	<1	33	<1	0
Neutrophil count decreased	87	29	4	30	4	<1
Anemia	84	3	0	33	<1	0
Lymphocyte count decreased	63	12	<1	32	2	0
Platelet count decreased	53	<1	1	15	0	0
Alanine aminotransferase increased	41	4	<1	32	1	0
Aspartate aminotransferase increased	37	4	0	25	4	<1

Combination Therapy with Ribociclib (MONALEESA-3)

The safety of FASLODEX 500 mg plus ribociclib 600 mg versus FASLODEX plus placebo was evaluated in MONALEESA-3. The data described below reflect exposure to FASLODEX plus ribociclib in 483 out of 724 postmenopausal patients with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy or after disease progression on endocrine therapy who received at least one dose of FASLODEX plus ribociclib or placebo in MONALEESA-3. Median duration of treatment was 15.8 months for FASLODEX plus ribociclib and 12 months for FASLODEX plus placebo.

Dose reductions due to adverse reactions occurred in 32% of patients receiving FASLODEX plus ribociclib and in 3% of patients receiving FASLODEX plus placebo. Among patients receiving FASLODEX plus ribociclib, 8% were reported to have permanently discontinued both FASLODEX plus ribociclib, and 9% were reported to have discontinued ribociclib alone due to ARs. Among patients receiving FASLODEX plus placebo, 4% were reported to have permanently discontinued both FASLODEX and placebo and 2% were reported to have discontinued placebo alone due to ARs.

Adverse reactions leading to treatment discontinuation of FASLODEX plus ribociclib (as compared to FASLODEX plus placebo) were ALT increased (5% vs. 0%), AST increased (3% vs. 0.6%), and vomiting (1% vs. 0%).

The most common adverse reactions (reported at a frequency ≥20% on the FASLODEX plus ribociclib arm and ≥2% higher than FASLODEX plus placebo) were neutropenia, infections, leukopenia, cough, nausea, diarrhea, vomiting, constipation, pruritus, and rash. The most frequently reported Grade 3/4 adverse reactions (reported at a frequency ≥5%) in patients receiving FASLODEX plus ribociclib in descending frequency were neutropenia, leukopenia, infections, and abnormal liver function tests.
Adverse reactions and laboratory abnormalities occurring in patients in MONALEESA-3 are listed in Table 6 and Table 7, respectively.

Table 6: Adverse Reactions Occurring in ≥10% and ≥2% higher than FASLODEX plus Placebo Arm in MONALEESA-3 (All Grades)

Arm in MONALEESA-3 (All Grades) Adverse Reactions	FASLODEX plus Ribociclib N=483			FASLODEX plus Placebo N=241		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Infections and Infestations						
Infections[1]	42	5	0	30	2	0
Blood and Lymphatic System Disorders						
Neutropenia	69	46	7	2	0	0
Leukopenia	27	12	<1	<1	0	0
Anemia	17	3	0	5	2	0
Metabolism and Nutrition Disorders						
Decreased appetite	16	<1	0	13	0	0
Nervous System Disorders						
Dizziness	13	<1	0	8	0	0
Respiratory, Thoracic, and Mediastinal Disorders						
Cough	22	0	0	15	0	0

Dyspnea	15	1	<1	12	2	0
Gastrointestinal Disorders						
Nausea	45	1	0	28	<1	0
Diarrhea	29	<1	0	20	<1	0
Vomiting	27	1	0	13	0	0
Constipation	25	<1	0	12	0	0
Abdominal pain	17	1	0	13	<1	0
Skin and Subcutaneous Tissue Disorders						
Alopecia	19	0	0	5	0	0
Pruritus	20	<1	0	7	0	0
Rash	23	<1	0	7	0	0
General Disorders and Administration Site Conditions						
Edema peripheral	15	0	0	7	0	0
Pyrexia	11	<1	0	7	0	0
Investigations						
Alanine aminotransferase increased	15	7	2	5	<1	0
Aspartate aminotransferase increased	13	5	1	5	<1	0

Grading according to CTCAE 4.03. CTCAE=Common Terminology Criteria for Adverse Events; N=number of patients

[1] Infections; urinary tract infections; respiratory tract infections; gastroenteritis; sepsis (<1%).

Additional adverse reactions in MONALEESA-3 for patients receiving FASLODEX plus ribociclib included asthenia (14%), dyspepsia (10%), thrombocytopenia (9%), dry skin (8%), dysgeusia (7%), electrocardiogram QT prolonged (6%), dry mouth (5%), vertigo (5%), dry eye (5%), lacrimation increased (4%), erythema (4%), hypocalcemia (4%), blood bilirubin increased (1%), and syncope (1%).

Table 7: Laboratory Abnormalities Occurring in ≥10% of Patients in MONALEESA-3

Laboratory parameters	FASLODEX plus Ribociclib N=483			FASLODEX plus Placebo N=241		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Hematology						
Leukocyte count decreased	95	25	<1	26	<1	0
Neutrophil count decreased	92	46	7	21	<1	0

Hemoglobin decreased	60	4	0	35	3	0
Lymphocyte count decreased	69	14	1	35	4	<1
Platelet count decreased	33	<1	1	11	0	0
Chemistry						
Creatinine increased	65	<1	<1	33	<1	0
Gamma-glutamyl transferase increased	52	6	1	49	8	2
Aspartate aminotransferase increased	49	5	2	43	3	0
Alanine aminotransferase increased	44	8	3	37	2	0
Glucose serum decreased	23	0	0	18	0	0
Phosphorous decreased	18	5	0	8	<1	0
Albumin decreased	12	0	0	8	0	0

Reporting of suspected adverse reactions

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

https://sideeffects.health.gov.il

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 (see section 5.3).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Endocrine therapy, Antiestrogens, ATC code: L02BA03

Mechanism of action and pharmacodynamic effects

Fulvestrant is a competitive oestrogen receptor (ER) antagonist with an affinity comparable to estradiol. Fulvestrant blocks the trophic actions of oestrogens without any partial agonist (oestrogen-like) activity. The mechanism of action is associated with down-regulation of estrogen receptor protein levels.

Clinical studies in postmenopausal women with primary breast cancer have shown that fulvestrant significantly down-regulates 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 down-regulates ER and the proliferation marker Ki67, to a greater degree than fulvestrant 250 mg in breast tumours in postmenopausal neoadjuvant setting.

Clinical efficacy and safety in advanced breast cancer

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 8.

Table 8 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 500mg/Faslodex 250mg)		
				Hazard ratio	95%CI	p-value
PFS	K-M median in months: Hazard ratio					
ALL Patients		6.5	5.5	0.8	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) **AI subgroup (n=313) [a]**		30.6 24.1	23.9 20.8	0.79 0.86	0.63, 0.99 0.67, 1.11	0.038[c] 0.241[c]
Variable	**Type of estimate; treatment comparison**	**Faslodex 500mg (N=362)**	**Faslodex 250mg (N=374)**	**Comparison between groups (Faslodex 500 mg/Faslodex 250 mg)**		
				Absolute Difference in%	**95%CI**	
ORR[d] **ALL Patients** **AE subgroup (n=296)** **AI subgroup (n=205) [a]**	**%of patients with OR; Absolute difference in%**	 13.8 18.1 7.3	 14.6 19.1 8.3	 -0.8 -1.0 -1.0	 -5.8,6.3 -8.2,9.3 -5.5, 9.8	
CBR[e] **ALL Patients** **AE subgroup (n=423)** **AI subgroup (n=313) [a]**	**%of patients with CB; Absolute difference in%**	 45.6 52.4 36.2	 39.6 45.1 32.3	 6.0 7.3 3.9	 -1.1, 13.3 -2.2, 16.6 -6.1, 15.2	

a Faslodex is indicated in patients whose disease had recurred or progressed on an antiestrogen 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 (i.e. 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:Antiestrogen.

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 9 and Figure 1.

Table 9 Summary of results of the primary efficacy endpoint (PFS) and key secondary efficacy endpoints (Investigator Assessment, Intent-To-Treat Population) – FALCON study

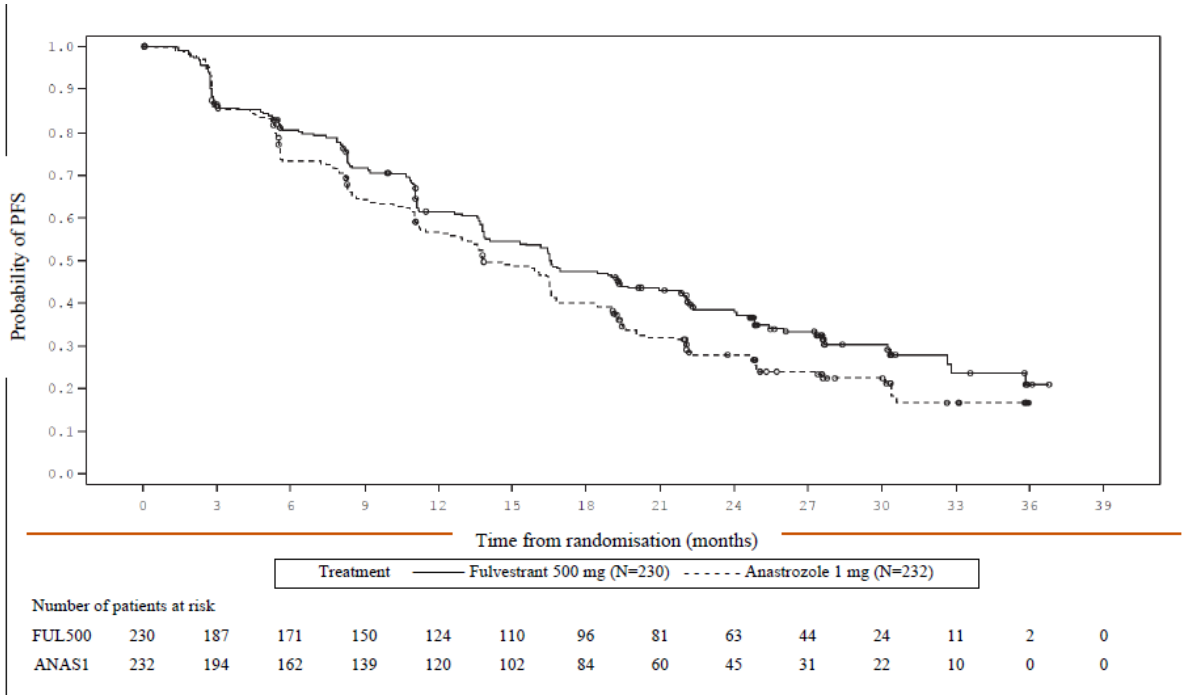
	Faslodex 500 mg (N=230)	Anastrozole 1 mg (N=232)
Progression-Free Survival		
Number of PFS Events (%)	143 (62.2%)	166 (71.6%)

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 versus the daily administration of 1 mg

anastrozole (aromatase 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).

Effects on the postmenopausal endometrium

Preclinical data do not suggest a stimulatory effect of fulvestrant on the postmenopausal endometrium (see section 5.3). A 2-week study in healthy postmenopausal volunteers treated with 20 µg per day 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.

Paediatric population

Faslodex is not indicated for use in children.

An open-label Phase 2 study investigated the safety, efficacy and pharmacokinetics of fulvestrant in 30 girls aged 1 to 8 years with Progressive Precocious Puberty associated with McCune Albright Syndrome (MAS). The paediatric patients received 4 mg/kg monthly intramuscular dose of fulvestrant.

This 12-month study investigated a range of MAS endpoints and showed a reduction in the frequency of vaginal bleeding and a reduction in the rate of bone age advancement. The steady-state trough concentrations of fulvestrant in children in this study were consistent with that in adults (see section 5.2). There were no new safety concerns arising from this small study, but 5-year data are yet not available.

The efficacy of FASLODEX 500 mg in combination with palbociclib 125 mg was compared to FASLODEX 500 mg plus placebo in PALOMA-3.

Combination Therapy

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

FASLODEX 500 mg in Combination with Palbociclib 125 mg (PALOMA-3).

PALOMA-3 (NCT-1942135) was an international, randomized, double-blind, parallel group, multi-centers study of FASLODEX plus palbociclib versus FASLODEX plus placebo conducted in women with HR-positive, HER2-negative advanced breast cancer, regardless of their menopausal status, whose disease progressed on or after prior endocrine therapy.

A total of 521 pre/postmenopausal women 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. Palbociclib was given orally at a dose of 125 mg daily for 21 consecutive days followed by 7 days off treatment. Fulvestrant 500 mg was administered as two 5 mL injections each containing fulvestrant 250 mg/5 mL, one in each buttock, on Days 1, 15, 29, and every 28 (+/- 3) days thereafter. Pre/perimenopausal women were enrolled in the study and received the LHRH agonist goserelin for at least 4 weeks prior to and for the duration of PALOMA-3.

Patients continued to receive assigned treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurred first. The major efficacy outcome of the study was investigator-assessed PFS evaluated according to RECIST v 1.1.

Patients enrolled in this study had a median age of 57 years (range 29 to 88). The majority of patients on study were White (74%), all patients had an ECOG PS of 0 or 1, and 80% were postmenopausal. All patients had received prior systemic therapy and 75% of patients had received a previous chemotherapy regimen. Twenty-five percent of patients had received no prior therapy in the metastatic disease setting, 60% had visceral metastases, and 23% had bone only disease.

The results from the investigator-assessed PFS and final OS data from the PALOMA-3 are summarized in Table 10.

The relevant Kaplan-Meier plots are shown in Figures 2 and 3, respectively. Consistent PFS results were observed across patient subgroups of disease site, sensitivity to prior hormonal therapy, and menopausal status. After a median follow-up time of 45 months, the final OS results were not statistically significant.

Table 10: Efficacy Results in PALOMA-3 – (Investigator Assessment, ITT Population)

	FASLODEX plus palbociclib	**FASLODEX plus placebo**
Progression-Free Survival for ITT	**(N=347)**	**(N=174)**
Number of PFS Events (%)	145 (41.8%)	114 (65.5%)
Median PFS (months) (95% CI)	9.5 (9.2-11.0)	4.6 (3.5-5.6)
Hazard Ratio (95% CI) and p-value	0.461 (0.360-0.591) p <0.0001	
Objective Response for Patients with Measurable Disease	**N=267**	**N=174**
Objective response rate[1] (%, 95% CI)	24.6 (19.6-30.2)	10.9 (6.2-17.3)
Overall Survival for ITT population	**N=347**	**N=174**
Number of OS events (%)	201 (57.9)	109 (62.6)
Median OS (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=0.08572,3	

N=number of patients; PFS=progression-free survival; CI=confidence interval; ITT=Intent-to-Treat; OS=overall survival.

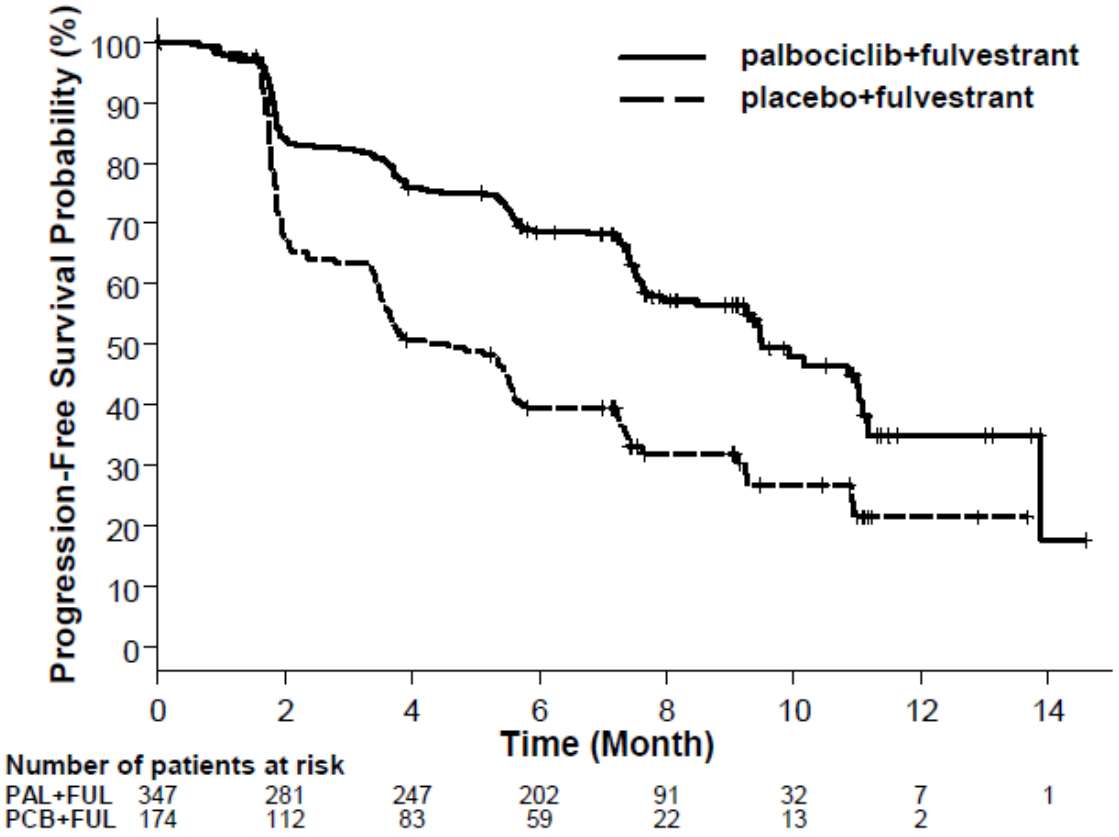
1. Responses are based on confirmed responses.

2. Not statistically significant at the pre-specified 2-sided alpha level of 0.047.

3. 2-sided p-value from the log-rank test stratified by the presence of visceral metastases and sensitivity to prior endocrine therapy per randomization.

Figure 2

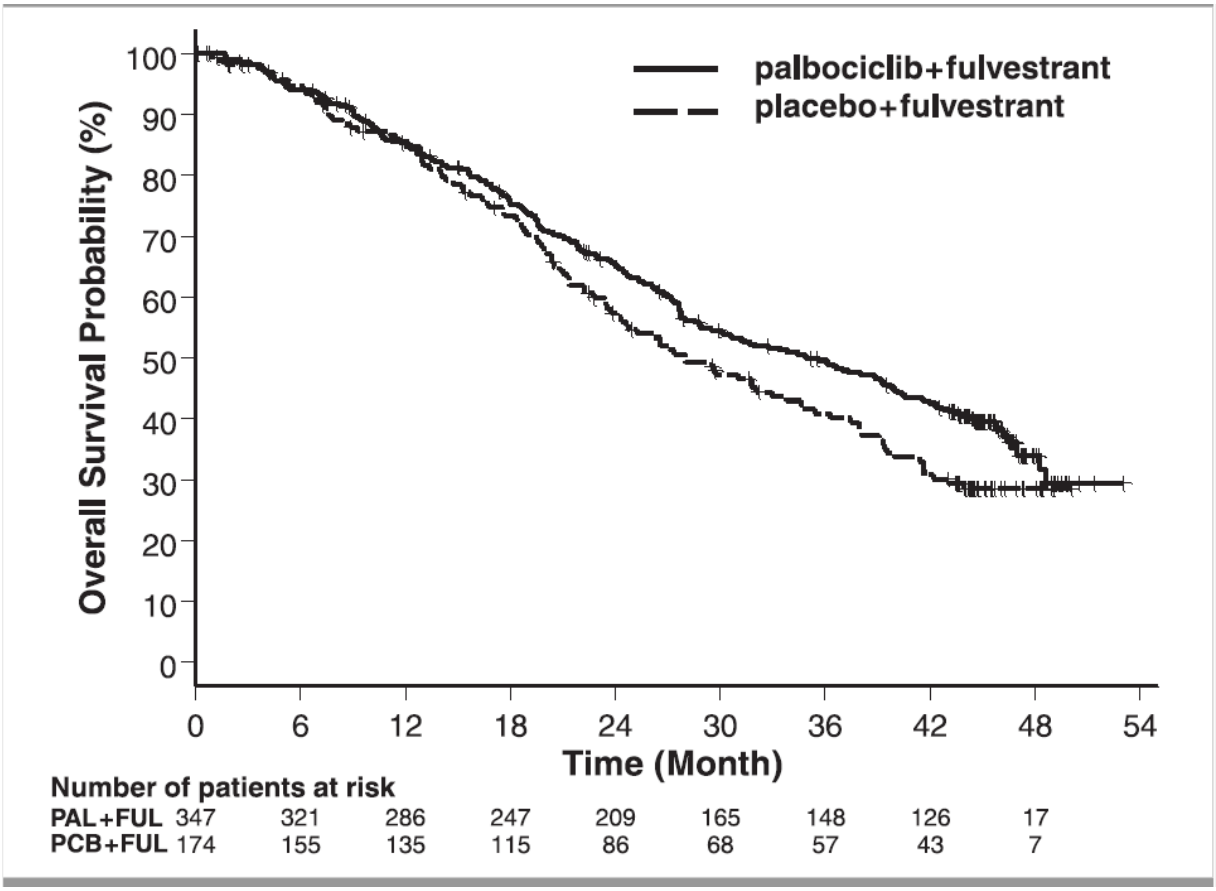
Kaplan-Meier Plot of Progression-Free Survival (Investigator Assessment, ITT Population) - PALOMA-3



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

Figure 3

Kaplan-Meier Plot of Overall Survival (ITT Population) – PALOMA-3



FUL=fulvestrant; PAL=palbociclib; PCB=placebo

FASLODEX 500 mg in Combination with Abemaciclib 150 mg (MONARCH 2)

MONARCH 2 (NCT02107703) was a randomized, placebo-controlled, multi-center 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 11, Figure 4, and Figure 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 11: 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. Datafrom 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)

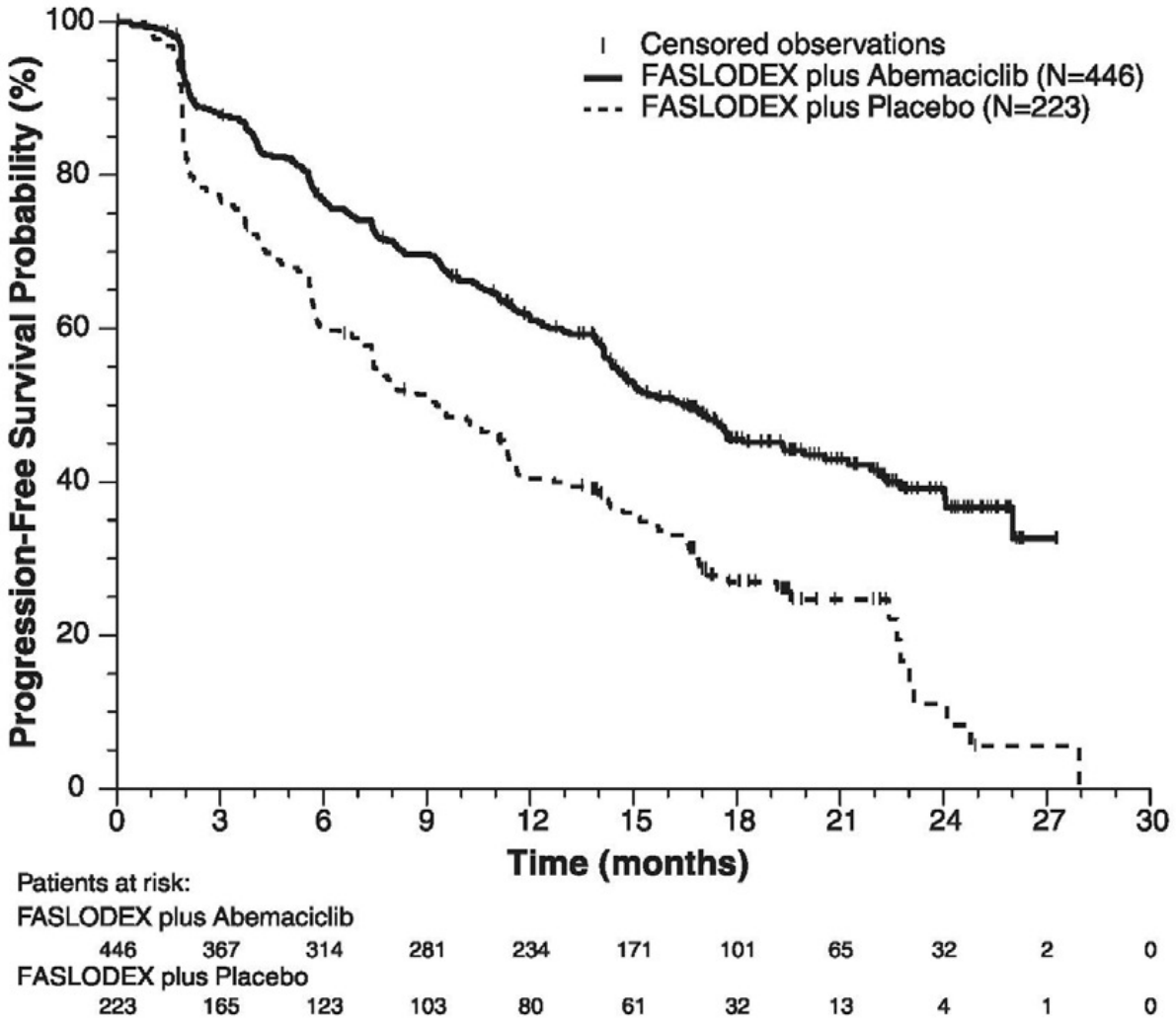
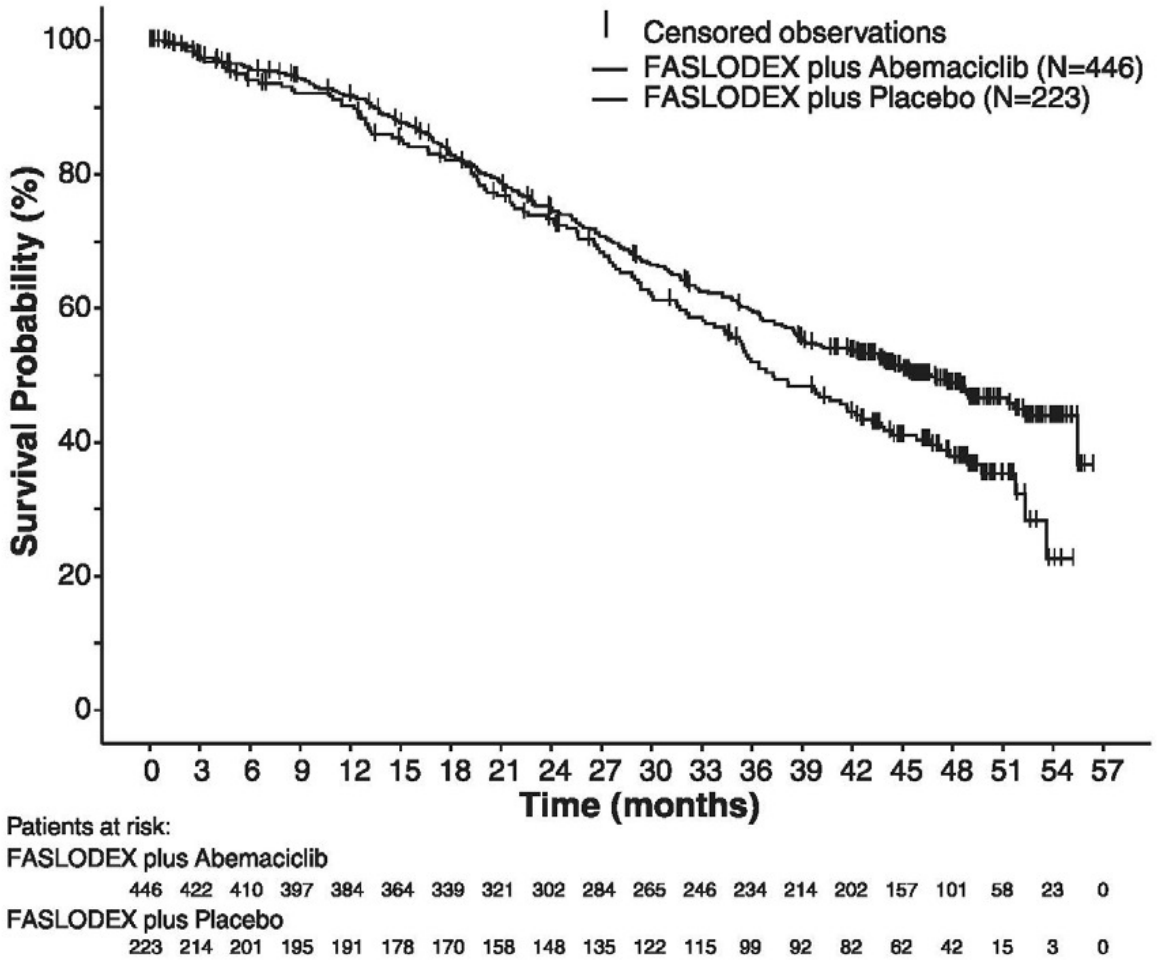


Figure 5 Kaplan-Meier Curves of Overall Survival: FASLODEX plus Abemaciclibversus FASLODEX plus Placebo (MONARCH 2)



Postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy or after disease progression on endocrine therapy

FASLODEX 500 mg in Combination with Ribociclib 600 mg (MONALEESA-3)

MONALEESA-3 (NCT 02422615) 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 12, Figure 6, and Figure 7. Consistent results were observed in stratification factor subgroups of disease site and prior endocrine treatment for advanced disease.

Table 12: 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]	<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)

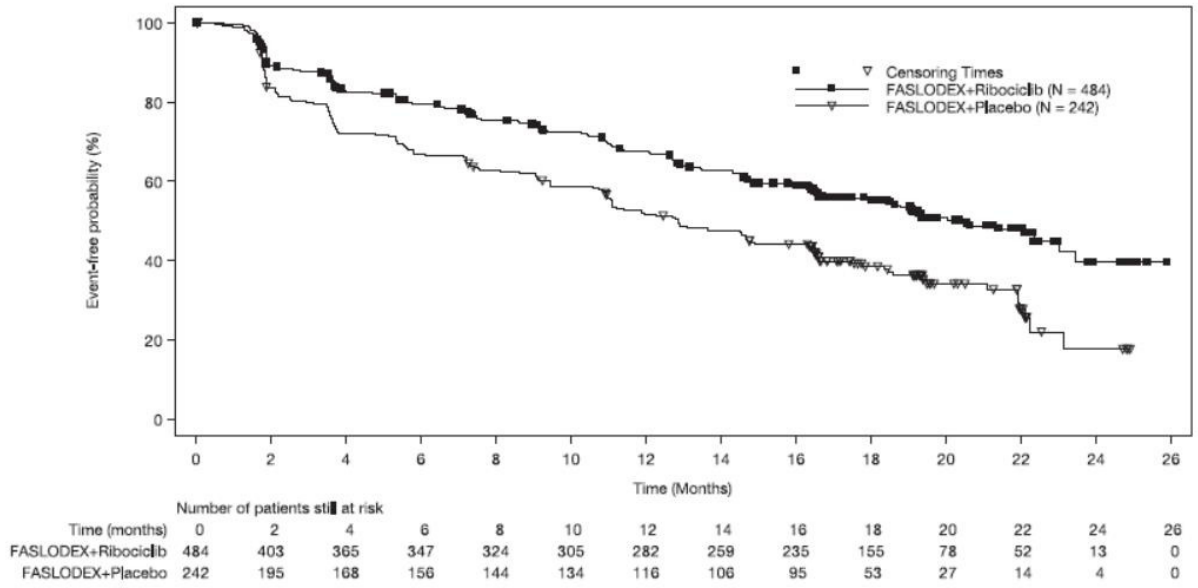
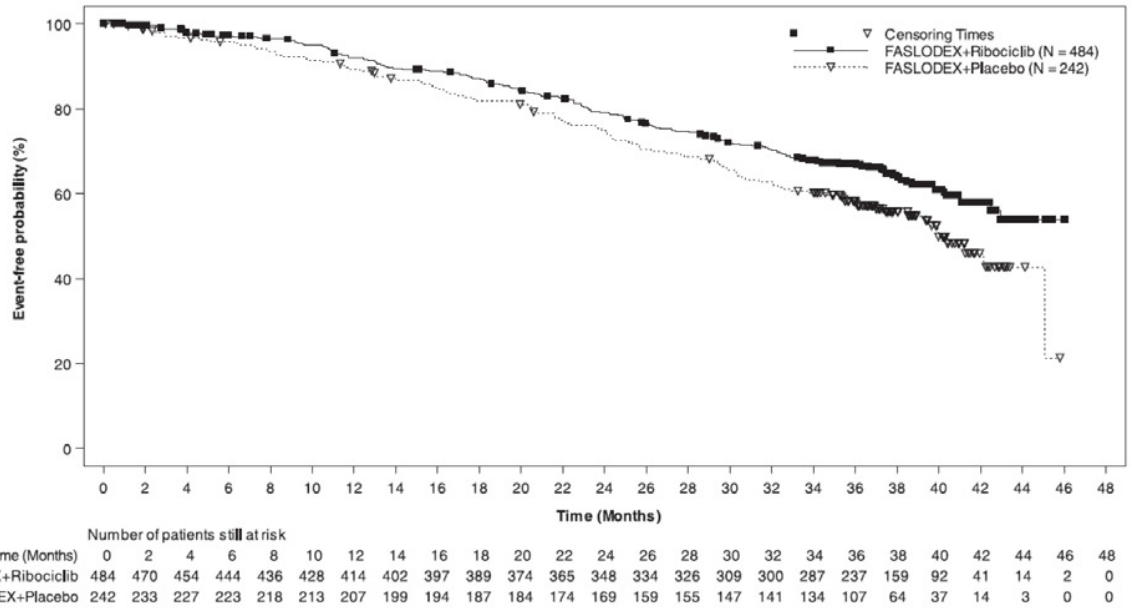


Figure 7 Kaplan-Meier plot of Overall Survival – MONALEESA-3 (Intent -to-Treat Population)



Number of patients still at risk

Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48
FASLODEX+Ribociclib	484	470	454	444	436	428	414	402	397	389	374	365	348	334	326	309	300	287	237	159	92	41	14	2	0
FASLODEX+Placebo	242	233	227	223	218	213	207	199	194	187	184	174	169	159	155	147	141	134	107	64	37	14	3	0	0

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.

Biotransformation

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 CYP3A4 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 subjects. 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.

Paediatric population

The pharmacokinetics of fulvestrant has been evaluated in a clinical study conducted in 30 girls with Progressive Precocious Puberty associated with McCune Albright Syndrome (see section 5.1). The paediatric patients were aged 1 to 8 years and received 4 mg/kg monthly intramuscular dose of fulvestrant. The geometric mean (standard deviation) steady state trough concentration (Cmin,ss) and AUCss was 4.2 (0.9) ng/mL and 3680 (1020) ng*hr/mL, respectively. Although the data collected were limited, the steady-state trough concentrations of fulvestrant in children appear to be consistent with those in adults.

Drug-Drug Interactions:

There are no known drug-drug interactions. Fulvestrant does not significantly inhibit any of the major CYP isoenzymes, including CYP 1A2, 2C9, 2C19, 2D6, and 3A4 in vitro, and studies of co-administration of fulvestrant with midazolam indicate that therapeutic doses of fulvestrant have no

inhibitory effects on CYP 3A4 or alter blood levels of drug metabolized by that enzyme. Although fulvestrant is partly metabolized by CYP 3A4, a clinical study with rifampin, an inducer of CYP 3A4, showed no effect on the pharmacokinetics of fulvestrant. Also, results from a healthy volunteer study with ketoconazole, a potent inhibitor of CYP 3A4, indicated that ketoconazole had no effect on the pharmacokinetics of fulvestrant and dosage adjustment is not necessary in patients co-prescribed CYP 3A4 inhibitors or inducers [see Interaction with other medicinal products and other forms of nteraction (4.5)]. Data from a clinical trial in patients with breast cancer showed that there was no clinically relevant drug interaction when fulvestrantis co-administered with palbociclib, abemaciclib, or ribociclib.

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

Benzyl benzoate
Ethanol 96%
Benzyl alcohol
Castor oil

6.2 Incompatibilities

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

6.3 Shelf life

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

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 Nature and contents of container

The pre-filled syringe presentation consists of:
Two clear type 1 glass pre-filled syringes with polystyrene plunger rod. Each syringe has a nominal content of 5 ml Faslodex solution and is fitted with a tamper evident closure.
Two safety needles (BD SafetyGlide™) for connection to the barrel are also provided.

6.6 Special precautions for disposal and other handling

Instructions for administration

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 section 4.4).

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

For each of the two syringes:

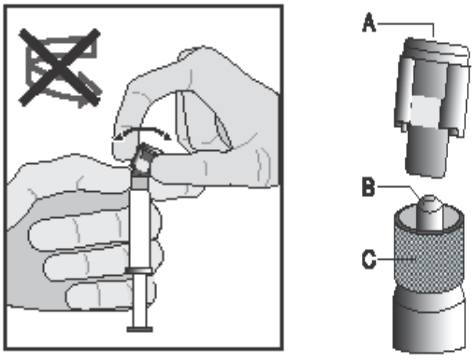
Remove glass syringe barrel from tray and check that it is not damaged.

• Peal open the safety needle (SafetyGlide™) outer packaging.

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

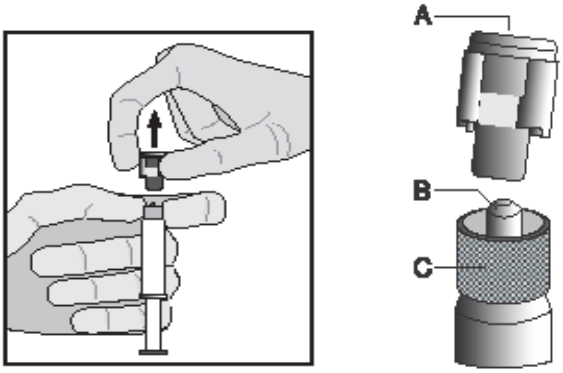
• Hold the syringe upright on the ribbed part (C). With the other hand, take hold of the cap (A) and carefully tilt back and forth until the cap disconnects and can be pulled off, do not twist (see Figure 1).

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 Luer-Lok and twist until firmly seated (see 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.

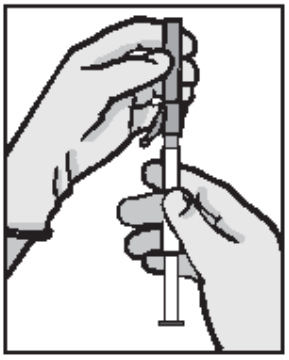


Figure3

• 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).

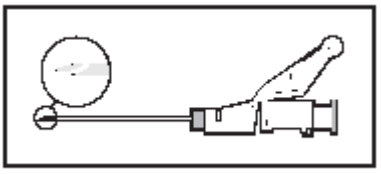


Figure 4

• After injection, immediately apply a single-finger stroke to the activation assisted lever arm to activate the shielding mechanism (see Figure 5).
NOTE: Activate away from self and others. Listen for click and visually confirm needle tip is fully covered.

Figure 5

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.

7. DRUG REGISTRATION NUMBER

132 67 31114-02

8. MANUFACTURER

AstraZeneca UK Limited
Macclesfield, Cheshire, UK.

9. LICENSE HOLDER

AstraZeneca (Israel) Ltd.,
1 Atirei Yeda St.,
Kfar Saba 4464301.

Revised in September 2023 according to MOH guidelines.