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SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
Lynparza 100 mg film-coated tablets
Lynparza 150 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Lynparza 100 mg film-coated tablets
Each film-coated tablet contains 100 mg olaparib.

Lynparza 150 mg film-coated tablets
Each film-coated tablet contains 150 mg olaparib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Film-coated tablet (tablet).

Lynparza 100 mg film-coated tablets
Yellow to dark yellow, oval, bi-convex tablet, debossed with 'OP100' on one side and plain on the other side.

Lynparza 150 mg film-coated tablets
Green to green/grey, oval, bi-convex tablet, debossed with 'OP150' on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Ovarian cancer
Maintenance Treatment of Recurrent Ovarian Cancer:
Lynparza is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.

Germline BRCA-mutated HER2-negative Metastatic Breast Cancer
Lynparza is indicated in patients with deleterious or suspected deleterious *gBRCAm*, HER2-negative metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor (HR)- positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy.

4.2 Posology and method of administration
Treatment with Lynparza should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

Posology
Lynparza is available as 100 mg and 150 mg tablets.

The recommended dose of Lynparza is 300 mg (two 150 mg tablets) taken twice daily, equivalent to a total daily dose of 600 mg. The 100 mg tablet is available for dose reduction.

Ovarian cancer

Patients should start treatment with Lynparza no later than 8 weeks after completion of their final dose of the platinum-containing regimen.

It is recommended that treatment be continued until progression of the underlying disease. There are no data on retreatment with Lynparza following subsequent relapse (see section 5.1).

Important differences in posology between Lynparza tablets and capsules

Lynparza tablets (100 mg and 150 mg) should not be substituted for Lynparza capsules (50 mg) on a milligram-to-milligram basis due to differences in the dosing and bioavailability of each formulation. Therefore, the specific dose recommendations for each formulation should be followed.

Missing dose

If a patient misses a dose of Lynparza, they should take their next normal dose at its scheduled time.

Dose adjustments for adverse reactions

Treatment may be interrupted to manage adverse reactions such as nausea, vomiting, diarrhoea, and anaemia and dose reduction can be considered (see section 4.8).

The recommended dose reduction is to 250 mg (one 150 mg tablet and one 100 mg tablet) twice daily (equivalent to a total daily dose of 500 mg).

If a further dose reduction is required, then reduction to 200 mg (two 100 mg tablets) twice daily (equivalent to a total daily dose of 400 mg) is recommended.

Dose adjustments for co-administration with CYP3A inhibitors

Concomitant use of strong or moderate CYP3A inhibitors is not recommended and alternative agents should be considered. If a strong CYP3A inhibitor must be co-administered, the recommended Lynparza dose reduction is to 100 mg (one 100 mg tablet) taken twice daily (equivalent to a total daily dose of 200 mg). If a moderate CYP3A inhibitor must be co-administered, the recommended Lynparza dose reduction is to 150 mg (one 150 mg tablet) taken twice daily (equivalent to a total daily dose of 300 mg) (see sections 4.4 and 4.5).

Special populations

Elderly

No adjustment in starting dose is required for elderly patients. There are limited clinical data in patients aged 75 years and over.

Renal impairment

For patients with moderate renal impairment (creatinine clearance 31 to 50 ml/min) the recommended dose of Lynparza is 200 mg (two 100 mg tablets) twice daily (equivalent to a total daily dose of 400 mg) (see section 5.2).

Lynparza can be administered in patients with mild renal impairment (creatinine clearance 51 to 80 ml/min) with no dose adjustment.

Lynparza is not recommended for use in patients with severe renal impairment or end-stage renal disease (creatinine clearance ≤ 30 ml/min), as safety and pharmacokinetics have not been studied in these patients. Lynparza may only be used in patients with severe renal impairment if the benefit outweighs the potential risk, and the patient should be carefully monitored for renal function and adverse events.

Hepatic impairment

Lynparza can be administered to patients with mild or moderate hepatic impairment (Child-Pugh classification A or B) with no dose adjustment (see section 5.2). Lynparza is not recommended for use in patients with severe hepatic impairment (Child-Pugh classification C), as safety and pharmacokinetics have not been studied in these patients.

Non-Caucasian patients
There are limited clinical data available in non-Caucasian patients. However, no dose adjustment is required on the basis of ethnicity (see section 5.2).

Patients with performance status 2 to 4
There are very limited clinical data available in patients with performance status 2 to 4.

Paediatric population
.Lynparza tablets is not indicated for children.

Method of administration
Lynparza is for oral use.
Lynparza tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Lynparza tablets may be taken without regard to meals.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Breast-feeding during treatment and for 1 month after the last dose (see section 4.6).

4.4 Special warnings and precautions for use
Haematological toxicity
Haematological toxicity has been reported in patients treated with Lynparza, including clinical diagnoses and/or laboratory findings of generally mild or moderate (CTCAE grade 1 or 2) anaemia, neutropenia, thrombocytopenia and lymphopenia. Patients should not start treatment with Lynparza until they have recovered from haematological toxicity caused by previous anticancer therapy (haemoglobin, platelet and neutrophil levels should be ≤CTCAE grade 1). Baseline testing, followed by monthly monitoring, of complete blood counts is recommended for the first 12 months of treatment and periodically after this time to monitor for clinically significant changes in any parameter during treatment (see section 4.8).

If a patient develops severe haematological toxicity or blood transfusion dependence, treatment with Lynparza should be interrupted and appropriate haematological testing should be initiated. If the blood parameters remain clinically abnormal after 4 weeks of Lynparza dose interruption, bone marro analysis and/or blood cytogenetic analysis are recommended.

Myelodysplastic syndrome/Acute myeloid leukaemia
The incidence of myelodysplastic syndrome/acute myeloid leukaemia (MDS/AML) in patients treated in clinical trials with Lynparza monotherapy, including long-term survival follow-up, was <1.5% and the majority of events had a fatal outcome. The duration of therapy with olaparib in patients who developed MDS/AML varied from <6 months to >2 years; data with longer durations of exposure are limited. All patients had potential contributing factors for the development of MDS/AML, having received previous chemotherapy with platinum agents. Many had also received other DNA damaging agents and radiotherapy. The majority of reports were in germline breast cancer susceptibility gene 1 or 2 (*gBRCA*1/2) mutation carriers. Some of the patients had a history of previous cancer or of bone marrow dysplasia. If MDS and/or AML are confirmed while on treatment with Lynparza, it is recommended that Lynparza should be discontinued and the patient be treated appropriately.

Pneumonitis

Pneumonitis, including events with a fatal outcome, has been reported in <1.0% of patients treated with Lynparza in clinical studies. Reports of pneumonitis had no consistent clinical pattern and were confounded by a number of pre-disposing factors (cancer and/or metastases in lungs, underlying pulmonary disease, smoking history, and/or previous chemotherapy and radiotherapy). If patients present with new or worsening respiratory symptoms such as dyspnoea, cough and fever, or an abnormal chest radiologic finding is observed, Lynparza treatment should be interrupted and prompt investigation initiated. If pneumonitis is confirmed, Lynparza treatment should be discontinued and the patient treated appropriately.

Embryofoetal toxicity
Based on its mechanism of action (PARP inhibition), Lynparza could cause foetal harm when administered to a pregnant woman. Nonclinical studies in rats have shown that olaparib causes adverse effects on embryofoetal survival and induces major foetal malformations at exposures below those expected at the recommended human dose of 300 mg twice daily.

Based on findings from genetic toxicity and animal reproduction studies, advise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment and for 3 months following the last dose of Lynparza

Pregnancy/contraception
Lynparza should not be used during pregnancy and in women of childbearing potential not using reliable contraception during therapy and for 1 month after receiving the last dose of Lynparza (see section 4.6).

Interactions
Lynparza co-administration with strong or moderate CYP3A inhibitors is not recommended (see section 4.5). If a strong or moderate CYP3A inhibitor must be co-administered, the dose of Lynparza should be reduced (see sections 4.2 and 4.5).
Lynparza co-administration with strong or moderate CYP3A inducers is not recommended. In the event that a patient already receiving Lynparza requires treatment with a strong or moderate CYP3A inducer, the prescriber should be aware that the efficacy of Lynparza may be substantially reduced (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction
Pharmacodynamic interactions
Clinical studies of olaparib in combination with other anticancer medicinal products, including DNA damaging agents, indicate a potentiation and prolongation of myelosuppressive toxicity. The recommended Lynparza monotherapy dose is not suitable for combination with myelosuppressive anticancer medicinal products.
Combination of olaparib with vaccines or immunosuppressant agents has not been studied. Therefore, caution should be taken if these medicinal products are co-administered with Lynparza and patients should be closely monitored.

Pharmacokinetic interactions
Effect of other medicinal products on olaparib
CYP3A4/5 are the isozymes predominantly responsible for the metabolic clearance of olaparib.

A clinical study to evaluate the impact of itraconazole, a known CYP3A inhibitor, has shown that co-administration with olaparib increased mean olaparib Cmax by 42% (90% CI: 33-52%) and mean AUC by 170% (90% CI: 144-197%). Therefore, known strong (e.g. itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, boceprevir, telaprevir) or moderate (e.g. erythromycin, diltiazem, fluconazole, verapamil) inhibitors of this isozyme are not recommended with Lynparza (see section 4.4). If strong or moderate CYP3A inhibitors must be co-administered, the dose of Lynparza should be reduced. The recommended Lynparza dose reduction is to 100 mg taken twice daily (equivalent to a total daily dose of 200 mg) with a strong CYP3A inhibitor or 150 mg taken twice daily

(equivalent to a total daily dose of 300 mg) with a moderate CYP3A inhibitor (see sections 4.2 and 4.4). It is also not recommended to consume grapefruit juice while on Lynparza therapy as it is a CYP3A inhibitor.

A clinical study to evaluate the impact of rifampicin, a known CYP3A inducer, has shown that co-administration with olaparib decreased olaparib mean Cmax by 71% (90% CI: 76-67%) and mean AUC by 87% (90% CI: 89-84%). Therefore, known strong inducers of this isozyme (e.g. phenytoin, rifampicin, rifapentine, carbamazepine, nevirapine, phenobarbital, and St John's Wort) are not recommended with Lynparza, as it is possible that the efficacy of Lynparza could be substantially reduced. The magnitude of the effect of moderate to strong inducers (e.g. efavirenz, rifabutin) on olaparib exposure is not established, therefore the co-administration of Lynparza with these medicinal products is also not recommended (see section 4.4).

Effect of olaparib on other medicinal products
Olaparib inhibits CYP3A4 *in vitro* and is predicted to be a mild CYP3A inhibitor *in vivo*. Therefore, caution should be exercised when sensitive CYP3A substrates or substrates with a narrow therapeutic margin (e.g. simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine) are combined with olaparib. Appropriate clinical monitoring is recommended for patients receiving CYP3A substrates with a narrow therapeutic margin concomitantly with olaparib.

Induction of CYP1A2, 2B6 and 3A4 has been shown *in vitro* with CYP2B6 being most likely to be induced to a clinically relevant extent. The potential for olaparib to induce CYP2C9, CYP2C19 and P-gp can also not be excluded. Therefore, olaparib upon co-administration may reduce the exposure to substrates of these metabolic enzymes and transport protein. The efficacy of some hormonal contraceptives may be reduced if co-administered with olaparib (see sections 4.4 and 4.6).
In vitro, olaparib inhibits the efflux transporter P-gp (IC50 = 76 μM), therefore it cannot be excluded that olaparib may cause clinically relevant drug interactions with substrates of P-gp (e.g. simvastatin, pravastatin, dabigatran, digoxin and colchicine). Appropriate clinical monitoring is recommended for patients receiving this type of medicinal product concomitantly.

In vitro, olaparib has been shown to be an inhibitor of BCRP, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K. It cannot be excluded that olaparib may increase the exposure to substrates of BCRP (e.g. methotrexate, rosuvastatin), OATP1B1 (e.g. bosentan, glibenclamide, repaglinide, statins and valsartan), OCT1 (e.g. metformin), OCT2 (e.g. serum creatinine), OAT3 (e.g. furosemide and methotrexate), MATE1 (e.g. metformin) and MATE2K (e.g. metformin). In particular, caution shouldbe exercised if olaparib is administered in combination with any statin.

Combination with anastrozole, letrozole and tamoxifen
A clinical study has been performed to assess the combination of olaparib with anastrozole, letrozole or tamoxifen. No significant interaction was observed with anastrozole or letrozole whereas tamoxifen decreased exposure to olaparib by 27%. The clinical relevance of this effect is unknown. Olaparib does not affect the pharmacokinetics of tamoxifen.

4.6 Fertility, pregnancy and lactation
Women of childbearing potential/contraception in females
Women of childbearing potential should not become pregnant while on Lynparza and not be pregnant at the beginning of treatment. A pregnancy test should be performed on all women of childbearing potential prior to treatment. Women of childbearing potential must use effective contraception during therapy and for 1 month after receiving the last dose of Lynparza (see section 4.4). Since it cannot be excluded that olaparib may reduce exposure to substrates of CYP2C9 through enzyme induction, the efficacy of some hormonal contraceptives may be reduced if co-administered with olaparib. Therefore,
an additional non-hormonal contraceptive method and regular pregnancy tests should be considered during treatment (see section 4.5).

Pregnancy
Studies in animals have shown reproductive toxicity including serious teratogenic effects and effects on embryofoetal survival in the rat at maternal systemic exposures lower than those in humans at therapeutic doses (see section 5.3). There are no data from the use of olaparib in pregnant women, however, based on the mode of action of olaparib, Lynparza should not be used during pregnancy and in women of childbearing potential not using reliable contraception during therapy and for 1 month after receiving the last dose of Lynparza. (See previous paragraph: "Women of childbearing potential/contraception in females" for further information about birth control and pregnancy testing.)

Males
Based on findings in genetic toxicity and animal reproduction studies, advise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment and for 3 months following the last dose of Lynparza. Advise male patients not to donate sperm during therapy and for 3 months following the last dose of Lynparza

Breast-feeding
There are no animal studies on the excretion of olaparib in breast milk. It is unknown whether olaparib/or its metabolites are excreted in human milk. Lynparza is contraindicated during breast-feeding and for 1 month after receiving the last dose, given the pharmacologic property of the product (see section 4.3).

Fertility
There are no clinical data on fertility. In animal studies, no effect on conception was observed but there are adverse effects on embryofoetal survival (see section 5.3).

4.7 Effects on ability to drive and use machines
Lynparza has moderate influence on the ability to drive and use machines. Patients who take Lynparza may experience fatigue, asthenia or dizziness. Patients who experience these symptoms should observe caution when driving or using machines.

4.8 Undesirable effects

Ovarian Cancer

Summary of the safety profile
Lynparza monotherapy has been associated with adverse reactions generally of mild or moderate severity (CTCAE 1 or 2) and generally not requiring treatment discontinuation. The most frequently observed adverse reactions across clinical trials in patients receiving Lynparza monotherapy (≥ 10%) were nausea, vomiting, diarrhoea, dyspepsia, fatigue, headache, dysgeusia, decreased appetite, dizziness, and anaemia.

Tabulated list of adverse reactions
The safety profile is based on pooled data from 1,248 patients treated with Lynparza monotherapy in clinical trials in the therapeutic indication at the recommended dose.
The following adverse reactions have been identified in clinical trials with patients receiving Lynparza monotherapy where patient exposure is known. Adverse drug reactions are listed by MedDRA System Organ Class (SOC) and then by MedDRA preferred term in Table 1. Within each SOC, preferred terms are arranged by decreasing frequency and then by decreasing seriousness. Frequencies of occurrence of adverse reactions are defined as: very common (≥ 1/10); common (□□1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1000); very rare (< 1/10,000); not known (cannot be estimated from available data).

Table 1 Tabulated list of adverse reactions:

	Adverse reactions	
MedDRA System Organ Class	**Frequency of All CTCAE grades**	**Frequency of CTCAE grade 3 and above**
Blood and lymphatic system disorders	**Very common** Anaemia[a] **Common** Neutropenia[a], Thrombocytopenia[a], Leukopenia[a] **Uncommon** Lymphopenia	**Very common** Anaemia[a] **Common** Neutropenia[a], Thrombocytopenia[a], Leukopenia[a] **Uncommon** Lymphopenia
Immune system disorders	**Common** Rash[a] **Uncommon** Hypersensitivity[a], Dermatitis[a]	-
Metabolism and nutrition disorders	**Very common** Decreased appetite	**Uncommon** Decreased appetite
Nervous system disorders	**Very common** Dizziness, Headache, Dysgeusia	**Uncommon** Dizziness, Headache
Respiratory, thoracic and mediastinal disorders	**Very common** Cough[a]	**Uncommon** Cough[a]
Gastrointestinal disorders	**Very common** Vomiting, Diarrhoea, Nausea, Dyspepsia **Common** Stomatitis, Upper abdominal pain	**Common** Vomiting, Diarrhoea, Nausea **Uncommon** Stomatitis, Upper abdominal pain
General disorders and administration site conditions	**Very common** Fatigue (including asthenia)	**Common** Fatigue (including asthenia)
Investigations	**Common** Increase in blood creatinine **Uncommon** Mean corpuscular volume elevation[b]	**Uncommon** Increase in blood creatinine

[a] Anaemia includes preferred terms (PTs) of anaemia, haemoglobin decreased, red blood cell count decreased, erythropenia and haematocrit decreased; Neutropenia includes PTs of neutropenia, granulocytopenia, granulocyte count decreased and neutrophil count decreased, febrile neutropenia, neutropenic infection and neutropenic sepsis; Thrombocytopenia includes PTs of thrombocytopenia, platelet count decreased, platelet production decreased and

plateletcrit decreased; Leukopenia includes PTs of leukopenia and white blood cell count decreased; Cough includes PTs of cough and productive cough; Rash includes PTs of rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, exfoliative rash and generalised erythema; Hypersensitivity includes
PTs of hypersensitivity and drug hypersensitivity; Dermatitis includes PTs of dermatitis, dermatitis allergic and dermatitis exfoliative.
[b] Represents the incidence of laboratory findings of elevations in mean corpuscular volume from baseline to above the upper limit of normal (ULN), not of reported adverse reactions.

Description of selected adverse reactions
Haematological toxicity
Anaemia and other haematological toxicities were generally low grade (CTCAE grade 1 or 2), however, there were reports of CTCAE grade 3 and higher events. Anaemia was the most common CTCAE grade ≥3 adverse reaction reported in clinical studies. Median time to first onset of anaemia was approximately 4 weeks (approximately 7 weeks for CTCAE grade ≥3 events). Anaemia was managed with dose interruptions and dose reductions (see section 4.2), and where appropriate with blood transfusions. In SOLO2, the incidence of anaemia adverse reactions was 43.6% (CTCAE grade ≥3 19.5%) and the incidences of dose interruptions, reductions and discontinuations for anaemia were 16.9%, 8.2% and 3.1%, respectively; 17.9% of patients treated with olaparib needed one or more blood transfusions. An exposure-response relationship between olaparib and decreases in haemoglobin has been demonstrated. In clinical studies with Lynparza the incidence of CTCAE grade ≥ 2 shifts (decreases) from baseline in haemoglobin was 20%, absolute neutrophils 15%, platelets 5%, lymphocytes 30% and leucocytes 20% (all % approximate).

The incidence of elevations in mean corpuscular volume from low or normal at baseline to above the ULN was approximately 55%. Levels appeared to return to normal after treatment discontinuation and did not appear to have any clinical consequences.

Baseline testing, followed by monthly monitoring of complete blood counts is recommended for the first 12 months of treatment and periodically after this time to monitor for clinically significant changes in any parameter during treatment which may require dose interruption or reduction and/or further treatment (see sections 4.2 and 4.4).

Other laboratory findings
In clinical studies with Lynparza the incidence of CTCAE grade ≥ 2 shifts (elevations) from baseline in blood creatinine was approximately 15%. Data from a double-blind placebo-controlled study showed median increase up to 23% from baseline remaining consistent over time and returning to baseline after treatment discontinuation, with no apparent clinical sequelae. 90% of patients had creatinine values of CTCAE grade 0 at baseline and 10% were CTCAE grade 1 at baseline.

Nausea and vomiting
Nausea was generally reported very early, with first onset within the first month of Lynparza treatment in the majority of patients. Vomiting was reported early, with first onset within the first two months of Lynparza treatment in the majority of patients. Both nausea and vomiting were reported to be intermittent for the majority of patients and can be managed by dose interruption, dose reduction and/or antiemetic therapy. Antiemetic prophylaxis is not required.

Treatment of *gBRCAm* HER2-negative Metastatic Breast Cancer
OlympiAD
The safety of Lynparza tablets as monotherapy was also evaluated in *gBRCAm* patients with HER2-negative metastatic breast cancer who had previously received up to two lines of chemotherapy for the treatment of metastatic disease in OlympiAD. This study was a randomized, open-label, multi-center study in which 296 patients received either Lynparza 300 mg twice daily (n=205) or a chemotherapy(capecitabine, eribulin, or vinorelbine) of the healthcare provider's choice (n=91) until disease progression or unacceptable toxicity.

The median duration of study treatment was 8.2 months in patients who received Lynparza and 3.4 months in patients who received chemotherapy. Dose interruptions due to an adverse reaction of any grade occurred in 35% of patients receiving Lynparza and 28% of those receiving chemotherapy; dose reductions due to an adverse reaction occurred in 25% of Lynparza patients and 31% of chemotherapy patients. Discontinuation occurred in 5% of Lynparza patients and 8% in chemotherapy patients.
Table 2 summarizes the adverse reactions that occurred in at least 20% of patients who received Lynparza in OlympiAD. Table 3 presents the laboratory abnormalities that occurred in at least 25% of patients who received Lynparza in OlympiAD.

Table 2 Adverse Reactions[a] in OlympiAD (≥20% of Patients Who Received Lynparza)

Adverse Reactions	**Lynparza tablets n=205**		**Chemotherapy n=91**	
	Grades 1-4 %	**Grades 3-4 %**	**Grades 1-4 %**	**Grades 3-4 %**
Blood and lymphatic disorders				
Anemia[b]	40	16	26	4
Leukopenia[c]	25	5	31	13
Neutropenia[d]	27	9	50	26
Gastrointestinal disorders				
Nausea	58	0	35	1
Vomiting	30	0	15	1
Diarrhea	21	1	22	0
Infections and infestations				
Respiratory tract infection[e]	27	1	22	0
General disorders and administration site conditions				
Fatigue (including asthenia)	37	4	36	1
Nervous system disorders				
Headache	20	1	15	2

a. Graded according to NCI CTCAE 4.0.
b. Represents grouped terms consisting of anemia (anemia erythropenia, hematocrit decreased, hemoglobin decreased and red blood cell count decreased).
c. Represents grouped terms consisting of leukopenia (leukopenia and white blood cell count decreased).
d. Represents grouped terms consisting of neutropenia (febrile neutropenia, granulocyte count decreased, granulocytopenia, neutropenia, neutropenic infection, neutropenic sepsis, neutrophil count decreased).
e. Represents grouped terms consisting of bronchitis, influenza, lower respiratory tract infection, nasopharyngitis, pharyngitis, respiratory tract infection, rhinitis, sinusitis, upper respiratory tract infection, upper respiratory tract infection bacterial.

In addition, adverse reactions in OlympiAD that occurred in <20% of patients receiving Lynparza were cough, decreased appetite, thrombocytopenia, dysgeusia, lymphopenia, dizziness, dyspepsia, stomatitis, upper abdominal pain, rash, increase in serum creatinine and dermatitis.

Table 3 Laboratory Abnormalities Reported ≥25% of Patients in OlympiAD

Laboratory Parameter[a]	**Lynparza tablets n[b]= 205**		**Chemotherapy n[b]= 91**	
	Grades 1-4 %	**Grades 3-4 %**	**Grades 1-4 %**	**Grades 3-4 %**
Increase in mean corpuscular volume[c]	71	-	33	-
Decrease in hemoglobin	82	17	66	3
Decrease in leukocytes	71	8	70	23
Decrease in lymphocytes	73	21	63	3

Decrease in absolute neutrophil count	46	11	65	38
Decrease in platelets	33	3	28	0

a. Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.
b. This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.
c. Represents the proportion of subjects whose mean corpuscular volume was > ULN.

Other special populations
Limited safety data are available in elderly (age 75 ≥ years) and non-Caucasian patients.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il)

4.9 Overdose
There is limited experience of overdose with olaparib. No unexpected adverse reactions were reported in a small number of patients who took a daily dose of up to 900 mg of olaparib tablets over two days. Symptoms of overdose are not established and there is no specific treatment in the event of Lynparza overdose. In the event of an overdose, physicians should follow general supportive measures and should treat the patient symptomatically.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: antineoplastic agents, other antineoplastic agents, ATC code: L01XX46

Mechanism of action and pharmacodynamic effects
Olaparib is a potent inhibitor of human poly (ADP-ribose) polymerase enzymes (PARP-1, PARP-2, and PARP-3), and has been shown to inhibit the growth of selected tumour cell lines *in vitro* and tumour growth *in vivo* either as a standalone treatment or in combination with established chemotherapies.

PARPs are required for the efficient repair of DNA single strand breaks and an important aspect of PARP-induced repair requires that after chromatin modification, PARP auto-modifies itself and dissociates from the DNA to facilitate access for base excision repair (BER) enzymes. When olaparib is bound to the active site of DNA-associated PARP it prevents the dissociation of PARP and traps it on the DNA, thus blocking repair. In replicating cells this also leads to the formation of DNA double-strand breaks (DSBs) when replication forks meet the PARP-DNA adducts. In normal cells, homologous recombination repair (HRR) pathway is effective at repairing these DNA DSBs. In cancers that lack functional components of HRR such as BRCA1 or 2, DNA DSBs cannot be repaired
accurately or effectively. Instead, alternative and error-prone pathways are activated, such as the classical non-homologous end joining (NHEJ) pathway, leading to increased genomic instability. After a number of rounds of replication, genomic instability can reach insupportable levels and result in cancer cell death, as cancer cells already have a high DNA damage load relative to normal cells. In the absence of *BRCA1* or *BRCA2* mutations, HRR pathway may be compromised by other mechanisms, although the causative aberrancy and penetrance are not fully elucidated. Absence of fully functional HRR pathway is one of the key determinants of platinum sensitivity in ovarian and other cancers.

In *BRCA1/2*-deficient *in vivo* models, olaparib given after platinum treatment resulted in a delay in tumour progression and an increase in overall survival compared to platinum treatment alone that correlated with the period of olaparib maintenance treatment.

Detection of *BRCA1/2* mutation

If *BRCA1/2* mutation status is determined, it should be conducted by an experienced laboratory using a validated test method.

Genetic counselling for patients tested for mutations in breast cancer susceptibility genes 1/2 (BRCA1/2) should be performed according to local regulations.

Clinical efficacy and safety

SOLO2 study (D0816C00002)

The safety and efficacy of olaparib as maintenance therapy were studied in a Phase III randomised, double-blind, placebo-controlled trial in patients with germline *BRCA1/2*-mutated platinum-sensitive relapsed (PSR) ovarian, fallopian tube or primary peritoneal cancer. The study compared the efficacy of Lynparza maintenance treatment (300 mg [2 x 150 mg tablets] twice daily) taken until progression with placebo treatment in 295 patients with high-grade serous or endometrioid PSR ovarian cancer (2:1 randomisation: 196 olaparib and 99 placebo) who were in response (CR [complete response] or PR [partial response]) following completion of platinum-containing chemotherapy.

Patients who have received two or more platinum-containing regimens and whose disease had recurred > 6 months after completion of penultimate platinum-based chemotherapy were enrolled. Patients could not have received prior olaparib or other PARP inhibitor treatment. Patients could have received prior bevacizumab, except in the regimen immediately prior to randomisation.

All patients had evidence of germline *BRCA1/2* mutation (*gBRCA1/2m*) at baseline. Patients with *BRCA1/2* mutations were identified either from germline testing in blood via a local test or the Myriad CLIA Integrated BRAC*Analysis*® test or from testing a tumour sample using a local test. Large rearrangements in the *BRCA1/2* genes were detected in 4.7% (14/295) of the randomised patients.

Demographic and baseline characteristics were generally well balanced between the olaparib and placebo arms. Median age was 56 years in both arms. Ovarian cancer was the primary tumour in > 80% of the patients. The most common histological type was serous (> 90%), endometrioid histology was reported in 6% of the patients. In the olaparib arm 55% of the patients had only 2 prior lines of treatment with 45% receiving 3 or more prior lines of treatment. In the placebo arm 61% of patients had received only 2 prior lines with 39% receiving 3 or more prior lines of treatment. Most patients were ECOG performance status 0 (81%). Platinum free interval was > 12 months in 60% and > 6-12 months in 40% of the patients. Response to prior platinum chemotherapy was complete in 47% and partial in 53% of the patients. In the olaparib and placebo arms, 17% and 20% of patients had prior bevacizumab, respectively.

The primary endpoint was progression free survival (PFS) determined by investigator assessment using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Secondary efficacy endpoints included time from randomisation to second progression or death (PFS2); OS (overall survival), time from randomisation to discontinuation of treatment or death (TDT), time from randomisation to first subsequent anti-cancer therapy or death (TFST), time from randomisation to start of second subsequent anti-cancer therapy or death (TSST); and health related quality of life (HRQoL).

The study met its primary objective demonstrating a statistically significant improvement in investigator assessed PFS for olaparib compared with placebo with a hazard ratio (HR) of 0.30 (95% CI 0.22-0.41; $p<0.0001$; median 19.1 months olaparib vs 5.5 months placebo). The investigator assessment of PFS was supported with a blinded independent central radiological review of PFS (HR 0.25; 95% CI 0.18-0.35; $p<0.0001$; median 30.2 months for olaparib and 5.5 months placebo). At 2 years, 43% olaparib-treated patients remained progression free compared with only 15% placebo-treated patients.

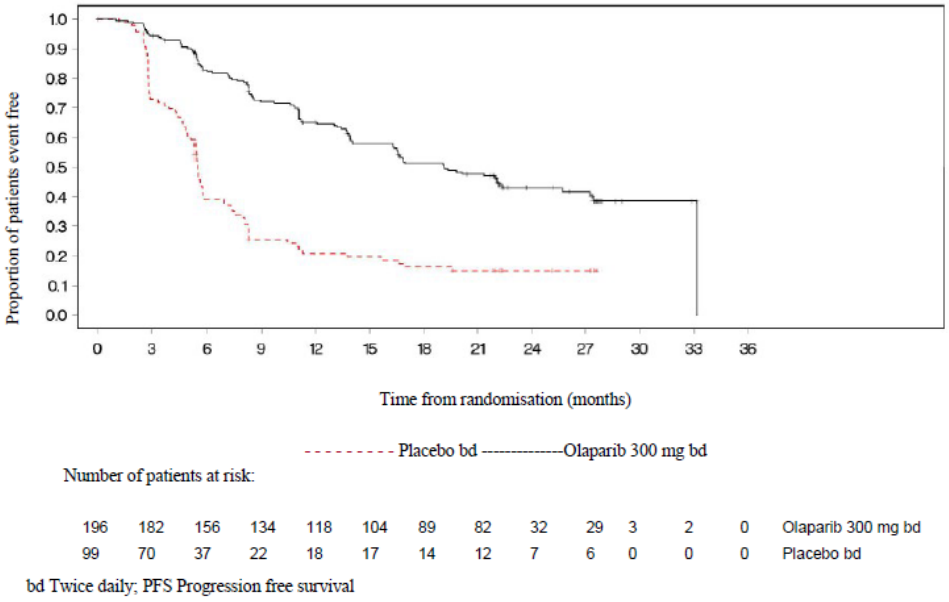
A summary of the primary objective outcome for patients with g*BRCA1/2m* PSR ovarian cancer in SOLO2 is presented in Table 2 and Figure 1.

Table 2 Summary of primary objective outcome for patients with g*BRCA1/2m* PSR ovarian cancer in SOLO2

	Olaparib 300 mg tablet bd	Placebo
PFS (63% maturity)		
Number of events: Total number of patients (%)	107:196 (55)	80:99 (81)
Median time (months) (95% CI)	19.1 (16.3-25.7)	5.5 (5.2-5.8)
HR (95% CI) [a]	0.30 (0.22-0.41)	
P value (2-sided)	p<0.0001	

[a] HR= Hazard Ratio. A value <1 favours olaparib. The analysis was performed using a log-rank test stratified by response to previous platinum chemotherapy (CR or PR), and time to disease progression (>6-12 months and >12 months) in the penultimate platinum-based chemotherapy.
bd Twice daily; PFS progression-free survival; CI confidence interval;

Figure 1 SOLO2: Kaplan-Meier plot of PFS in patients with g*BRCA1/2m* PSR ovarian cancer (63% maturity - investigator assessment)



bd Twice daily; PFS Progression free survival

The secondary endpoints TFST and PFS2 demonstrated a persistent and statistically significant improvement for olaparib compared with placebo (Table 3).

Table 3 Summary of key secondary objective outcomes for patients with g*BRCA1/2m* PSR ovarian cancer in SOLO2

	Olaparib 300 mg tablet bd	Placebo
TFST (58% maturity)		
Number of events: Total number of patients (%)	92:196 (47)	79:99 (80)
Median time (months) (95% CI)	27.9 (22.6-NR)	7.1 (6.3-8.3)
HR (95% CI) a	0.28 (0.21-0.38)	
P value* (2-sided)	p<0.0001	
PFS2 (40% maturity)		
Number of events: Total number of patients (%)	70:196 (36)	49:99 (50)
Median time (months) (95% CI)	NR (24.1-NR)	18.4 (15.4-22.8)
HR (95% CI) a	0.50 (0.34-0.72)	
P value (2-sided)	p=0.0002	

* Not controlled for multiplicity
[a] HR= Hazard Ratio. A value <1 favours olaparib. The analysis was performed using a log-rank test stratified by response to previous platinum chemotherapy (CR or PR), and time to disease progression (>6-12 months and >12 months) in the penultimate platinum-based chemotherapy.
bd Twice daily; NR not reached; CI confidence interval; PFS2 time from randomisation to second progression or death; TFST Time from randomisation to start of first subsequent therapy or death.

Among the patients entering the trial with measurable disease (target lesions at baseline), an objective response rate of 41% was achieved in the Lynparza arm versus 17% on placebo. Of patients treated with Lynparza, who entered the study with evidence of disease (target or non-target lesions at baseline), 15.0% experienced complete response compared with 9.1% of patients on placebo.

At the time of the analysis of PFS the median duration of treatment was 19.4 months for olaparib and 5.6 months for placebo. The majority of patients remained on the 300 mg bd starting dose of olaparib. The incidence of dose interruptions, reductions, discontinuations due to an adverse event was 45.1%, 25.1% and 10.8%, respectively. Dose interruptions occurred most frequently in the first 3 months and dose reductions in the first 3-6 months of treatment. The most frequent adverse reactions leading to dose interruption or dose reduction were anaemia, nausea and vomiting.

Patient-reported outcome (PRO) data indicate no difference for the olaparib-treated patients as compared to placebo as assessed by the change from baseline in the Trial Outcome Index (TOI) of the Functional Assessment of Cancer Therapy – Ovarian (FACT-O).

Study 19 (D0810C00019)
The safety and efficacy of olaparib as a maintenance therapy in the treatment of PSR ovarian, including fallopian tube or primary peritoneal cancer patients, following treatment with two or more platinum containing regimens, were studied in a large Phase II randomised, double-blind, placebo-controlled trial (study 19). The study compared the efficacy of Lynparza capsule maintenance treatment (400 mg [8 x 50 mg capsules] twice daily) taken until progression with placebo treatment in 265 (136 olaparib and 129 placebo) PSR high grade serous ovarian cancer patients who were in response (CR or PR) following completion of platinum-containing chemotherapy. The primary endpoint was PFS based on investigator assessment using RECIST 1.0. Secondary efficacy endpoints included OS, disease control rate (DCR) defined as confirmed CR/PR + SD (stable disease), HRQoL and disease related symptoms. Exploratory analyses of TFST and TSST were also performed.
Patients whose disease had recurred >6 months after completion of penultimate platinum-based chemotherapy were enrolled. Enrolment did not require evidence of *BRCA1/2* mutation (*BRCA* mutation status for some patients was determined retrospectively). Patients could not have received prior olaparib or other PARP inhibitor treatment. Patients could have received prior bevacizumab, except in the regimen immediately prior to randomisation. Retreatment with olaparib was not permitted following progression on olaparib.

Patients with *BRCA1/2* mutations were identified either from germline testing in blood via a local test or the Myriad CLIA Integrated BRACAnalysis® test or from testing a tumour sample using a test performed by Foundation Medicine. Large rearrangements in the *BRCA1/2* genes were detected in 7.4% (10/136) of the randomised patients.

Demographic and baseline characteristics were generally well balanced between the olaparib and placebo arms. Median age was 59 years in both arms. Ovarian cancer was the primary tumour in 86% of the patients. In the olaparib arm 44% of the patients had only 2 prior lines of treatment with 56% receiving 3 or more prior lines of treatment. In the placebo arm 49% of patients had received only 2 prior lines with 51% receiving 3 or more prior lines of treatment. Most patients were ECOG performance status 0 (77%). Platinum free interval was > 12 months in 60% and > 6-12 months in 40% of the patients. Response to prior platinum chemotherapy was complete in 45% and partial in 55% of the patients. In the olaparib and placebo arms, 6% and 5% of patients had prior bevacizumab, respectively.

The study met its primary objective demonstrating a statistically significant improvement in PFS for olaparib compared with placebo in the overall population with a HR of 0.35 (95% CI 0.25-0.49; p<0.00001; median 8.4 months olaparib vs 4.8 months placebo). At the final OS analysis (data cut off [DCO] 9 May 2016) at 79% maturity, the hazard ratio comparing olaparib with placebo was 0.73 (95% CI 0.55-0.95; p=0.02138 [did not meet pre-specified significance level of < 0.0095]; median 29.8 months olaparib versus 27.8 months placebo). In the olaparib-treated group, 23.5% (n=32/136) of patients remained on treatment for ≥2 years as compared with 3.9% (n=5/128) of the patients on placebo. Although patient numbers were limited, 13.2% (n=18/136) of the patients in the olaparib-treated group remained on treatment for ≥5 years as compared with 0.8% (n=1/128) in the placebo group.

Preplanned subgroup analysis identified patients with *BRCA1/2*-mutated ovarian cancer (n=136, 51.3%; including 20 patients identified with a somatic tumour *BRCA1/2* mutation) as the subgroup that derived the greatest clinical benefit from olaparib maintenance monotherapy. A benefit was also observed in patients with *BRCA1/2* wild-type/variants of uncertain significance (*BRCA1/2 wt*/VUS), although of a lesser magnitude. There was no strategy for multiple testing in place for the sub-group analyses.

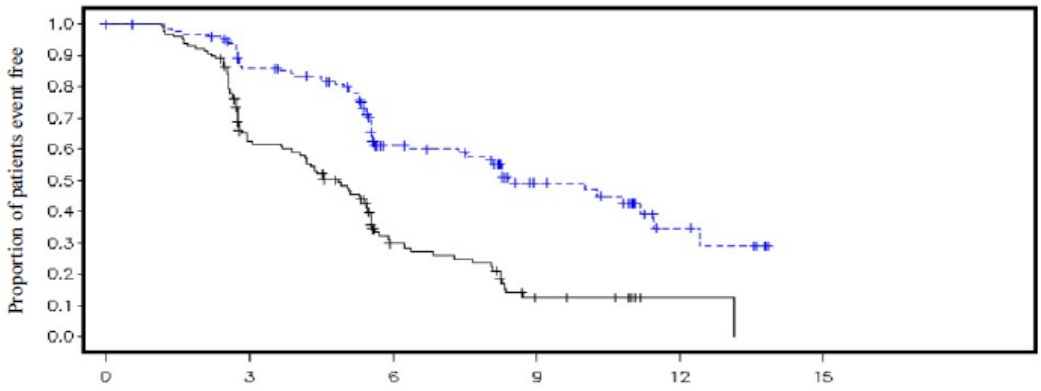
A summary of the primary objective outcome for patients with *BRCA1/2*-mutated and *BRCA1/2 wt*/VUS PSR ovarian cancer in Study 19 is presented in Table 4 and for all patients in Study 19 in Table 4 and Figure 2.

Table 4 Summary of primary objective outcome for all patients and patients with *BRCA1/2*-mutated and *BRCA1/2 wt*/VUS PSR ovarian cancer in study 19

	All patients[a]		***BRCA1/2*-mutated**		***BRCA1/2 wt*/VUS**	
	Olaparib 400 mg capsule bd	**Placebo**	**Olaparib 400 mg capsule bd**	**Placebo**	**Olaparib 400 mg capsule bd**	**Placebo**
PFS – DCO 30 June 2010						
Number of events: Total number of patients (%)	60:136 (44)	94:129 (73)	26:74 (35)	46:62 (74)	32:57 (56)	44:61 (72)
Median time (months) (95% CI)	8.4 (7.4-11.5)	4.8 (4.0-5.5)	11.2 (8.3-NR)	4.3 (3.0-5.4)	7.4 (5.5-10.3)	5.5 (3.7-5.6)
HR (95% CI) [b]	0.35 (0.25-0.49)		0.18 (0.10–0.31)		0.54 (0.34-0.85)	
P value (2-sided)	p<0.00001		p<0.00001		p=0.00745	

[a] All patients comprises of the following subgroups: *BRCA1/2*-mutated, *BRCA1/2 wt*/VUS and *BRCA1/2* status unknown (11 patients with status unknown, not shown as a separate subgroup in table).
[b] HR= Hazard Ratio. A value <1 favours olaparib. The analysis was performed using a Cox proportional hazards model with factors for treatment, ethnic descent, platinum sensitivity and response to final platinum therapy.
bd Twice daily; PFS progression-free survival; DCO data cut off; CI confidence interval; NR not reached.

Figure 2 Study 19: Kaplan-Meier plot of PFS in the FAS (58% maturity – investigator assessment) DCO 30 June 2010



Time from randomisation (months)

----------Placebo bd - - - - - - - - - Olaparib 400 mg bd

Number of patients at risk:

136	106	53	24	7	0	Olaparib 400 mg bd
129	72	24	7	1	0	Placebo

bd Twice daily; DCO Data cut-off; FAS Full analysis set; PFS progression-free survival

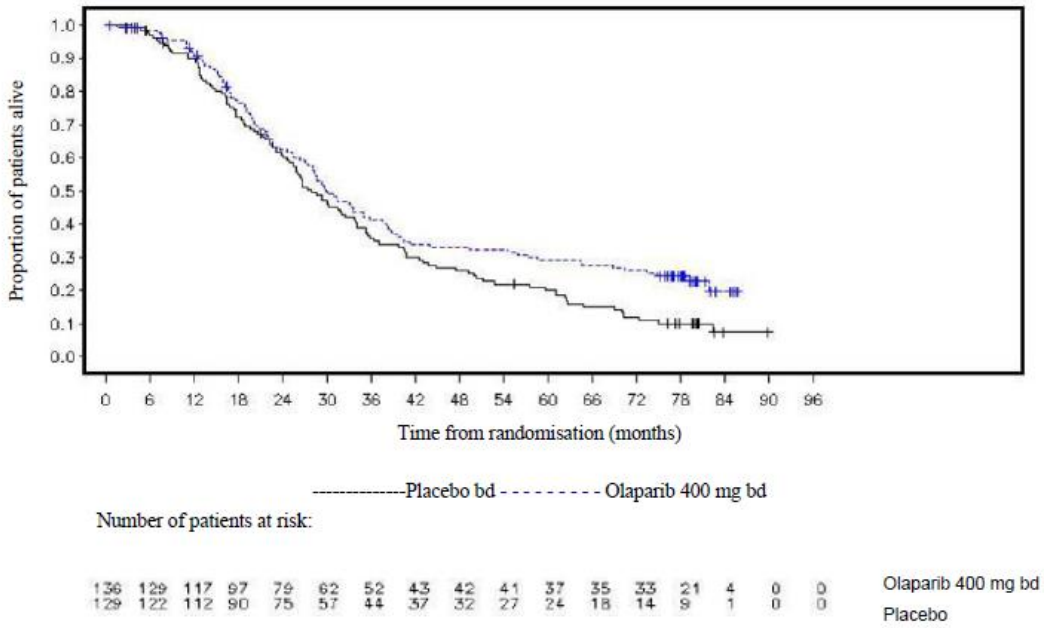
A summary of key secondary objective outcomes for patients with *BRCA1/2*-mutated and *BRCA1/2 wt*/VUS PSR ovarian cancer in Study 19 is presented in Table 5 and for all patients in Study 19 in Table 5 and Figure 3.

Table 5 Summary of key secondary objective outcomes for all patients and patients with *BRCA1*/2-mutated and *BRCA1/2* wt/VUS PSR ovarian cancer in study 19

	All patients[a]		*BRCA1/2*-mutated		*BRCA1/2 wt*/VUS	
	Olaparib 400 mg capsule bd	**Placebo**	**Olaparib 400 mg capsule bd**	**Placebo**	**Olaparib 400 mg capsule bd**	**Placebo**
OS - DCO 09 May 2016						
Number of events: Total number of patients (%)	98:136 (72)	112:129 (87)	49:74 (66)	50:62 (81) [c]	45:57 (79)	57:61 (93)
Median time (months) (95% CI)	29.8 (26.9-35.7)	27.8 (24.9-33.7)	34.9 (29.2-54.6)	30.2 (23.1-40.7)	24.5 (19.8-35.0)	26.6 (23.1-32.5)
HR (95% CI)[b]	0.73 (0.55–0.95)		0.62 (0.42–0.93)		0.84 (0.57-1.25)	
P value* (2-sided)	p=0.02138		p=0.02140		p=0.39749	
TFST – DCO 09 May 2016						
Number of events: Total number of patients (%)	106:136 (78)	124:128 (97)	55:74 (74)	59:62 (95)	47:57 (83)	60:61 (98)
Median time (months) (95% CI)	13.3 (11.3-15.7)	6.7 (5.7-8.2)	15.6 (11.9-28.2)	6.2 (5.3-9.2)	12.9 (7.8-15.3)	6.9 (5.7-9.3)
HR (95% CI)[b]	0.39 (0.30–0.52)		0.33 (0.22-0.49)		0.45 (0.30-0.66)	
P value* (2-sided)	p<0.00001		p<0.00001		p=0.00006	

* There was no strategy for multiple testing in place for the sub-group analyses or for the all patients TFST.
[a] All patients comprises of the following subgroups: *BRCA1/2*-mutated, *BRCA1/2 wt*/VUS and *BRCA1/2* status unknown (11 patients with status unknown, not shown as a separate subgroup in table).
[b] HR= Hazard Ratio. A value <1 favours olaparib. The analysis was performed using a Cox proportional hazards model with factors for treatment, ethnic descent, platinum sensitivity and response to final platinum therapy.
[c] Approximately a quarter of placebo-treated patients in the *BRCA*-mutated subgroup (14/62; 22.6%) received a subsequent PARP inhibitor.
bd Twice daily; OS Overall survival; DCO data cut off; CI confidence interval; TFST time from randomisation to start of first subsequent therapy or death.

Figure 3 Study 19: Kaplan Meier plot of OS in the FAS (79% maturity) DCO 09 May 2016



bd Twice daily; DCO Data cut off; FAS Full analysis set; OS Overall survival

At the time of the analysis of PFS the median duration of treatment was 8 months for olaparib and 4 months for placebo. The majority of patients remained on the 400 mg bd starting dose of olaparib. The incidence of dose interruptions, reductions, discontinuations due to an adverse event was 34.6%, 25.7% and 5.9%, respectively. Dose interruptions and reductions occurred most frequently in the first 3 months of treatment. The most frequent adverse reactions leading to dose interruption or dose Olaparib 400 mg bd Placebo Proportion of patients alive reduction were nausea, anaemia, vomiting, neutropenia and fatigue. The incidence of anaemia adverse reactions was 22.8% (CTCAE grade ≥3 7.4%).

Patient-reported outcome (PRO) data indicate no difference for the olaparib-treated patients as compared to placebo as measured by improvement and worsening rates in the Trial Outcome Index (TOI) and Functional Analysis of Cancer Therapy–Ovarian total score (FACT-O total).

Treatment of *gBRCAm* HER2-negative Metastatic Breast Cancer

OlympiAD

OlympiAD (NCT02000622) was an open-label study in which patients (n=302) with *gBRCAm* HER2-negative metastatic breast cancer were randomized 2:1 to receive Lynparza 300 mg tablets or healthcare provider's choice of chemotherapy (capecitabine, eribulin, or vinorelbine, at standard doses) until progression or unacceptable toxicity. Randomization was stratified by prior use of chemotherapy for metastatic disease (yes vs no), hormone receptor status (hormone receptor positive vs triple negative), and previous use of platinum-based chemotherapy (yes vs no). Patients were required to have received treatment with an anthracycline (unless contraindicated) and a taxane, in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor-positive disease must have progressed on at least 1 endocrine therapy (adjuvant or metastatic), or have disease that the treating healthcare provider believed to be inappropriate for endocrine therapy. Patients with prior platinum therapy were required to have no evidence of disease progress during platinum treatment. No prior treatment with a PARP inhibitor was

permitted. Of the 302 patients randomized onto OlympiAD, 299 were tested with the BRACAnalysis CDx® and 297 were confirmed to have deleterious or suspected deleterious *gBRCAm* status; 202 were randomized to the Lynparza arm and 95 to the healthcare provider's choice of chemotherapy arm.

Among the 205 patients treated with Lynparza, the median age was 44 years (range: 22 to 76), 65% were White, 4% were males and all the patients had an ECOG PS of 0 or 1. Approximately 50% of patients had triple-negative tumors and 50% had estrogen receptor and/or progesterone receptor positive tumors and the proportions were balanced across treatment arms. Patients in each treatment arm had received a median of 1 prior chemotherapy regimen for metastatic disease; approximately 30% had not received a prior chemotherapy regimen for metastatic breast cancer. Twenty-one percent of patients in the Lynparza arm and 14% in the chemotherapy arm had received platinum therapy for metastatic disease. Seven percent of patients in each treatment arm had received platinum therapy for localized disease.

The major efficacy outcome measure was PFS assessed by blinded independent central review (BICR) using RECIST version 1.1. A statistically significant improvement in PFS was demonstrated for the Lynparza arm compared to the chemotherapy arm. Efficacy data for OlympiAD are displayed in Table 4 and Figure 4. Consistent results were observed across patient subgroups defined by study stratification factors. An exploratory analysis of investigator-assessed PFS was consistent with the BICR-assessed PFS results.

Table 4 Efficacy Results - OlympiAD (BICR-assessed)

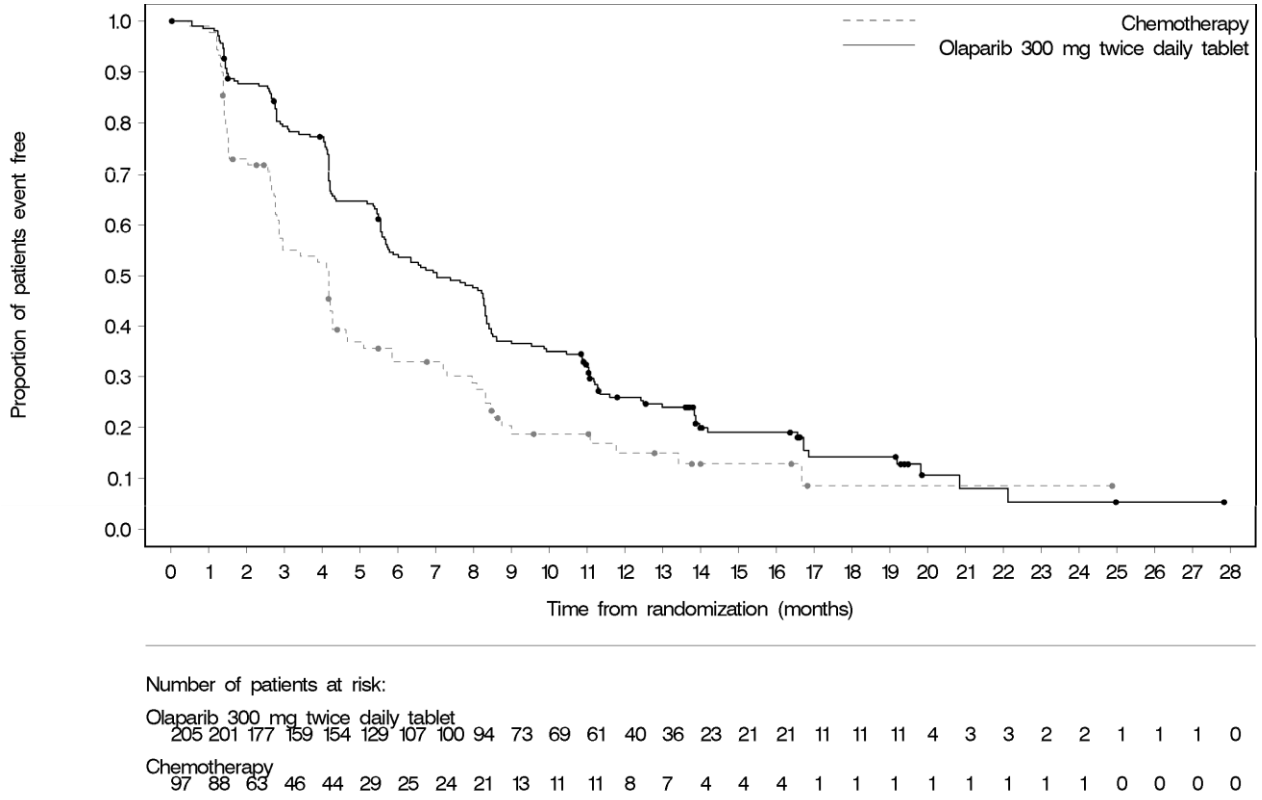
	Lynparza tablets (n=205)	**Chemotherapy (n=97)**
Progression-Free Survival		
Number of events (%)	163 (80%)	71 (73%)
Median, months	7.0	4.2
Hazard ratio (95% CI)[a]	0.58 (0.43, 0.80)	
p-value[b]	0.0009	
Patients with Measurable Disease	n=167	n=66
Objective Response Rate (95% CI)[c]	52% (44, 60)	23% (13, 35)
Overall Survival		
Number of events (%)	130 (63%)	62 (64%)
Median, months	19.3	17.1
Hazard ratio (95% CI)[a]	0.90 (0.66, 1.23)	

a. Hazard ratio is derived from a stratified log-rank test, stratified by ER, PgR negative versus ER and/or PgR positive and prior chemotherapy (yes versus no).

b. For PFS, p-value (2-sided) was compared to 0.05.

c. Response based on confirmed responses. The confirmed complete response rate was 7.8% for Lynparza compared to 1.5% for chemotherapy arm.

Figure 4: Kaplan-Meier Curves of Progression-Free Survival – OlympiAD



5.2 Pharmacokinetic properties

The pharmacokinetics of olaparib at the 300 mg tablet dose are characterised by an apparent plasma clearance of ~7 L/h, an apparent volume of distribution of ~158 L and a terminal half-life of 15 hours. On multiple dosing, an AUC accumulation ratio of 1.8 was observed and PK appeared to be time-dependent to a small extent.

Absorption

Following oral administration of olaparib via the tablet formulation (2 x 150 mg), absorption is rapid with median peak plasma concentrations typically achieved 1.5 hours after dosing. Co-administration with food slowed the rate (tmax delayed by 2.5 hours and Cmax reduced by approximately 21%) but did not significantly affect the extent of absorption of olaparib (AUC increased 8%). Consequently, Lynparza may be taken without regard to food (see section 4.2).

Distribution

The *in vitro* plasma protein binding is approximately 82% at 10 µg/mL which is approximately Cmax. *In vitro*, human plasma protein binding of olaparib was dose-dependent; the fraction bound was approximately 91% at 1 µg/mL, reducing to 82% at 10 µg/mL and to 70% at 40 µg/mL. In solutions of purified proteins, the olaparib fraction bound to albumin was approximately 56%, which was independent of olaparib concentrations. Using the same assay, the fraction bound to alpha-1 acid glycoprotein was 29% at 10 µg/mL with a trend of decreased binding at higher concentrations.

Biotransformation
In vitro, CYP3A4/5 were shown to be the enzymes primarily responsible for the metabolism of olaparib (see section 4.5).
Following oral dosing of 14C-olaparib to female patients, unchanged olaparib accounted for the majority of the circulating radioactivity in plasma (70%) and was the major component found in both urine and faeces (15% and 6% of the dose respectively). The metabolism of olaparib is extensive. The majority of the metabolism was attributable to oxidation reactions with a number of the components produced undergoing subsequent glucuronide or sulfate conjugation. Up to 20, 37 and 20 metabolites were detected in plasma, urine and faeces respectively, the majority of them representing < 1% of the dosed material. A ring-opened piperazin-3-ol moiety, and two mono-oxygenated metabolites (each ~10%) were the major circulating components, with one of the mono-oxygenated metabolites also being the major metabolite in the excreta (6% and 5% of the urinary and faecal radioactivity respectively).

In vitro, olaparib produced little/no inhibition of UGT2B7, or CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 or 2E1 and is not expected to be a clinically significant time dependent inhibitor of any of these CYP enzymes. Olaparib inhibited UGT1A1 *in vitro*, however, PBPK simulations suggest this is not of clinical importance. *In vitro*, olaparib is a substrate of the efflux transporter P-gp, however, this is unlikely to be of clinical significance (see section 4.5).

In vitro, data also show that olaparib is not a substrate for OATP1B1, OATP1B3, OCT1, BCRP or MRP2 and is not an inhibitor of OATP1B3, OAT1 or MRP2.

Elimination
Following a single dose of 14C-olaparib, ~86% of the dosed radioactivity was recovered within a 7-day collection period, ~44% via the urine and ~42% via the faeces. Majority of the material was excreted as metabolites.

Special populations
In population based PK analyses, patient age, bodyweight, or race (including White and Japanese patients) were not significant covariates.

Renal impairment
In patients with mild renal impairment (creatinine clearance 51 to 80 ml/min), AUC increased by 24% and Cmax by 15% compared with patients with normal renal function. No Lynparza dose adjustment is required for patients with mild renal impairment.

In patients with moderate renal impairment (creatinine clearance 31 to 50 ml/min), AUC increased by 44% and Cmax by 26% compared with patients with normal renal function. Lynparza dose adjustment is recommended for patients with moderate renal impairment (see section 4.2).
There are no data in patients with severe renal impairment or end-stage renal disease (creatinine clearance < 30 ml/min).

Hepatic impairment
In patients with mild hepatic impairment (Child-Pugh classification A), AUC increased by 15% and Cmax by 13% and in patients with moderate hepatic impairment (Child-Pugh classification B), AUC increased by 8% and Cmax decreased by 13% compared with patients with normal hepatic function. No Lynparza dose adjustment is required for patients with mild or moderate hepatic impairment (see section 4.2). There are no data in patients with severe hepatic impairment (Child-Pugh classification C).

Paediatric population

No studies have been conducted to investigate the pharmacokinetics of olaparib in paediatric patients.

5.3 Preclinical safety data

Genotoxicity

Olaparib showed no mutagenic potential, but was clastogenic in mammalian cells *in vitro*. When dosed orally to rats, olaparib induced micronuclei in bone marrow. This clastogenicity is consistent with the known pharmacology of olaparib and indicates potential for genotoxicity in man.

Repeat-dose toxicity

In repeat-dose toxicity studies of up to 6 months duration in rats and dogs, daily oral doses of olaparib were well-tolerated. The major primary target organ for toxicity in both species was the bone marrow, with associated changes in peripheral haematology parameters. These changes were reversible within 4 weeks of cessation of dosing. In rats, minimal degenerative effects on gastrointestinal tract were also noted. These findings occurred at exposures below those seen clinically. Studies using human bone marrow cells also showed that direct exposure to olaparib can result in toxicity to bone marrow cells in *ex vivo* assays.

Reproductive toxicology

In a female fertility study where rats were dosed until implantation, although extended oestrus was observed in some animals, mating performance and pregnancy rate was not affected. However, there was a slight reduction in embryofoetal survival.

In rat embryofoetal development studies, and at dose levels that did not induce significant maternal toxicity, olaparib caused reduced embryofoetal survival, reduced foetal weight and foetal developmental abnormalities, including major eye malformations (e.g. anophthalmia, microphthalmia), vertebral/rib malformation, and visceral and skeletal abnormalities.

Carcinogenicity

Carcinogenicity studies have not been conducted with olaparib.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Copovidone k28
Mannitol
Silica, colloidal anhydrous
Sodium stearyl fumarate

Tablet coating

Hypromellose
Titanium dioxide
Macrogol 400
Iron oxide yellow
Iron oxide black (150 mg tablets only)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

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

6.4 Special precautions for storage
Store in the original package in order to protect from moisture.
This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container
Alu/Alu non-perforated blister containing 8 film-coated tablets.
Pack sizes:
56 film-coated tablets (7 blisters).
Multipack containing 112 (2 packs of 56) film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Manufacturer
AstraZeneca UK limited Silk Road Business Park,
Macclesfield, Cheshire SK10 2NA, UK

8. License holder and Importer
AstraZeneca (Israel) Ltd, POB 1455, Hod Hasharon 4524075, Israel.