23 October 2014
DOC_REF_ID
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lynparza

International non-proprietary name: olaparib

Procedure No. EMEA/H/C/003726/II/0051/G

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AML	acute myeloid leukaemia
AUC	area under plasma concentration-time curve from zero to infinity
AUC_{ss}	area under plasma concentration-time curve from zero to infinity at steady state
bd	twice daily
BICR	blinded independent central review
BIG	Breast International Group
BRCA	breast cancer susceptibility gene
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
Cmax	maximum plasma concentration
$C_{max,ss}$	maximum plasma concentration at steady state
CNS	central nervous system
CPS&EG	clinical stage (CS), oestrogen receptor status (E), nuclear grade (G), and post-treatment pathologic stage (PS) – a disease scoring system
CRF	case report form
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DBL	database lock
DCO	data cut-off
DDFS	distant disease free survival
DDI	drug-drug interaction
DDR	DNA damage response
DFS	disease free survival
DNA	deoxyribonucleic acid

DSB	double strand break
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EFS	event free survival
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
ER	oestrogen receptor
ESMO	European Society for Medical Oncology
EU	European Union
FAS	full analysis set
FACIT	Functional Assessment of Chronic Illness Therapy
FFPE	formalin fixed paraffin embedded
FIGO	International Federation of Gynecology and Obstetrics
FISH	fluorescence in-situ hybridisation
GCP	Good Clinical Practice
GI	gastrointestinal
GLS	Geometric least squares
HER2	human epidermal growth factor receptor 2
HR	hazard ratio
HRD	homologous recombination deficiencies
HRQoL	health-related quality of life
HRR	homologous recombination repair
HRRm	homologous recombination repair mutation
ICH	International Council for Harmonisation
IDFS	invasive disease free survival
IDMC	Independent Data Monitoring Committee
IHC	immunohistochemistry
ITT	intention-to-treat
LS	least squares
MAH	Marketing authorisation holder
MDS	myelodysplastic syndrome
MRI	magnetic resonance imaging

n	number of patients
N	total number of patients
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NRG	NCI supported National Clinical Trials Network Group
od	once daily
ORR	objective response rate
OS	overall survival
PARP	polyadenosine 5'diphosphoribose polymerase
PBRER	Periodic Benefit-risk Evaluation Report
pCR	pathological complete response
PD-1	programmed cell death protein-1
PD-L1	programmed death-ligand 1
PFS	progression free survival
PFS2	time to second progression
PgR	progesterone receptor
PK	pharmacokinetic(s)
PRO	patient reported outcome
PSR	platinum-sensitive relapsed
PT	preferred term
QLC-C30	quality of questionnaire core 30 item module
QoL	quality of life
RECIST 1.1	response evaluation criteria in solid tumours version 1.1
RMP	risk management plan
RMST	restricted mean survival time
ROW	rest of world
rPFS	radiological progression-free survival
RSI	Reference Safety Information
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Safety analysis set
SD	standard deviation

SSB	single strand break
STEEP	standardised terms for efficacy endpoints
TNBC	triple negative breast cancer
VUS	genetic mutation of uncertain significance.
vs	versus

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, AstraZeneca AB submitted to the European Medicines Agency on 11 October 2021 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB
B.I.z	B.I.z - Quality change - Active substance - Other variation	Type IB	None

C.I.6.a - Extension of indication to include adjuvant treatment of breast cancer for Lynparza (for tablets); as a consequence, sections 4.1, 4.2, 4.5, 4.8 and 5.1 of the SmPC are updated. In addition, sections 4.8 of the SmPC for Lynparza hard capsules are revised based on the updated safety data analysis. The Package Leaflet is updated in accordance. Version 23 of the RMP has also been submitted.

B.I.z – to reassess the control strategy for potentially mutagenic impurities in the active substance in view of the proposed extension of indication to an earlier line of cancer treatment.

The group of variations requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0250/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0250/2020 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Alexandre Moreau Co-Rapporteur: Karin Janssen van Doorn

Timetable	Actual dates
Submission date	11 October 2021
Start of procedure:	30 October 2021
CHMP Rapporteur Assessment Report	22 December 2021
PRAC Rapporteur Assessment Report	3 January 2022
CHMP Co-Rapporteur Critique	5 January 2022
PRAC Outcome	13 January 2022
CHMP members comments	17 January 2022
Updated CHMP Rapporteur(s) (Joint) Assessment Report	21 January 2022
Request for supplementary information (RSI)	27 January 2022
CHMP Rapporteur Assessment Report	22 March 2022
PRAC Rapporteur Assessment Report	25 March 2022
PRAC members comments	30 March 2022
PRAC Outcome	7 April 2022
CHMP members comments	11 April 2022
Updated CHMP Rapporteur Assessment Report	20 April 2022
Request for supplementary information (RSI)	22 April 2022
CHMP Rapporteur Assessment Report	10 June 2022
CHMP members comments	13 June 2022
Updated CHMP Rapporteur Assessment Report	23 June 2022
Opinion	23 June 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Breast cancer is the most common cancer in the world, with an estimated 2.2 million new cases in 2020 globally (11.7% of all new cancers). Breast cancer is also the fifth most common cause of death from cancer, with an estimated 684,000 deaths in 2020. In the European Community in 2020, the number of cases of breast cancer in women and men was 355,457 and the number of deaths was 91,826 (ECIS 2020). Over 90% of patients with breast cancer are diagnosed at an early stage (Cardoso et al. 2018b).

Nearly 30% of women with cancer confined to the breast and 75% of women with nodal involvement will ultimately relapse (Rosen et al 1989). Metastatic breast cancer remains an incurable disease with an estimated 5-year OS of 25% (Cardoso et al 2009).

Breast cancer is a heterogeneous disease and optimal treatment depends on pathological and molecular characterization of the tumour. Early-stage Breast cancer (Stages I to III) is defined as disease confined to the breast with or without regional lymph node involvement and in the absence of metastatic disease. Treatment for Stages I to III breast cancer usually includes surgery and radiation therapy, with the addition of chemotherapy for patients with high risk of recurrence, either before (neoadjuvant) or after (adjuvant) surgery. Other drug therapies including endocrine and anti-HER2 therapy are additionally given depending on ER and/or PgR and HER2 status.

The presence of micrometastases or clinically occult tumour present after surgery with a potential to metastasize confer both morbidity and mortality. Pretreatment clinical stage (CS), estrogen receptor status (E), histological grade (G), and post-treatment pathologic stage (PS) can be used to estimate relapse probability with higher risk conferred by higher CPS, ER negativity and Grade 3 (Jeruss et al 2008, Mittendorf et al 2011).

Claimed therapeutic indication

The MAH applied for the following indication:

Olaparib is indicated as monotherapy for the adjuvant treatment of adult patients with BRCA mutated, HER2-negative, high risk early breast cancer who have previously been treated with neoadjuvant or adjuvant chemotherapy.

The recommended indication is as follows:

Lynparza is indicated as:

- *monotherapy or in combination with endocrine therapy for the adjuvant treatment of adult patients with germline BRCA1/2-mutations who have HER2-negative, high risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy (see SmPC sections 4.1, 4.2 and 5.1).*

Before Lynparza treatment is initiated for adjuvant treatment of HER2 negative high risk early breast cancer, patients must have confirmation of deleterious or suspected deleterious gBRCA1/2 mutation using a validated test (see SmPC sections 4.2 and 5.1).

Biologic features – BRCA Mutations in Breast Cancer

In the general population, germline BRCA mutation carriers have an increased relative risk of breast cancer (Kuchenbaecker et al 2017, Antoniou et al 2003). Onset of gBRCAm associated breast cancer is early (Mavaddat et al 2012), as also evidenced by the OlympiA and the OlympiAD trial populations where the median age of study participants at the time of randomisation following completion of neo/adjuvant treatment in OlympiA was 42 years (Tutt et al 2021) and at the time of randomisation with advanced/metastatic disease in OlympiAD was 45 years (Robson et al 2017).

BRCAm breast cancer is most frequently HER2 negative (IHC 0, 1+ or 2+/FISH non-amplified) breast cancer, which can be either ER and/or PgR positive (ER and/or PgR IHC nuclear staining ≥1%) or TNBC (ER and/or PgR IHC nuclear staining <1%). The development of HER2 positive BRCAm breast cancer, whilst it does occur, is rare (Mavaddat et al 2012, Evans et al 2016, Winter et al 2016).

Approximately 3% to 5% of patients with breast cancer carry BRCA1/2 mutations (Dorling et al 2021; Malone et al 2006). Approximately 70% of BRCA1 mutation carriers who develop breast cancers present with TNBC; in contrast, breast cancer patients carrying mutations in the BRCA2 gene are more likely to be positive for expression of the ER and/or PgR (Mavaddat et al 2012, Song et al 2020).

BRCAm breast cancer is associated with high-risk features with a poor prognosis for patients. BRCA1/2 breast cancer hallmarks include high histological grade, continuous pushing margins, TP-53 mutations, loss of RAD51 focus information, extreme genomic instability and sensitivity to DNA crosslinking agents, with BRCA1 tumours additionally more frequently basal-like and ER-negative (Turner et al 2004). TNBC, which is more frequently associated with BRCA1m, generally has a poor prognosis despite high sensitivity to chemotherapy (Metzger-Filho et al 2012) with early recurrence between the first and third year after diagnosis, frequently in association with visceral and/or brain metastases and a shorter period between time of recurrence and death (Dent et al 2007). Germline BRCA-associated hormone receptor–positive breast cancer is also associated with intrinsically less favourable biology with more high- and intermediate-risk disease and less low-risk disease compared to controls (Shah et al 2016). Within BRCAm tumours, the proportions with high-risk features are very similar for each gene, regardless of the mutation being germline or somatic (Winter et al 2016). When compared to BRCA wildtype primary breast carcinomas, tumours harbouring a BRCA1/2 mutation (gBRCA1 n=10, gBRCA2 n=10, sBRCA1 n=4, sBRCA2 n=5), showed a higher proportion of patients with higher risk features including N1-N3, grade 3 tumours, ER/PR negative disease and basal subtype (Winter et al 2016).

The development of metastatic disease in BRCAm breast cancer is also associated with a poor prognosis. Song et al 2020 reported that breast cancer patients with a BRCA1 mutation frequently experience metastasis to lung and distant lymph nodes, and BRCA2 mutation carriers most often to bone and liver; the data also indicate that at least one-half of patients with BRCA1-associated or BRCA2-associated metastatic breast cancer will develop CNS metastases. Involvement of CNS and other non-CNS distant sites (relative to locoregional recurrence or contralateral disease) as first recurrence events were associated with increased mortality risk.

Management

The decision to treat patients with early breast cancer with neoadjuvant or adjuvant chemotherapy in addition to surgery/radiotherapy is driven by the consideration of clinical characteristics, tumour stage and pathology. Randomised clinical trials have found no significant differences in long-term outcomes when systemic chemotherapy is given before or after surgery (Mauri et al 2005, Rastogi et al 2008).

For TNBC, neoadjuvant/adjuvant chemotherapy has been the main systemic treatment option for patients. Chemotherapy treatment of patients with early stage ER and/or PgR positive HER2 negative breast cancer depend on the individual risk of recurrence and presumed responsiveness to endocrine therapy (ESMO 2019, NCCN Guidelines). For hormone receptor positive patients with ≥4 positive nodes at definitive surgery, NCCN guidelines recommend that all patients should receive adjuvant chemotherapy followed by endocrine therapy (NCCN Guidelines); additional chemotherapy is also recommended to patients with hormone receptor positive cancers that have high risk characteristics, such as high-grade tumour, large tumour size (≥2 cm), pathologically involved lymph nodes, and/or high recurrence score (OncotypeDX 21-gene or other multigene assay). Adjuvant endocrine therapy is recommended following neo/adjuvant chemotherapy for all ER and/or PgR positive HER2 negative patients (NCCN Guidelines; ESMO 2019).

Standard neo/adjuvant chemotherapy for HER2 negative early disease is an anthracycline alkylator, and taxane-containing regimen. The ESMO Guidelines (ESMO 2019) recommend that a sequential anthracycline/taxane-based regimen be standard for the majority of patients. The NCCN and ESMO guidelines consider there is insufficient evidence for the routine use of platinum in neoadjuvant regimens for TNBC patients. Whilst platinum compounds are not routinely recommended, the addition of a platinum compound may be considered in high risk TNBC patients with deleterious BRCA1/2 mutations (ESMO 2019) and in selected patients where better local control is desirable (NCCN Guidelines). In high risk TNBC patients not achieving pCR after standard neoadjuvant chemotherapy, the addition of adjuvant capecitabine postoperatively may be considered (NCCN Guidelines, ESMO 2019).

2.1.2. About the product

Olaparib, is a potent oral human polyadenosine 5'diphosphoribose polymerase (PARP) inhibitor that exploits deficiencies in DNA repair pathways to preferentially target cancer cells carrying such deficiencies. Dysfunctional homologous recombination repair (HRR) in tumour cells results in reliance on error prone repair pathways, leading to an accumulation of DNA damage and cell death in tumour cells. Lynparza is approved in EU for the treatment of ovarian cancer, breast cancer, adenocarcinoma of the pancreas and prostate cancer (see section 4.1 of the SmPC).

The antitumour effects of the PARP inhibitor olaparib is dependent on an underlying defect in a cancer cell's DNA damage response (DDR) mechanisms, rather than a direct interaction with a mutated gene or protein. These defects in DDR mechanisms arise from cells with homologous recombination deficiencies (HRD), of which BRCA mutations are one subtype. Olaparib traps PARP at the sites of single-strand DNA damage and prevents their repair (Murai et al 2012). During replication, the single strand breaks (SSBs) trapped with PARP are converted to double strand break (DSBs). These DSBs are normally repaired by a high-fidelity process known as HRR. BRCA mutated tumours with HRD cannot accurately repair the DNA damage, which may become lethal to cells as it accumulates.

Breast cancers harbouring mutations in BRCA1 or BRCA2 result in tumour cells lacking BRCA protein functionality that are deficient in homologous recombination, making BRCA mutated breast cancer appropriate for treatment with PARP inhibitors whereby the process of synthetic lethality can be exploited.

2.2. Quality aspects

This Type II variation is being grouped with a consequential quality Type IB variation (category B.I.z) reassessing the control strategy for potentially mutagenic impurities.

In view of the proposed extension of the patient population to an earlier line of cancer treatment (i.e., adjuvant setting), the Applicant has reassessed the control strategy for potentially mutagenic impurities to consider a non ICH S9 patient population, in line with ICH M7 guidance. Consequently, the Applicant has submitted an updated Quality Overall Summary in Module 2.3 and updates in Module 3, S.3.2 Impurities and S.4.5 Justification of Specification for Drug Substance.

2.3. Discussion on quality aspects

The Applicant stated that nothing has changed in the quality of the olaparib active substance or Lynparza Tablets, and the way they are manufactured has not changed. The Applicant considers that there is no change to the drug substance specification required as the existing control strategy is appropriate for a non ICH S9 population.

The recommended dose of olaparib tablets is 300 mg (two 150 mg tablets) taken twice daily, equivalent to a total daily dose of 600 mg per day. It is recommended that treatment in the early breast cancer setting be continued for a maximum of 12 months. The threshold of toxicological concern (TTC) limit of 10 µg/day has been proposed based on ICH M7, applying a less than lifetime (LTL) exposure where the expected duration of the use of the product is less than 10 years. Based on this, the permitted limit for mutagenic impurity in olaparib drug substance would equate to 16.7 ppm using a staged TTC of 10 µg/d and a MDD of 600 mg.

As a reminder, olaparib showed no mutagenic potential in the Ames bacterial mutation tests but was clastogenic in an *in vitro* chromosome aberration test.

Following review of the initially submitted data, the control of potentially mutagenic impurities was not considered acceptable for the proposed additional indication. In addition, the applicant was asked to revise the nitrosamine risk-assessment. The applicant submitted satisfactory responses to the questions raised.

At the time of the CHMP opinion, a post-approval measure (PAM) was agreed with the MAH and is put forward as recommendation: to provide the results of a GLP Ames test for one impurity.

Active substance

A Risk Assessment of Potentially Mutagenic Impurities (PMI) has been provided in the revised section 3.2.S.3.2.

Mutagenic impurities have been evaluated using a (Q)SAR analysis employing two complementary methodologies (DEREK), a rule based expert system (SAR), and Leadscope modeller, a statistical QSAR model, Expert evaluation of SAR predictions, in vivo/in vitro mutagenicity testing. This evaluation takes into account all the starting materials, intermediates, reagents, as well as potential impurities and degradation products of both the active substance and finished product. For each compound, it includes its chemical structure, origin, mutagenicity risk assessment results, Ames assessment when applicable, and ICH M7 classification (class 1 to 5).

Eight compounds were predicted to be mutagenic by (Q)SAR analysis. Of those, the mutagenicity of five compounds was confirmed. Impurities which are reported as known animal carcinogens were not assessed using the QSAR modeller but have been treated as Class 1 in accordance with ICH M7.

The classification of certain impurities as class 5 compounds was not acceptable based on Amberg's publication only. In absence of relevant additional data, the Applicant was asked to categorize these impurities as Class 3 compounds.

The risk of one impurity being present either in the intermediate or in the final active substance can be considered as unlikely since the conditions required to form this impurity are not employed.

Two of the remaining structures were ruled out based on negative results in mutagenicity tests or based on structural analogy to a compound which was non-mutagenic in an Ames test.

One impurity gives a positive prediction in Derek Nexus and it is categorized as Class 5 compound based on a negative result in Ames test. However, some issues have been raised on this test and a GLP Ames test is requested in order to confirm the negative results. Currently, the impurity is not specifically named on the olaparib specification but is controlled as "Any individual unspecified impurity". The current control strategy for the impurity is acceptable provided that the negative results are confirmed (see conclusion).

All the other impurities were classified as Class 5 compounds based on two negative predictions which is sufficient to conclude that these impurities are of no mutagenic concern according to ICH M7. Based on this, no further action is required for these impurities that include all the specified impurities of the drug substance and the potential degradation impurity of the drug product

Omission of test for potentially mutagenic impurities has been justified in the revised section 3.2.S.4.5.

One class 1 impurity is controlled via option 4, as described in ICH M7. The removal of this impurity through the downstream processes was demonstrated by purging studies. No further action is required given the effective purge.

A further class 1 impurity is controlled via option 3, as described in ICH M7. Levels of this impurity have been reported as well below the specification limit, no further action is required.

One class 3 impurity is controlled via option 4, as described in ICH M7, in order to ensure that olaparib meets the established toxicological limit. The predicted purge factor of this class 3 impurity through the whole process has been determined. Given a purge ratio well above 1000, no specification is required for this mutagenic impurity as per ICH M7 guidance.

Further class 3 impurities are also controlled via option 4, as described in ICH M7.

One impurity is currently controlled under "Unspecified Impurity". The predicted purge factor of this impurity through the whole process has been determined. Given a purge ratio well above 1000, no specification is required as per ICH M7 guidance.

One impurity is currently specified with a limit, while two related impurities are controlled as any other impurity. Based on this, and considering their purge through the whole process, these impurities can be controlled via option 4, as described in ICH M7.

Finished product

Given the proposed extension of the patient population to an earlier line of cancer treatment (i.e. adjuvant setting), the control strategy for potential nitrosamines in the drug product has been reassessed. No significant risk of presence of nitrosamine impurities in the finished product has been identified.

2.4. Conclusion on quality aspects

Based on the review of the data on quality, the CHMP considers that the control strategy for potential mutagenic impurities is acceptable for the proposed (adjuvant) indication. The data provided sufficiently

support the proposed changes. Relevant sections of Module 3 have been updated accordingly. The MAH is recommended to provide the results of a GLP Ames test for one impurity (see also non-clinical aspects).

2.5. Non-clinical aspects

2.5.1. Introduction

The Applicant has submitted an updated Nonclinical Overview. The nonclinical package of studies was reviewed in accordance with the ICH M3(R2) guidance and an abbreviated package was proposed in view of the high-risk nature of the intended patient population i.e. BRCAm HER2-negative high risk early breast cancer. No additional nonclinical studies to further investigate carcinogenicity, reproductive toxicity or the safety of metabolites were submitted (see discussion on non-clinical aspects).

2.5.2. Ecotoxicity/environmental risk assessment

An updated Environmental Risk Assessment (ERA) was submitted.

Table 1: Summary of Environmental risk assessment

Substance (INN/Invented Name): olaparib			
CAS-number (if available): 763113-22-0			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	**OECD107 (study 06-0182/C)**	**1.55**	< 4.5**: not PBT or vPvB**
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log P_{ow}	1.55	**Not PBT nor vPvB**
	BCF	NA	
Persistence	DT_{50} or ready biodegradability	DT50, total system, 20°C = 260 (S1) & 251 (S2) DT50, total system, 12°C = 551 (S1) & 534 (S2)	
Toxicity	NOEC	0.32 mg/L	
PBT-statement:	The compound is not considered as PBT nor vPvB.		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	**0.40**	**µg/L**	**> 0.01µg/L**
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Hydrolysis	OECD 111	<10 % (120 hours) at pH 5, 7 and 9	Hydrolytically stable.
Ready Biodegradability Test	OECD 301F	Negligible biodegradation (Day 28: <6%)	Not readily biodegradable
Aerobic Transformation in Aquatic Sediment systems	OECD 308 (08-0028/C)	DT50 values at 20°C LOM DT50water = 7.06 days HOM DT50water = 4.22 days LOM DT50total system = 251 days HOM DT50total system = 260 days DT50 values at 12°C LOM DT50water = 15.0 days	Sediment toxicity study triggered.

		HOM DT50water = 8.96 days LOM DT50total system = 534 days HOM DT50total system = 551 days No metabolites >10% were observed.	
Adsorption-Desorption	**OECD 106(study 12-0285/A)**	*High Organic Carbon (HOC) sediment mean* **K_d =111** **K_{oc} = 1986** *Low Organic Carbon (LOC) sediment* mean **K_d = 3.8** **K_{oc} = 27487**	*KFoc values indicated that [^{14}C]Olaparib was of* ***low mobility in the HOC sediment*** *(KFoc 500-2000), and* ***immobile in the LOC sediment*** *(KFoc >5000)*
Adsorption /desorption tosludge	**OPPTS 835.1110 (study 08-0028/B)**	$Kd_{sludge(ads)}$ = **25**	*[^{14}C]AZD2281 did not show significant adsorption to sewage sludge and therefore, is not predicted to adsorb to bio-solids during wastewater treatment. A Kd value of 25 was calculated assuming a linear adsorption isotherm*

Phase IIa Effect studies

Study type	Test protocol	Endpoint	value	Unit	Remarks
Algae, Growth Inhibition Test/*Species*	**OECD 201 (study 06-0182/F)**	NOEC	83	mg/L	*EC_{50} = > 83 mg/L*
Daphnia sp. Reproduction Test	**OECD 211 (study 06-0182/H)**	NOEC	0.32	µg/L	*21 day LOEC = 1.0 mg/L*
Fish, Early Life Stage Toxicity Test/*Species*	**OECD 210 (study 06-0182/I)**	NOEC	0.32	µg/L	*32 day LOEC 1.0 mg/L*
Activated Sludge, Respiration Inhibition Test	**OECD 209 (study 06-0182/E)**	NOEC	100	µg/L	*3 hour EC_{50} > 100 mg/L*

$PNEC_{microorganism}$ = 10 000 µg/L
$PNEC_{surfacewater}$ = 32 µg/L
$PEC_{groundwater}$ = 0.1 µg/L
$PNEC_{groundwater}$ = 32 µg/L

$PEC_{surfacewater}$/$PNEC_{microorganism}$ = 4.0 x 10-5: Olaparib is unlikely to present a risk to microorganisms
$PEC_{surfacewater}$/$PNEC_{surfacewater}$ = 1.25 x 10-2: Olaparib is unlikely to present a risk to organisms in surface water
$PEC_{groundwater}$/$PNEC_{groundwater}$ = 3.13 x 10-3: Olaparib is unlikely to present a risk to the groundwater environment

Phase IIb Studies

Toxicity to *Chironomus riparius*	**OECD 218 (study 08-0028/D)**	*28 d NOEC = 0.6 mg/kg dry sediment and; NOEC normalised to 10% o.c. = 2.61 mg/Kg* *28 d LOEC = 1.25 mg/kg dry sediment, based on development rate*
Toxicity to *Lumbriculus variegatus*	**OECD 225 (study 123A-124)**	*28 day NOEC = 86 mg/kg dry weight*
Toxicity to Hyalella azteca	**U.S. EPA 600/R-99/064 (study 123A-125)**	*28 day NOEC = 89.6 mg/kg dry weight*

$PEC_{sediment}$ = 48.6 µg/kg (dry weight)
$PNEC_{sediment}$ = 260 µg/kg (NOEC from the chironomus test (normalised to 10% o.c.) / 10)
$PEC/PNEC_{sediment}$ = 0.19: Olaparib is unlikely to present a risk to sediment dwelling organisms

2.5.3. Discussion on non-clinical aspects

With this application, Lynparza is proposed to be indicated in early breast cancer that falls under ICH M3(R2) for non-advanced cancers.

No additional non-clinical studies were submitted in support of this application. The non-clinical and clinical risks are considered to be well characterised and the adverse effects in animals are sufficiently known.

Olaparib is not mutagenic but causes clastogenicity consistent with the mechanism of action. The potential for genotoxicity in humans is mentioned in section 5.3 of the SmPC and a subsection on myelodysplastic syndrome/acute myeloid leukemia (MDS/AML) is included in sections 4.4 and 4.8 of the SmPC. New primary malignancies (NPM) and MDS/AML are also described as important potential risk and important identified risk, respectively, in the olaparib risk management plan (RMP). Since 2014, these risks have been proactively monitored during clinical development, which included solicited reporting of adverse events (AEs) during the overall survival follow-up phase in the majority of MAH-sponsored clinical trials.

Olaparib has shown embryo-foetal toxicity and teratogenicity. The product information includes adequate warnings in relation to pregnancy and contraception. The duration of contraception use following the end of treatment for women of childbearing potential was revised in line with the document 'Response from SWP to CMDh questions regarding genotoxicity and contraception' (EMA/CHMP/SWP/74077/2020). Lynparza should not be used during pregnancy and in women of childbearing potential not using reliable contraception during therapy and for 6 months after receiving the last dose of Lynparza (see sections 4.4 and 4.6). Breastfeeding during treatment and for 1 month after the last dose is a contraindication due to the pharmacological properties of the product (see SmPC section 4.3).

M18 (a product of phase 1 metabolic pathways) was identified as the only major circulating metabolite in humans (15.8% of total drug-related exposure). This metabolite was also found in humans. Because M18 was less potent than olaparib in primary pharmacology and structurally similar to olaparib, additional risks are considered unlikely.

A complete and acceptable environmental risk assessment was submitted for Lynparza. Olaparib was found to be very persistent in the environment (DT50 > 180 days). Olaparib did not demonstrate any other environmental risks. The conclusions of this updated ERA are consistent with that of the previously submitted ERA. The patient use of Lynparza is not predicted to present a risk to the environment.

An Ames study provided for one of the impurities (see quality aspects) did not show any mutagenic potential of the impurity up to a concentration of 500 µg/well without S9 and up to 1600 µg/well with S9. However, the study provided was not GLP compliant and the MAH is recommended to provide the results of a GLP Ames test for the impurity. It is recommended that the maximum doses with and without S9 are selected as the highest doses where a precipitate is observed without interfering with scoring. Triple plating is recommended at each dose level and the use of the preincubation method is encouraged.

2.5.4. Conclusion on the non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP. The risks associated with olaparib have been characterised based on available non-clinical and clinical data and are adequately described in the Lynparza EU SmPC and addressed in the EU Risk Management Plan (RMP).

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of olaparib. Considering the above data, olaparib is not expected to pose a risk to the environment.

2.6. Clinical aspects

2.6.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 2: Tabular overview of clinical studies

Type of study	Study identifier, status	Objective(s) of the study	Study design/type of control	Test product, dosage regimen, route of administration	No of patients randomised /treated	Patient population	Location of study report
Efficacy, safety, PK	D081CC00006 (OlympiA [BIG 6-13, NSABP B 55]) Ongoing; interim (primary) superiority analysis (IDFS, DDFS, OS) completed	Determine the efficacy (assessed by IDFS) of olaparib compared to placebo	Phase III, randomised, double-blind, placebo-control, multicentre	Olaparib 300 mg bd tablet (oral) Matching placebo	1836/1815	Patients with germline *BRCA1/2* mutations and HER2 negative high-risk early breast cancer who have completed definitive local treatment and neoadjuvant or adjuvant chemotherapy	OlympiA CSR, Module 5.3.5.1

bd = twice daily; *BRCA* = breast cancer susceptibility gene; *BRCAm* = *BRCA* mutated; DDFS = distant disease free survival; HER2 = human epidermal growth factor receptor 2; IDFS = invasive disease free survival; OS = overall survival; PK = pharmacokinetics.

Source: OlympiA CSR, Module 5.3.5.1. Data cut-off 27 March 2020.

2.6.2. Pharmacokinetics

PK in breast cancer patients

No additional formal PK investigations were submitted in the context of the variation under review. However, the population-PK model was updated (Olaparib-MS-09) using data from patients with breast cancer investigated in OlympiA study.

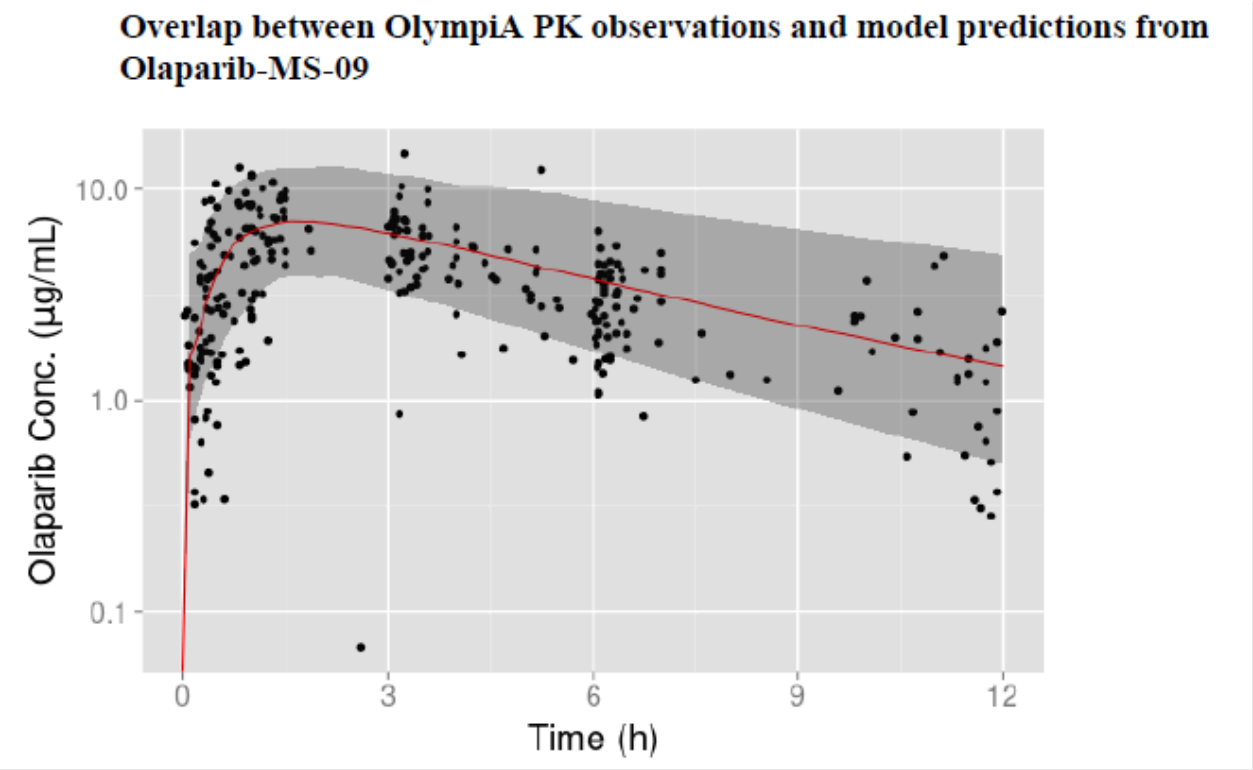


Figure 1: **Overlap between OlympiA PK observations and model predictions from Olaparib-MS-09**

The shaded area and dotted line represent the PK model predictions at 300mg bd from Olaparib-MS-09 (n=497) (2.5th, 50th and 97.5th percentiles). The black dots are the observed olaparib PK data in OlympiA after the 300 mg bd dose (n=69). Source: Olaparib-MS-09

Effect of intrinsic Factors on the PK of Olaparib

The updated pop-PK analysis (Olaparib-MS-09) did not identify gender, race, tumour location, age or body weight as significant covariates. Additionally, BRCA1/2 status was not identified as a significant covariate.

Effect of Extrinsic Factors on the PK of Olaparib

Considering that the claimed indication implies co-administration of olaparib and anti-hormonal drugs such as tamoxifen, and letrozole and anastrozole, the potential for DDI interaction of olaparib and antihormonal drugs was investigated. Study D081CC00001 was conducted to evaluate the DDI between olaparib and anti-hormonal agents at steady state, such as anastrozole (1 mg od), letrozole (2.5 mg od) and tamoxifen (20 mg od). It was an open label, non-randomised, parallel group, multicentre, Phase I study to assess the safety and the effect of olaparib at steady state on the PK of the anti-hormonal agents anastrozole, letrozole and tamoxifen at steady state, and the effect of the anti-hormonal agents on olaparib, following administration in patients with advanced solid cancer. Part A of the study (mandatory) assessed the effect of olaparib on the PK parameters of anastrozole, letrozole and tamoxifen and vice versa; Part B allowed patients (if eligible) continued access to olaparib after the PK phase and provided additional safety data.

The main findings of Study D081CC00001are summarised below.

Table 3: Effect of tamoxifen on olaparib

Olaparib PK parameter	Olaparib +tamoxifen		Olaparib		Point estimate of GLSmean ratio tamoxifen + olaparib	90% CI of GLSmean ratio tamoxifen + olaparib
	N	GLSmean	N	GLSmean		
$C_{max\ ss}$ (µg/mL)	19	7.553	26	9.444	0.80	0.71, 0.90
AUC_{ss} (µg.h/mL)	18	44.81	25	61.58	0.73	0.63, 0.84

AUC_{ss} Area under the plasma concentration time curve over the dosing interval at steady state, $C_{max,ss}$ Maximum plasma concentration at steady state; CI Confidence interval; GLS Geometric least squares; PK Pharmacokinetic.

Data Source: Table 14 from CSR D081CC00001 in Module 5.3.3.2.

When olaparib (300 mg tablet) was co-administered with tamoxifen (20 mg od), there was a decrease in olaparib Geometric least squares (GLS) mean AUCss of 27% (mean ratio: 0.73; 90% CI: 0.63, 0.84), and a decrease in steady state GLS mean Cmaxby 20% (mean ratio: 0.80; 90% CI: 0.71, 0.90).

Table 4: Effect of olaparib on tamoxifen

Tamoxifen PK parameter	Olaparib +tamoxifen		Tamoxifen		Point estimate of GLSmean ratio tamoxifen + olaparib	90% CI of GLSmean ratio tamoxifen + olaparib
	N	GLSmean	N	GLSmean		
$C_{max\ ss}$ (µg/mL)	18	147.9	24	130.3	1.13	1.06, 1.22
AUC_{ss} (µg.h/mL)	18	2583	24	2233	1.16	1.11, 1.21

AUC_{ss} Area under the plasma concentration time curve over the dosing interval at steady state; $C_{max,ss}$ Maximum plasma concentration at steady state; CI Confidence interval; GLS Geometric least squares; PK Pharmacokinetic.

Effects of Other anti-hormonal Drugs (anastrozole and letrozole) on the PK of Olaparib

The anti-hormonal drugs, anastrozole (1 mg od) and letrozole (2.5 mg od) had no relevant impact on the steady state exposure to olaparib (300 mg bd) when given in combination. The mean ratio (90%CI) for olaparib AUCss and Cmax,ss were 0.89, (0.76-1.05) and 0.94(0.84-1.04) when co-administered with anastrozole; and the GLS mean ratio for olaparib AUCssand Cmax,sswere 1.15 (1.07-1.25) and 1.09 (0.99-1.21) for Cmax,ss when co-administered with letrozole.

Effects of Olaparib on the PK of Other anti-hormonal Drugs (anastrozole and letrozole)

Olaparib had no marked effect on the exposure to anastrozole or letrozole at steady state. The GLS mean ratio (90%CI) on anastrozole AUCss and Cmax,ss were 0.86, (0.80-0.93) and 0.90 (0.84-0.97) respectively; and the mean ratio on letrozole AUCss and Cmax,ss were 0.95 (0.91-0.99) and 0.94 (0.914-0.98) for Cmax,ss respectively.

PK/PD modelling /Exposure-Response relationshipExposure-Efficacy Relationship

In OlympiA, Kaplan-Meier curves for IDFS stratified by the tertile exposure for any of the exposure metrics showed no apparent exposure-response trend. In addition, Cox proportional hazard analysis based on AUC_{ss} values spanning over the range of 13.2 µg.h/mL to 101 µg.h/mL could not detect a statistically significant correlation between this exposure metric and IDFS. In patients with PK data who received concomitant tamoxifen and were demonstrated to have lower exposure of olaparib, the Kaplan-Meier curve was similar to that of patients with PK data who did not receive concomitant tamoxifen (**Figure 2**).

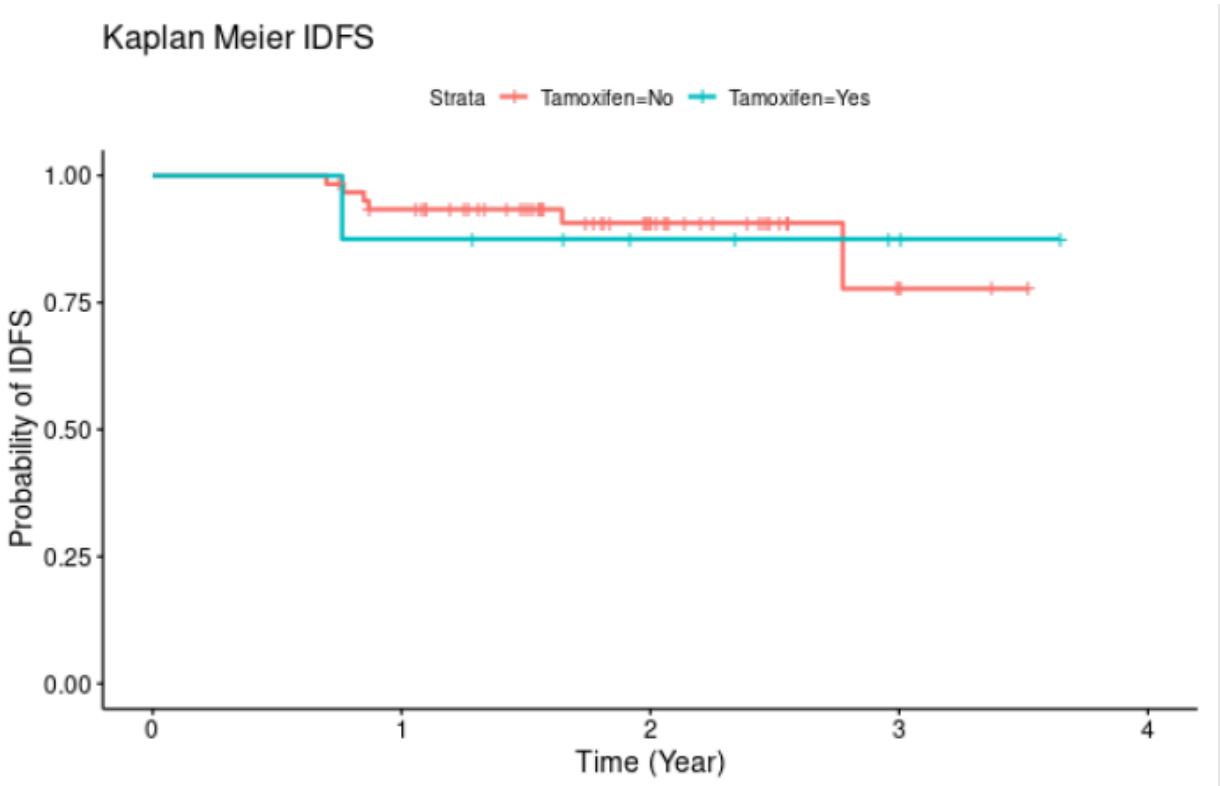


Figure 2: Kaplan Meier Curves for patients with PK data on concomittant tamoxifen (n =8) and for patients with PK data not on concomittant (n=61) in OlympiA

Similarly, graphical analyses in OlympiAD did not reveal any apparent relationship in breast cancer patients between olaparib exposure metrics and PFS, OS, or PFS2.

Exposure-Safety Relationship

The most recent exposure-safety analysis based on pooled data from monotherapy studies with the tablet formulation (Olaparib-MS-09) suggested daily C_{max} and daily AUC behaved similarly as the best predictor for safety endpoints. Similar to the previous analyses, it identified relatively weak exposure-response relationships between at least one of the exposure metrics of olaparib and anaemia, decreased appetite, fatigue, nausea, vomiting, and diarrhoea. Anaemia had a statistically significant relationship with all exposure metrics while there was no increased dysgeusia, headache and neutropenia event rate detected for any for the exposure metrics.

2.6.3. Discussion on clinical pharmacology

The tablet formulation was used in study OlympiA. The proposed recommended total dose of olaparib in the indication under review is 600 mg per day. The drug is recommended to be administered as two 150 mg tablets (300 mg) taken twice daily. The 100 mg strength could be used for dose reduction when needed.

No complementary formal PK investigations were provided in the context of the variation under review. However, the already assessed pop-PK model was updated by the inclusion of data from study OlympiA. The PKs of olaparib in the target patients was assessed and compared to the PK profile characterised in other cancer patients. Also, based on the updated model, the exposure-response (Efficacy and safety) relationship in target patients was investigated.

Exposure to olaparib in the OlympiA study, collected from breast cancer patients, was shown to be similar to that observed in previous studies with the olaparib 300mg bd tablet.

The potential for DDI for olaparib as a victim or perpetrator has been previously investigated and characterized. The results of study D081CC00001 (effect of anti-hormonal agents on olaparib) were previously submitted in procedure EMEA/H/C/003726/X/0016/G supporting the use of the tablet formulation. Based on this study, it was concluded that no significant interaction was observed with anastrozole or letrozole whereas tamoxifen decreased exposure to olaparib by 27%. However, results from PK/PD modelling suggested that the exposure response for efficacy in breast cancer was flat at the 300 mg bd dose level. Therefore, the reduction in olaparib exposure due to co-administration of tamoxifen is not considered clinically relevant. Section 4.5 of the SmPC has been updated accordingly.

The potential for DDI of olaparib with exemestane and goserelin has not been investigated. Nevertheless, the potential for relevant PK-based DDI between olaparib and exemestane or goserelin is unlikely given the different metabolic pathways, the clinical data available and the PBPK predictions.

The Exposure-Response (efficacy-safety) relationship was investigated in the proposed target population included in study OlympiA. The outcome of this analysis is consistent with that described for patients in other indications.

2.6.4. Conclusions on clinical pharmacology

No significant difference in PKs characteristics was observed in breast cancer patients from the OlympiA study compared to the PK profile of olaparib tablet formulation observed in previous studies in approved indications.

2.7. Clinical efficacy

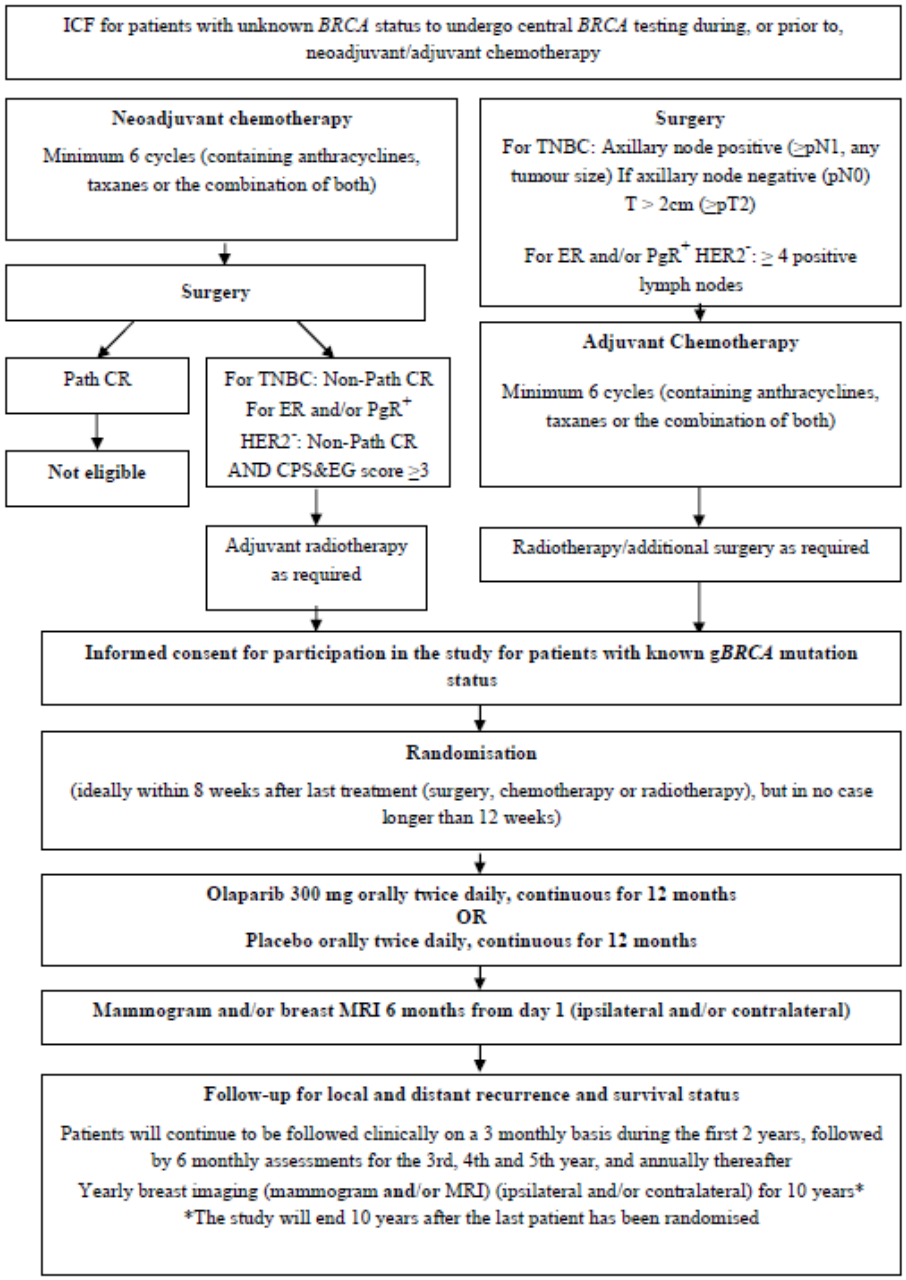
2.7.1. Main study

Study D081CC00006 (OlympiA)

Methods

OlympiA was a randomised, double-blind, parallel group, placebo-controlled multi-centre Phase III study to assess the efficacy and safety of olaparib versus placebo as adjuvant treatment in patients with germline BRCA1/2 mutations and HER2 negative high-risk early breast cancer who had completed definitive local treatment and neoadjuvant or adjuvant chemotherapy.

The study flow chart for the OlympiA study is provided in **Figure 3**.



bd = twice daily; *BRCA* = breast cancer susceptibility gene; *BRCAm* = *BRCA* mutated; CPS&EG = clinical stage (CS), oestrogen receptor status (E), nuclear grade (G), and post treatment pathologic stage (PS)- a disease scoring system; CR = complete response ER = oestrogen receptor; *gBRCA* = germline *BRCA*; HER2 = human epidermal growth factor receptor 2; ICF = informed consent form; IDFS = invasive disease free survival; MRI = magnetic resonance imaging; OS = overall survival; PgR = progesterone receptor; PK = pharmacokinetics TNBC = triple negative breast cancer.

Figure 3: Study Design - OlympiA

Study participants

Main inclusion criteria

For inclusion in the study patients should fulfil the following criteria:

1. Provision of informed consent prior to any study specific procedures

2. Female or male patients must be ≥18 years of age

3A. For patients who underwent initial surgery and received adjuvant chemotherapy

- TNBC patients must have been axillary node-positive (≥pN1, any tumour size) or axillary node-negative (pN0) with invasive primary tumour pathological size > 2 cm (≥pT2)
- ER and/or PgR positive/HER 2 negative patients must have had ≥4 pathologically confirmed positive lymph nodes

3B. For patients who underwent neoadjuvant chemotherapy followed by surgery

1. TNBC patients must have residual invasive breast cancer in the breast and/or resected lymph nodes (non pCR)
2. ER and/or PgR positive/HER 2 negative patients must have residual invasive cancer in the breast and/or the resected lymph nodes (non pCR) AND a CPS&EG score ≥3.

4. Histologically confirmed non-metastatic primary invasive adenocarcinoma of the breast that is one of the two following phenotypes:

a) TNBC defined as:

- ER and PgR negative defined as IHC nuclear staining <1%.

AND

- HER2 negative (not eligible for anti-HER2 therapy) defined as:
    - IHC 0, 1+ without ISH OR
    - IHC 2+ and ISH non-amplified with ratio less than 2.0 and if reported, average HER2 copy number < 4 signals/cells OR
    - ISH non-amplified with ratio less than 2.0 and if reported, average HER2 copy number < 4 signals/cells (without IHC)

b) ER and/or PgR positive, HER2 negative breast cancer defined as:

- ER and/or PgR positive defined as IHC nuclear staining ≥1%.

AND

- HER2 negative (not eligible for anti-HER2 therapy) defined as:
    - IHC 0, 1+ without ISH OR
    - IHC 2+ and ISH non-amplified with ratio less than 2.0 and if reported, average HER2 copy number < 4 signals/cells OR
    - ISH non-amplified with ratio less than 2.0 and if reported, average HER2 copy number < 4 signals/cells (without IHC)

Patients with multifocal or multicentric invasive disease are eligible as long as all the lesions for which HER2 characterization is available are HER2 negative.

Patients with synchronous bilateral invasive disease are eligible as long as all the lesions assessed for HER2 on both sides are negative.

In both the above cases the lesion considered at highest risk for recurrence based on the investigator's discretion will be used for eligibility determination.

5. Documented germline mutation in BRCA1 or BRCA2 that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function). Local gBRCA testing results, if available, will be used for establishing eligibility. If local gBRCA testing results are not available, central testing will be provided for those patients who otherwise appear to be eligible.

6A. Completed adequate breast surgery defined as:

- The inked margins of breast conservation surgery or mastectomy must be histologically free of invasive breast cancer and ductal carcinoma in situ with the exception of the posterior margin if this margin is the pectoralis major fascia or the anterior margin if this is the dermis. Patients with resection margins positive for lobular carcinoma in situ are eligible.
- Patients with breast conservation must have adjuvant radiotherapy. Patients having mastectomy may have adjuvant radiotherapy according to local policy and/or international guidelines.

6B. Completed adequate axilla surgery defined as:

Adjuvant Chemotherapy Patients:

- Sentinel lymph node biopsy alone if negative or if lymph node(s) only contain micrometastases (≤ 2.0 mm) **OR**
- Positive sentinel lymph node biopsy followed by axillary nodal dissection or radiotherapy as per local guidelines **OR**
- Axillary dissection

Neoadjuvant Chemotherapy Patients:

- Sentinel lymph node biopsy performed *before* neoadjuvant chemotherapy:
    - If negative or if lymph node(s) only contain micrometastases (≤2.0 mm) additional axillary surgery is not required
    - If positive, axillary node dissection or axillary nodal radiotherapy should follow completion of neoadjuvant chemotherapy
- Sentinel lymph node biopsy performed *after* neoadjuvant chemotherapy:
    - If negative, additional axillary surgery not mandated
    - If positive (micrometastases are regarded as positive), additional axillary surgery is required unless the patient is enrolled in a Phase III multicenter clinical trial proposing radiotherapy as alternative treatment of the axilla. The trial must be pre-approved by the OlympiA Executive Committee
- Axillary dissection

7. Completed at least 6 cycles of neoadjuvant or adjuvant chemotherapy containing anthracyclines, taxanes or the combination of both. Prior platinum as potentially curative treatment for prior cancer (e.g. ovarian) or as adjuvant or neoadjuvant treatment for breast cancer is allowed. (For neoadjuvant patients all chemotherapy should be delivered prior to surgery. No further cycles of chemotherapy post-surgery are allowed.)

8. Patients must have adequate organ and bone marrow function measured within 28 days prior to randomisation with no blood transfusions (packed red blood cells and/or platelet transfusions) in the past 28 days prior to testing for organ and bone marrow function as defined below:

- Haemoglobin ≥10.0 g/dL
- Absolute neutrophil count (ANC) ≥1.5 x 10^9/L
- Platelet count ≥100 x 10^9/L
- Total Bilirubin ≤ ULN (institutional upper limit of normal) except elevated total bilirubin <1.5 x ULN due to Gilbert's disease or similar syndrome involving slow conjugation of bilirubin
- AST (SGOT)/ALT (SGPT) ≤2.5 x ULN
- ALP ≤2.5 x ULN

To rule out metastatic breast cancer, patients with screening ALT/AST or ALP above institutional upper limit of normal should have liver ultrasound, CT or MRI at any time point between diagnosis of current breast cancer and randomisation. Screening bone scan is required if ALP and/or corrected calcium level are above the institutional upper limit. (Note: PET CT scan may be used as an alternative imaging technique).

9. Serum or plasma creatinine ≤1.5 x ULN

10. ECOG performance status 0-1

11A. Women who are not postmenopausal or have not undergone hysterectomy must have documented negative pregnancy test within 28 days prior to randomisation:

Postmenopausal is defined as:

- Age ≥60 years
- Age <60 years and amenorrheic for 1 year or more in the absence of chemotherapy and/or hormonal treatment
- Follicle stimulating hormone (FSH) and plasma estradiol levels in the postmenopausal range for women under 60 years
- Radiation-induced oophorectomy with last menses >1 year ago
- Bilateral oophorectomy

11B. Women of childbearing potential and their partners, who are sexually active, must agree to the use of two highly effective forms of contraception in combination.

12. Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations

13. Formalin fixed, paraffin embedded (FFPE) tumour sample from the primary tumour, mandatory*.

*NOTE: For adjuvant patients, this refers to the surgical specimen; for neoadjuvant patients, both the pre-treatment core biopsy and the surgical specimen with residual disease are requested but only one is mandatory.

14. Patient should be randomised in the trial ideally within a maximum of 8 weeks of completion of their last treatment (surgery, chemotherapy or radiotherapy), but in no case longer than 12 weeks.

Main exclusion criteria:

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. Involvement in the planning and/or conduct of the study.

2. Patients who do not have deleterious or suspected deleterious gBRCA1 and/or 2 mutations but only have BRCA1 and/or BRCA2 mutations that are considered to be non-detrimental (e.g., "Variants of uncertain clinical significance" or "Variant of unknown significance" or "Variant, favour polymorphism" or "benign polymorphism" etc.).

3. Previous randomisation in the present study.

4. Evidence of metastatic breast cancer. Patient considered at high risk of having disseminated disease (i.e. those with locally advanced disease, clinical N2-3 or pathological N1-3 with the exception of pN1a in adjuvant patients) should have a CT/MRI scan of the Thorax/Abdomen/Pelvis or any other area as clinically indicated and a bone scan at any point between diagnosis of the current breast cancer and randomisation to rule out metastatic breast cancer. (Note PET/ CT scan may be used as an alternative imaging technique and precludes the need for bone scan). Patients with screening ALT/AST or ALP above institutional upper limit of normal should have liver ultrasound, CT or MRI at any time point between diagnosis of current breast cancer and randomisation. Screening bone scan is required if ALP and/or corrected calcium level are above the institutional upper limit. (Note PET/ CT scan may be used as an alternative imaging technique).

5. Exposure to an investigational product within 30 days or five half-lives (whichever is the longer) prior to randomisation.

6. Any previous treatment with a PARP inhibitor, including olaparib and/or known hypersensitivity to any of the excipients of study treatment.

7. Patients with second primary malignancy. Exceptions are:

- adequately treated non-melanoma skin cancer, curatively treated in situ cancer of the cervix, Ductal Carcinoma in situ (DCIS) of the breast, stage 1 grade 1 endometrial carcinoma.
- other solid tumours and lymphomas (without bone marrow involvement) diagnosed ≥5 years prior to randomisation and treated with no evidence of disease recurrence and for whom no more than one line of chemotherapy was applied.

8. Resting ECG with QTc >470 msec detected on 2 or more time points within a 24-hour period or family history of long QT syndrome. If ECG demonstrates QTc >470 msec, patient will be eligible only if repeat ECG demonstrates QTc ≤470 msec.

9. Patients receiving systemic chemotherapy within 3 weeks prior to randomisation.

10. Patients receiving adjuvant radiotherapy within 2 weeks prior to randomisation.

11. Concomitant use of known strong CYP3A inhibitors (e.g., itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (e.g., ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil). The required washout period prior to starting study treatment is 2 weeks. Concomitant use of known strong (e.g., phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate CYP3A inducers (e.g., bosentan, efavirenz, modafinil). The required washout period prior to starting study treatment is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents.

12. Persistent toxicities (≥CTCAE grade 2) caused by previous cancer therapy, excluding alopecia and CTCAE grade 2 peripheral neuropathy.

13. Patients with current or past history of haematologic malignancies and any clonal non-malignant haematological disorder which predisposes the patient to develop a haematological malignancy. Exception: lymphoma (refer to Exclusion Criterion 7).

14. Major surgery within 2 weeks prior to randomisation: patients must have recovered from any effects of any major surgery.

CPS&ES score

In the OlympiA study, non-pCR combined with CPS&EG score ≥ 3 was implemented within the eligibility criteria to select "high risk" ER and/or PgR positive, HER2 negative gBRCAm patients following neoadjuvant chemotherapy whose risk of recurrence would be expected to be comparable to that of a TNBC non-pCR population.

In clinical practice, there is no universal system/tool on how to define a 'high-risk' patient for subgroups of early breast cancer, and definition of high-risk breast cancer may be based on local/regional clinical guidelines (Cardoso et al 2019, NCCN Guidelines 2021). However, non-pCR post neoadjuvant chemotherapy, high tumour burden, nodal involvement, aggressive biology and young age are among the common 'high-risk' factors (Cardoso et al 2019, NCCN Guidelines 2021). To illustrate the correlation between the CPS&EG scoring system and the conventional high-risk criteria, **Table *5*** shows how AJCC (TNM) staging, oestrogen receptor status and tumour nuclear grade were utilized to assign points to the CPS&EG scoring system. With higher pre-treatment clinical staging (per AJCC criteria) and post-treatment pathological staging (per AJCC criteria), more points were assigned. In addition, points were given to well-recognized high-risk factors, such as ER negativity and tumour nuclear grade 3 based on the CPS&EG scoring system.

Table 5: CPS&EG score[a]

Stage/feature		AJCC staging[b]	Points
Clinical Stage (pre-treatment)	I	T1N0; T0N1mi; T1N1mi	0
	IIA	T0N1; T1N1; T2N0	0
	IIB	T2N1; T3N0	1
	IIIA	T0-3 N2; T3N1	1
	IIIB	T4 N0-2	2
	IIIC	ANY T N3	2
Pathologic Stage (post-treatment)	0	ypT0/is ypN0	0
	I	ypT1ypN0; ypT0ypN1mi; ypT1ypN1mi	0
	IIA	ypT0ypN1; ypT1ypN1; ypT2ypN0	1
	IIB	ypT2ypN1; ypT3ypN0	1
	IIIA	ypT0-2 ypN2; ypT3ypN1	1
	IIIB	ypT4 ypN0-2	1
	IIIC	Any ypT ypN3	2
Receptor status	ER negative [c]		1
Nuclear grade[d]	Nuclear grade 3		1

[a] Calculation instructions: Add the points for Clinical Stage + Pathologic Stage + ER status + Nuclear grade to derive a sum (CPS&EG score) between 0 and 6.
[b] AJCC: American Joint Committee on Cancer (https://cancerstaging.org/Pages/default.aspx).
[c] ER: Estrogen receptor; definitions for ER negativity see eligibility criteria Section 4.1.4.a.
[d] In the unlikely situation nuclear grade cannot be determined, regular histologic grade should be used; if only Nottingham overall grade is reported, the Nottingham overall grade must be 9 to be scored as 1 point in the CPS&EG score (http://pathology.jhu.edu/breast/grade.php).

BRCA Testing Methodologies

Data on gBRCA mutation status for OlympiA was to be obtained from a combination of locally generated BRCA mutation status obtained from medical records and reported in the CRFs, and/or assessment at a central laboratory, Myriad Genetic Laboratories Inc. BRCA testing of all patients in China was to be conducted locally by BGI Laboratory.

Germline BRCA testing conducted for OlympiA by Myriad was performed either using their CLIA-based assay, BRACAnalysis, or BRACAnalysis CDx.

Local testing laboratories could use a variety of methods to detect BRCA variants. Locally identified BRCA mutations were to be taken from medical records and reported within the CRF, however details of the specific methods used to detect the variants were not required to be provided. Confirmatory testing of locally reported mutations was to be subsequently performed by central testing at Myriad.

Treatments

Patients were randomised in a 1:1 ratio to receive either olaparib tablets 300 mg bd or the matching placebo tablets orally bd for up to a maximum of 12 months.

The 100 mg olaparib tablets were used to manage dose reductions.

Patients were allowed to have concurrent treatment with endocrine therapy as per local guidelines.

Objectives

Primary objective

The primary objective was to assess the effect of adjuvant treatment with olaparib on Invasive Disease Free Survival (IDFS).

Safety objective

To assess the safety and tolerability of adjuvant treatment with Olaparib.

Secondary objectives

- To assess the effect of adjuvant treatment with olaparib on overall survival (OS)
- To assess the effect of adjuvant treatment with olaparib on Distant Disease Free Survival (DDFS)
- To assess the effect of adjuvant treatment with olaparib on the incidence of new primary contralateral invasive breast cancer, primary contralateral non-invasive breast cancer, new primary ovarian cancer, new primary fallopian tube cancer and new primary peritoneal cancer
- To assess the effect of olaparib on patient reported outcomes using the FACIT-Fatigue and EORTC QLQ-C30 questionnaires
- To assess the efficacy of olaparib in patients identified as having a deleterious or suspected deleterious variant in either of the BRCA genes using variants identified with current and future germline BRCA mutation assays (gene sequencing and large rearrangement analysis)

6. To determine the exposure to olaparib (in plasma) in patients receiving olaparib as adjuvant therapy

Exploratory objectives

- To assess the consistency of treatment effects on efficacy endpoints across potential or expected prognostic factors, including the baseline stratification factors with special emphasis on hormone receptor status
- To explore methods for estimating overall survival (OS) adjusting for the impact of confounding by subsequent therapies, specifically the control arm receiving subsequent Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerisation (PARP) inhibitors or platinum salts
- To explore whether resistance mechanisms to olaparib can be identified through analysis of tumour and blood sample derivatives (cells, plasma and protein and nucleic acid derivatives) - archival tumour samples (mandatory), tumour sample at recurrence (optional) and blood samples at baseline, 30 days post study treatment and on disease recurrence (mandatory)

  For adjuvant patients, this refers to the surgical specimen; for neoadjuvant patients, both the pre-treatment core biopsy and the surgical specimen with residual disease are requested but only one is mandatory.
- To determine the frequency of and describe the nature of BRCA mutation/s in tumour samples and to compare this with germline BRCA mutation status
- To conduct future exploratory research into factors that may influence development of cancer and/or response to treatment (where response is defined broadly to include efficacy, tolerability or safety). This may be performed on the collected and stored tumour and blood samples
- To collect and store DNA according to each country's local and ethical procedures for future exploratory research into genes/genetic variation that may influence response (i.e. distribution, safety, tolerability and efficacy) to study treatments and/or susceptibility to disease (optional)

Outcomes/endpoints

Primary endpoint

Invasive Disease Free Survival (IDFS) defined as the time from randomisation to date of first recurrence, where recurrence is defined according to the standardised terms for efficacy endpoints (STEEP) system definition as one of the following:

- Ipsilateral invasive breast tumour recurrence: Invasive breast cancer involving the same breast parenchyma as the original primary.
- Regional invasive breast cancer recurrence: Invasive breast cancer in the axilla, regional lymph nodes, chest wall, and skin of the ipsilateral breast.
- Distant recurrence: Metastatic disease-breast cancer that has either been biopsy confirmed or radiologically diagnosed as recurrent invasive breast cancer.
- Death attributable to any cause, including breast cancer, non-breast cancer, or unknown cause.
- Contralateral invasive breast cancer.
- New primary non-breast invasive cancers (i.e., excluding new in situ carcinomas of any site). New primary non-breast invasive cancers include haematologic cancers and MDS. Squamous or basal cell skin cancers will not be counted as primary endpoint events.

Secondary endpoints

- Overall survival (OS) defined as the time from the date of randomisation until death due to any cause.
- Distant disease free survival (DDFS) defined as the time from randomisation until documented evidence of first distant recurrence of breast cancer. Distant recurrence included the following events:
    - Distant recurrence: Metastatic disease-breast cancer that had either been biopsy confirmed or radiologically diagnosed as recurrent invasive breast cancer.
    - Death attributable to any cause, including breast cancer, non-breast cancer, or unknown cause.
    - New primary non-breast invasive cancer.
- New primary contralateral breast cancers (invasive and non-invasive), new primary ovarian cancer, new primary fallopian tube cancer and new primary peritoneal cancers in patients at risk for these events
- HRQoL/PROs: FACIT-Fatigue symptom scale score and EORTC-QLQ-C30 global health status, functional, and symptoms scales/items scores
- IDFS, DDFS and OS based on patients with gBRCA mutations confirmed by the central test (only required if population differs from the ITT (intention to treat) population)
- Pharmacokinetic analysis

Safety endpoints: Adverse Events (AE), physical examination, vital signs including blood pressure (BP), pulse, and laboratory findings including clinical chemistry and haematology

Exploratory endpoints:

- Potential retrospective biomarker (mandatory) & pharmacogenetic research (optional)
- Adjusted overall survival estimates (if applicable)

Sample size

A total of 1800 patients were to be randomised into the study to achieve 330 IDFS events. If the true HR for the comparison of olaparib versus placebo in terms of IDFS was 0.7 then with 330 events, the analysis of IDFS will have 90% power to demonstrate a statistically significant difference in IDFS, assuming a 2-sided 5% significance level. The critical HR value at the primary analysis at 330 events was 0.805.

During the study, the Steering Committee was to monitor the recruited patient population and actual event rate whilst remaining blinded to treatment. If the data suggested that the original sample size assumptions were incorrect such that achieving the required number of events with the current number of patients did not seem feasible, then in consultation with the IDMC a decision could be made to increase the number of patients recruited into the study to achieve the required 330 events.

Sample Size Consideration for PRO Endpoints

It was assumed that half of triple negative patients and a quarter of hormone receptor positive patients would have received neoadjuvant chemotherapy and it was anticipated that 95% of patients enrolled in the study would complete the HRQoL instrument. In addition, adjusting downward to allow for 20% of missing

data at the 12 months assessment point, it was expected that data from 633 neoadjuvant and 735 adjuvant patients would be available (assuming that 15% of the total 1800 enrolled patients were ER and/or PgR positive, HER2 negative). These would be sufficient to provide statistical power of 93% and 96% correspondingly to detect a difference of 3 points on the FACIT-Fatigue scale score between treatment arms assuming a SD of 10.9 (Cella et al 2002b; estimated SD of mean baseline score) and controlling α-level at 0.05. No multiple comparisons adjustment was employed since these outcomes evaluated the toxicity of the study treatment. A collection of PROs and QoL from all patients enrolled in the main study was expected to provide sufficient statistical power to detect important differences between the 2 treatment arms.

Randomisation

Patients were randomised in a 1:1 ratio to either olaparib or placebo for up to a maximum of 12 months.

Randomisation used permuted blocks and was stratified by:

- hormone receptor status (ER and/or PgR positive/HER2 negative vs TNBC),
- prior neoadjuvant vs adjuvant chemotherapy,
- prior platinum use for breast cancer (yes vs no).

Blinding (masking)

OlympiA was a double-blind study.

Statistical methods

A superiority interim analysis of IDFS was protocolled to occur when half of the events required for the primary IDFS analysis (165 events) had been observed from the first 50% of patients recruited (i.e., from the first 900 patients). The IDFS interim analysis was to be performed on all 1836 recruited patients, whilst additionally providing a cohort of 900 patients with a similar level of maturity to that planned for the primary IDFS analysis.

Statistical methods

IDFS (Time from randomisation to invasive disease recurrence or death due to any cause):

- Primary analysis stratified log-rank test and Cox regression
- Key supportive analysis: stratified Cox regression in randomised patients confirmed as gBRCAm positive by central Myriad test (if different from FAS [ITT])

DDFS (Time from randomisation to distant recurrence or death due to any cause):

- Stratified log-rank test and Cox regression
- Key supportive analysis: stratified Cox regression in randomised patients confirmed as gBRCAm positive by central Myriad test (if different from FAS [ITT])

OS (Time from randomisation to death due to any cause):

- Stratified log-rank test and Cox regression
- Key supportive analysis: stratified Cox regression in randomised patients confirmed as gBRCAm positive by central Myriad test (if different from FAS [ITT])

- Incidence of contralateral invasive breast cancer, contralateral non-invasive breast cancer, new primary ovarian cancer, new primary fallopian tube cancer, and new primary peritoneal cancer: Fine and Gray models

FACIT-Fatigue:

- Primary analysis MMRM at 6 and 12 months
- Sensitivity analysis MMRM

EORTC QLQ-C30 GI symptoms and EORTC QLQ-C30 HRQoL: mixed model for repeated measures (MMRM)

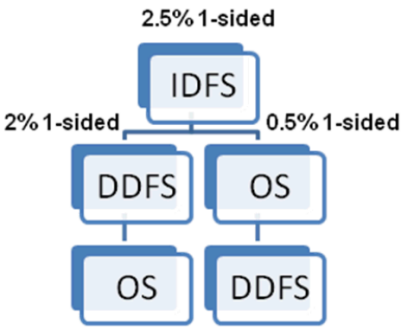
For the primary analysis, invasive disease free survival, p-values were calculated using a log-rank test stratified by the stratification factors determined by the pooling strategy. The hazard ratio (HR) was estimated using a Cox proportional hazards model with the same stratification factors as the log-rank test. The 2-sided 95% CIs were calculated using the profile likelihood approach. IDFS times were summarised using Kaplan-Meier (KM) survival curves and the percentages of surviving subjects who were invasive disease free at 1 year, 2 years, and 3 years from the time of randomisation were estimated from the KM curves. Approximate 95% confidence limits were calculated, based on Greenwood's formula for the standard error of the KM estimate.

Four IDFS sensitivity analyses were performed to assess the robustness of the primary analysis: including only patients with central pathology review data for hormone receptor status (ER and PgR), using unadjusted analysis, using interval censoring, and using the restricted mean survival time (RMST) method.

Exploratory subgroup analyses of IDFS in the full analysis set (FAS) were conducted to assess the consistency of treatment effect across potential or expected prognostic factors, including the baseline stratification factors.

A multiple testing procedure was employed across the IDFS, DDFS, and OS endpoints to strongly control the overall type I error at 5% 2-sided, accounting for any interim analyses on IDFS, DDFS and OS and also planned further analyses post the primary IDFS Data Cut Off (DCO).

A hierarchical testing strategy was employed where IDFS was tested first using the full test mass (i.e., full 5%, 2-sided alpha), then DDFS and OS were tested if IDFS was significant based on a weighted proportion of the test mass (4% for DDFS and 1% for OS, 2-sided) which was recycled to secondary endpoints not yet rejected. Testing stopped when the entire test mass was allocated to non-rejected endpoints (Figure 4).



DDFS = distant disease free survival; IDFS = invasive disease free survival; OS = overall survival.

Figure 4 OlympiA: Multiple testing procedure

Invasive disease free survival was planned to be analysed at the interim (165 IDFS events in the first 900 patients) and the primary (330 IDFS events) IDFS analysis. If IDFS was statistically significant at the interim based on the ITT population then secondary endpoints were formally tested at the interim based on the

MTP outlined above. To account for multiple analyses on each endpoint a separate alpha spending function was applied to each endpoint (Glimm et al 2010). It was anticipated that further analyses of DDFS and OS with more mature follow-up may have been required for which some alpha would be reserved for significance testing.

Study populations

- Full analysis set (FAS)
    - Intention-to-treat (ITT): This included all randomised patients and compared the treatment arms on the basis of randomised treatment, regardless of the treatment actually received. Note: it was anticipated that all patients would be randomised by the time of the interim analysis.
    - Mature cohort ITT population: This included the first 900 randomised patients only and compared the treatment arms on the basis of randomised treatment, regardless of the treatment actually received. This analysis was to be regarded as supportive, to aid interpretation of the result in the ITT population based on interim data. Statistical significance was not required for the mature cohort population.

  The primary analysis population was all patients randomised (ITT). A subgroup analysis (supportive) based on prior chemotherapy (adjuvant or neoadjuvant), prior platinum therapy (yes or no) and hormone receptor status (ER and/or PgR positive, HER2 negative versus TNBC) was conducted to check for consistency in the treatment effect.

- Safety Analysis Set (SAS): All patients who received at least one dose of randomised study treatment, olaparib or placebo, were to be included in the SAS. If a patient received at least one dose of olaparib he/she was included in the olaparib arm for safety summaries (ie, olaparib arm included patients randomised to olaparib who received at least one dose of olaparib or placebo patients who received at least one dose of olaparib in error at any time). If a patient randomised to olaparib received only placebo treatment, then he/she was summarised as part of the placebo arm.
- PK Analysis Set: Approximately 150 patients randomised to olaparib/placebo will have provided PK samples at those sites that had confirmed that they were able to collect the PK assessment samples. Placebo samples were not analysed unless specified. Pharmacokinetic sampling was performed in a subset of patients who had signed the optional PK informed consent. Pharmacokinetic data were analysed according to treatment received. This population comprised those that were randomised to olaparib who received at least one dose of study treatment, had at least one PK sample collected, and did not violate or deviate from the Clinical Study Protocol (CSP) in ways that would have significantly affected the PK analyses.
- PRO Analysis Set: This population comprised patients who consented to participate in the PRO assessment portion of the study, who started treatment and who provided evaluable baseline FACIT-Fatigue or EORTC QLQ-C30 data, where evaluable means that at least one sub-scale baseline score was determined. Baseline was defined as the last result on or before the first day of study drug. For patients who were randomised but not treated, baseline was not derived and they were to be excluded from the PRO analysis set. Since the PRO analysis set included those with an evaluable baseline score for either the FACIT-Fatigue or the EORTC QLQ-C30, the analyses for each questionnaire were based on a subset of the PRO analysis set with an evaluable baseline for that questionnaire. The PRO analysis was to be summarised by planned treatment arm.

Patient reported outcomes

Hypotheses

The hypotheses and measurement strategy focused on the fact that patients in the study would be starting with significant decrements in HRQoL and high rates of symptoms at study entry (baseline) due to previous chemotherapy and local treatments (surgery with or without radiation therapy). Therefore, the following hypotheses were proposed based on the expected toxicities of olaparib.

Primary PRO Hypothesis

Patients receiving olaparib may experience greater fatigue severity during treatment than those receiving placebo as measured by the FACIT-Fatigue scale at 6 and 12 months after randomisation.

No multiple comparisons adjustments were to be employed since these outcomes evaluate the toxicity of the study treatment.

Secondary PRO Hypotheses

- Patients receiving olaparib may experience greater GI symptoms (nausea/vomiting, diarrhoea, and pain) severity during treatment than those receiving placebo as measured at 6 and 12 months after randomisation but no difference expected by 24 months after randomisation.
- There will be no difference in fatigue post-discontinuation of study treatment as measured at 18 and 24 months.
- There will be no difference in QoL between the two treatment arms as measured by the global health status/QoL score and other functional sub-scales from the EORTC QLQ-C30 at 6, 12, 18, and 24 months after randomisation and patients will demonstrate improvements in functioning over time.

All secondary analyses were considered exploratory and therefore no adjustments for multiplicity were to be made.

The FACIT-Fatigue and EORTC QLQ-C30 questionnaires were completed at baseline (prior to randomisation) and every 6 months for a period of 2 years.

Results

Participant flow

Germline *BRCA* testing results in OlympiA and routes to randomisation

In total, 14387 patients were screened for entry into OlympiA. This includes 203 patients with unknown gBRCA status (due to no sample available for testing and no pre-existing local gBRCA result), resulting in 14184 patients with pre-existing available local gBRCA result or a blood sample available for testing. Of these patients, 1114 patients had a pre-existing gBRCA result from local testing, 2515 patients were screened prospectively in China using the BGI test, 10554 patients were screened prospectively using the Myriad CLIA or CDx gBRCA test and 1 patient was prospectively tested at Myriad under the SOLO3 study. Within patients meeting the OlympiA study eligibility criteria, 1114 patients were randomised based on an existing local gBRCA result, 474 based on a Myriad gBRCA CLIA or CDx result, 247 based on a gBRCA result from BGI testing in China and the remaining patient was prospectively tested at Myriad under the SOLO3 study (no result was reported under OlympiA study ID). In total, 1836 patients were randomised onto the OlympiA study.

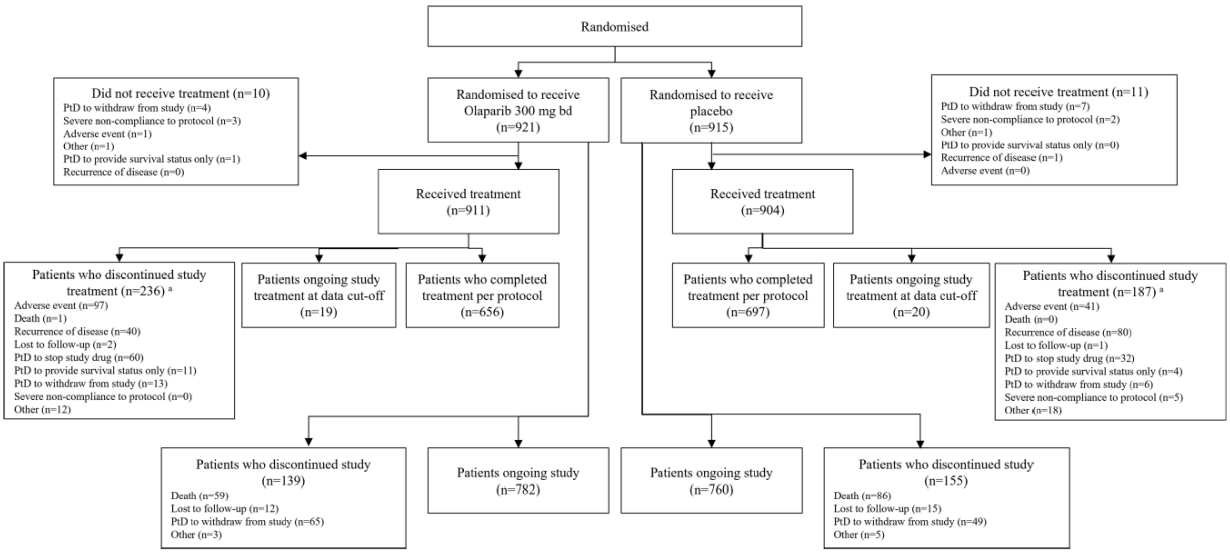
Participant flow

A total of 1836 patients with breast cancer and gBRCA1/2 mutations were randomised to receive either olaparib 300 mg bd (n=921) or placebo (n=915). At the DCO date (27 March 2020), 1353 patients (73.7%) had completed study treatment per CSP and 39 patients (2.1%) were still receiving study treatment.

Of 1836 patients randomized, 21 patients did not receive their planned study medication (10 patients in the olaparib arm, 11 patients in the placebo arm).

A higher proportion of olaparib-treated patients than placebo-treated patients discontinued study treatment due to AEs (97 patients [10.5%] versus 41 patients [4.5%]) and patient decision to stop study drug (60 patients [6.5%] versus 32 patients [3.5%]). A lower proportion of olaparib-treated patients than placebo-treated patients discontinued study treatment due to recurrence of disease (40 patients [4.3%] versus 80 patients [8.7%]).

The majority of patients (73.7%) completed 12 months of treatment per protocol, with a similar proportion of patients in each treatment arm: 19 patients and 20 patients are still ongoing study treatment at data cut-off in olaparib and placebo arm respectively.



[a] Does not include patients who did not receive treatment.
n = number of patients in the category or analysis; PtD = patient decision
Source: Table 14.1.1.1 and Table 14.1.1.2.

Figure 5: Patient disposition in OlympiA

Recruitment

A total of 1836 patients with breast cancer and gBRCA1/2 mutations were randomised from 546 centres in 23 countries worldwide: Austria, Argentina, Australia, Belgium, Canada, China, France, Germany, Israel, Japan, United Kingdom and Northern Ireland, Hungary, Iceland, Italy, Netherlands, Poland, Portugal, Province of China, Republic of Korea, Spain, Sweden, Switzerland, Taiwan, USA.

First patient enrolled: 22 April 2014

Last subject enrolled: 17 April 2019

Data cut-off date: 27 March 2020

Conduct of the study

Premature unblinding

A total of 133 participants were prematurely unblinded as follows (DCO):

- olaparib arm: n=45 patients [4.9%]. One patient was unblinded prior to the investigator-assessed IDFS event and 36 patients were unblinded on or after an IDFS event. Eight patients did not have an IDFS event; all of which were unblinded after discontinuation of randomised study treatment.
- placebo arm: n=88 patients [9.6%]. Two patients were unblinded prior to investigator-assessed IDFS event and 82 patients were unblinded on or after an IDFS event. Four patients did not have an IDFS event; all of which were unblinded after discontinuation of randomised study treatment.

Protocol deviations

The number of patients with important protocol deviations and important GCP violations in each treatment arm and overall is summarised in **Table 6**.

Table 6. Patients with Important Protocol Deviations (FAS)

	Number (%) of patients		
	Olaparib 300 mg bd (N=921)	Placebo (N=915)	Total (N=1836)
Number of patients with at least one important protocol deviation excl. important GCP violations [a]	**130 (14.1)**	**122 (13.3)**	**252 (13.7)**
No histologically confirmed non-metastatic primary invasive adenocarcinoma of the breast	3 (0.3)	0	3 (0.2)
No documented germline mutation in *BRCA1* or *BRCA2*	3 (0.3)	3 (0.3)	6 (0.3)
Randomised but did not receive any study treatment	10 (1.1)	11 (1.2)	21 (1.1)
Not fulfilling criteria for high risk disease	25 (2.7)	12 (1.3)	37 (2.0)
Inadequate breast surgery and/or radiotherapy	7 (0.8)	8 (0.9)	15 (0.8)
Inadequate axilla surgery	5 (0.5)	1 (0.1)	6 (0.3)
Completed less than 6 cycles of neoadjuvant or adjuvant chemotherapy containing anthracyclines, taxanes or the combination of both	7 (0.8)	15 (1.6)	22 (1.2)
Peri-operative chemotherapy (patients who had both neoadjuvant and adjuvant therapy; 'unquantifiable risk of disease relapse')	4 (0.4)	6 (0.7)	10 (0.5)
Evidence of metastatic disease (to include only those patients who had suspicion or confirmation of recurrence prior to randomisation)	2 (0.2)	4 (0.4)	6 (0.3)
No staging or insufficient staging	67 (7.3)	66 (7.2)	133 (7.2)
Prior PARP inhibitor use	0	0	0
Prior cancer <5 years ago including MDS/t-AML	0	2 (0.2)	2 (0.1)
Received no study treatment whatsoever for a period of more than 7 days due to errors in dispensing of medication	5 (0.5)	4 (0.4)	9 (0.5)
Received an alternative study treatment to that which they were randomised	0	0	0
Received prohibited concomitant medication	5 (0.5)	4 (0.4)	9 (0.5)
Lack of confirmatory exams for events that count towards the analysis endpoints, efficacy and safety	0	1 (0.1)	1 (0.1)
Received additional anti-cancer therapy prior to IDFS event [b]	0	0	0
Received other investigational agent prior to IDFS event	0	0	0

	Number (%) of patients		
	Olaparib 300 mg bd (N=921)	Placebo (N=915)	Total (N=1836)
Number of patients with at least one important GCP violation	**41 (4.5)**	**39 (4.3)**	**80 (4.4)**
GCP violation relating to informed consent	26 (2.8)	22 (2.4)	48 (2.6)
GCP violation relating to serious adverse events	2 (0.2)	10 (1.1)	12 (0.7)
GCP violation: Other	13 (1.4)	7 (0.8)	20 (1.1)

[a] Important protocol deviations were those that could have had a strong influence on the interpretation of the efficacy or safety results. Excluding GCP violations.

[b] Other than hormone therapy permitted in the protocol.

The same patient may have had more than one important protocol deviation.

There was a data privacy breach with a patient's details sent by email, but all correspondence was deleted without a patient ID recorded so this important protocol deviation could not be included in the table.

bd = twice daily; *BRCA* = breast cancer susceptibility gene; FAS = full analysis set; GCP = Good Clinical Practice; IDFS = invasive disease free survival; MDS = myelodysplastic syndrome; N = total number of patients; PARP = polyadenosine 5'diphosphoribose polymerase; t-AML therapy-related acute myeloid leukaemia.

Source: Table 14.1.2.

Protocol amendment

Important amendments to the original CSP (ROW CSP: Version 1.0, dated 25 October 2013), including when those amendments came into effect with respect to the recruitment of patients, and other significant changes to study conduct are shown in Table 7.

Table 7 : Protocol Amendments Related to Changes in Study Conduct

RoW CSP Version/US CSP amendment (Date)	Key details of amendment	Main reason(s) for amendment
Amendments made after the start of patient recruitment		
ROW CSP: 3.0 (21Oct2015) US CSP Amendment 2.0 (19Oct2015)	Target patient population for the study updated to include ER and/or PgR positive high-risk HER2 negative patient population.	Extrapolations from the metastatic setting supported the expectations that these patients would also benefit from adjuvant olaparib treatment.
	New secondary PK objective and endpoint included: To determine the exposure to olaparib (in plasma) in patients receiving olaparib as adjuvant therapy.	Implemented PK analysis in a subset of patients who signed an optional PK Informed consent.
	Addition of hormone receptor status (ER and/or PgR positive, HER2 negative versus TNBC) to the stratification factors.	Addition of ER and/or PgR positive high-risk HER2 negative patient population.
	New exploratory study objective included: To assess the consistency of treatment effects on efficacy endpoints across potential or expected prognostic factors, including the baseline stratification factors with special emphasis on hormone receptor status.	Stratification factors updated.
	Randomisation window wording changed to say patients were to be randomised in the study ideally within a maximum of 8 weeks of completing their last treatment modality (chemotherapy and definitive local or locoregional treatment), but in no case longer than 12 weeks.	Randomisation window extended.

RoW CSP Version/US CSP amendment (Date)	Key details of amendment	Main reason(s) for amendment
	Following changes made to inclusion criteria: 3 and 4: updated to include specific requirements and definitions for ER and/or PgR positive, HER 2 negative patients. 5: clarified that local *gBRCA* testing results, if available, could be used for establishing eligibility and that if local *gBRCA* testing results were not available, central testing would be provided for those patients who otherwise appeared to be eligible. 6: definitions for completed adequate breast surgery and completed adequate axilla surgery clarified. 7: clarified that for neoadjuvant patients all chemotherapy should be delivered prior to surgery and that no further cycles of chemotherapy post surgery are allowed 8: removal of 'no blood transfusions in the past 28 days' and clarification that CT/MRI was to be performed at any time point between diagnosis of current breast cancer and randomisation. 9: addition of 'plasma' creatinine 11: updated to clarify definition of female patients of childbearing potential and the requirements for birth control. 13: updated to clarify requirements for mandatory tumour sample collection from adjuvant and neoadjuvant patients. 14: added to state that patients should be randomised in the study ideally within a maximum of 8 weeks of completion of their last treatment, but in no case longer than 12 weeks. Following changes made to exclusion criteria: 4: clarification that liver ultrasound/CT/MRI was to be performed at any time point between diagnosis of current breast cancer and randomisation. 9 and 10: timing of systemic radiotherapy and adjuvant radiotherapy, respectively, changed to within 3 weeks prior to randomisation and within 2 weeks prior to randomisation, not start of study treatment. 13: clarification that AML did not have to be treatment related, and patients with features suggestive of MDS/AML were also excluded. 14: timing of major surgery changed to within 2 weeks prior to randomisation, not start of study treatment.	Inclusion and exclusion criteria updated.

RoW CSP Version/US CSP amendment (Date)	Key details of amendment	Main reason(s) for amendment
	Number of study centres increased from approximately 300 to 500 in the US and ROW countries and number of patients randomised increased from 1320 to 1500 patients. Approximately 150 randomised patients were to be analysed for PK at sites that were able to collect the PK assessment samples.	Implemented PK analysis in a subset of patients who signed an optional PK Informed consent.
	PK analysis included in the study schedule and PK methods added: The plasma concentration-time data were to be analysed by non-linear mixed effects modelling in order to evaluate the PK characteristics of olaparib, quantify variability in the PK, identify demographic or pathophysiological covariates, which may explain the observed variability and explore exposure-response relationships. PK sample timings/collection/handling and sample analysis details included.	
	Family history of cancer added to the study schedule for collection at screening.	Collection of the family cancer history.
ROW CSP: 4.0 (23Mar2017) US CSP Amendment 4.0 (25Jul2017)	Inclusion criterion 4 wording changed to remove "All ER and PgR assessments that are locally available must be negative" from the TNBC definition and "Any tumour that has been locally assessed as ER and/or PgR positive in either the core biopsy or the surgical specimen is considered to be ER and/or PgR positive" removed from the ER and/or PgR positive, HER2 negative breast cancer definition.	Wording was overly restrictive for patients with tumours classified as TNBC based on the receptor status analysis from the core needle biopsy, but who had low levels of peroxidase staining for ER and PgR in their post-neoadjuvant surgical specimen.
ROW CSP: 5.0 (18May2018) US CSP Amendment 6.0 (27Jul2018)	Number of study centres increased from approximately 500 to 700 in the US and ROW countries and number of patients randomised increased from 1500 to 1800 patients.	The simulations that were run support the addition of the ER positive cohort to the study were too pessimistic with respect to event rates for the triple negative adjuvant population. Based on extracted study data new predictions were run which indicated the need to increase the sample size to 1800.
	The estimation for study recruitment was increased to 5 years.	To account for the 300 extra patients.
	Removal of the minimum 24-month follow-up from the DCO for the primary analysis.	The expected high event rate in the first 2 years had not been seen.
	Confirmed that the interim analysis would be triggered by events in the first 900 patients (previously 750 patients).	To account for the continued randomisation of patients.

Baseline data

The demographic and key baseline characteristics of FAS and Myriad gBRCAm patients are summarised in Table 8.

The Myriad gBRCAm patient population excluded patients with only a local or Breast International Group (BIG) result. Out of 1836 patients enrolled into OlympiA, 1623 were confirmed as g*BRCA*m by central testing, either prospectively (n=474) or retrospectively (n=1149, based on local or BIG result).

Table 8: Patient Demographics (FAS: Overall and Myriad gBRCAm Patients DCO 27 March 2020)

	Number (%) of patients					
	Full analysis set			**Myriad *gBRCAm* patients**		
	Olaparib 300 mg bd (N=921)	**Placebo (N=915)**	**Total (N=1836)**	**Olaparib 300 mg bd (N=816)**	**Placebo (N=807)**	**Total (N=1623)**
Sponsor						
AstraZeneca	810 (87.9)	806 (88.1)	1616 (88.0)	712 (87.3%)	704 (87.2%)	1416 (87.2%)
NRG	111 (12.1)	109 (11.9)	220 (12.0)	104 (12.7%)	103 (12.8%)	207 (12.8%)
Geographic region						
North America	122 (13.2)	132 (14.4)	254 (13.8)	114 (14.0%)	126 (15.6%)	240 (14.8%)
South America	16 (1.7)	12 (1.3)	28 (1.5)	14 (1.7%)	12 (1.5%)	26 (1.6%)
Europe	481 (52.2)	452 (49.4)	933 (50.8)	466 (57.1%)	437 (54.2%)	903 (55.6%)
Asia Pacific and South Africa [a]	302 (32.8)	319 (34.9)	621 (33.8)	222 (27.2%)	232 (28.7%)	454 (28.0%)
Age (years) [b]						
Mean (SD)	43.0 (9.82)	43.6 (10.12)	43.3 (9.97)	42.9 (9.89)	43.8 (10.13)	43.4 (10.02)
Median (range)	42.0 (22-77)	43.0 (24-78)	42.0 (22-78)	42.0 (22-77)	43.0 (24-78)	42.0 (22-78)
Age groups						
<30 years	51 (5.5)	59 (6.4)	110 (6.0)	46 (5.6%)	47 (5.8%)	93 (5.7%)
30-39 years	333 (36.2)	306 (33.4)	639 (34.8)	296 (36.3%)	267 (33.1%)	563 (34.7%)
40-49 years	315 (34.2)	308 (33.7)	623 (33.9)	275 (33.7%)	278 (34.4%)	553 (34.1%)
50-59 years	166 (18.0)	172 (18.8)	338 (18.4)	150 (18.4%)	150 (18.6%)	300 (18.5%)
60-69 years	48 (5.2)	66 (7.2)	114 (6.2)	41 (5.0%)	61 (7.6%)	102 (6.3%)
≥70 years	8 (0.9)	4 (0.4)	12 (0.7)	8 (1.0%)	4 (0.5%)	12 (0.7%)
Age groups (alternative categorisation)						

	Number (%) of patients					
	Full analysis set			Myriad *gBRCAm* patients		
	Olaparib 300 mg bd (N=921)	Placebo (N=915)	Total (N=1836)	Olaparib 300 mg bd (N=816)	Placebo (N=807)	Total (N=1623)
<65 years	892 (96.9)	883 (96.5)	1775 (96.7)	790 (96.8%)	775 (96.0%)	1565 (96.4%)
65-84	29 (3.1)	32 (3.5)	61 (3.3)	26 (3.2%)	32 (4.0%)	58 (3.6%)
≥85	0	0	0	0	0	0
Sex						
Female	919 (99.8)	911 (99.6)	1830 (99.7)	814 (99.8%)	803 (99.5%)	1617 (99.6%)
Male	2 (0.2)	4 (0.4)	6 (0.3)	2 (0.2%)	4 (0.5%)	6 (0.4%)
Race						
White	626 (68.0)	599 (65.5)	1225 (66.7)	602 (73.8%)	580 (71.9%)	1182 (72.8%)
Asian	259 (28.1)	272 (29.7)	531 (28.9)	180 (22.1%)	186 (23.0%)	366 (22.6%)
Black or African American	19 (2.1)	29 (3.2)	48 (2.6)	19 (2.3%)	27 (3.3%)	46 (2.8%)
Native Hawaiian or other Pacific Islander	1 (0.1)	0	1 (0.1)	1 (0.1%)	0 (0.0%)	1 (0.1%)
American Indian or Alaska native	3 (0.3)	1 (0.1)	4 (0.2)	3 (0.4%)	1 (0.1%)	4 (0.2%)
Other	3 (0.3)	6 (0.7)	9 (0.5)	3 (0.4%)	5 (0.6%)	8 (0.5%)
Missing [c]	10 (1.1)	8 (0.9)	18 (1.0)	8 (1.0%)	8 (1.0%)	16 (1.0%)

[a] There were no patients from South Africa in the study.

Age was calculated as the patient's age at randomisation.

'Not reported', 'Not recorded', and 'Unknown' are included as missing.

bd = twice daily; FAS = full analysis set; *gBRCAm* = germline *BRCA* mutations; N = total number of patients; SD = standard deviation.

Baseline patient characteristics of height, weight, BMI, menopausal status, and ECOG performance status for the FAS are summarised in Table 9.

Table 9 : Baseline patient characteristics (FAS)

	Olaparib 300 mg bd (N=921)	Placebo (N=915)	Overall (N=1836)
Height (cm)			
Mean	162.9	163.1	163.0
SD	6.75	6.91	6.83
Median	162.2	163.0	163.0
Min	143	117	117
Max	183	185	185
Missing	3 (0.3%)	3 (0.3%)	6 (0.3%)
Weight (kg)			
Mean	68.1	69.2	68.7
SD	16.56	16.38	16.47
Median	65.0	65.4	65.0
Min	39	38	38
Max	162	146	162
Missing	1 (0.1%)	0 (0.0%)	1 (0.1%)
Weight group (kg)			
<55 kg	179 (19.4%)	149 (16.3%)	328 (17.9%)
[55 - 75 kg)	487 (52.9%)	489 (53.4%)	976 (53.2%)
>= 75 kg	254 (27.6%)	277 (30.3%)	531 (28.9%)
Missing	1 (0.1%)	0 (0.0%)	1 (0.1%)
Body mass index (kg/m2) [1]			
Mean	25.6	25.9	25.8
SD	5.71	5.58	5.65
Median	24.2	24.7	24.5
Min	16	16	16
Max	59	57	59
Missing	3 (0.3%)	3 (0.3%)	6 (0.3%)
Body mass index (kg/m2) group			
< 18.5 kg/m2	34 (3.7%)	25 (2.7%)	59 (3.2%)
[18.5 kg/m2 - 25 kg/m2)	469 (50.9%)	451 (49.3%)	920 (50.1%)
[25 kg/m2 - 30 kg/m2)	251 (27.3%)	248 (27.1%)	499 (27.2%)
>= 30 kg/m2	164 (17.8%)	188 (20.5%)	352 (19.2%)
Missing	3 (0.3%)	3 (0.3%)	6 (0.3%)
Menopausal status [2]			
Premenopausal	572 (62.1%)	553 (60.4%)	1125 (61.3%)
Postmenopausal	347 (37.7%)	358 (39.1%)	705 (38.4%)
Male	2 (0.2%)	4 (0.4%)	6 (0.3%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
ECOG performance status			
0: Fully Active	824 (89.5%)	804 (87.9%)	1628 (88.7%)
1: Restricted work	97 (10.5%)	111 (12.1%)	208 (11.3%)
2: Ambulatory	0 (0.0%)	0 (0.0%)	0 (0.0%)
3: Limited self-care	0 (0.0%)	0 (0.0%)	0 (0.0%)
4: Disabled	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing [3]	0 (0.0%)	0 (0.0%)	0 (0.0%)

[1] Body Mass Index = weight (kg) / (height (m)^2)
[2] Menopausal status is collected at screening.
[3] Includes ECOG 'not performed' and 'missing'.

The baseline patient and disease characteristics of FAS are summarised in

Table **10**.

Table 10 : Baseline Patient and Disease Characteristics (FAS)

	Number (%) Patients		
	Olaparib 300 mg bd (N=921)	**Placebo (N=915)**	**Total (N=1836)**
Hormone Receptor Status			
TNBC [a]	753 (81.8)	758 (82.8)	1511 (82.3)
ER and/or PgR positive, HER2-negative	168 (18.2)	157 (17.2)	325 (17.7)
Prior Platinum			
No	674 (73.2)	677 (74.0)	1351 (73.6)
Yes	247 (26.8)	238 (26.0)	485 (26.4)
Prior Chemotherapy			
Adjuvant	461 (50.1)	455 (49.7)	916 (49.9)
Neoadjuvant	460 (49.9)	460 (50.3)	920 (50.1)
Prior Chemotherapy by Hormone Receptor Status			
Adjuvant TNBC	397 (43.1)	390 (42.6)	787 (42.9)
Adjuvant ER and/or PgR positive, HER2-negative	64 (6.9)	65 (7.1)	129 (7.0)
Neoadjuvant TNBC [a]	356 (38.7)	368 (40.2)	724 (39.4)
Neoadjuvant ER and/or PgR positive, HER2-negative	104 (11.3)	92 (10.1)	196 (10.7)
Baseline *BRCA* Status			
BRCA1	656 (71.2)	669 (73.1)	1325 (72.2)
BRCA2	260 (28.2)	238 (26.0)	498 (27.1)
BRCA1&2	2 (0.2)	5 (0.5)	7 (0.4)

	Number (%) Patients		
	Olaparib 300 mg bd (N=921)	**Placebo (N=915)**	**Total (N=1836)**
No *gBRCA* mutation	2 (0.2)	3 (0.3)	5 (0.3)
Missing	1 (0.1)	0	1 (0.1)
Prior Neoadjuvant/Adjuvant Chemotherapy for Primary Breast Cancer			
Anthracycline and taxane regimen	871 (94.6)	849 (92.8)	1720 (93.7)
Anthracycline regimen (without taxane)	7 (0.8)	13 (1.4)	20 (1.1)
Taxane regimen (without anthracycline)	43 (4.7)	52 (5.7)	95 (5.2)
Missing	0	1 (0.1)	1 (0.1)
Primary Breast Cancer Surgery Prior to Randomisation			
Primary breast cancer surgery	921 (100.0)	913 (99.8)	1834 (99.9)
Non-conservative surgery	698 (75.8)	673 (73.6)	1371 (74.7)
Conservative surgery	223 (24.2)	240 (26.2)	463 (25.2)
Unknown [b]	0	2 (0.2)	2 (0.1)

[a] Post randomisation 2 patients (included as TNBC) were found not to have confirmed negative HER2 status. These patients were captured as important protocol deviations in category 'No histologically confirmed non-metastatic primary invasive adenocarcinoma of the breast'.

[b] E106578 (placebo) was reported to have right mastectomy (DCIS) in 2001 in the concomitant procedure of the eCRF, the patient received axillary lymph node dissection (pN1) prior to entering OlympiA study. E112449 (placebo) was reported to have occult breast carcinoma on the histology report and no visible tumour in the breast per MRI; the patient received axillary lymph node dissection (pN1) prior to entering OlympiA study.

bd = twice daily; *BRCA* = breast cancer susceptibility gene; eCRF = electronic case report form; ER = oestrogen receptor; *gBRCA* = germline *BRCA*; HER2 = human epidermal growth factor receptor 2; N = total number of patients; PgR = progesterone receptor; TNBC = triple negative breast cancer.

Source: Table 14.1.6, Table 14.1.7, Table 14.1.15.1, and Appendix 16.1.13, Table 2838.1, and Table 2842.2.

Pathological characteristics of primary breast cancer are summarised in Table 11.

Table 11 : Pathological Characteristics of Primary Breast Cancer at Baseline (FAS Population)

Number (%) of patients			
	Full analysis set		
	Olaparib 300 mg bd (N=921)	Placebo (N=915)	Total (N=1836)
Clinical stage of distant metastases			
M0	826 (89.7)	815 (89.1)	1641 (89.4)
M1	0	0	0
Missing	95 (10.3)	100 (10.9)	195 (10.6)
Clinical AJCC stage			
IA	103 (11.2)	85 (9.3)	188 (10.2)
IB	0	0	0
IIA	329 (35.7)	334 (36.5)	663 (36.1)
IIB	190 (20.6)	195 (21.3)	385 (21.0)
IIIA	128 (13.9)	111 (12.1)	239 (13.0)
IIIB	28 (3.0)	30 (3.3)	58 (3.2)
IIIC	42 (4.6)	56 (6.1)	98 (5.3)
IV	0	0	0
Missing	101 (11.0)	104 (11.4)	205 (11.2)
Pathological stage of distant metastases			
M0	921 (100)	915 (100)	1836 (100)
M1	0	0	0
Missing	0	0	0

AJCC = American Joint Committee on Cancer; bd = twice daily; *BRCA* = breast cancer susceptibility gene; FAS = full analysis set; *gBRCAm* = germline *BRCA* mutations; N = total number of patients; NOS = not otherwise specified.

Source: Table 14.1.17.1 and Table 14.1.17.1.2.

The concordance between overall hormone receptor status by local versus central laboratory result is presented in Table 12.

Table 12 : OlympiA: Central ER/PgR Expression Levels in Patients Locally identified as TNBC and Hormone Receptor Positive (FAS Population)

	Local TNBC (per eCRF) N = 1509	Local Hormone Receptor Positive (per eCRF) N = 325
Central hormone receptor positive, n (%)	106 (7.0)	240 (73.8)
Central ER 1% to < 10%	37 (2.5)	13 (4.0)
Central ER ≥ 10%	33 (2.2)	222 (68.3)
Central ER negative but PgR positive	36 (2.4)	5 (1.5)
Central hormone receptor negative, n (%)	1064 (70.5)	40 (12.3)
Central hormone receptor status missing, n (%)	339 (22.5)	45 (13.8)
Central ER% [a], n	1183	282
Mean (Std Dev)	1.3 (8.9)	62.0 (39.2)
Median (Q1 – Q3)	0 (0 - 0)	80.0 (15.0 – 95.0)
min – max	0 – 99	0 – 99
Central PgR% [a], n	1174	277
Mean (Std Dev)	0.6 (4.8)	29.6 (35.0)
Median (Q1 – Q3)	0 (0 – 0)	10.0 (0 – 60.0)
min – max	0 – 99	0 – 99

[a] Summary statistics for central ER% and PgR% include all central results.
Hormone receptor positive is defined as ER-positive and/or PgR positive
Two patients are excluded from the summary of the TNBC subset because they do not have confirmed HER2-negative status.
Central laboratory results were not available in China.
eCRF = electronic case report form; ER = oestrogen receptor; FAS = full analysis set; PgR = progesterone receptor; Q1-Q3 = interquartile range; StdDev = standard deviation; TNBC = triple negative breast cancer.
Source IEMT 3056.1, Appendix C.

A total of 50 patients were centrally identified as ER low (1% to 10% expression). Out of these 50 patients, the majority (41 patients [82%]) did not receive any concurrent endocrine therapy. 37 patients (74.0%) were identified as local TNBC patients and 13 (26.0%) as local Hormone Positive patients.

Prior and concomitant therapy

Previous disease-related cytotoxic chemotherapy treatments are summarised in Table 13 and prior and concurrent hormonal therapies in Table 14.

Table 13: Prior Chemotherapy, Bisphosphonates and Immunotherapy for Primary Breast Cancer in ≥5% of Patients Overall (FAS)

	Number (%) of patients		
	Olaparib 300 mg bd (N=921)	Placebo (N=915)	Total (N=1836)
Prior therapy in the adjuvant setting			
Antineoplastic agents	**465 (50.5)**	**461 (50.4)**	**926 (50.4)**
Anthracyclines and related substances	**439 (47.7)**	**423 (46.2)**	**862 (46.9)**
Doxorubicin	183 (19.9)	188 (20.5)	371 (20.2)
Epirubicin	238 (25.8)	221 (24.2)	459 (25.0)
Nitrogen mustard analogues	**442 (48.0)**	**432 (47.2)**	**874 (47.6)**
Cyclophosphamide	442 (48.0)	431 (47.1)	873 (47.5)
Platinum compounds	**80 (8.7)**	**72 (7.9)**	**152 (8.3)**
Carboplatin	76 (8.3)	67 (7.3)	143 (7.8)
Pyrimidine analogues	**84 (9.1)**	**67 (7.3)**	**151 (8.2)**
Flourouracil	84 (9.1)	63 (6.9)	147 (8.0)
Taxanes	**457 (49.6)**	**449 (49.1)**	**906 (49.3)**
Docetaxel	194 (21.1)	169 (18.5)	363 (19.8)
Paclitaxel	263 (28.6)	272 (29.7)	535 (29.1)
Prior therapy in the neoadjuvant setting			
Antineoplastic agents	**460 (49.9)**	**461 (50.4)**	**921 (50.2)**
Anthracyclines and related substances	**440 (47.8)**	**439 (48.0)**	**879 (47.9)**
Doxorubicin	207 (22.5)	207 (22.6)	414 (22.5)
Epirubicin	226 (24.5)	226 (24.7)	452 (24.6)
Nitrogen mustard analogues	**425 (46.1)**	**428 (46.8)**	**853 (46.5)**
Cyclophosphamide	425 (46.1)	428 (46.8)	853 (46.5)
Platinum compounds	**167 (18.1)**	**168 (18.4)**	**335 (18.2)**
Carboplatin	160 (17.4)	155 (16.9)	315 (17.2)
Pyrimidine analogues	**74 (8.0)**	**82 (9.0)**	**156 (8.5)**
Flourouracil	73 (7.9)	79 (8.6)	152 (8.3)
Taxanes	**457 (49.6)**	**454 (49.6)**	**911 (49.6)**
Docetaxel	149 (16.2)	150 (16.4)	299 (16.3)
Paclitaxel	293 (31.8)	287 (31.4)	580 (31.6)

Each treatment was counted a maximum of once per patient.

Categorised according to the WHO Drug Dictionary B2 Enhanced with Herbal Dictionary (release date March 2018).

Patients received adjuvant endocrine therapy per local policy and/or international guidelines. Overall, 291 (89.5%) of the ER and/or PgR positive, HER2 negative patients received concurrent hormone therapy including 146 patients (86.9%) in the olaparib arm and 145 patients (92.4%) in the placebo arm.

Table 14 : Prior and/or Concurrent Hormone Therapy for Primary Breast Cancer in the ER and/or PgR Positive, HER2 Negative Subgroup in ≥10% of Patients Overall (FAS)

	Olaparib 300 mg bd (N=168)	Placebo (N=157)	Overall (N=325)
All HR+/HER2- patients [1]	**168 (100.0%)**	**157 (100.0%)**	**325 (100.0%)**
Any prior and/or concurrent hormone therapy	**146 (86.9%)**	**145 (92.4%)**	**291 (89.5%)**
Diagnostic agents	1 (0.6%)	0 (0.0%)	1 (0.3%)
Tests for fertility disturbances	1 (0.6%)	0 (0.0%)	1 (0.3%)
Gonadorelin	1 (0.6%)	0 (0.0%)	1 (0.3%)
Endocrine therapy	146 (86.9%)	145 (92.4%)	291 (89.5%)
Anti-estrogens	73 (43.5%)	64 (40.8%)	137 (42.2%)
Tamoxifen	73 (43.5%)	62 (39.5%)	135 (41.5%)
Toremifene	0 (0.0%)	2 (1.3%)	2 (0.6%)
Aromatase inhibitors	85 (50.6%)	89 (56.7%)	174 (53.5%)
Anastrozole	26 (15.5%)	31 (19.7%)	57 (17.5%)
Exemestane	23 (13.7%)	27 (17.2%)	50 (15.4%)
Letrozole	43 (25.6%)	39 (24.8%)	82 (25.2%)
Gonadotropin releasing hormone analogues	37 (22.0%)	35 (22.3%)	72 (22.2%)
Goserelin	28 (16.7%)	20 (12.7%)	48 (14.8%)
Goserelin acetate	0 (0.0%)	1 (0.6%)	1 (0.3%)
Leuprorelin	8 (4.8%)	12 (7.6%)	20 (6.2%)
Triptorelin	1 (0.6%)	3 (1.9%)	4 (1.2%)
Triptorelin acetate	2 (1.2%)	0 (0.0%)	2 (0.6%)
Pituitary and hypothalamic hormones and analogues	4 (2.4%)	2 (1.3%)	6 (1.8%)
Gonadotropin-releasing hormones	4 (2.4%)	2 (1.3%)	6 (1.8%)
Gonadorelin	2 (1.2%)	2 (1.3%)	4 (1.2%)
Gonadotropin-releasing hormones	2 (1.2%)	0 (0.0%)	2 (0.6%)
Any prior hormone therapy	**8 (4.8%)**	**11 (7.0%)**	**19 (5.8%)**
Endocrine therapy	8 (4.8%)	11 (7.0%)	19 (5.8%)
Anti-estrogens	1 (0.6%)	3 (1.9%)	4 (1.2%)
Tamoxifen	1 (0.6%)	3 (1.9%)	4 (1.2%)
Aromatase inhibitors	4 (2.4%)	3 (1.9%)	7 (2.2%)
Anastrozole	1 (0.6%)	0 (0.0%)	1 (0.3%)
Exemestane	0 (0.0%)	2 (1.3%)	2 (0.6%)
Letrozole	3 (1.8%)	1 (0.6%)	4 (1.2%)
Gonadotropin releasing hormone analogues	3 (1.8%)	5 (3.2%)	8 (2.5%)
Goserelin	3 (1.8%)	3 (1.9%)	6 (1.8%)
Leuprorelin	0 (0.0%)	1 (0.6%)	1 (0.3%)
Triptorelin	0 (0.0%)	1 (0.6%)	1 (0.3%)
Any concurrent hormone therapy	**146 (86.9%)**	**145 (92.4%)**	**291 (89.5%)**
Diagnostic agents	1 (0.6%)	0 (0.0%)	1 (0.3%)
Tests for fertility disturbances	1 (0.6%)	0 (0.0%)	1 (0.3%)
Gonadorelin	1 (0.6%)	0 (0.0%)	1 (0.3%)
Endocrine therapy	146 (86.9%)	145 (92.4%)	291 (89.5%)
Anti-estrogens	72 (42.9%)	61 (38.9%)	133 (40.9%)
Tamoxifen	72 (42.9%)	59 (37.6%)	131 (40.3%)
Toremifene	0 (0.0%)	2 (1.3%)	2 (0.6%)
Aromatase inhibitors	83 (49.4%)	88 (56.1%)	171 (52.6%)
Anastrozole	25 (14.9%)	31 (19.7%)	56 (17.2%)
Exemestane	23 (13.7%)	25 (15.9%)	48 (14.8%)
Letrozole	41 (24.4%)	38 (24.2%)	79 (24.3%)
Gonadotropin releasing hormone analogues	35 (20.8%)	32 (20.4%)	67 (20.6%)
Goserelin	25 (14.9%)	18 (11.5%)	43 (13.2%)
Goserelin acetate	0 (0.0%)	1 (0.6%)	1 (0.3%)
Leuprorelin	8 (4.8%)	11 (7.0%)	19 (5.8%)
Triptorelin	1 (0.6%)	2 (1.3%)	3 (0.9%)
Triptorelin acetate	2 (1.2%)	0 (0.0%)	2 (0.6%)
Pituitary and hypothalamic hormones and analogues	4 (2.4%)	2 (1.3%)	6 (1.8%)
Gonadotropin-releasing hormones	4 (2.4%)	2 (1.3%)	6 (1.8%)
Gonadorelin	2 (1.2%)	2 (1.3%)	4 (1.2%)
Gonadotropin-releasing hormones	2 (1.2%)	0 (0.0%)	2 (0.6%)

Numbers analysed

The analysis sets and the number of patients in each analysis set are summarised in Table 15.

Table 15 : Analysis sets and number of patients in each analysis set

	Olaparib 300 mg bd (N=921)	Placebo (N=915)	Overall (N=1836)
Patients randomised	921 (100.0%)	915 (100.0%)	1836 (100.0%)
Patients in full analysis set	921 (100.0%)	915 (100.0%)	1836 (100.0%)
Patients not in full analysis set	0 (0.0%)	0 (0.0%)	0 (0.0%)
Patients in safety analysis set	911 (98.9%)	904 (98.8%)	1815 (98.9%)
Patients not in safety analysis set	10 (1.1%)	11 (1.2%)	21 (1.1%)
No treatment received	10 (1.1%)	11 (1.2%)	21 (1.1%)
Patients in the mature cohort	449 (48.8%)	451 (49.3%)	900 (49.0%)
Patients consented for PK assessments	90 (9.8%)	98 (10.7%)	188 (10.2%)
Patients included in PK analysis set	71 (7.7%)	0 (0.0%)	71 (3.9%)
Patients not included in PK analysis set	19 (2.1%)	98 (10.7%)	117 (6.4%)
No pharmacokinetic analysis done	17 (1.8%)	0 (0.0%)	17 (0.9%)
No treatment received	2 (0.2%)	0 (0.0%)	2 (0.1%)
Not on olaparib	0 (0.0%)	98 (10.7%)	98 (5.3%)
Patients consented for PRO assessments	908 (98.6%)	897 (98.0%)	1805 (98.3%)
Patients included in PRO analysis set	876 (95.1%)	875 (95.6%)	1751 (95.4%)
Patients not included in PRO analysis set	32 (3.5%)	22 (2.4%)	54 (2.9%)
No evaluable baseline QoL questionnaire	22 (2.4%)	11 (1.2%)	33 (1.8%)
No treatment received	10 (1.1%)	11 (1.2%)	21 (1.1%)
Protocol version at randomisation (full analysis set)			
RoW			
Version 1	178 (19.3%)	182 (19.9%)	360 (19.6%)
Version 2	266 (28.9%)	254 (27.8%)	520 (28.3%)
Version 4	263 (28.6%)	263 (28.7%)	526 (28.6%)
Version 5	103 (11.2%)	107 (11.7%)	210 (11.4%)
US			
Version 1	23 (2.5%)	25 (2.7%)	48 (2.6%)
Version 2	35 (3.8%)	36 (3.9%)	71 (3.9%)
Version 3	7 (0.8%)	8 (0.9%)	15 (0.8%)
Version 5	30 (3.3%)	33 (3.6%)	63 (3.4%)
Version 6	16 (1.7%)	7 (0.8%)	23 (1.3%)

Full analysis set - All randomised patients with a signed informed consent.
Mature cohort analysis set - first 900 randomised patients only.
PRO analysis set - patients who consent to participate in the Patient Reported Outcome (PRO) assessment portion of the study, who started treatment and completed at least the baseline PRO questionnaire.
Safety analysis set - all patients who received at least one dose of study treatment.
PK analysis set - patients who signed the optional PK informed consent form, were randomised to the olaparib arm, received at least one dose of study treatment and had at least one PK sample collected.
QoL - Quality of life

Outcomes and estimation

Primary variable

Primary endpoint: IDFS by investigator assessment (FAS, DCO 27 March 2020, **15.5% maturity**)

As the pre-defined statistical threshold for superiority of olaparib versus placebo for IDFS was met at the interim analysis (2-sided, 0.005 significance level), the superiority interim analysis reported constitutes the primary IDFS analysis for this study.

Median duration of follow-up was 2.3 years in the olaparib arm and 2.5 years in the placebo arm. The IDFS status based on investigator assessment at the time of the DCO is presented in Table 16.

Table 16 : Summary of Type of First IDFS Event (FAS)

	Number (%) of patients	
	Olaparib 300 mg bd (N=921)	**Placebo (N=915)**
IDFS events	**106 (11.5)**	**178 (19.5)**
Distant CNS recurrence	**22 (2.4)**	**36 (3.9)**
Brain metastasis	21 (2.3)	36 (3.9)
Meningitis carcinomatosa	1 (0.1)	0
Distant excl. CNS recurrence	**50 (5.4)**	**84 (9.2)**
Bone	5 (0.5)	14 (1.5)
Skin nodes (other than local or regional)	0	0
Lymph nodes (other than local or regional)	5 (0.5)	9 (1.0)
Lung	16 (1.7)	34 (3.7)
Liver	20 (2.2)	23 (2.5)
Pleural effusion	3 (0.3)	4 (0.4)
Other	1 (0.1)	0
Regional (ipsilateral) recurrence	**6 (0.7)**	**14 (1.5)**
Axillary lymph nodes	6 (0.7)	9 (1.0)
Infraclavicular lymph nodes	0	0
Supraclavicular lymph nodes	0	3 (0.3)
Internal mammary lymph nodes	0	1 (0.1)
Skin or soft tissue within the regional area	0	1 (0.1)
Local (ipsilateral) recurrence	**7 (0.8)**	**11 (1.2)**
Breast surgical scar	1 (0.1)	3 (0.3)
Breast	3 (0.3)	4 (0.4)
Anterior chest wall	2 (0.2)	2 (0.2)
Skin or soft tissue within the local area	1 (0.1)	2 (0.2)
Contralateral invasive breast cancer	**8 (0.9)**	**12 (1.3)**
New primary cancers	**11 (1.2)**	**21 (2.3)**
New primary invasive non-breast ovarian cancer	2 (0.2)	8 (0.9)
Ovarian cancer	1 (0.1)	4 (0.4)
Fallopian tube cancer	1 (0.1)	4 (0.4)
Peritoneal cancer	0	0
New primary invasive non-breast non-ovarian cancers	9 (1.0)	13 (1.4)
Deaths without a prior IDFS event	**2 (0.2)**	**0**

If 2 recurrence events were reported within 2 months of each other, this was referred to as a simultaneous event and was considered to be a single event. In this situation the worst case was taken as the event 'type' but the date of recurrence was the earliest date of the 2 events.

bd = twice daily; CNS = central nervous system; FAS = full analysis set; IDFS = invasive disease free survival.

Source: Table 14.2.1.

Table 17 : Analysis of IDFS (FAS)

	Olaparib 300 mg bd (N=921)	Placebo (N=915)
Olaparib vs placebo		
Number of events (%)	106 (11.5)	178 (19.5)
Estimate of HR [a]	0.581	
99.5% CI for HR [b, c]	0.409, 0.816	
95% CI for HR [c, d]	0.455, 0.737	
log-rank test: p-value [e]	0.0000073	
Median clinical follow-up time, years [f]	**2.3**	**2.5**
Minimum/Maximum	0/5.5	0/5.5
Percentage (95% CI) of patients invasive disease free at [g]		
1 year	93.3 (91.4, 94.8)	88.4 (86.1, 90.4)
2 years	89.2 (86.8, 91.3)	81.5 (78.6, 84.0)
3 years	85.9 (82.8, 88.4)	77.1 (73.7, 80.1)

[a] Estimate of the treatment HR was based on the stratified Cox's Proportional Hazards Model, <1 indicates a lower risk with olaparib compared with placebo arm. Stratification factors were the same as those used in the stratified log-rank test.

[b] Inferential, according to the alpha spending rules for the interim analysis.

[c] The CI for the HR was estimated using the profile likelihood approach.

[d] Exploratory, not inferential.

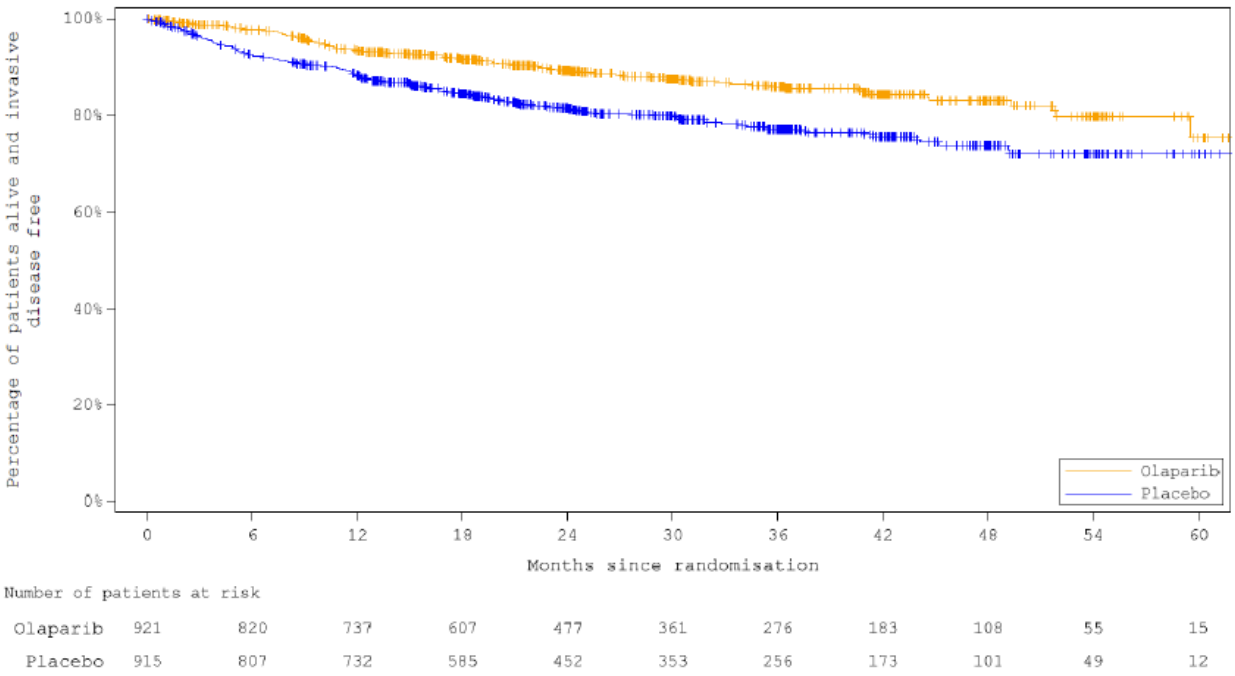
[e] P-value from a stratified log-rank test. Stratification was by chemotherapy type (2 levels: adjuvant versus neoadjuvant), hormone receptor status (2 levels: ER and/or PgR positive, HER2 negative versus TNBC), and prior platinum therapy (2 levels: yes versus no). Stratification factors were based upon the categories used in the randomisation system and were chosen by the pooling strategy. Once the pooling strategy was applied, only the hormone receptor status stratification factor was selected.

[f] Median clinical follow-up was calculated using the reverse censoring method.

[g] Percentage of patients were from the KM estimates and the 95% CIs were calculated using Greenwood's formula.

bd = twice daily; CI = confidence interval; FAS = full analysis set; ER = oestrogen receptor; HER2 = human epidermal growth factor receptor 2; HR = hazard ratio; IDFS = invasive disease free survival; KM = Kaplan-Meier PgR = progesterone receptor; TNBC = triple negative breast cancer.

Source: Table 14.2.3.



FAS = full analysis set; IDFS = invasive disease free survival.
Source: Figure 14.2.1.

Figure 6 : Kaplan-Meier Plot of IDFS (FAS)

Secondary variables

DDFS by investigator assessment (FAS, DCO 27 March 2020, 13% maturity)

Table 18 : Analysis of DDFS (FAS)

	Olaparib 300 mg bd (N=921)	Placebo (N=915)
Olaparib vs placebo		
Number of events (%)	89 (9.7)	152 (16.6)
Estimate of HR [a]	0.574	
99.5% CI for HR [b, c]	0.392, 0.831	
95% CI for HR [b, d]	0.441, 0.744	
log-rank test: p-value [e]	0.0000257	
Median clinical follow-up time, years	**2.3**	**2.5**
Minimum/Maximum	0/5.5	0/5.5
Percentage (95% CI) of patients distant disease free at [f]		
1 year	94.3 (92.4, 95.6)	90.2 (88.1, 92.0)
2 years	90.0 (87.6, 92.0)	83.9 (81.2, 86.3)
3 years	87.5 (84.6, 89.9)	80.4 (77.2, 83.3)

[a] Estimate of the treatment HR was based on the stratified Cox's Proportional Hazards Model, <1 indicates a lower risk with olaparib compared with placebo arm. Stratification factors were the same as those used in the stratified log-rank test.

[b] The CI for the HR was estimated using the profile likelihood approach.

[c] Inferential, according to the alpha spending rules for the interim analysis.

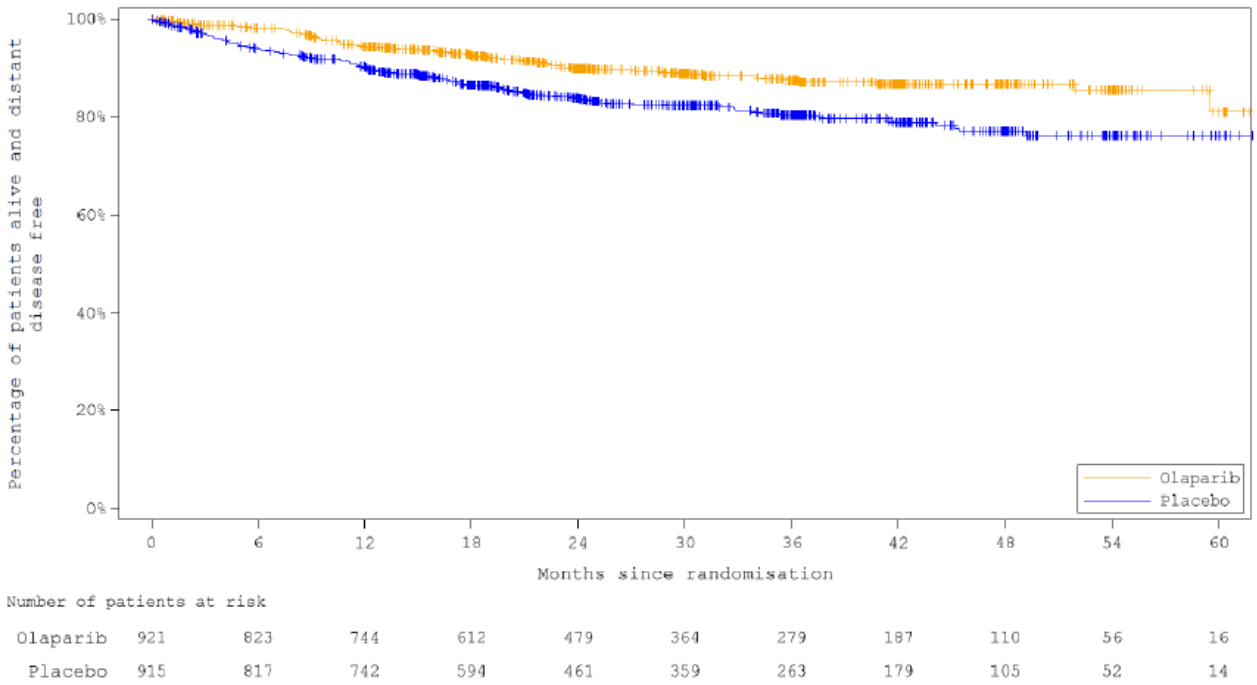
[d] Exploratory, not inferential.

[e] P-value from a stratified log-rank test. Stratification was by chemotherapy type (2 levels: adjuvant versus neoadjuvant), hormone receptor status (2 levels: ER and/or PgR positive, HER2 negative versus TNBC), and prior platinum therapy (2 levels: yes versus no). Stratification factors were based upon the categories used in the randomisation system and were chosen by the pooling strategy. Once the pooling strategy was applied, only the hormone receptor status stratification factor was selected.

[f] Percentage of patients were from the KM estimates and the 95% CIs were calculated using Greenwood's formula.

bd = twice daily; CI = confidence interval; DDFS = distant disease free survival; ER = oestrogen receptor; FAS = full analysis set; HER2 = human epidermal growth factor receptor 2; HR = hazard ratio; KM = Kaplan-Meier; PgR = progesterone receptor; TNBC = triple negative breast cancer.

Source: Table 14.2.10.



DDFS = distant disease free survival; FAS = full analysis set.
Source: Figure 14.2.20.1.

Figure 7 : Kaplan-Meier plot of DDFS (FAS)

OS by investigator assessment (FAS, DCO2 12 July 2021, 10% maturity)

The MAH provided updated OS results from the second planned interim analysis (DCO2 12 July 2021). Median duration of follow-up for OS was 3.5 years in the olaparib arm and 3.6 years in the placebo arm.

Table 19 : Updated Analysis of OS (FAS)

		DCO1: 27 March 2020		DCO2 12 July 2021	
		Olaparib 300 mg bd (N=921)	Placebo (N=915)	Olaparib 300 mg bd (N=921)	Placebo (N=915)
	4 years	-	-	86.5 (83.8, 88.8)	79.1 (76.0, 81.8)
OS					
Number of events/total number of patients (%)		59/921 (6.4)	86/915 (9.4)	75/921 (8.1)	109/915 (11.9)
Hazard ratio [b]		0.683		0.678	
99% CI for hazard ratio [c,d]		0.438, 1.053		-	
98.5% CI for hazard ratio [c,d]		-		0.468, 0.973	
95% CI for hazard ratio [d,e]		0.488, 0.950		0.503, 0.907	
p-value, 2-sided [f]		0.0236		0.0091	
Median survival follow-up time, years [g]		2.4	2.5	3.5	3.6
Percentage (95% CI) of patients alive at [h]	1 year	98.1 (96.9, 98.8)	96.9 (95.5, 97.9)	98.0 (96.9, 98.8)	96.9 (95.5, 97.9)
	2 years	94.8 (93.0, 96.2)	92.3 (90.1, 94.0)	95.0 (93.3, 96.2)	92.8 (90.9, 94.3)
	3 years	92.0 (89.6, 93.9)	88.3 (85.4, 90.7)	92.8 (90.8, 94.4)	89.1 (86.7, 91.0)
	4 years	-	-	89.8 (87.2, 91.9)	86.4 (83.6, 88.7)

[a] Invasive disease free survival is defined as time from randomisation to date of first recurrence, where recurrence is defined (per STEEP definition) as loco-regional, distant recurrence, contralateral invasive breast cancer, second primary non-breast invasive malignancy, or death from any cause.

[b] Estimate of the treatment hazard ratio was based on the stratified Cox's Proportional Hazards Model, <1 indicates a lower risk with olaparib compared with placebo arm. Stratification factors were the same as those used in the stratified log-rank test.

[c] Inferential, according to the alpha spending rules for each DCO, pre-defined in the statistical analysis plan (Table 10, Section 5).

[d] The CI for the hazard ratio was estimated using the profile likelihood approach.

[e] Exploratory, not inferential.

[f] P-value from a stratified log-rank test. Stratification was by chemotherapy type (2 levels: adjuvant versus neoadjuvant), hormone receptor status (2 levels: ER and/or PgR positive, HER2 negative versus TNBC), and prior platinum therapy (2 levels: yes versus no). Stratification factors were based upon the categories used in the randomisation system and were chosen by the pooling strategy. Once the pooling strategy was applied, only the hormone receptor status stratification factor was selected.

[e] P-value from a stratified log-rank test. Stratification was by chemotherapy type (2 levels: adjuvant versus neoadjuvant), hormone receptor status (2 levels: ER and/or PgR positive, HER2 negative versus TNBC), and prior platinum therapy (2 levels: yes versus no). Stratification factors were based upon the categories used in the randomisation system and were chosen by the pooling strategy. Once the pooling strategy was applied, only the hormone receptor status stratification factor was selected.

[f] Percentage of patients were from the KM estimates and the 95% CIs were calculated using Greenwood's formula.

bd = twice daily; CI = confidence interval; ER = oestrogen receptor positive; FAS = full analysis set; HER2 = human epidermal growth factor receptor 2; HR = hazard ratio; KM = Kaplan Meier; OS = overall survival; PgR = progesterone receptor positive; TNBC = triple negative breast cancer.

Source: Table 14.2.7.

Cancers Occurring Post Randomisation

Table 20 presents all cancers occurring post randomisation (COPRs), which included not only the incidence of cancers of special interest as listed in the secondary efficacy endpoint, but also the incidence of new primary non-breast, non-ovarian cancers including MDS/AML.

New primary malignancies (NPM) are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. Invasive non-breast new primary cancers were confirmed by clinical or radiological examination, with positive histology or cytology when the lesion was easily accessible for biopsy. These events were captured in eCRF on the "Second Primary Malignancy" form.

In comparison, breast cancer relapses in the OlympiA study includes ipsilateral invasive breast tumour recurrence, regional invasive breast cancer recurrence, distant recurrence, and contralateral invasive breast

cancer if determined as recurrence by the investigator. Locoregional recurrence of the disease (ipsilateral, regional and contralateral invasive breast cancer) should be cytologically/histologically confirmed. Distant recurrence were diagnosed by radiological examination and/or histopathological confirmation when metastatic lesion was easily accessible for biopsy.

Table 20 : Summary of Cancers Occurring Post-Randomisation (FAS)

	Olaparib 300 mg bd (N=921)	Placebo (N=915)
Number (%) of patients with:		
Contralateral invasive breast cancer	12 (1.3)	14 (1.5)
Contralateral non-invasive breast cancer	2 (0.2)	3 (0.3)
New primary ovarian [a]	2 (0.2) [b]	8 (0.9)
New primary ovarian cancer	1 (0.1)	4 (0.4)
New primary fallopian tube cancer	1 (0.1)	4 (0.4)
New primary peritoneal cancer	0	0
New primary invasive non-breast non-ovarian cancers	9 (1.0)	14 (1.5)

[a] Includes new primary ovarian, fallopian, and peritoneal cancers, without considering competing risks.

[b] One patient was captured in the database with ovarian cancer recurrence.

Summary of cancers without considering competing risks.

For contralateral breast cancers, this includes all cancers, both new and recurrent.

bd = twice daily; FAS = full analysis set.

Source: Table 14.2.14.

Health-related Quality of Life

FACIT-Fatigue score and EORTC QLQ-C30 global health status/QoL score were secondary outcome measures.

PRO analyses were based on the PRO analysis set (N=876 patients in the olaparib arm and N=875 in the placebo arm).

Table 21 : Compliance Rate for QoL Questionnaires by Group and Visit (PRO Analysis Set)

	Compliance rate (%) [a]				
	Baseline	6 Months	12 Months	18 Months	24 Months
Olaparib (N=876)					
FACIT-Fatigue	99.4	84.0	81.8	72.2	66.8
EORTC QLQ-C30	100	84.8	82.2	72.4	66.8
Placebo (N=875)					
FACIT-Fatigue	99.7	90.9	86.0	73.6	68.7
EORTC QLQ-C30	99.9	91.6	86.9	74.2	69.3

[a] Number of evaluable forms divided by the number of expected forms.

EORTC QLQ-30 = European Organisation for Research and Treatment of Cancer quality of life questionnaire; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue Measurement questionnaire; PRO = patient reported outcome; QoL = quality of life.

Source: Table 14.2.25.02.

FACIT-Fatigue

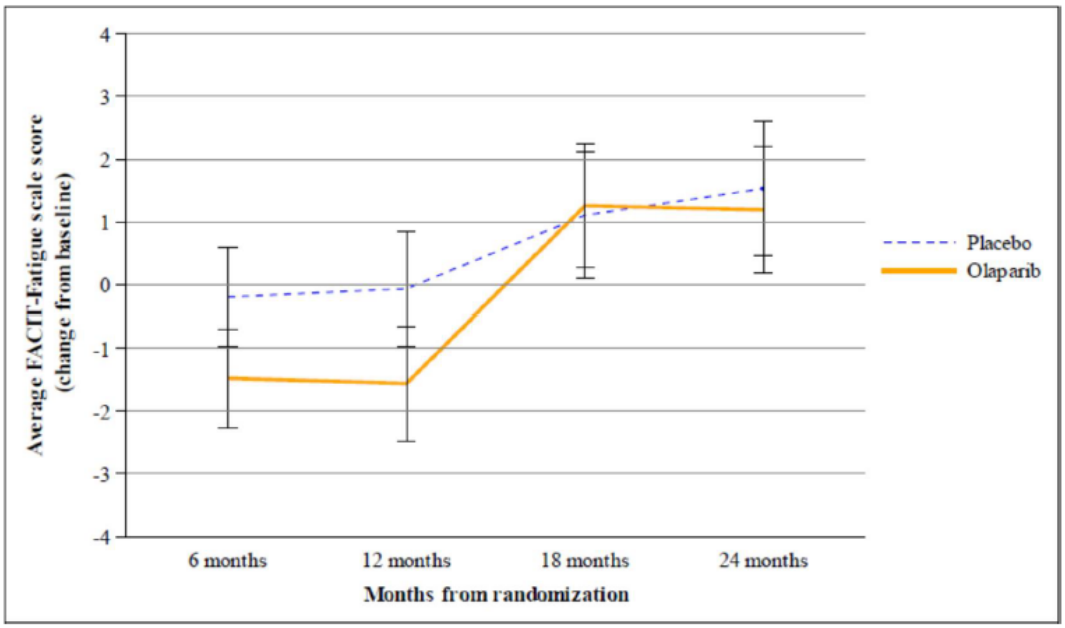
The FACIT-Fatigue score ranges from 0 to 52 with higher scores indicating less fatigue, and a score difference of 3 points defined as clinically meaningful. Separate analyses were conducted for patients who had received prior neoadjuvant chemotherapy and patients who had received standard post-surgical adjuvant chemotherapy because the timing of chemotherapy had the potential to impact fatigue outcome differently.

Change from baseline at 6 and 12 months for FACIT-Fatigue in patients receiving neoadjuvant and adjuvant chemotherapy is presented in Table 22.

Regarding FACIT-Fatigue Score, differences that were detected were not clinically meaningful (adjusted LS mean change scores between the olaparib and placebo at Months 6 and 12 for both the prior neoadjuvant (-1.3 at 6 months; p=0.024 [nominal], -1.5 at 12 months; p=0.025 [nominal]) and adjuvant (-1.3 at 6 months; p=0.017 [nominal], and -1.3 at 12 months; p=0.027 [nominal]) treatment groups).

Table 22 : Change from Baseline for FACIT-Fatigue Score at 6 and 12 Months (MMRM; PRO Analysis Set) – Neoadjuvant

	6 months		12 months	
Parameter	**LS Mean**	**95% CI**	**LS Mean**	**95% CI**
Patients who had completed neoadjuvant chemotherapy				
Olaparib 300 mg bd (n=371)	-1.5	-2.2, -0.7	-1.5	-2.4, -0.6
Placebo (n=356)	-0.2	-1.0, 0.6	0.0	-0.9, 0.9
Difference	-1.3	-2.4, -0.2	-1.5	-2.8, -0.2
P-value	0.024		0.025	



FACIT-Fatigue score ranges from 0 to 52 with higher score indicating less fatigue; a score difference of 3 points was defined as clinically meaningful. Adjusted LS mean changes and 95% CI are obtained from MMRM analysis of the change from baseline. The model includes treatment, time and treatment by time interaction, corresponding baseline score and the baseline score by time interaction.

CI = confidence interval; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue Measurement questionnaire; LS = least squares; MMRM = mixed model for repeated measures; PRO = patient reported outcome.

Source: Figure 14.2.24.01.

Figure 8: Mean Change from Baseline for FACIT-Fatigue (Prior Neoadjuvant Patients; PRO Analysis Set)

Table 23 : Change from Baseline for FACIT-Fatigue Score at 6 and 12 Months (MMRM; PRO Analysis Set) – Adjuvant

	6 months		12 months	
Parameter	**LS Mean**	**95% CI**	**LS Mean**	**95% CI**
Patients who had completed adjuvant chemotherapy				
Olaparib 300 mg bd (n=375)	-0.7	-1.4, 0.1	-0.8	-1.6, -0.0
Placebo (n=403)	0.6	-0.1, 1.3	0.5	-0.3, 1.2
Difference	-1.3	-2.3, -0.2	-1.3	-2.4, 0.1
P-value	0.017		0.027	

Only patients with an evaluable baseline form were included.

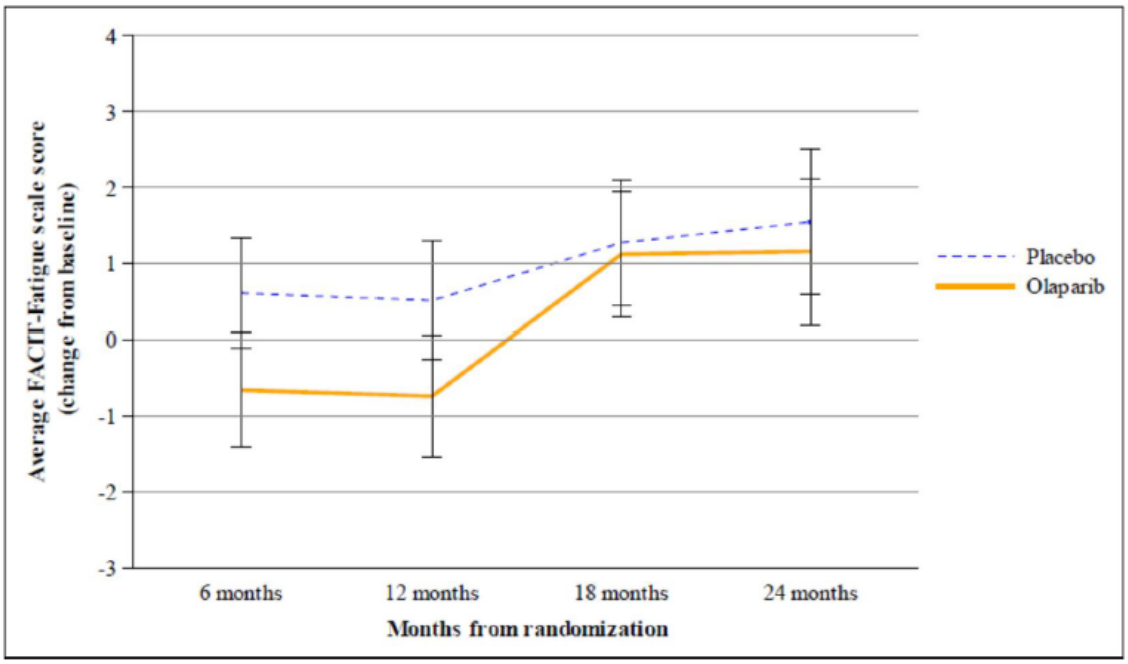
Adjusted least-square mean changes, p-values (2-sided) and 95% CI were obtained from MMRM analysis of the change from baseline. The model included treatment, time and treatment by time interaction, corresponding baseline score, and the baseline score by time interaction.

FACIT-Fatigue ranges from 0 to 52 with higher score indicating less fatigue.

Difference was the values for olaparib minus placebo.

bd = twice daily; CI = confidence interval; FACIT = functional assessment of chronic illness therapy; LS = least squares; MMRM = mixed model for repeated measures; PRO = patient reported outcome.

Source: Table 14.2.25.11 and Table 14.2.25.12.



FACIT-Fatigue score ranges from 0 to 52 with higher score indicating less fatigue a score difference of 3 points defined as clinically meaningful. Adjusted LS mean changes and 95% CI are obtained from MMRM analysis of the change from baseline. The model includes treatment, time and treatment by time interaction, corresponding baseline score and the baseline score by time interaction.

CI = confidence interval; FACIT = functional assessment of chronic illness therapy; LS = least squares; MMRM = mixed model for repeated measures; PRO = patient reported outcome.

Source: Figure 14.2.24.02.

Figure 9 : Mean Change from Baseline for FACIT-Fatigue (Prior Adjuvant Patients; PRO Analysis Set)

EORTC QLQ-C30

All EORTC QLQ-C30 scales range in score from 0 to 100, with higher scores on HRQoL and functioning scores indicating better HRQoL/functioning and higher scores on symptom scales indicating worse symptom severity.

Mean (SD) EORTC QLQ-C30 global health status/QoL and functioning subscale scores generally remained stable for both the olaparib and placebo arms at Months 6 and 12. Small improvements from baseline were observed in global health status/QoL, role functioning, and social functioning in both arms at Months 18 and 24, with no statistical meaningful differences.

Mean (SD) EORTC QLQ-C30 GI symptom scores (nausea/vomiting) were increased in the olaparib arm versus the placebo arm after 6 and 12 months of treatment as expected given the known safety profile of olaparib. At Months 18 and 24, scores returned to baseline and were comparable between the olaparib and placebo arms, with no clinically meaningful differences observed (**Table 24**). For the prior neoadjuvant group, small increases in scores for diarrhoea were observed in the olaparib arm versus the placebo arm after 6 and 12 months of treatment, with scores returning to baseline and comparable to placebo at 18 and 24 months. For the adjuvant group, diarrhoea scores generally remained stable for both the olaparib and placebo arms across all timepoints.

Change from baseline for EORTC QLQ-C30 subscale scores in patients receiving neoadjuvant and adjuvant chemotherapy are presented in Table 24.

Table 24 : Model Based Change from Baseline for EORTC QLQ-C30 Subscale Measures (PRO Analysis Set) – Neoadjuvant

	6 months		12 months		18 months		24 months	
Parameter	**Mean**	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**
Patients who had completed neoadjuvant chemotherapy								
EORTC QLQ-C30 Global health status QoL								
Olaparib 300 mg bd (n=380)	-0.2	-2.0, 1.6	0.4	-1.7, 2.4	3.6	1.4, 5.7	2.3	-0.3, 5.0
Placebo (n=358)	0.5	-1.3, 2.4	2.8	0.8, 4.8	4.2	2.0, 6.4	6.9	4.2, 9.7
Difference	-0.7	-3.3, 1.9	-2.5	-5.3, 0.4	-0.6	-3.7, 2.5	-4.6	-8.4, -0.8
P-value	0.590		0.090		0.688		0.018	
EORTC QLQ-C30 Nausea and vomiting symptom scale								
Olaparib 300 mg bd (n=383)	7.6	6.2, 9.0	7.3	6.0, 8.7	0.7	-0.4, 1.8	1.3	0.0, 2.6
Placebo (n=359)	1.6	0.2, 3.1	1.0	-0.4, 2.4	0.4	-0.8, 1.5	-0.1	-1.5, 1.2
Difference	6.0	4.0, 8.0	6.3	4.4, 8.2	0.4	-1.2, 1.9	1.4	-0.4, 3.3
P-value	<0.001		<0.001		0.664		0.120	
EORTC QLQ-C30 Diarrhoea symptom scale								
Olaparib 300 mg bd (n=380)	1.6	-0.0, 3.3	4.0	1.9, 6.1	2.7	0.5, 4.9	1.3	-1.0, 3.5
Placebo (n=357)	1.3	-0.4, 3.0	2.0	-0.1, 4.1	1.5	-0.7, 3.8	-0.5	-2.9, 1.8
Difference	0.3	-2.0, 2.7	2.0	-1.0, 4.9	1.1	-2.0, 4.3	1.8	-1.5, 5.0
P-value	0.776		0.187		0.488		0.282	

	6 months		12 months		18 months		24 months	
Parameter	**Mean**	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**
Patients who had completed adjuvant chemotherapy								
EORTC QLQ-C30 Global health status QoL								
Olaparib 300 mg bd (n=383)	-0.4	-2.1, 1.3	0.7	-1.0, 2.5	2.8	1.0, 4.7	4.1	1.8, 6.3
Placebo (n=406)	2.3	0.7, 3.9	3.3	1.6, 5.0	5.5	3.6, 7.4	4.9	2.6, 7.1
Difference	-2.7	-5.0, -0.4	-2.5	-5.0, -0.1	-2.6	-5.3, 0.0	-0.8	-4.0, 2.4
P-value	0.023		0.043		0.053		0.619	
EORTC QLQ-C30 Nausea and vomiting symptom scale								
Olaparib 300 mg bd (n=385)	6.9	5.5, 8.2	5.5	4.2, 6.7	0.7	-0.5, 1.8	-0.0	-1.3, 1.3
Placebo (n=406)	1.6	0.3, 2.9	1.0	-0.2, 2.1	1.0	-0.2, 2.1	0.6	-0.6, 1.9
Difference	5.3	3.4, 7.2	4.5	2.8, 6.2	-0.3	-1.9, 1.3	-0.6	-2.5, 1.2
P-value	<0.001		<0.001		0.718		0.481	
EORTC QLQ-C30 Diarrhoea symptom scale								
Olaparib 300 mg bd (n=384)	0.0	-1.7, 1.8	1.5	-0.1, 3.1	-0.2	-1.8, 1.4	-1.6	-3.2, 0.1
Placebo (n=406)	1.7	0.1, 3.4	1.4	-0.2, 3.0	-0.6	-2.2, 1.0	-0.6	-2.2, 1.1
Difference	-1.7	-4.1, 0.7	0.1	-2.2, 2.4	0.4	-1.9, 2.7	-1.0	-3.4, 1.4
P-value	0.167		0.901		0.736		0.405	

Only patients with an evaluable baseline form were included.

Adjusted least-square mean changes, p-values (2-sided) and 95% CI were obtained from MMRM analysis of the change from baseline. The model included treatment, time and treatment by time interaction, corresponding baseline score, and the baseline score by time interaction.

All EORTC QLQ-C30 scales range in score from 0 to 100. Higher score indicates better QoL/functioning or worse symptom severity.

Difference was the values for olaparib minus placebo.

bd = twice daily; CI = confidence interval; EORTC QLQ-30 = European Organisation for Research and Treatment of Cancer quality of life questionnaire; MMRM = mixed model for repeated measures; PRO = patient reported outcome; QoL = quality of life.

Source: Table 14.2.25.15 and Table 14.2.25.16.

Ancillary analyses

Sensitivity Analyses

Table 25 : Sensitivity Analyses of IDFS (FAS) (DCO1: 27 March 2020)

Analysis	Group	N [a]	Treatment effect		
			Number (%) of patients with events	Comparison between groups	
				HR	95% CI
Patients with central pathology review data [b]	Olaparib 300 mg bd	732	86 (11.7)	0.535 [c]	0.409, 0.696 [d]
	Placebo	720	151 (21.0)		
Unadjusted analysis (unstratified Cox model fitted)	Olaparib 300 mg bd	921	106 (11.5)	0.581 [e]	0.455, 0.737 [d]
	Placebo	915	178 (19.5)		
Interval censoring [f]	Olaparib 300 mg bd	921	106 (11.5)	0.580 [c]	0.456, 0.738 [g]
	Placebo	915	178 (19.5)		

[a] Number of patients included in sensitivity analysis.

[b] Includes patients that had both central and local hormone receptor status results. Central pathology review data were not available for China. See Table 14.1.8.3 for tabulation of the concordance between central and local results. Stratification factors for hormone receptor status was according to the central pathology review.

[c] Estimate of the treatment HR was based on the stratified Cox's Proportional Hazards Model, <1 indicates a lower risk with olaparib compared with placebo arm.

[d] The 95% CI for the HR was estimated using the profile likelihood approach.

[e] Estimate of the treatment HR was based on the unstratified Cox's Proportional Hazards Model, <1 indicates a lower risk with olaparib compared with placebo arm.

[f] For patients experiencing an event, and without follow-up according to the CSP (defined as over 18 months between the event and the last visit), the interval from the last date at which the subject was known to be IDFS free to the date of recurrence or death, was used.

[g] The 95% Wald CI for the HR.

Percentages are of the number of patients in the population subgroup in question.

Mis-stratification sensitivity analysis was not triggered as ≤5% of randomised patients were incorrectly stratified (ie, randomisation system data did not match baseline data). Sensitivity analysis excluding patients with important protocol deviations that may affect the efficacy of the study therapy (did not have the intended disease or indication; did not receive any randomised therapy) was not triggered as ≤10% of patients in either treatment group had important protocol deviations.

bd = twice daily; CI = confidence interval; CSP = Clinical Study Protocol; FAS = full analysis set; HR = hazard ratio; IDFS = invasive disease free survival.

Source: Table 14.2.6.2.

Table 26 : Sensitivity Analyses of DDFS (FAS) (DCO1: 27 March 2020)

	Olaparib 300 mg bd (N=921)	Placebo (N=915)
Patients with central pathology review data [a]		
Olaparib vs placebo, n (%) [b]	732	720
Number of events (%)	71 (9.7)	127 (17.6)
Estimate of HR (95% CI) [c, d]	0.530 (0.395, 0.706)	
Unadjusted analysis [e]		
Olaparib vs placebo, n (%) [b]	921	915
Number of events (%)	89 (9.7)	152 (16.6)
Estimate of HR (95% CI) [d, f]	0.575 (0.441, 0.745)	

[a] Includes patients that had both central and local hormone receptor status results. Central pathology review data were not available for China. See Table 14.1.8.3 for the concordance between central and local results.

[b] Number of patients included in sensitivity analysis.

[c] Estimate of the treatment HR was based on the stratified Cox's Proportional Hazards Model, <1 indicates a lower risk with olaparib compared with placebo arm. Stratification factors for prior platinum therapy and chemotherapy were the same as those used in the analysis of DDFS, stratification factor for hormone receptor status was according to the central pathology review.

[d] The 95% CI for the HR was estimated using the profile likelihood approach.

[e] An unstratified Cox model was fitted.

[f] Estimate of the treatment HR was based on the stratified Cox's Proportional Hazards Model, <1 indicates a lower risk with olaparib compared with placebo arm. Cox model was unstratified.

Percentages are of the number of patients in the population subgroup in question.

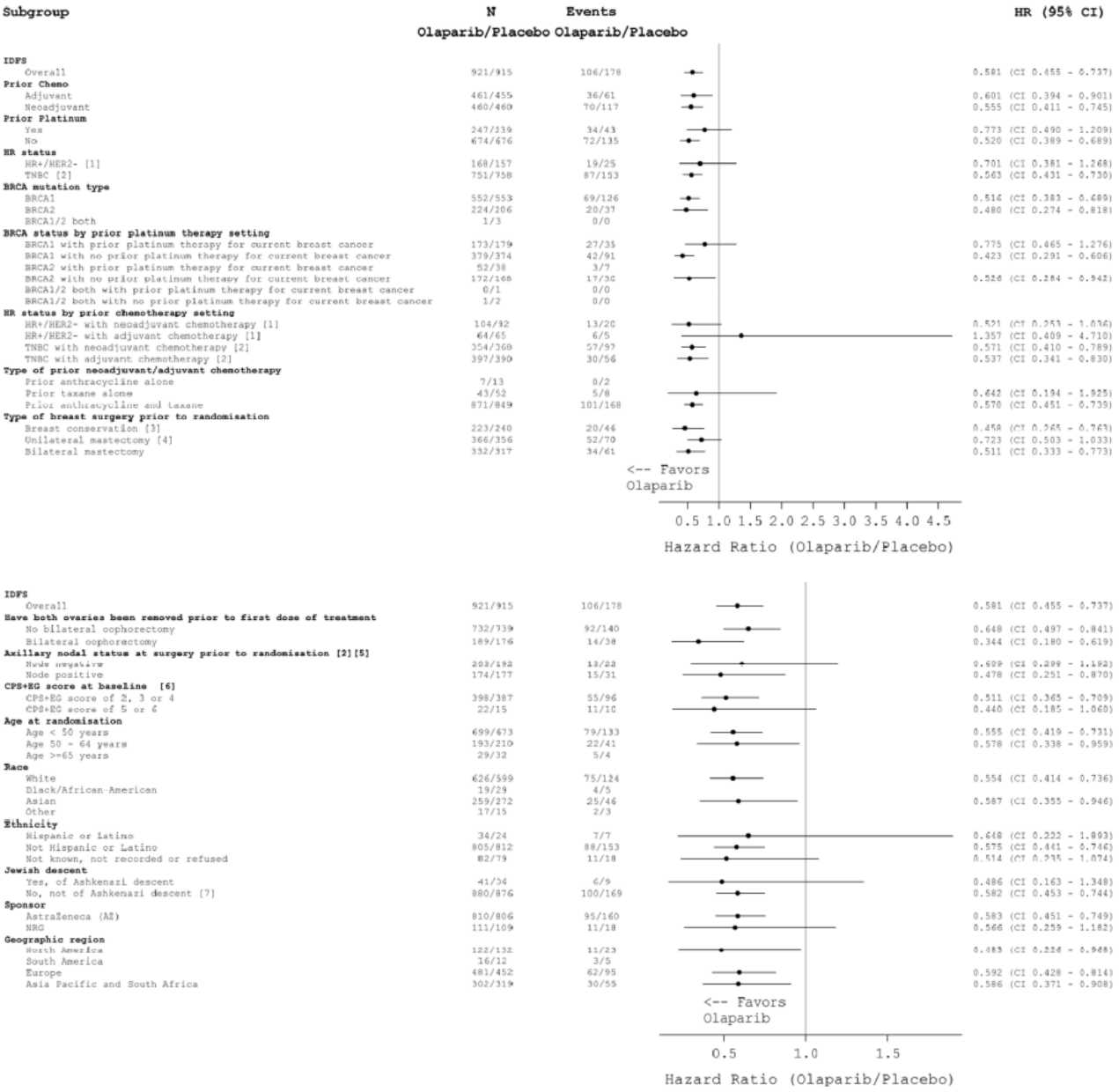
See Table 14.2.10 for the main analysis of DDFS.

bd = twice daily; CI = confidence interval; DDFS = distant disease free survival; FAS = full analysis set; HR = hazard ratio.

Source: Table 14.2.12.2.

Subgroup analyses

Subgroup Analyses of IDFS (DCO1: 27 March 2020)



1 HR+ was defined as ER positive and/or PgR positive.

2 Two patients were excluded from the summary of the TNBC subset because they did not have confirmed negative HER2 status.

3 Breast conservation was defined as partial mastectomy/breast quadrantectomy/breast segmentectomy/breast lumpectomy and breast re-excision of margins.

4 Unilateral mastectomy was defined as modified radical mastectomy, radical mastectomy (Halsted), or simple mastectomy.

5 Triple negative breast cancer, adjuvant patients only, with sentinel node sampling or axillary node dissection.

6 Post-neoadjuvant group only.

7 Not Ashkenazi Jewish means that the patient was either Jewish but not Ashkenazi Jewish, not Jewish, or descent recorded as unknown.

Note: Ten olaparib-treated patients and 8 placebo-treated patients in the missing race category (see Table 14.1.4.1) were analysed in race subgroup "other".

Figure 10 : Forest Plot of IDFS Subgroup Analyses (FAS) *(DCO1: 27 March 2020)*

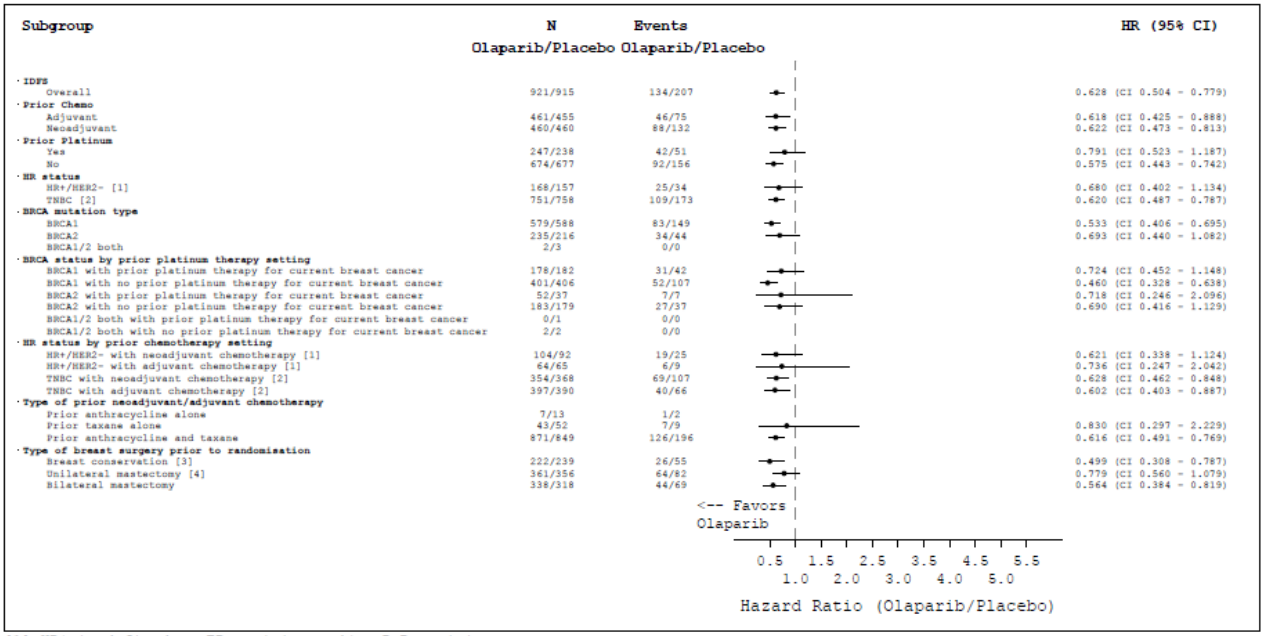
Table 27: OlympiA: Summary of IDFS by Hormone Receptor Status (DCO1: 27 March 2020)

	IDFS		
Population	**Number of Events/Number of Patients (%)**		
	Olaparib 300 mg bd	**Placebo**	**IDFS Hazard Ratio (95% CI)**
FAS (local ER/PgR/HER2 status)			
TNBC (N=1509)	87/751 (11.6)	153/758 (20.2)	0.563 (0.431, 0.730)
ER and/or PgR positive, HER2 negative (N=325)	19/168 (11.3)	25/157 (15.9)	0.701 (0.381, 1.268)
Hormone Receptor Status by Central Pathology Review [b]			
TNBC (N=1106)	70/563 (12.4)	117/543 (21.5)	0.548 (0.406, 0.735)
ER and/or PgR positive, HER2 negative (N=346)	16/169 (9.5)	34/177 (19.2)	0.486 (0.261, 0.864)
ER expression level by Central Pathology Review [b] (Central Hormone Receptor Positive Population)			
ER negative: ER < 1% (N=41)	3/20 (15.0)	4/21 (19.0)	NC
ER low: ER ≥ 1% and < 10% (N=50)	4/17 (23.5)	13/33 (39.4)	NC
ER strongly positive: ER ≥ 10% (N=255)	9/132 (6.8)	17/123 (13.8)	0.463 (0.197, 1.016)

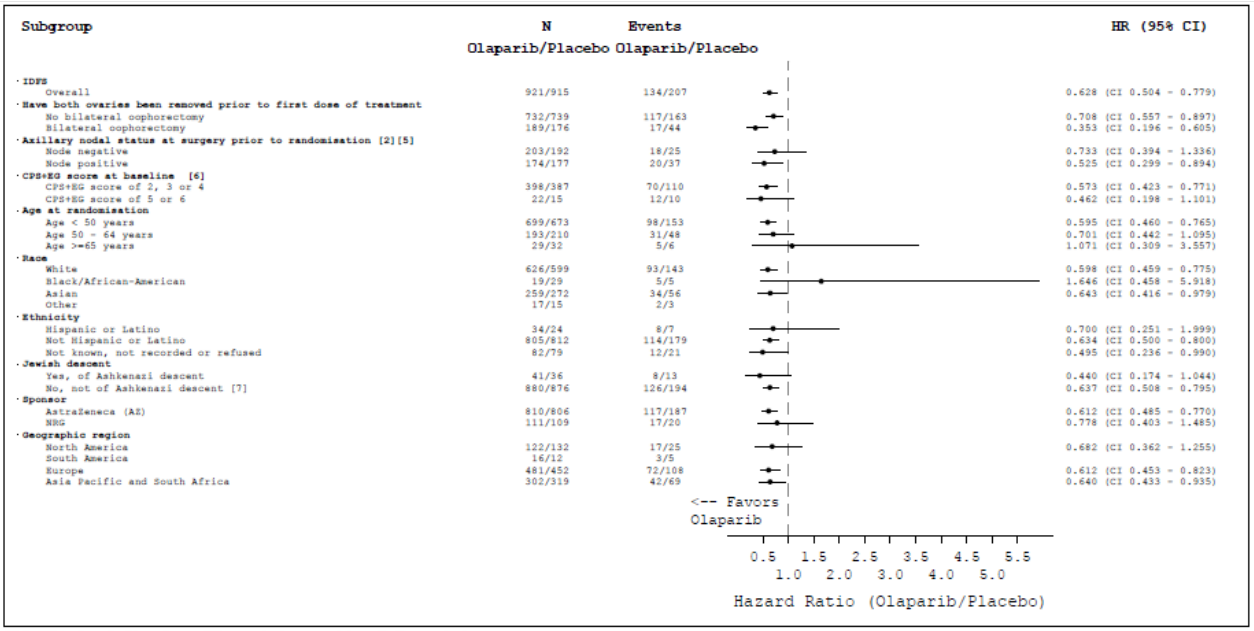
[a] Exploratory, not inferential.
[b] Excludes patients recruited in China.

Two patients are excluded from the summary of the TNBC subset because they do not have confirmed hormone receptor negative status.
bd = twice daily; CI = confidence interval; ER = oestrogen receptor; FAS = Full Analysis Set; HER2 = human epidermal growth factor receptor 2; IDFS = invasive disease free survival; NC = Not calculated;
PgR = progesterone receptor; TNBC = triple negative breast cancer.
Hazard Ratios are not presented for any subgroup levels with less than 5 events in either treatment arm.
Source: Table 14.2.13.1, OlympiA CSR, Module 5.3.5.1; IEMT 2848.2.1, Efficacy Outputs, Module 5.3.5.3. IEMT 3079.1; (DCO1: 27 March 2020).

Subgroup Analyses of IDFS (DCO2: 12 July 2021)



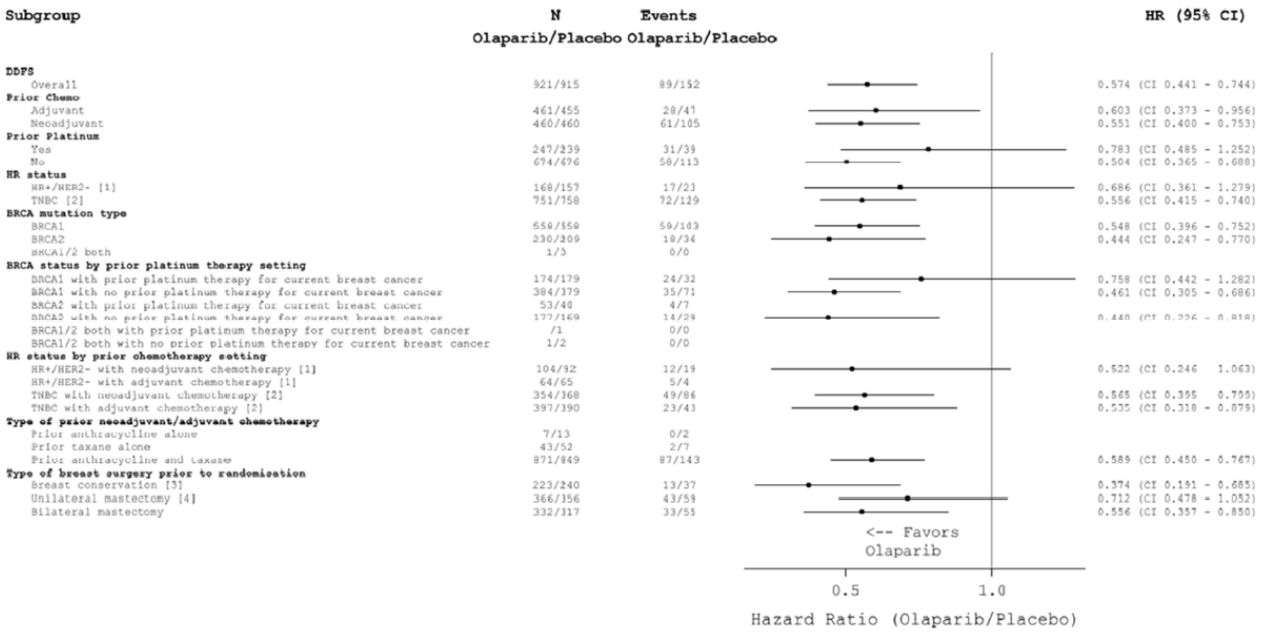
[1] HR+ is defined as ER positive and/or PgR positive.
[2] Two patients are excluded from the summary of the TNBC subset because they do not have confirmed negative HER2 status.
[3] Breast conservation defined as partial mastectomy / breast quadrantectomy / breast segmentectomy / breast lumpectomy and breast re-excision of margins.
[4] Unilateral mastectomy defined as modified radical mastectomy, radical mastectomy (Halsted) or simple mastectomy.
[5] TNBC, adjuvant patients only, with sentinel node sampling or axillary node dissection.
[6] Post neoadjuvant group only.
[7] Not Ashkenazi Jewish can mean that the patient is either Jewish but not Ashkenazi Jewish, not Jewish or descent recorded as unknown.

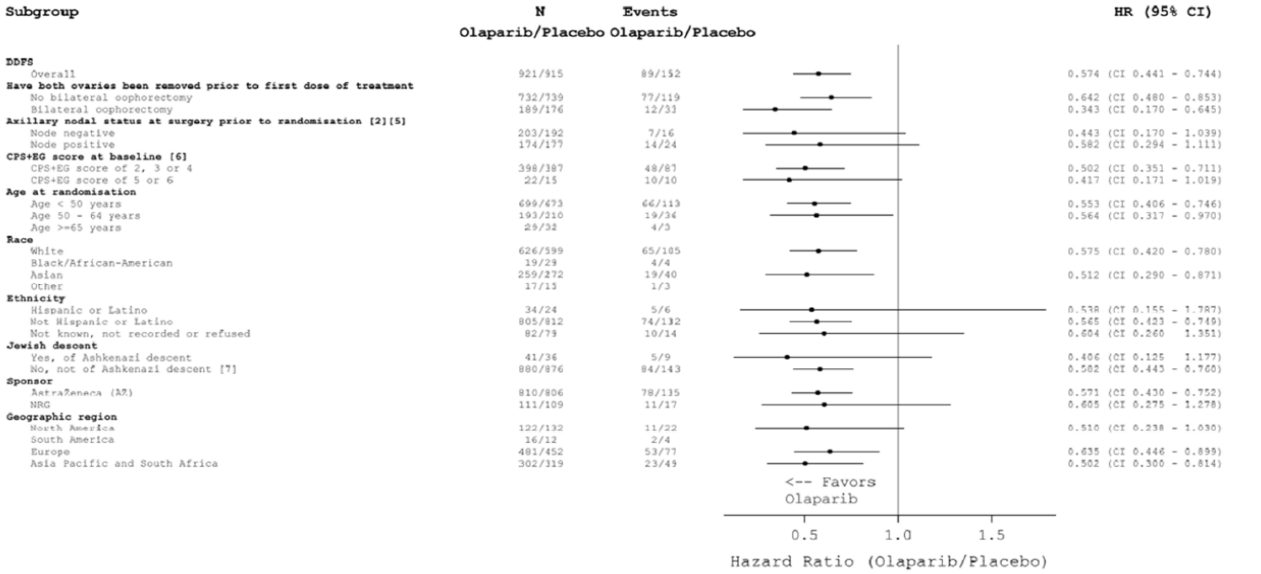


[1] HR+ is defined as ER positive and/or PgR positive.
[2] Two patients are excluded from the summary of the TNBC subset because they do not have confirmed negative HER2 status.
[3] Breast conservation defined as partial mastectomy / breast quadrantectomy / breast segmentectomy / breast lumpectomy and breast re-excision of margins.
[4] Unilateral mastectomy defined as modified radical mastectomy, radical mastectomy (Halsted) or simple mastectomy.
[5] TNBC, adjuvant patients only, with sentinel node sampling or axillary node dissection.
[6] Post neoadjuvant group only.
[7] Not Ashkenazi Jewish can mean that the patient is either Jewish but not Ashkenazi Jewish, not Jewish or descent recorded as unknown.

Figure 11 : Forest Plot of IDFS (FAS) *(DCO2: 12 July 2021)*

Subgroup Analyses of DDFS (DCO1: 27 March 2020)





1 HR+ was defined as ER positive and/or PgR positive.

2 Two patients were excluded from the summary of the TNBC subset because they did not have confirmed negative HER2 status.

3 Breast conservation was defined as partial mastectomy/breast quadrantectomy/breast segmentectomy/breast lumpectomy and breast re-excision of margins.

4 Unilateral mastectomy was defined as modified radical mastectomy, radical mastectomy (Halsted), or simple mastectomy.

5 Triple negative breast cancer, adjuvant patients only, with sentinel node sampling or axillary node dissection.

6 Post-neoadjuvant group only.

7 Not Ashkenazi Jewish means that the patient was either Jewish but not Ashkenazi Jewish, not Jewish, or descent recorded as unknown.

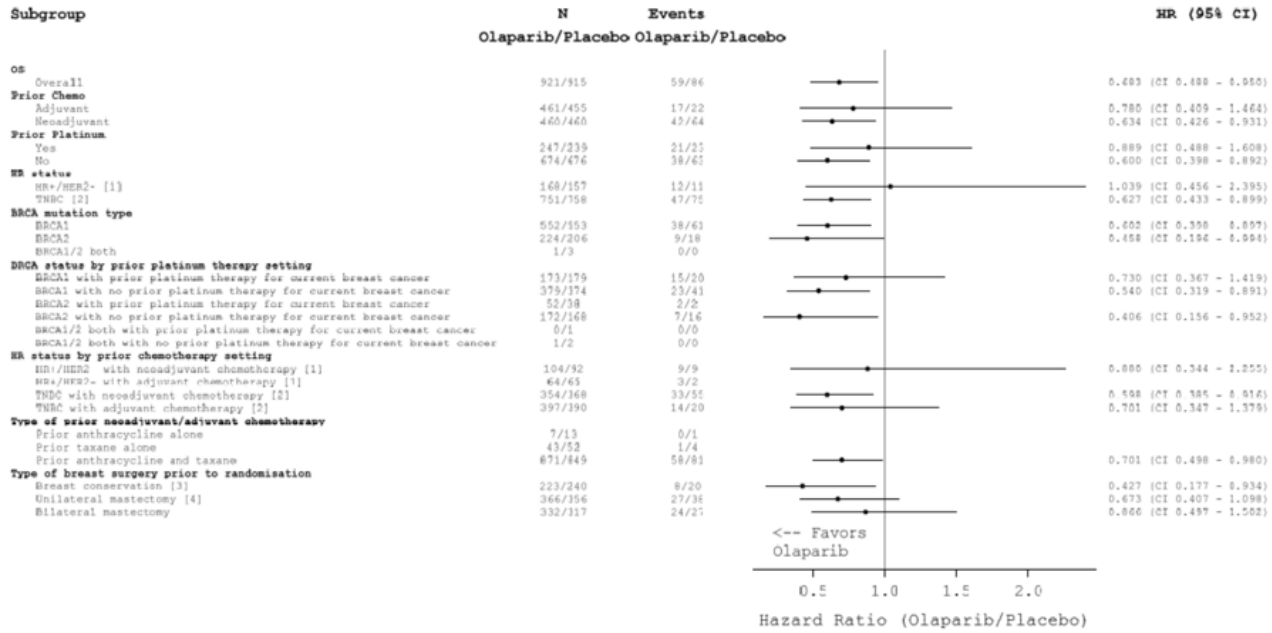
Note: Ten olaparib-treated patients and 8 placebo-treated patients in the missing race category (see Table 14.1.4.1) were analysed in race subgroup "other".

BRCA = breast cancer susceptibility gene; CI = confidence interval; CPS+EG = clinical stage (CS), oestrogen receptor status (E), nuclear grade (G), and post-treatment pathologic stage (PS) – a disease scoring system; DDFS = distant disease free survival; ER = oestrogen receptor; FAS = full analysis set; HER2 = human epidermal growth factor receptor 2; HR = hazard ratio; HR+ = hormone receptor positive; HR status = hormone receptor status; PgR = progesterone receptor; TNBC = triple negative breast cancer.

Source: Figure 14.2.22.2.1.

Figure 12 : Forest Plot of DDFS (FAS) *(DCO1: 27 March 2020)*

Subgroup Analyses of OS (DCO1: 27 March 2020)



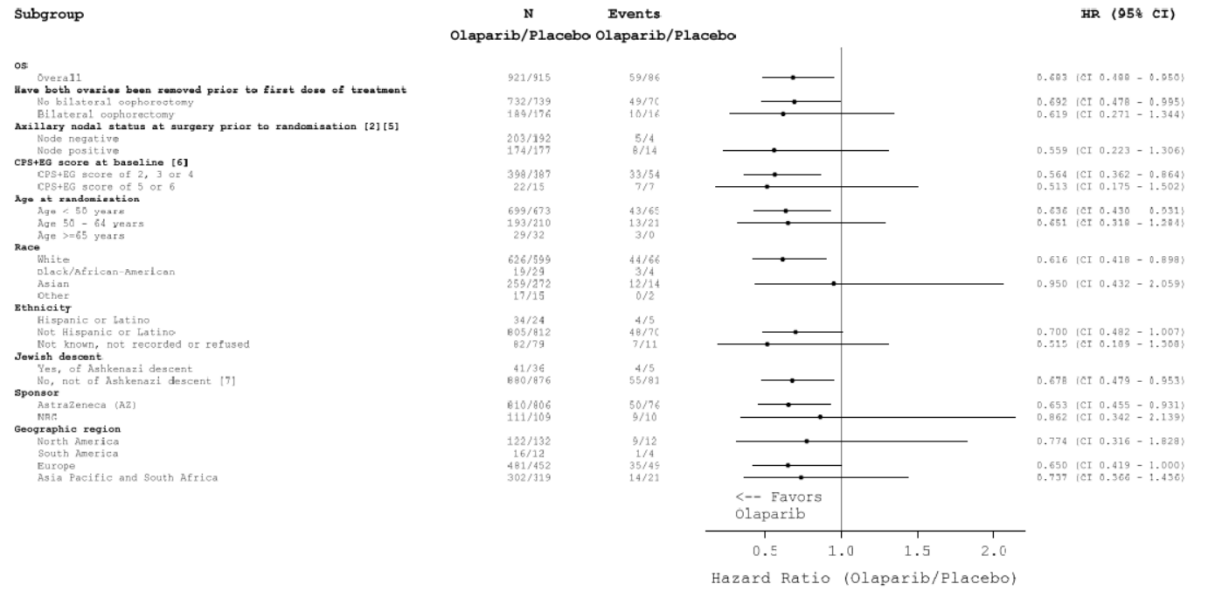
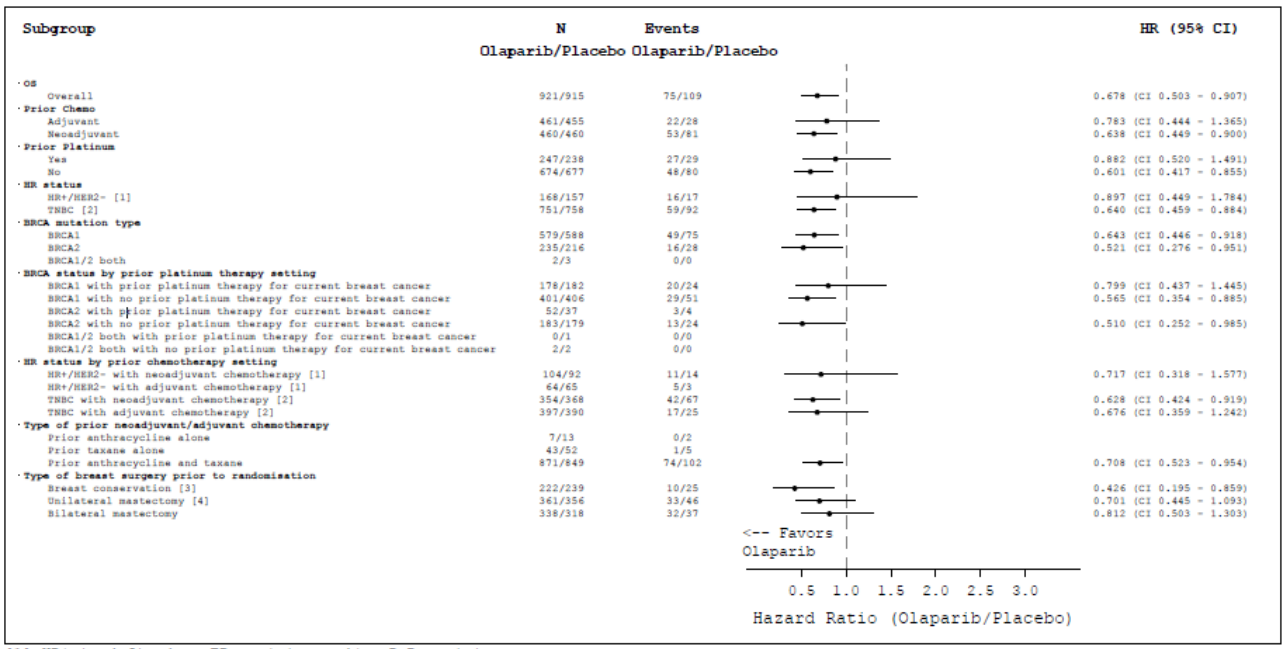
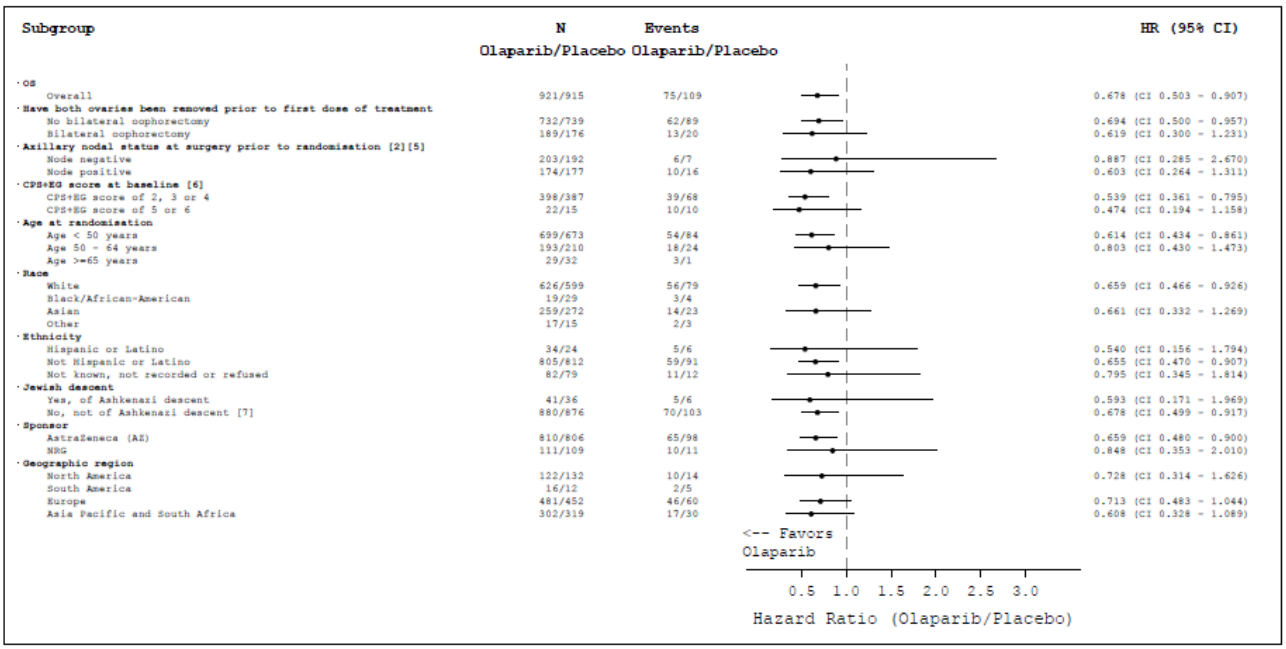


Figure 13 : Forest Plot of OS Subgroup Analyses (DCO1: March 2020)

Subgroup Analyses of OS (DCO2: 12 July 2021)



[1] HR+ is defined as ER positive and/or PgR positive.
[2] Two patients are excluded from the summary of the TNBC subset because they do not have confirmed negative HER2 status.
[3] Breast conservation defined as partial mastectomy / breast quadrantectomy / breast segmentectomy / breast lumpectomy and breast re-excision of margins.
[4] Unilateral mastectomy defined as modified radical mastectomy, radical mastectomy (Halsted) or simple mastectomy.
[5] TNBC, adjuvant patients only, with sentinel node sampling or axillary node dissection.
[6] Post neoadjuvant group only.
[7] Not Ashkenazi Jewish can mean that the patient is either Jewish but not Ashkenazi Jewish, not Jewish or descent recorded as unknown.



[1] HR+ is defined as ER positive and/or PgR positive.
[2] Two patients are excluded from the summary of the TNBC subset because they do not have confirmed negative HER2 status.
[3] Breast conservation defined as partial mastectomy / breast quadrantectomy / breast segmentectomy / breast lumpectomy and breast re-excision of margins.
[4] Unilateral mastectomy defined as modified radical mastectomy, radical mastectomy (Halsted) or simple mastectomy.
[5] TNBC, adjuvant patients only, with sentinel node sampling or axillary node dissection.
[6] Post neoadjuvant group only.
[7] Not Ashkenazi Jewish can mean that the patient is either Jewish but not Ashkenazi Jewish, not Jewish or descent recorded as unknown.

Figure 12: Forest Plot of OS Subgroup Analyses *(DCO2: 12 July 2021)*

Descriptive analyses of IDFS (DCO2: 12 July 2021)

Updated descriptive analyses of IDFS based on more mature data (with median follow-up of 3.5 years) conducted at the time of the pre-planned second OS interim analysis (DCO2: 12 July 2021) were provided. These were undertaken in the overall ITT population including the subgroup analysis of patients with ER and/or PgR positive, HER2-negative status who had received adjuvant chemotherapy.

Table 28: OlympiA: Summary of IFDS by hormone receptor status (per local status) and prior chemotherapy

Population	IDFS		
	Number of Events/Number of Patients (%)		
	Olaparib 300 mg bd	Placebo	IDFS Hazard Ratio (95% CI)
Primary Analysis IDFS Subgroup analysis (DCO1 27 March 2020)			
Overall population	106/921 (11.5)	178/915 (19.5)	0.581 (0.455, 0.737)
TNBC	87/751 (11.6)	153/758 (20.2)	0.563 (0.431, 0.730)
TNBC prior neoadjuvant chemotherapy	57/354 (16.1)	97/368 (26.4)	0.571 (0.410, 0.789)
TNBC prior adjuvant chemotherapy	30/397 (7.6)	56/390 (14.4)	0.537 (0.341, 0.830)
ER and/or PgR positive, HER2 negative	19/168 (11.3)	25/157 (15.9)	0.701 (0.381, 1.268)
ER and/or PgR positive, HER2 negative, prior neoadjuvant chemotherapy	13/104 (12.5)	20/92 (21.7)	0.521 (0.253, 1.036)
ER and/or PgR positive, HER2 negative, prior adjuvant chemotherapy	6/64 (9.4)	5/65 (7.7)	1.357 (0.409, 4.710)
Updated IDFS subgroup analysis (DCO2 12 July 2021)			
Overall population	134/921 (14.5)	207/915 (22.6)	0.628 (0.504 - 0.779)
TNBC	109/751 (14.5)	173/758 (22.8)	0.620 (0.487 - 0.787)
TNBC prior neoadjuvant chemotherapy	69/354 (19.5)	107/368 (29.1)	0.628 (0.462 - 0.848)
TNBC prior adjuvant chemotherapy	40/397 (10.1)	66/390 (16.9)	0.602 (0.403 - 0.887)
ER and/or PgR positive, HER2 negative	25/168 (14.9)	34/157 (21.7)	0.680 (0.402 - 1.134)
ER and/or PgR positive, HER2 negative, prior neoadjuvant chemotherapy	19/104 (18.3)	25/92 (21.7)	0.621 (0.338 - 1.124)
ER and/or PgR positive, HER2 negative, prior adjuvant chemotherapy	6/64 (9.4)	9/65 (13.8)	0.736 (0.247 - 2.042)

Two patients are excluded from the summary of the TNBC subset because they do not have confirmed hormone receptor negative status.
bd = twice daily; CI = confidence interval; ER = oestrogen receptor; FAS = Full Analysis Set; HER2 = human epidermal growth factor receptor 2; PgR = progesterone receptor; TNBC = triple negative breast cancer.
Source: Table 14.2.13.1, OlympiA CSR (DCO1: 27 March 2020); Figure 14.2.22.1.1 in Appendix B (DCO2: 12 July 2021).

Myriad gBRCAm Patients

Table 29: Supportive Analyses of IDFS, DDFS, and OS in Confirmed Myriad gBRCAm Patients (FAS) (DCO2: 12 July 2021)

	Olaparib 300 mg bd (N=816)	Placebo (N=807)
IDFS		
Number of events (%)	117 (14.3)	193 (23.9)
Estimate of HR [a]	0.571	
95% CI for HR [b]	0.453, 0.717	
Median clinical follow-up time, years [c]	**3.5**	**3.5**
Minimum/Maximum	0/6.7	0/6.6
Percentage (95% CI) of patients invasive disease free at [d]		
1 year	93.4 (91.4, 95.0)	87.9 (85.3, 90.0)
2 years	89.8 (87.4, 91.7)	80.2 (77.2, 82.8)
3 years	86.3 (83.5, 88.7)	75.7 (72.4, 78.6)
4 years	82.9 (79.6, 85.7)	74.0 (70.6, 77.2)
DDFS		
Number of events (%)	94 (11.5)	159 (19.7)
Estimate of HR [a]	0.561	
95% CI for HR [b]	0.433, 0.722	
Median clinical follow-up time, years [c]	**3.5**	**3.5**
Minimum/Maximum	0/6.7	0/6.6
Percentage (95% CI) of patients distant disease free at [d]		
1 year	94.4 (92.6, 95.9)	89.8 (87.4, 91.7)
2 years	90.8 (88.5, 92.7)	83.0 (80.1, 85.5)
3 years	88.5 (85.9, 90.6)	79.7 (76.6, 82.5)
4 years	86.8 (83.9, 89.2)	78.0 (74.7, 81.0)

	Olaparib 300 mg bd (N=816)	Placebo (N=807)
OS		
Number of events (%)	65 (8.0)	103 (12.8)
Estimate of HR [a]	0.607	
95% CI for HR [b]	0.443, 0.826	
Median clinical follow-up time, years [c]	**3.5**	**3.5**
Minimum/Maximum	0/6.8	0/6.7
Percentage (95% CI) of patients alive at [d]		
1 year	98.0 (96.8, 98.8)	96.8 (95.3, 97.8)
2 years	94.9 (93.0, 96.2)	92.2 (90.1, 93.9)
3 years	92.9 (90.8, 94.5)	87.9 (85.3, 90.1)
4 years	90.2 (87.5, 92.4)	85.2 (82.1, 87.7)

[a] Estimate of the treatment HR was based on the stratified Cox's Proportional Hazards Model, <1 indicates a lower risk with olaparib compared with placebo arm. Stratification factors were the same as those used in the analysis of IDFS, DDFS, or OS in the FAS.

[b] The 95% CI for the HR was estimated using the profile likelihood approach.

[c] Median clinical follow-up was calculated using the reverse censoring method.

[d] Percentage of patients were from the KM estimates and the 95% CIs were calculated using Greenwood's formula.

Excludes patients with only a local or Beijing Genomics Institute result. Myriad data was not available for China. Percentages are of the number of patients in the population subgroup in question.

bd = twice daily; CI = confidence interval; DDFS = distant disease free survival; FAS = full analysis set; *gBRCAm* = germline *BRCA* mutated; HR = hazard ratio; IDFS = invasive disease free survival; KM = Kaplan-Meier; N = total number of patients; OS = overall survival.

Source: Table 14.2.6.1, Table 14.2.9.1, and Table 14.2.12.1.

Summary of main study

The following table summarise the efficacy results from the main study OlympiA supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 30: Summary of Key Efficacy Outcome Variables (FAS)

Title: A randomised, double-blind, parallel group, placebo-controlled multi-centre Phase III study to assess the efficacy and safety of olaparib versus placebo as adjuvant treatment in patients with germline BRCA1/2 mutations and high risk HER2 negative primary breast cancer who have completed definitive local treatment and neoadjuvant or adjuvant chemotherapy (OlympiA).			
Study identifier	D081CC00006		
Design	Randomised, double-blind, parallel group, placebo-controlled multi-centre Phase III study		
Hypothesis	Superiority (interim analysis)		
Treatments groups	Olaparib	300 mg (2 x 150 mg tablets) orally bd continuous N=921 (FAS)	
	Placebo	Matching placebo N=915 (FAS)	
Endpoints and definitions	Primary endpoint	IDFS (Invasive Disease Free Survival)	Time from randomisation to invasive disease recurrence or death due to any cause
	Secondary endpoint	DDFS (Distant Disease Free Survival)	Time from randomisation to distant recurrence or death due to any cause
	Secondary endpoint	OS (Overall Survival)	Time from randomisation to death due to any cause
Results and Analysis			
	FAS		
	Olaparib (N=921)	**Placebo (N=915)**	
IDFS (15.5% maturity in FAS) – DCO1 (25 March 2020)			
Number of events/total number of patients (%)	106/921 (11.5)	178/915 (19.5)	
HR[a] (99.5% CI)[b]	0.581 (0.409, 0.816)[c]		
95% CI[b,d]	(0.455, 0.737)		
p-value (2-sided)[e]	0.0000073		
Patients invasive disease free at 36 months (%)[f] (95% CI)	85.9 (82.8, 88.4)	77.1 (73.7, 80.1)	
DDFS (13% maturity in FAS) – DCO1 (25 March 2020)			
Number of events/total number of patients (%)	89/921 (9.7)	152/915 (16.6)	
HR[a] (99.5% CI)[b,c]	0.574 (0.392, 0.831)		
95% CI[b,d]	(0.441, 0.744)		

p-value (2-sided) [e]	0.0000257	
Patients distant disease free at 36 months (%)[f] (95%CI)	87.5 (84.6, 89.9)	80.4 (77.2, 83.3)
OS (10.0% maturity in FAS) – DCO2 (12 July 2021)		
Number of events/total number of patients (%)	75/921 (8)	109/915 (12)
HR[a] (98.5% CI) [b,c]	0.68 (0.47, 0.97)	
p-value (2-sided)[e]	0.0091	
Percentage (95% CI) of patients alive at 3 years [f]	92.8 (09.8, 94.4)	89.1 (86.7, 91.0)
Percentage (95% CI) of patients alive at 4 years [f]	89.8 (87.2, 91.9)	86.4 (83.6, 88.7)

[a] Estimate of the treatment HR was based on the stratified Cox's Proportional Hazards Model, <1 indicates a lower risk with olaparib compared with placebo arm. Stratification factors were the same as those used in the stratified log-rank test.

[b] The CI for the HR was estimated using the profile likelihood approach.

[c] Inferential, according to the alpha spending rules for the interim analysis.

[d] Exploratory, not inferential

[e] P-value from a stratified log-rank test. Stratification was by chemotherapy type (2 levels: adjuvant vs neoadjuvant), hormone receptor status (2 levels: ER and/or PgR positive, HER2 negative vs TNBC), and prior platinum therapy (2 levels: yes vs no). Stratification factors were based upon the categories used in the randomisation system and were chosen by the pooling strategy. Once the pooling strategy was applied, only the hormone receptor status stratification factor was selected.

[f] Percentages of patients were from the Kaplan-Meier estimates and the 95% CIs were calculated using Greenwood's formula.

CI = confidence interval; DDFS = distant disease free survival; FAS = full Analysis Set; HR = hazard ratio; IDFS = invasive disease free survival; N = total number of patients; OS = overall survival

Supportive studies

The pivotal study OlympiA only included patients with germline mutations of BRCA (gBRCAm). The MAH submitted additional clinical evidence to support the claimed indication that included patients with both germline and somatic BRCA mutations.

Table 31 summarises efficacy data for olaparib and other PARP inhibitors in gBRCAm, tBRCAm, and sBRCAm metastatic breast cancer patients.

Table 31: Summary of Clinical Outcomes by Germline/Somatic BRCA Status in Metastatic Breast Cancer Patients

Study	Subtype	*BRCAm* status	Number of patients	Prior lines of chemotherapy for metastatic disease	Treatment	Median PFS months	ORR	Additional information
Monotherapy/Combination Studies with Olaparib								
OlympiAD (Study D0819C00003; NCT02000622) final analysis	TNBC and ER and/or PgR positive/HER2-negative	*gBRCAm*	205	0-2	Olaparib monotherapy	7.03 (95% CI: 5.68, 8.31)	52.1%[a] (95% CI, 44.2%, 59.9%)	
	TNBC	*gBRCAm*	62	1-2	Olaparib monotherapy	5.4 (95% CI: 4.0, 5.9)	47.1%[a] (95% CI: 32.9%, 61.5%)	
LUCY (Study D0816C00018; NCT03286842)	TNBC and ER and/or PgR positive/HER2-negative	*gBRCAm*	252	0-2	Olaparib monotherapy	8.2 (95% CI: 7.0, 9.2)	49.6% (95% CI, 43.3%, 55.9%)[d]	
	TNBC and ER and/or PgR positive/HER2-negative	*sBRCAm*	3	0-2	Olaparib monotherapy	NA	2/3 patients had best response as stable disease	Median TDT: 8.4 months (95% CI, 0.7, 12.1)
Walsh et al 2021	TNBC and ER and/or PgR positive/HER2-negative	*sBRCAm*	4	2-8	Olaparib monotherapy	6.5 (range: 5-9)	100.0%	
TBCRC 048 NCT03344965 (Tung et al 2020)	TNBC and ER and/or PgR positive/HER2-negative	*sBRCAm*	16	0-2	Olaparib monotherapy	6.3 (90% CI: 4.4, NA)	50.0%[a] (90% CI: 28%, 72%)	
VIOLETTE (Study D5336C00001; NCT03330847) final analysis	TNBC	*sBRCAm*[c]	4	1-2	Olaparib monotherapy	NA	50%[a] (75% (3/4) unconfirmed ORR)	
	TNBC	*sBRCA*[c]	6	1/2	Olaparib combination with DDRi[b]	NA	67% (4/6 unconfirmed ORR)[e]	
Monotherapy/Combination Studies with Other PARP Inhibitors								
EMBRACA (Litton et al 2018	TNBC and ER and/or PgR	*gBRCAm*	287	0-3	Talazoparib monotherapy	8.6 (95% CI: 7.2, 9.3)	62.6%[d] (95% CI: 55.8%, 69.0%)	
ViTAL (Loirat et al 2021)	TNBC and ER and/or PgR	*sBRCAm*	5	0-2+	Talazoparib monotherapy	NA	NA	Median TDT 9.1 months (95% CI: 0.7, NE)

Study	Subtype	*BRCAm* status	Number of patients	Prior lines of chemotherapy for metastatic disease	Treatment	Median PFS months	ORR	Additional information
RUBY (Patsouris et al 2021)	TNBC and ER and/or PgR	*sBRCAm*	5	1/2	Rucaparib monotherapy	NA	20%	1 additional patient had stable disease
Vinayak et al 2019	TNBC	*tBRCAm*	15	0-3	Niraparib + Pembrolizumab	8.3 (95% CI: 2.1, NA)	47% (90% CI: 24%, 70%)	
	TNBC	*sBRCAm* (out of 15 *tBRCAm*)	2	0-3	Niraparib + Pembrolizumab	NA	100% (1 CR and 1 PR)	
Real World Evidence Studies								
Real World Clinico-Genomic Database (Batalini et al 2021)	TNBC and ER and/or PgR	*gBRCAm*	44	1-4+	PARPi or PARPi combination	rwPFS 5.5 (range: 4.3, 7.2)	NA	
	TNBC and ER and/or PgR	*sBRCAm* [c]	9	1-4+	PARPi or PARPi combination	rwPFS 7.1 (range: 1.4, 12.4)	NA	

[a] ORR data are for confirmed responses (by BICR); these were defined as a recorded response of either confirmed or partial response, confirmed by repeat imaging not less than 4 weeks after the visit when the response was first observed.
[b] All patients in the combination arms had a full dose of Olaparib monotherapy.
[c] *sBRCAm* was determined by Foundation Medicine Inc SGZ computational validated algorithm (Sun et al 2018).
[d] ORR data are determined by investigators.
[e] Unconfirmed ORR as confirmation of response was not required in VIOLETTE.
BICR = blinded independent central review; *BRCA* = breast cancer susceptibility gene; *BRCAm* = *BRCA* mutated; CI = confidence interval; CR =complete response; DDRi = DNA damage response inhibitor; ER = oestrogen receptor; *gBRCAm* = germline *BRCA* mutated; HER2 = human epidermal growth factor receptor 2; NA = not available/computable; NE = not evaluable; ORR = objective response rate; PARP = poly adenosine diphosphate-ribose polymerase; PARPi = PARP inhibitor; PFS = progression free survival; PgR = progesterone receptor; PR = partial response; rwPFS = real world progression free survival; *sBRCAm* = somatic *BRCA* mutated; *tBRCAm* = tumour *BRCA* mutated; TDT = time to discontinuation of study treatment; TNBC = triple negative breast cancer.
Source: Table 14.2.1.1 and Table 14.2.3.1.2, LUCY Study; IEMT000197, VIOLETTE study. Sources for other data are as per published references.

2.7.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The applicant provided data from the randomised, double blind, controlled, multi-centre phase III study OlympiA to support the proposed use of olaparib as monotherapy for the adjuvant treatment of adult patients with BRCA1/2-mutations (germline / somatic) who have HER2 negative high risk early breast cancer who have previously been treated with neoadjuvant or adjuvant chemotherapy.

The dose of olaparib in OlympiA (300 mg bd tablets) was selected based on data from the Phase I study, D0810C00024 (Study 24). Study 24 was a formulation comparison study and the findings provided information on the efficacy, PK/PD, safety and tolerability profiles of the olaparib tablet. Study 24 explored the safety data and tumour shrinkage data across a number of different doses and schedules of olaparib tablet or capsule in an advanced gBRCA mutated ovarian cancer population. The results of this study supported the use of 300 mg bd tablet dose for Phase III studies.

On 28 February 2019 (EMEA/H/C/003726/II/0020) Olaparib 100mg/150mg tablets were approved in a breast cancer indication for the treatment in monotherapy of adult patients with germline BRCA1/2-mutations, who have HER2 negative locally advanced or metastatic breast cancer (based on the results of the pivotal study OlympiAD).

Considering the data from study OlympiA, the proposed recommended dose of Lynparza in monotherapy or in combination with endocrine therapy in the treatment of early breast cancer is 300 mg (two 150 mg tablets) taken twice daily, equivalent to a total daily dose of 600 mg (see SmPC section 4.2). The 100 mg tablet is available for dose reduction. Prescribers should refer to the full product information of the endocrine

therapy combination partner(s) (aromatase inhibitor/anti-oestrogen agent and/or LHRH) for the recommended posology.

For what concern treatment duration, the choice of the one-year duration was based on the available efficacy and safety information (due to potential safety issues, e.g. MDS/AML) at the time of the study design in the early breast cancer setting. Therefore, it is recommended that patients are treated for up to 1 year, or until disease recurrence, or unacceptable toxicity, whichever occurs first.

OlympiA study was designed as a comparative study of olaparib monotherapy versus placebo. At the time of study onset, endocrine therapies for patients with HR+/HER2- breast cancer were the only available treatment options after completion of neoadjuvant/adjuvant, anthracycline/taxane chemotherapy. Patients with HR+/HER2- breast cancer included in OlympiA were allowed to have concurrent treatment with endocrine therapy as per local guidelines. Overall, 89.5% of them received an endocrine concomitant therapy during study (see discussion below). The control arm of OlympiA study for RH+/HER2- patients is therefore considered to be placebo + endocrine therapy for this group of patients.

The choice of comparator was also discussed in light of available results from a clinical trial evaluating capecitabine in the adjuvant treatment of TNBC breast cancer (Masuda et al 2017, CREATE-X study). Based on the results of the CREATE-X trial (a trial in Asian patients with HER2-negative residual invasive breast cancer after neoadjuvant chemotherapy [containing anthracycline, taxane, or both]), the NCCN guidelines and ESMO guidelines for early breast cancer were updated to recommend that capecitabine may be offered to high risk TNBC patients following optimal neoadjuvant chemotherapy (Cardoso et al 2019, NCCN Guidelines 2021). However, these results were published three years after the initiation of study OlympiA and the use of additional adjuvant therapy after randomised therapy was not permitted in study OlympiA. Capecitabine is not approved in the EU as adjuvant treatment for breast cancer. Overall, the choice of comparator arm in study OlympiA is acceptable.

The OlympiA study was double blinded which is expected to minimise the risk of bias that could affect the interpretation of the IDFS primary endpoint. A somewhat significant rate of premature unblinding was observed, with a twice higher rate in the placebo arm as compared to olaparib arm. However, these treatments disclosures were compliant to protocol rules and mainly due to treatment discontinuations. A differential efficacy and the need to adequately treat patients' condition when their allocated treatment was stopped could explain this imbalance in unblinding rates.

Patient distribution was generally well balanced between the 2 treatment arms with regard to baseline demographics, disease characteristics, prior medication and therapy.

The majority of hormone receptor positive patients received concurrent endocrine therapy (86.9% in olaparib arm and 92.4% in placebo arm) mainly based on aromatase inhibitors (52.6%, n=171) and tamoxifen (40.3%, n=131). This is consistent with clinical practice and the most recent ESMO Guideline (Cardoso et al 2019) and NCCN Guidelines (NCCN Guidelines 2021). The 34 (10.5%) hormone receptor positive patients who did not receive endocrine therapy were mostly primarily ER zero/PgR positive or ER low (1 to 10%). Current clinical practice guidelines recommend the use of endocrine therapy in ER positive breast cancer defined as ≥1% by immunohistochemistry (IHC) (ESMO, 2019). It is acknowledged that there is currently limited data on the overall benefit of endocrine therapies for patients with low level (1% to 10%) ER expression (Iwamoto et al 2012; Allison et al 2020 ; Burstein et al 2021 ; Schrodi et al 2021; Villegas et al 2021) and the clinical decision to treat with endocrine therapy in OlympiA was made by the treating physician. To adequately reflect the studied population the indication has been reworded to include the use of olaparib is either as monotherapy or in combination with endocrine therapy (see SmPC section 4.1).

The imbalances between arms recorded in the use of individual endocrine therapy agents in hormone receptor positive patients in OlympiA are not considered to introduce any major biases on the efficacy results of the study.

The definitions of high risk of recurrence for patients who received adjuvant chemotherapy (inclusion criteria #3A) and for TNBC patients who received neoadjuvant therapy (inclusion criteria #3B1) are considered acceptable. In OlympiA, high risk early breast cancer patients were selected as follows:

- patients who received prior neoadjuvant chemotherapy: patients with either triple negative breast cancer (TNBC) or hormone receptor positive breast cancer must have had residual invasive cancer in the breast and/or the resected lymph nodes (non-pathologic complete response) at the time of surgery. Additionally, patients with hormone receptor positive breast cancer must have had a CPS&EG score of ≥3 based on pre-treatment clinical and post-treatment pathologic stage (CPS), estrogen receptor (ER) status and histologic grade as shown in Table 9 of the SmPC.

- patients who have received prior adjuvant chemotherapy: triple negative breast cancer (TNBC) patients must have had node positive disease or node negative disease with a ≥2 cm primary tumour; HR positive, HER2-negative patients must have had ≥4 pathologically confirmed positive lymph nodes.

The MAH provided clarifications regarding the CPS&EG scoring system and its use as a prognostic score following neoadjuvant chemotherapy in several retrospective studies including a large population of patients (Mittendorf et al 2011, Abdelsattar et al 2016, Marmé et al 2016). This staging system globally showed a statistically significant stepwise reduction in breast cancer-specific survival with increasing CPS&EG score and was able to separate patients into more refined subgroups. The SmPC has been revised to provide more details about the CPS&EG Scoring and transparent instructions on how high-risk ER and/or PgR positive, HER2-negative breast cancer patients were selected in OlympiA in the neoadjuvant setting (see SmPC section 5.1).

The primary objective of OlympiA was to evaluate the effect of adjuvant treatment with olaparib for patients with HER2-negative (HR+/HER2- or TNBC) early-stage breast cancer on IDFS which is considered acceptable. A multiple testing procedure was employed across the IDFS, DDFS, and OS endpoints to strongly control the overall type I error at 5% 2-sided, accounting for any interim analyses on IDFS, DDFS and OS. At the DCO1 date (27 March 2020), a 2-sided significance level of 0.005 was assigned to the analysis for IDFS and DDFS and a 2-sided significance level of 0.01 was assigned to the analysis for OS. Secondary efficacy endpoints included DDFS, OS and PRO collected on pertinent scales regarding olaparib safety profile and olaparib indication (FACIT-Fatigue, EORTC QLQ-C30).

A protocol amendment was put in place in 2015 (ROW CSP 3.0 [21 Oct 2015]) to update the target population to include HR+/HER2- patients. Prior to this amendment only TNBC patients were included. Only 17.7% of HR+/HER2- patients were included in OlympiA representing a total of 325 patients. It is agreed that this amendment is not considered to have affected the interpretation of study results since IDFS HR+/HER2- subgroup analyses showed HR point estimate consistent with overall IDFS results (HR 0.70; 95% CI: 0.38, 1.27 and HR 0.59; 95% CI: 0.46, 0.74 respectively).

Important protocol deviations were reported in 252 patients (13.7%) and were balanced between the treatment arms (130 patients [14.1%] and 122 patients [13.3%] in the olaparib arm and placebo arm, respectively). The most common important deviation observed in both treatment arms was no staging or insufficient staging as required by exclusion criterion 4 with 67 patients (7.3%) in the olaparib arm and 66 patients (7.2%) in the placebo arm not having all the required tests performed prior to randomisation. A total of 10.2% of patients with AJCC clinical stage IA were included in the study. This population is not covered by the claimed indication. A post hoc analysis was provided excluding all patients with an important protocol deviations related to eligibility (n=223) (data not shown). Results of this post hoc exploratory

analysis of IDFS suggested a consistent treatment effect in the intended study population, when compared with the FAS (HR 0.52; 95% CI 0.40, 0.68; p<0.001).

Efficacy data and additional analyses

OlympiA met its primary endpoint showing a statistically significant improvement in IDFS for olaparib-treated patients compared to placebo-treated patients, reducing the risk of recurrence of disease at any given point in time by 42% in patients with gBRCAm, high risk early-stage breast cancer after standard of care neo/adjuvant chemotherapy and surgery (HR 0.58; 99.5% CI: 0.41, 0.82; p=0.0000073). The difference in the proportion of patients free of invasive disease at 3 years was 8.8% (95%CI, 4.5%-13.0%) in favour of olaparib. This benefit is considered clinically meaningful.

The results of the sensitivity analyses of IDFS (including only patients with central pathology review data for hormone receptor status [ER and PgR], using unadjusted analysis, using interval censoring, and using RMST method) are considered consistent with the primary analysis of IDFS.

The subgroup analyses showed consistent effects with the primary analysis of IDFS in the FAS with a treatment benefit of olaparib over placebo evidenced across most of the pre-defined subgroups. The subgroup of patients with HR+/HER2- status who had received adjuvant chemotherapy (6 events in 64 olaparib-treated patients vs 5 events in 65 placebo-treated patients) showed a HR point estimate >1 (HR 1.36; 95% CI: 0.41, 4.71) at DCO 1 (27 March 2020).

Updated descriptive analyses of IDFS based on more mature data (with median follow-up of 3.5 years) conducted at the time of the pre-planned second OS interim analysis (DCO2: 12 July 2021) were provided. The updated analysis with increased number of events in the hormone receptor positive prior adjuvant subgroup (9.4% and 13.8% events for the olaparib and placebo arm respectively) showed an improved hazard ratio for IDFS of 0.736 (95% CI: 0.247, 2.042). The hazard ratio in this subgroup of patients with longer follow up and increased maturity of events is consistent with the ITT outcome supporting a treatment benefit for olaparib in these patients.

Treatment with olaparib compared to placebo conferred a numerical benefit in DDFS supporting the positive outcome of IDFS.

The MAH provided updated OS results from the second planned interim analysis (DCO2 12 July 2021). Median duration of follow-up for OS was 3.5 years in the olaparib arm and 3.6 years in the placebo arm. The OS results showed statistically 32.2% numerical reduction in the risk of death at any given point in time (HR 0.68, 98.5% CI: 0.47, 0.97, p=0.0091). At all-time points, a higher proportion of patients in the olaparib arm compared with the placebo arm remained alive (1 year [98.0%], 2 years [95.0%], 3 years [92.8%] and 4 years [89.8%] compared with 96.9%, 92.8%, 89.1% and 86.4% respectively). The subgroup analyses showed consistent effects with the analysis of OS in the FAS, with a treatment benefit of olaparib over placebo evidenced across all the pre-defined subgroups (including the HR+/HER2- population).

The incidences of contralateral breast cancers (invasive and non-invasive), new primary ovarian cancer, new primary fallopian tube cancer, and new primary peritoneal cancer without considering competing risks were numerically lower in the olaparib arm compared with the placebo arm. However, it remains difficult to draw conclusion based on this low number of cases, in addition longer follow up would be necessary to assess if this potential benefit persists on long term.

No clinically meaningful differences in HRQoL were observed between patients receiving olaparib and placebo over the course of the study especially on adverse events of special interest (nausea/vomiting and diarrhea) and fatigue scores based on results collected on pertinent scales regarding olaparib safety profile (FACIT-Fatigue, EORTC QLQ-C30). However, no formal hypothesis testing was performed regarding PROs.

Methodologically robust PRO data are needed to be able to conclude on a potential clinical benefit (The use of patient-reported outcome (PRO) measures in oncology studies - Appendix 2 to the guideline on the evaluation of anticancer medicinal products in man; 1 April 2016 EMA/CHMP/292464/2014).

The MAH submitted a justification to support the claimed indication that include patients with both germline and somatic BRCA mutations. The MAH presented data available with olaparib in the metastatic setting and data available from other PARP inhibitors. These data support a strong biological rationale and suggest antitumour activity in patients with sBRCA in this adjuvant setting. In addition, similarities between the target population (sBRCAm in adjuvant setting) and the studied population are acknowledged. However, the extrapolation of the efficacy associated with olaparib observed in patients with germline BRCA mutations to patients with tumours with somatic BRCA mutations in the early breast cancer setting is considered premature considering the remaining uncertainties. Further evidence to support efficacy in patients with sBRCAm and to address uncertainties related to safety is required including clinical data with longer follow-up (see also discussion on clinical safety). The indication is thus restricted to germline BRCAm patients only (see SmPC section 4.1). Section 4.2 of the SmPC has been updated accordingly reflecting that patients must have confirmation of deleterious or suspected deleterious g*BRCA1/2* mutation using a validated test before Lynparza treatment is initiated for adjuvant treatment of HER2 negative high risk early breast cancer.

2.7.3. Conclusions on the clinical efficacy

A clinically relevant benefit of olaparib has been shown for both the subgroups of TNBC patients in monotherapy and HR+/HER2- patients in association with endocrine therapy as adjuvant treatment of adult patients with germline BRCA1/2-mutations who have high risk early breast cancer who have previously been treated with neoadjuvant or adjuvant chemotherapy.

Since patients with a somatic mutation were excluded from study OlympiA due to unavailability of an appropriate diagnostic test based on tissue analysis at that time, there are no clinical data available on the responsiveness of breast tumours with sBRCA mutation to olaparib in the early setting. The benefit remains uncertain in patients with sBRCA1/2 mutations treated in early breast cancer setting. In the absence of data supporting extrapolation to patients with somatic mutation the indication has been restricted to germline BRCAm patients only.

2.8. Clinical safety

Introduction

Across the entire clinical programme, as of 15 June 2021, approximately 17923 patients are estimated to have received treatment with olaparib.

The safety assessment was based primarily on data from OlympiA, the pivotal Phase III study in gBRCAm primary breast cancer patients, where 911 patients received olaparib (300 mg bd tablet).

Data from OlympiA was supported by data from a pooled safety database of olaparib 300 mg bd tablet data from 17 AstraZeneca sponsored monotherapy studies (n=3045 [including 911 patients from OlympiA]) as described in **Table 32** and larger pools of olaparib studies (olaparib monotherapy combined therapeutic dose pool, n=3988) at the DCO 27 March 2020 (DCO1). The MAH provided updated safety data with the DCO 12 July 2021 (DCO2). At DCO2, safety data from 18 studies were pooled to provide data for a total of 3155 patients with advanced solid tumours, 1289 of whom had breast cancer. Between DCO1 and DCO2,

the total number of patients in the 300 mg bd pool has increased by 110 patients; this was due to addition of data from patients who received olaparib 300 mg bd monotherapy in the VIOLETTE study. Data have also been updated for the OlympiA and SOLO3 studies.

The primary comparison of safety was between the olaparib and placebo arms within the OlympiA study and the olaparib 300 mg bd tablet pool. In addition, data were presented for the larger therapeutic dose pool of olaparib studies in summaries of MDS/AML and important potential risks.

Table 32: Number of Patients in the 300 mg bd Pool (DCO: 12 July 2021)

Study/pooled dataset	**Number of patients intended for the 300 mg bd cohort and received olaparib (all tumour types)**
Total exposed	**3155**
D081CC00006 (OlympiA): Phase III *gBRCA1/2m* HER2 negative high-risk early breast cancer patients who have completed definitive local treatment and either neoadjuvant or adjuvant chemotherapy	911
D0818C00001 (SOLO1): Phase III FIGO Stage III-IV ovarian cancer SOLO1 China cohort [a]	260 40
D0816C00002 (SOLO2): Phase III platinum-sensitive serous ovarian cancer SOLO2: China cohort [a]	195 22
Study D0816C00010 (SOLO3): Phase III *gBRCAm* ≥third line ovarian cancer patients	178
D0819C00003 (OlympiAD): Phase III HER2-negative breast cancer patients with *gBRCA1/2* mutation	205
Study D081DC00007 (PROfound): Phase III HRRm metastatic castration-resistant prostate cancer (mCRPC)	256
Study D081FC00001 (POLO): Phase III *gBRCAm* metastatic pancreatic adenocarcinoma patients whose disease has not progressed on first-line platinum-based chemotherapy.	90
Study D0816C00020 (OPINION): Phase IIIb, patients with platinum-sensitive relapsed non-germline *BRCA* mutated ovarian cancer	279
Study D0816L00003 (LIGHT): Phase II, patients with different HRD tumour status and with platinum-sensitive and endometrioid ovarian, fallopian tube, or primary peritoneal cancer	271
Study D5336C00001 (VIOLETTE): Phase II, second- or third-line metastatic TNBC patients stratified by alterations in HRR related genes (including *BRCA1/2*) (Patient Population E [Stratum A]; olaparib monotherapy)	110
Study 24: Phase I Relative Bioavailability (300 mg tablet bd patients only, Groups 4 and 6)	24
Study 04: Phase I Food interaction & QT	57

Study/pooled dataset	**Number of patients intended for the 300 mg bd cohort and received olaparib (all tumour types)**
Study 06: Phase I Renal impairment study	43
Study 07: Phase I CYP3A4 inhibition and QT	56
Study 08: Phase I CYP induction	19
Study D081CC00001: Phase I anti-hormonal PK study	69
Study D081BC00001: Phase I Japan Monotherapy study	19
D0816C00005: Phase I hepatic impairment study	31
D081BC00002: China PK study	20

Patient exposure

Overall Extent of Exposure: OlympiA Study

All except for 21 of the 1836 randomised patients in OlympiA received study treatment (10 patients randomised to olaparib and 11 patients randomised to placebo). The OlympiA Safety Analysis Set (SAS) consists of 1815 patients (911 who received olaparib and 904 who received placebo).

The DCO for the interim analysis for OlympiA was 27 March 2020 (DCO1). At the time of the DCO1, 1353 patients (73.7%) had completed study treatment per protocol and 39 patients (2.1%) were still receiving study treatment (19 patients [2.1%] in the olaparib arm and 20 patients [2.2%] in the placebo arm). At the time of the DCO2 (12 July 2021), no patients remained on study treatment in OlympiA; 1389 patients (75.7% of those randomised) had completed treatment per protocol and 426 patients (23.2% of those randomised) had discontinued study treatment. In total, 674 patients (73.2% of those randomised) in the olaparib arm and 715 patients (78.1% of those randomised) in the placebo arm completed treatment per protocol. As observed at DCO1, the most common reason for early discontinuation in the olaparib arm was AEs (98 patients [10.6%] in the olaparib versus 41 patients [4.5%] in the placebo arm) and in the placebo arm it was recurrence of disease (80 patients [8.7%] in the placebo arm versus 40 patients [4.3%] in the olaparib arm). A lower proportion of patients in the olaparib arm than the placebo arm died on study (75 patients [8.1%] versus 106 patients [11.6%] in the FAS, respectively (**Table 44**).

The treatment duration in OlympiA was capped at 12 months. A summary of the number of patients receiving treatment by months is presented in **Table 33**. A similar proportion of patients in both treatment arms continued to receive treatment over 12 months treatment duration.

The majority of patients (76.1% in the olaparib arm and 81.7% in the placebo arm) received ≥11 months with most patients discontinuing treatment after 11.5 months (73.9% in the olaparib arm and 79.4% in the placebo arm). Only a small number of patients received ≥12.5 months of randomised treatment (1.9% of patients in the olaparib arm and 0.9% of patients in the placebo arm).

Table 33: OlympiA: Overall Extent of Exposure (SAS)

Cumulative exposure over time (months) [a]	Number (%) of patients			
	Olaparib 300 mg bd (N=911)		Placebo (N=904)	
	27 Mar 2020 DCO	12 Jul 2021 DCO	27 Mar 2020 DCO	12 Jul 2021 DCO
>0 months	910 (99.9)	910 (99.9)	903 (99.9)	903 (99.9)
≥1 month	848 (93.1)	848 (93.1)	872 (96.5)	872 (96.5)
≥2 months	824 (90.5)	824 (90.5)	847 (93.7)	847 (93.7)
≥3 months	801 (87.9)	801 (87.9)	836 (92.5)	836 (92.5)
≥4 months	782 (85.8)	782 (85.8)	821 (90.8)	821 (90.8)
≥5 months	769 (84.4)	769 (84.4)	805 (89.0)	805 (89.0)
≥6 months	757 (83.1)	757 (83.1)	794 (87.8)	794 (87.8)
≥7 months	752 (82.5)	752 (82.5)	782 (86.5)	782 (86.5)
≥8 months	739 (81.1)	739 (81.1)	771 (85.3)	771 (85.3)
≥9 months	719 (78.9)	719 (78.9)	758 (83.8)	758 (83.8)
≥10 months	706 (77.5)	707 (77.6)	753 (83.3)	753 (83.3)
≥11 months	685 (75.2)	693 (76.1)	733 (81.1)	739 (81.7)
12 months	401 (44.0)	414 (45.4)	449 (49.7)	465 (51.4)

[g] Rows are cumulative and patients were included if they had taken treatment up to and including that day.

Patients with partial treatment end dates were excluded.

bd = Twice daily; CSR = Clinical study report; DCO = Data cut-off; N = Total number of patients; SAS = Safety analysis set.

Source: Table 14.3.1.3, OlympiA CSR, Module 5.3.5.1 and Safety Update Table 14.3.1.3.

Table 34: OlympiA: Duration of Exposure (SAS)

Treatment duration		Olaparib 300 mg bd (N=911)		Placebo (N=904)	
		27 Mar 2020 DCO	**12 Jul 2021 DCO**	**27 Mar 2020 DCO**	**12 Jul 2021 DCO**
Total intended exposure (days) [a]	Mean (standard deviation)	306.5 (114.80)	307.2 (115.02)	322.4 (97.54)	323.1 (97.72)
	Median (range)	364.0 (1-492)	364.0 (1-492)	364.0 (2-414)	365.0 (2-414)
Actual treatment exposure (days) [b]	Mean (standard deviation)	294.4 (113.90)	295.0 (114.09)	315.1 (97.59)	315.7 (97.77)
	Median (range)	350.0 (1-420)	350.0 (1-420)	358.0 (2-404)	359.0 (2-404)
Number of days on 300 mg treatment bd [c]	Mean (standard deviation)	245.2 (141.68)	245.8 (142.05)	306.3 (107.51)	307.0 (107.67)
	Median (range)	338.0 (1-420)	341.0 (1-420)	358.0 (2-404)	358.0 (2-404)

[h] Total intended exposure (days) = (last dose date - first dose date + 1).

Actual treatment exposure (days) = intended exposure - total duration of dose interruptions, where intended exposure was calculated as above.

Number of days on 300 mg olaparib/placebo bd (actual exposure for the assigned starting dose).

Patients with partial treatment end dates were excluded.

bd = Twice daily; CSR = Clinical study report; DCO = Data cut-off; N = Total number of patients; SAS = Safety analysis set.

Source: Table 14.3.1.1, OlympiA CSR, Module 5.3.5.1 and Safety Update Table 14.3.1.1.

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The proportion of patients with dose interruptions or reductions was higher in the olaparib arm than in the placebo arm. The majority of patients in the olaparib arm had ≤2 interruptions and 79 patients (8.7%) had ≥3 interruptions. In both arms, AEs were the most common reason for dose reductions. The most common reason for dose interruption were AEs in the olaparib arm and surgery in the placebo arm.

Table 35*: Treatment dose reductions (SAS) (DCO 12 July 2021)*

	Olaparib 300 mg bd (N=911)	Placebo (N=904)
Patients with no dose reduction	683 (75.0%)	857 (94.8%)
Patients with a dose reduction	228 (25.0%)	47 (5.2%)
Total number of dose reductions	287	54
Number of patients with a dose reduction		
1 dose reduction	170 (18.7%)	40 (4.4%)
2 dose reductions	57 (6.3%)	7 (0.8%)
3 or more dose reductions	1 (0.1%)	0 (0.0%)
Reason for reduction [2]		
Adverse event	222 (24.4%)	35 (3.9%)
Dosing error	6 (0.7%)	10 (1.1%)
Administrative reasons	2 (0.2%)	1 (0.1%)
Other	0 (0.0%)	1 (0.1%)

[1] Dose reductions are based on investigator initiated decisions, reductions due to 'Subject non-compliance' are omitted.
[2] Reasons for dose reductions are not mutually exclusive for patients with multiple reductions although are counted only once per category.

Table 36 *: Treatment dose interruptions (SAS) (DCO 12 July 2021)*

	Olaparib 300 mg bd (N=911)	Placebo (N=904)
Patients with no dose interruption	401 (44.0%)	500 (55.3%)
Patients with a dose interruption	510 (56.0%)	404 (44.7%)
Patients with a dose interruption lasting at least 3 days	400 (43.9%)	279 (30.9%)
Number of patients with a dose interruption		
1 dose interruption	300 (32.9%)	272 (30.1%)
2 dose interruptions	131 (14.4%)	92 (10.2%)
3 or more dose interruptions	79 (8.7%)	40 (4.4%)
Reason for interruption [2]		
Adverse event	323 (35.5%)	126 (13.9%)
Surgery	224 (24.6%)	236 (26.1%)
Recurrence of disease	38 (4.2%)	79 (8.7%)
Dosing error	0 (0.0%)	3 (0.3%)
Administrative reasons	20 (2.2%)	25 (2.8%)
Other	6 (0.7%)	11 (1.2%)

[1] Dose interruptions are based on investigator initiated decisions, interruptions due to 'Subject non-compliance' are omitted.
[2] Reasons for dose interruptions are not mutually exclusive for patients with multiple interruptions although are counted only once per category.

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Table 37 : 300 mg bd Pool: Overall Extent of Exposure (SAS)

	Number (%) of patients	
	Olaparib 300 mg bd (N=3155)	
Treatment period	27 Mar 2020 DCO	12 Jul 2021 DCO
>0 month	3045 (100)	3155 (100)
≥1 month	2887 (94.8)	2981 (94.5)
≥3 months	2520 (82.8)	2577 (81.7)
≥6 months	2077 (68.2)	2107 (66.8)
≥12 months	983 (32.3)	996 (31.6)
≥18 months	548 (18.0)	548 (17.4)
≥24 months	365 (12.0)	366 (11.6)
≥36 months	109 (3.6)	117 (3.7)
≥48 months	82 (2.7)	92 (2.9)
≥60 months	58 (1.9)	65 (2.1)
≥72 months	9 (0.3)	9 (0.3)

Patients ongoing treatment at study closure may not necessarily appear in the final treatment day category as total treatment duration differs across patients.

Rows are cumulative and patients were included if they had taken treatment up to that day.

bd = Twice daily; DCO = Data cut-off; N = Total number of patients; SAS = Safety analysis set.

Source: Safety Update Table 2.7.4.1.9.2.

In OlympiA, patients were treated for a maximum of 12 months in comparison to the 300 mg bd pool where studies allowed patients to be treated for 24 months or until disease progression if they were continuing to receive benefit.

Demographics and Characteristics of Study Population

OlympiA Study

The demographic and disease characteristics of patients in OlympiA are summarised in **Table 8**.

Adverse events

Overview of AE

Comparison with olaparib 300mg bd pool

Table 38: OlympiA: Number of Events and Number (%) of patients who had at least one AE in any Category (SAS; DCO: 12 July 2021)

AE category [a]	Number (%) of patients		
	OlympiA SAS		
	Olaparib 300 mg bd (N=911)	Placebo (N=904)	Olaparib 300 mg bd pool (N=3155)
Any AE	836 (91.8)	756 (83.6)	3024 (95.8)
Any AE of CTCAE Grade ≥3	223 (24.5)	102 (11.3)	1155 (36.6)
Any AE with outcome=death	1 (0.1)	2 (0.2)	31 (1.0)
Any SAE (including events with outcome=death)	79 (8.7)	78 (8.6)	616 (19.5)
Any AE leading to discontinuation of olaparib or placebo	97 (10.6)	42 (4.6)	306 (9.7)
Any AE leading to dose reduction of olaparib or placebo [b]	213 (23.4)	33 (3.7)	711 (22.5)
Any AE leading to interruption of olaparib or placebo [c]	284 (31.2)	99 (11.0)	1191 (37.7)

[a] Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories.

[b] Includes AEs that led to a dose interruption/reduction and did not lead to permanent discontinuation of study treatment.

Includes AEs with an onset date between the date of first dose and 30 days following the date of last dose of study treatment.

At DCO2 (12 July 2021), AE causally related to olaparib/placebo were reported in 736 patients (80.8%) and 480 patients (53.1%) in the olaparib and placebo arm respectively.

Table 39: OlympiA: Adverse Events and Event Rate Reported in At Least 5% of Patients in Either Treatment Arm Arranged by System Organ Class and Preferred Term (SAS)

	Olaparib 300 mg bd (N=911)				Placebo (N=904)			
	27 Mar 2020 DCO		12 Jul 2021 DCO		27 Mar 2020 DCO		12 Jul 2021 DCO	
System organ class / MedDRA preferred term	Number (%) of patients	Event rate (per 1000 pt years) [a]	Number (%) of patients	Event rate (per 1000 pt years) [a]	Number (%) of patients	Event rate (per 1000 pt years) [a]	Number (%) of patients	Event rate (per 1000 pt years) [a]
Any AE	**835 (91.7)**	**7774**	**836 (91.8)**	**7790**	**753 (83.3)**	**3530**	**756 (83.6)**	**3576**
Gastrointestinal disorders	**654 (71.8)**	**2405**	**654 (71.8)**	**2393**	**427 (47.2)**	**827**	**429 (47.5)**	**830**
Nausea	518 (56.9)	1340	518 (56.9)	1335	211 (23.3)	303	212 (23.5)	303
Vomiting	206 (22.6)	305	206 (22.6)	304	74 (8.2)	91	74 (8.2)	90
Diarrhoea	160 (17.6)	226	160 (17.6)	225	124 (13.7)	161	124 (13.7)	160
Abdominal pain	86 (9.4)	111	86 (9.4)	111	68 (7.5)	83	68 (7.5)	83
Constipation	84 (9.2)	108	84 (9.2)	108	77 (8.5)	95	78 (8.6)	96
Stomatitis	81 (8.9)	105	81 (8.9)	104	36 (4.0)	43	36 (4.0)	43
Dyspepsia	55 (6.0)	70	55 (6.0)	69	37 (4.1)	44	37 (4.1)	44
General disorders and administration site conditions	**505 (55.4)**	**1131**	**505 (55.4)**	**1129**	**379 (41.9)**	**671**	**382 (42.3)**	**677**
Fatigue	365 (40.1)	665	365 (40.1)	662	245 (27.1)	363	246 (27.2)	364
Pain	68 (7.5)	86	68 (7.5)	86	74 (8.2)	91	74 (8.2)	90
Influenza like illness	57 (6.3)	71	58 (6.4)	72	43 (4.8)	51	44 (4.9)	52
Pyrexia	48 (5.3)	60	48 (5.3)	60	41 (4.5)	49	41 (4.5)	49
Nervous system disorders	**370 (40.6)**	**689**	**370 (40.6)**	**685**	**298 (33.0)**	**467**	**297 (32.9)**	**464**
Headache	180 (19.8)	258	179 (19.6)	255	152 (16.8)	202	152 (16.8)	201
Dysgeusia	107 (11.7)	144	107 (11.7)	144	38 (4.2)	45	38 (4.2)	45
Dizziness	104 (11.4)	137	104 (11.4)	136	67 (7.4)	82	66 (7.3)	80
Infections and infestations	**284 (31.2)**	**446**	**286 (31.4)**	**448**	**305 (33.7)**	**467**	**306 (33.8)**	**468**

System organ class / MedDRA preferred term	Olaparib 300 mg bd (N=911)				Placebo (N=904)			
	27 Mar 2020 DCO		12 Jul 2021 DCO		27 Mar 2020 DCO		12 Jul 2021 DCO	
	Number (%) of patients	Event rate (per 1000 pt years) [a]	Number (%) of patients	Event rate (per 1000 pt years) [a]	Number (%) of patients	Event rate (per 1000 pt years) [a]	Number (%) of patients	Event rate (per 1000 pt years) [a]
Upper respiratory tract infection	79 (8.7)	101	79 (8.7)	101	75 (8.3)	92	75 (8.3)	92
Nasopharyngitis	31 (3.4)	38	31 (3.4)	38	52 (5.8)	63	52 (5.8)	62
Investigations	**282 (31.0)**	**452**	**285 (31.3)**	**456**	**184 (20.4)**	**252**	**185 (20.5)**	**253**
Neutrophil count decreased	146 (16.0)	200	147 (16.1)	200	59 (6.5)	72	59 (6.5)	72
WBC count decreased	143 (15.7)	197	144 (15.8)	197	52 (5.8)	63	52 (5.8)	63
Lymphocyte count decreased	61 (6.7)	78	62 (6.8)	79	15 (1.7)	18	15 (1.7)	17
Musculoskeletal and connective tissue disorders	**280 (30.7)**	**445**	**280 (30.7)**	**442**	**307 (34.0)**	**477**	**307 (34.0)**	**476**
Arthralgia	84 (9.2)	109	89 (9.8)	115	107 (11.8)	135	114 (12.6)	145
Back pain	62 (6.8)	79	62 (6.8)	78	74 (8.2)	90	73 (8.1)	89
Pain in extremity	62 (6.8)	78	61 (6.7)	76	61 (6.7)	74	63 (7.0)	76
Myalgia	49 (5.4)	61	49 (5.4)	61	49 (5.4)	59	49 (5.4)	59
Blood and lymphatic system disorders	**228 (25.0)**	**339**	**229 (25.1)**	**339**	**43 (4.8)**	**51**	**43 (4.8)**	**51**
Anaemia	214 (23.5)	314	215 (23.6)	314	35 (3.9)	41	35 (3.9)	41
Respiratory, thoracic and mediastinal disorders	**170 (18.7)**	**238**	**171 (18.8)**	**238**	**163 (18.0)**	**215**	**164 (18.1)**	**215**
Cough	77 (8.5)	98	77 (8.5)	98	73 (8.1)	89	73 (8.1)	89
Metabolism and nutrition disorders	**154 (16.9)**	**214**	**155 (17.0)**	**215**	**88 (9.7)**	**110**	**88 (9.7)**	**109**
Decreased appetite	119 (13.1)	160	119 (13.1)	159	53 (5.9)	64	53 (5.9)	64
Vascular disorders	**121 (13.3)**	**163**	**121 (13.3)**	**162**	**136 (15.0)**	**177**	**135 (14.9)**	**175**
Hot flush	72 (7.9)	93	72 (7.9)	92	75 (8.3)	93	74 (8.2)	91
Psychiatric disorders	**118 (13.0)**	**156**	**120 (13.2)**	**158**	**128 (14.2)**	**164**	**128 (14.2)**	**163**
Insomnia	67 (7.4)	85	67 (7.4)	85	60 (6.6)	73	60 (6.6)	72

[a] For any event, each SOC and each PT, the event rate is presented and was defined as the number of patients with that AE (counting AEs from date of first dose up to 30 days following the date of last dose of study treatment) divided by the total number of days at risk across all patients in a given group multiplied by 365.25 × 1000. The denominator, total number of days at risk, was, (a) for patients who had the event, the number of days between date of first treatment to start date of the first event, (b) for patients who did not have the event, the number of days between date of first treatment and end of safety follow-up (where end of safety follow-up was defined as the minimum of 30 days following last dose of study treatment, withdrawal and death).

There were 12 patients (6 patients in the olaparib arm and 6 patients in the placebo arm) with 13 pre-existing AEs that worsened after treatment was started who were incorrectly censored in the calculation of the event rate and were not included in this table.

SOCs sorted by decreasing frequency and by decreasing frequency order in the olaparib arm for PT.

Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories.

Includes AEs with an onset date on or after the date of first dose and up to and including 30 days following the date of last dose of olaparib/placebo.

CTCAE Version 4.03. MedDRA Version 22.1 used for 27 March 2020 DCO and MedDRA Version 24.0 used for 12 July 2021 DCO.

AE = Adverse event; bd = Twice daily; CSR = Clinical study report; DCO = Data cut-off; MedDRA = Medical Dictionary for Regulatory Activities; N = Total number of patients; PT = Preferred term; pt = Patient; SAS = Safety analysis set; SOC = System organ class; WBC = White blood cell.

Source: Table 14.3.2.15, OlympiA CSR, Module 5.3.5.1, data on file, and Safety Update Table 14.3.2.15.

Comparison with olaparib 300mg bd pool

Table 40: **Most Common AEs (Reported in ≥5% of Patients in the Olaparib Arm of OlympiA or the 300 mg bd Pool; DCO: 12 July 2021)**

Preferred term	Number (%) of patients [a]		
	OlympiA SAS		
	Olaparib 300 mg bd (N=911)	Placebo (N=904)	Olaparib 300 mg bd pool (N=3155)
Any AE	**836 (91.8)**	**756 (83.6)**	**3024 (95.8)**
Nausea	518 (56.9)	212 (23.5)	1842 (58.4)
Fatigue	365 (40.1)	246 (27.2)	1238 (39.2)
Anaemia	215 (23.6)	35 (3.9)	1087 (34.5)
Vomiting	206 (22.6)	74 (8.2)	904 (28.7)
Headache	179 (19.6)	152 (16.8)	515 (16.3)
Diarrhoea	160 (17.6)	124 (13.7)	703 (22.3)
Neutrophil count decreased	147 (16.1)	59 (6.5)	281 (8.9)
WBC count decreased	144 (15.8)	52 (5.8)	284 (9.0)
Decreased appetite	119 (13.1)	53 (5.9)	609 (19.3)
Dysgeusia	107 (11.7)	38 (4.2)	365 (11.6)
Dizziness	104 (11.4)	66 (7.3)	367 (11.6)
Arthralgia	89 (9.8)	114 (12.6)	404 (12.8)
Abdominal pain	86 (9.4)	68 (7.5)	438 (13.9)
Constipation	84 (9.2)	78 (8.6)	488 (15.5)
Stomatitis	81 (8.9)	36 (4.0)	207 (6.6)
Upper respiratory tract infection	79 (8.7)	75 (8.3)	242 (7.7)
Cough	77 (8.5)	73 (8.1)	379 (12.0)
Hot flush	72 (7.9)	74 (8.2)	132 (4.2)
Pain	68 (7.5)	74 (8.2)	100 (3.2)
Insomnia	67 (7.4)	60 (6.6)	215 (6.8)
Back pain	62 (6.8)	73 (8.1)	339 (10.7)
Lymphocyte count decreased	62 (6.8)	15 (1.7)	112 (3.5)
Pain in extremity	61 (6.7)	63 (7.0)	199 (6.3)
Influenza like illness	58 (6.4)	44 (4.9)	146 (4.6)

Table 40: **Most Common AEs (Reported in ≥5% of Patients in the Olaparib Arm of OlympiA or the 300 mg bd Pool; DCO: 12 July 2021)**

	Number (%) of patients [a]		
	OlympiA SAS		
Preferred term	Olaparib 300 mg bd (N=911)	Placebo (N=904)	Olaparib 300 mg bd pool (N=3155)
Dyspepsia	55 (6.0)	37 (4.1)	282 (8.9)
Myalgia	49 (5.4)	49 (5.4)	163 (5.2)
Pyrexia	48 (5.3)	41 (4.5)	265 (8.4)
Abdominal pain upper	45 (4.9)	35 (3.9)	230 (7.3)
Urinary tract infection	39 (4.3)	43 (4.8)	240 (7.6)
Dyspnoea	38 (4.2)	30 (3.3)	303 (9.6)
Nasopharyngitis	31 (3.4)	52 (5.8)	186 (5.9)
Oedema peripheral	25 (2.7)	18 (2.0)	210 (6.7)
Asthenia	23 (2.5)	12 (1.3)	365 (11.6)
Blood creatinine increased	18 (2.0)	3 (0.3)	181 (5.7)
Thrombocytopenia	2 (0.2)	0	167 (5.3)
Neutropenia	0	0	259 (8.2)

[i] Sorted by decreasing order of frequency for PT in the olaparib arm of OlympiA, and then by decreasing order of frequency in the placebo arm.

Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories.

Includes AEs with an onset date between the date of first dose and 30 days following the date of last dose of study treatment.

MedDRA Version 24.0.

AE = Adverse event; bd = Twice daily; CSR = Clinical study report; DCO = Data cut-off; MedDRA = Medical Dictionary for Regulatory Activities; N = Total number of patients; PT = Preferred term; SAS = Safety analysis set; WBC = White blood cell.

Source: Safety Update Table 14.3.2.15 and Table 2.7.4.1.1.2.

CTCAE Grade ≥3 Adverse Events

At DCO2, adverse events of CTCAE Grade ≥3 occurred in 24.5% of patients in the olaparib arm and 11.3% of patients in the placebo arm. Anaemia was the only AE of CTCAE Grade ≥3 reported in ≥5% of patients (8.7% of patients in the olaparib arm vs 0.3% of patients in the placebo arm).

Table 41: Most Common AEs of CTCAE Grade ≥3 (Reported in ≥3 Patients in the Olaparib Arm of OlympiA or ≥2% of Patients in the 300 mg bd Pool; DCO: 12 July 2021)

System organ class / MedDRA preferred term	Number (%) of patients [a]		
	OlympiA SAS		
	Olaparib 300 mg bd (N=911)	Placebo (N=904)	Olaparib 300 mg bd pool (N=3155)
Patients with AE of CTCAE Grade ≥3	**223 (24.5)**	**102 (11.3)**	**1155 (36.6)**
Blood and lymphatic system disorders	**86 (9.4)**	**3 (0.3)**	**548 (17.4)**
Anaemia	79 (8.7)	3 (0.3)	462 (14.6)
Febrile neutropenia	6 (0.7)	0	12 (0.4)
Neutropenia	0	0	85 (2.7)
Investigations	**70 (7.7)**	**16 (1.8)**	**207 (6.6)**
Neutrophil count decreased	45 (4.9)	7 (0.8)	94 (3.0)
WBC count decreased	27 (3.0)	3 (0.3)	57 (1.8)
Lymphocyte count decreased	12 (1.3)	0	24 (0.8)
ALT increased	3 (0.3)	1 (0.1)	22 (0.7)
Infections and infestations	**21 (2.3)**	**18 (2.0)**	**124 (3.9)**
Mastitis	3 (0.3)	4 (0.4)	3 (0.1)
Device related infection	3 (0.3)	2 (0.2)	5 (0.2)
Gastroenteritis	3 (0.3)	0	7 (0.2)
General disorders and administration site conditions	**19 (2.1)**	**10 (1.1)**	**132 (4.2)**
Fatigue	16 (1.8)	6 (0.7)	75 (2.4)
Gastrointestinal disorders	**18 (2.0)**	**9 (1.0)**	**178 (5.6)**
Nausea	7 (0.8)	0	34 (1.1)
Vomiting	6 (0.7)	0	35 (1.1)
Diarrhoea	3 (0.3)	3 (0.3)	24 (0.8)
Nervous system disorders	**12 (1.3)**	**7 (0.8)**	**63 (2.0)**
Syncope	3 (0.3)	2 (0.2)	13 (0.4)
Vascular disorders	**8 (0.9)**	**10 (1.1)**	**49 (1.6)**
Hypertension	5 (0.5)	9 (1.0)	20 (0.6)
Embolism	3 (0.3)	0	9 (0.3)

Serious adverse event/deaths/other significant events

Serious adverse events

Table 42: Most Common SAEs (Reported in ≥3 Patients in the Olaparib Arm of OlympiA and/or Reported in ≥2% of Patients in the 300 mg bd Pool; DCO: 12 July 2021)

System organ class / MedDRA preferred term	Number (%) of patients [a]		
	OlympiA SAS		Olaparib 300 mg bd pool (N=3155)
	Olaparib 300 mg bd (N=911)	Placebo (N=904)	
Patients with any SAE	**79 (8.7%)**	**78 (8.6)**	**616 (19.5)**
Blood and lymphatic system disorders	**18 (2.0)**	**1 (0.1)**	**164 (5.2)**
Anaemia	15 (1.6)	1 (0.1)	137 (4.3)
Febrile neutropenia	3 (0.3)	0	8 (0.3)
Infections and infestations	**16 (1.8)**	**15 (1.7)**	**122 (3.9)**
Device related infection	3 (0.3)	2 (0.2)	4 (0.1)
Mastitis	3 (0.3)	6 (0.7)	3 (0.1)

[j] Sorted by decreasing order of frequency for SOC and PT in the olaparib arm of OlympiA and then by decreasing order of frequency in the placebo arm.

Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories.

Includes AEs with an onset date between the date of first dose and 30 days following the date of last dose of study treatment.

MedDRA Version 24.0.

AE = Adverse event; bd = Twice daily; CSR = Clinical study report; DCO = Data cut-off; MedDRA = Medical Dictionary for Regulatory Activities; N = Total number of patients; PT = Preferred term; SAE = Serious adverse event; SAS = Safety analysis set; SOC = System organ class.

Source: Safety Update Table 14.3.2.23.1 and Table 2.7.4.1.3.1

Deaths

At DCO2, 181 patients had died; 75 patients (8.1%) in the olaparib arm and 106 patients (11.6%) in the placebo arm. This represents an additional 36 patients (16 in the olaparib arm and 20 in the placebo arm) who died between DCO1 (27 March 2020) and DCO2 (12 July 2021). Consistent with data at DCO1, the majority of deaths reported in the study were related to the disease under investigation (171 of 181 deaths [94.5%]; 70 patients in the olaparib arm and 101 patients in the placebo arm). At DCO1, four patients experienced an AE with outcome of death (one patient [1.7%] in the olaparib arm [cardiac arrest] and 3 patients [3.5%] in the placebo arm [acute myeloid leukaemia, leukaemia, and ovarian cancer]) during study treatment or after the 30-day follow up. At DCO2 one additional patient experienced an AE with outcome of death after the 30-day follow up period; this patient was in the placebo arm and had a fatal AE of pancreatic carcinoma.

Table 43 Patients Who Died in OlympiA and the 300 mg bd Pool (DCO: 12 July 2021)

Category	Number (%) of patients		
	OlympiA SAS		Olaparib 300 mg bd pool (N=3155)
	Olaparib 300 mg bd (N=911)	Placebo (N=904)	
Total number of deaths	75 (8.2)	106 (11.7)	958 (30.4)
Death related to disease under investigation only and no AE with outcome of death	70 (7.7)	101 (11.2)	857 (27.2)
Death not related to disease and AE with outcome of death	1 (0.1)	2 (0.2)	21 (0.7)
Death not related to disease and AE with outcome of death (AE start date falling after 30 day follow-up period)	1 (0.1) [a]	2 (0.2)	10 (0.3)
Death related to disease and an AE with outcome of death	0	0	10 (0.3)
Death related to disease and an AE with outcome of death (AE start date falling after 30 day follow-up period)	0	0	1 (0.0)
Deaths not related to disease and no AE with outcome of death [b]	3 (0.3)	1 (0.1)	59 (1.9)

[k] In the olaparib arm, the AE with outcome of death (AE start date falling after 30 day follow up period) is the case of AML reported for one Patient.

[l] Patients who died and were not captured in the earlier categories, see Safety Update Table 2.7.4.1.2.4 for details.

Death related to disease under investigation was determined by the investigator.

Rows are mutually exclusive, patients are only reported in one category.

AE = Adverse event; bd = Twice daily; CSR = Clinical study report; DCO = Data cut-off; N = Total number of patients; SAS = Safety analysis set.

Source: Safety Update Table 2.7.4.1.2.5a and Table 2.7.4.1.2.5b.

Table 44 OlympiA: All Deaths (FAS)

Category	Number (%) of patients			
	Olaparib 300 mg bd (N=921)		Placebo (N=915)	
	27 Mar 2020 DCO	12 Jul 2021 DCO	27 Mar 2020 DCO	12 Jul 2021 DCO
Total number of deaths [a]	59 (6.4)	75 (8.1)	86 (9.4)	106 (11.6)
Primary cause of death [b]				
Breast cancer recurrence	55 (93.2)	70 (93.3)	82 (95.3)	101 (95.3)
Adverse event	1 (1.7)	1 (1.3)	3 (3.5)	4 (3.8)
Other [c]	3 (5.1)	3 (4.0)	1 (1.2)	1 (0.9)
Missing	0	1 (1.3)	0	0
Time to death from last dose [b]				
≤30 days	5 (8.5)	5 (6.7)	4 (4.7)	4 (3.8)
>30 days	54 (91.5)	70 (93.3)	82 (95.3)	102 (96.2)

[a] As reported on the CRF (Death page).

[b] Percentages were calculated from the number of patients who died.

[c] In the olaparib arm other includes pulmonary embolism (1 patient), AML (1 patient) and unknown cause of death (1 patient) and in the placebo arm includes 1 patient with an unknown cause of death.

Table is presented for the Full Analysis Set, (ie, showing treatment as randomised).

AE = Adverse event; bd = Twice daily; CRF = Case Report Form; CSR = Clinical study report; DCO = Data cut-off; FAS = Full analysis set; N = Total number of patients.

Source: Table 14.3.3.1 and Listing 14.3.3.3, OlympiA CSR, Module 5.3.5.1 and Safety Update Table 14.3.3.1.

Adverse drug reaction

When considering an event as an ADR for inclusion in the product information for olaparib, all available sources of data are considered, including: Non-clinical findings; Class effects; Plausibility in light of the drug's pharmacology (eg, PARP inhibition); Clinical data from individual studies, pooled analyses, and post-marketing reports: Comparative incidence rates for the event in placebo-controlled trials and where relevant, exposure-adjusted analyses, Indirect comparisons between single arm olaparib studies, or pooled datasets from the olaparib arms of multiple studies, and epidemiological data in the breast cancer population, Individual case/case series reviews, including assessment of time to onset of events and/or de-challenge/re-challenge data (where available), confounding factors (eg, concurrent medications; co-morbidities) and/or the presence or absence of single events which are strongly indicative of an ADR.

The safety profile is based on pooled data from 4098 patients with solid tumours treated with Lynparza monotherapy in clinical trials at the recommended dose.

Table 45: Frequency of AEs for Events Identified as ADRs Associated with Olaparib Treatment (Tablet Pool and Overall)

	Tablet monotherapy pool N=3155		Overall (tablet and capsule) N=4098			
System organ class/ Preferred Term	**All CTCAE Grades [a] n (%)**	**CTCAE Grades ≥3 [b] n (%)**	**All CTCAE Grades [a] n (%)**	**Frequency descriptor**	**CTCAE Grades ≥3 [b] n (%)**	**Frequency descriptor**
Blood and lymphatic system disorders						
Anaemia [c]	1110 (35.2)	466 (14.8)	1403 (34.2)	Very common	598 (14.6)	Very common
Neutropenia [c]	536 (17.0)	183 (5.8)	613 (15.0)	Very common	211 (5.1)	Common
Thrombocytopenia [c]	299 (9.5)	66 (2.1)	369 (9.0)	Common	87 (2.1)	Common
Lymphopenia [c]	180 (5.7)	41 (1.3)	193 (4.7)	Common	43 (1.0)	Common
Leukopenia [c]	432 (13.7)	83 (2.6)	492 (12.0)	Very common	104 (2.5)	Common
Gastrointestinal disorders						
Nausea	1842 (58.4)	34 (1.1)	2414 (58.9)	Very common	57 (1.4)	Common
Vomiting	904 (28.7)	35 (1.1)	1233 (30.1)	Very common	62 (1.5)	Common
Diarrhoea	703 (22.3)	24 (0.8)	919 (22.4)	Very common	39 (1.0)	Uncommon
Dyspepsia	282 (8.9)	1 (0.0)	438 (10.7)	Very common	1 (0.0)	Rare
Abdominal pain upper	230 (7.3)	2 (0.1)	318 (7.8)	Common	4 (0.1)	Rare
Stomatitis [c]	256 (8.1)	9 (0.3)	317 (7.7)	Common	12 (0.3)	Uncommon
General disorders and administration site conditions						
Fatigue and asthenia [c]	1563 (49.5)	111 (3.5)	2129 (52.0)	Very common	172 (4.2)	Common
Immune system disorders						
Hypersensitivity [c]	26 (0.8)	1 (0.0)	34 (0.8)	Uncommon	1 (0.0)	Rare
Angioedema	0	0	3 (0.1) [d]	Rare	-	-
Investigations						
Blood creatinine increased	181 (5.7)	1 (0.0)	236 (5.8)	Common	3 (0.1)	Rare
Mean cell volume increased	8 (0.3)	0	8 (0.2)	Uncommon	0	-
Metabolism and nutrition disorders						
Decreased appetite	609 (19.3)	18 (0.6)	802 (19.6)	Very common	24 (0.6)	Uncommon
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)						
MDS/AML [c,e]	12 (0.4)	12 (0.4)	15 (0.4)	Uncommon	15 (0.4)	Uncommon
Nervous system disorders						

	Tablet monotherapy pool N=3155		Overall (tablet and capsule) N=4098			
System organ class/ Preferred Term	**All CTCAE Grades [a] n (%)**	**CTCAE Grades ≥3 [b] n (%)**	**All CTCAE Grades [a] n (%)**	**Frequency descriptor**	**CTCAE Grades ≥3 [b] n (%)**	**Frequency descriptor**
Headache	515 (16.3)	8 (0.3)	668 (16.3)	Very common	10 (0.2)	Uncommon
Dysgeusia [c]	443 (14.0)	0	566 (13.8)	Very common	0	-
Dizziness	367 (11.6)	3 (0.1)	485 (11.8)	Very common	6 (0.1)	Uncommon
Respiratory, thoracic and mediastinal disorders						
Cough [c]	405 (12.8)	4 (0.1)	549 (13.4)	Very common	5 (0.1)	Uncommon
Dyspnoea [c]	330 (10.5)	26 (0.8)	471 (11.5)	Very common	43 (1.0)	Common
Skin and subcutaneous tissue disorders						
Rash [c]	235 (7.4)	4 (0.1)	342 (8.3)	Common	5 (0.1)	Uncommon
Dermatitis [c]	14 (0.4)	1 (0.0)	18 (0.4)	Uncommon	1 (0.0)	Rare
Erythema nodosum	2 (0.1)	0	2 (0.0)	Rare	0	-

[d] Patients with multiple ADRs are counted once for each grouped term.

[e] Each patient has only been represented with the maximum reported CTCAE grade within each ADR group.

[f] Anaemia includes PTs of anaemia, anaemia macrocytic, erythropenia, haematocrit decreased, haemoglobin decreased, normocytic anaemia, and red blood cell count decreased; Neutropenia includes PTs of febrile neutropenia, neutropenia, neutropenic infection, neutropenic sepsis, and neutrophil count decreased; Thrombocytopenia includes PTs of platelet count decreased and thrombocytopenia; Lymphopenia includes PTs of lymphocyte count decreased and lymphopenia; Leukopenia includes PTs of leukopenia and white blood cell count decreased; Cough includes PTs of cough and productive cough; Stomatitis includes PTs of aphthous ulcer, mouth ulceration, and stomatitis; Fatigue and Asthenia includes PTs of asthenia and fatigue; Hypersensitivity includes PTs of drug hypersensitivity and hypersensitivity; Rash includes PTs of erythema, exfoliative rash, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, and rash pruritic; Dermatitis includes PTs of dermatitis and dermatitis allergic; Dyspnoea includes PTs of dyspnoea and dyspnoea exertional; Dysgeusia includes PTs of dysgeusia and taste disorder; MDS/AML includes PTs of AML, MDS, and myeloid leukaemia.

[g] As observed in the post-marketing setting. No cases were observed in the olaparib monotherapy combined therapeutic dose pool, therefore incidence has been determined based on the rule of 3 (3/3988).

[h] The incidence of MDS/AML events reported in **Table 45** are not the same as reported in Section Myelodysplastic Syndrome/Acute Myeloid Leukaemia and **Table 46**. In **Table 45**, MDS/AML events are only reported for AEs with an onset date between the date of first dose of continuous treatment and 30 days following the date of last dose of continuous treatment and do not include events based on long-term collection of data beyond treatment discontinuation and 30-day follow-up. In Section Myelodysplastic Syndrome/Acute Myeloid Leukaemia and **Table 46**, MDS/AML events are reported based on the long-term collection of data beyond treatment discontinuation and 30-day follow-up.

Includes Adverse Events with an onset date between the date of first dose of continuous treatment and 30 days following the last dose of continuous treatment.

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); and very rare (<1/10,000) including isolated reports

ADR = adverse drug reaction; AE = adverse event; AML = acute myeloid leukaemia; CTCAE = Common Terminology Criteria for Adverse Events; DCO = data cut-off; MDS = myelodysplastic syndrome; n = number of patients with an event; N = total number of patients; PT = preferred term.

Source: Safety Update Tables 2.7.4.4.1.1 and 2.7.4.4.6 (DCO 12 July 2021).

Table 46: Frequency of ADR of MDS/AML in the 300 mg bd Pool and Overall (Olaparib Monotherapy Combined Therapeutic Dose Pool) for All Reported Events

	300 mg bd pool N=3155		Overall (olaparib monotherapy combined therapeutic dose pool [tablet and capsule]) N=4098			
System organ class/Preferred term	**All CTCAE Grades [a] n (%)**	**CTCAE Grades ≥3 [b] n (%)**	**All CTCAE Grades [a] n (%)**	**Frequency descriptor**	**CTCAE Grades ≥3 [b] n (%)**	**Frequency descriptor**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
MDS/AML [c]	28 (0.9)	26 (0.8)	34 (0.8)	Uncommon	32 (0.8)	Uncommon

[a] Patients with multiple ADRs are counted once for each grouped term.

[b] Each patient has only been represented with the maximum reported CTCAE grade within each ADR group.

[c] MDS/AML includes PTs of AML, MDS, and myeloid leukaemia.

Frequencies of occurrence of adverse reactions are defined as: very common (>1/10), common (>1/100 to <1/10), uncommon (>1/1000 to <1/100), rare (>1/10000 to <1/1000), very rare (<1/10000) including isolated reports.

Includes all reported AEs (ie, long-term collection of data beyond treatment discontinuation and 30-day follow-up).

ADR = adverse drug reaction; AE = adverse event; AML = acute myeloid leukaemia; bd = twice daily; CTCAE = Common Terminology Criteria for Adverse Events; DCO = data cut-off; MDS = myelodysplastic syndrome; n = number of patients with an event; N = total number of patients; PT = preferred term.

Source: Tables 2.7.4.4.1.4 and 2.7.4.4.6 (DCO 12 Jul 2021).

Table 47: Frequency of Adverse Laboratory Findings Associated with Olaparib Treatment in the Tablet Pool and Overall

	Tablet monotherapy pool		Overall (tablet and capsule)	
	27 Mar 2020 DCO	**12 Jul 2021 DCO**	**27 Mar 2020 DCO**	**12 Jul 2021 DCO**
Laboratory parameter	**≥2 CTCAE Grade changes n/N (%)**	**≥2 CTCAE Grade changes n/N (%)**	**≥2 CTCAE Grade changes n/N (%)**	**≥2 CTCAE Grade changes n/N (%)**
Haemoglobin [a]	632/3018 (20.9)	650/3126 (20.8)	825/3951 (20.9)	843/4059 (20.8)
Neutrophils [a]	496/2712 (18.3)	515/2820 (18.3)	615/3636 (16.9)	634/3744 (16.9)
Platelets [a]	130/3017 (4.3)	134/3125 (4.3)	183/3950 (4.6)	187/4058 (4.6)
Lymphocytes [a]	756/3007 (25.1)	784/3114 (25.2)	968/3759 (25.8)	996/3866 (25.8)
Leukocytes [a]	600/3004 (20.0)	616/3112 (19.8)	749/3937 (19.0)	765/4045 (18.9)
Increase in serum creatinine [a]	414/3018 (13.7)	426/3126 (13.6)	443/3950 (11.2)	455/4058 (11.2)
Increase in mean corpuscular volume [b]	1472/2723 (54.1)	1511/2830 (53.4)	1827/3583 (51.0)	1866/3690 (50.6)

[a] Represents patients who had any 2 Grade change (ie, 0 to 2 or higher, 1 to 3 or higher, or 2 to 4).

[b] Represents patients who had a change in mean corpuscular volume from low or normal to: >1 x ULN.

CTCAE = Common Terminology Criteria for Adverse Events; DCO = data cut-off; n = number of patients with an event; N = total number of patients; ULN = upper limit of normal.

Source: Tables 2.7.4.4.2.1.1, 2.7.4.4.2.1.3, 2.7.4.4.2.2.1, 2.7.4.4.2.2.3, Pooled Safety Outputs, Module 5.3.5.3 and Safety Update Tables 2.7.4.4.2.1.1, 2.7.4.4.2.1.3, 2.7.4.4.2.2.1, 2.7.4.4.2.2.3.

Haematological Toxicity

Anaemia

Anaemia is the most common haematological effect reported with olaparib treatment. The proposed product information includes anaemia as an adverse reaction of olaparib therapy. In OlympiA, the majority of events of anaemia were mild or moderate in intensity. Onset was early, generally in the first 3 months of starting olaparib although the risk of developing anaemia remained constant throughout exposure with no evidence of cumulative effect. AEs of anaemia were manageable by interrupting or reducing the olaparib dose or giving blood transfusions or other blood preparations in accordance with local practice. Adverse events of anaemia (grouped term) led to temporary dose interruptions in 11.4% of patients and to dose reduction in 8.5% of patients. In OlympiA, transfusions were reported as either concomitant medications or procedures during treatment and the 30-day follow-up period. Overall, 53 patients (5.8%) in the olaparib arm and 8 patients (0.9%) in the placebo arm received a transfusion, with 16 patients (1.8%) and 2 patients (0.2%) receiving >1 transfusion in the olaparib and placebo arms, respectively.

Between 2 and 3 months, 21 patients (2.3%) in the olaparib arm compared to 0 patients in the placebo arm required a transfusion. Over time, fewer transfusions were observed and at ≥12 months, there were 2 patients (0.2%) in the olaparib arm and 2 patients (0.2%) in the placebo arm who required transfusions. AEs of anaemia requiring discontinuation occurred in 1.8% of olaparib-treated patients and were consistent with the tablet pool.

Table 48: OlympiA and the 300 mg bd Pool: Patients Who Had at least One AE of Anaemia (SAS)

	Number (%) of patients				
	OlympiA SAS				**Olaparib 300 mg bd pool (N=3155)**
	Olaparib 300 mg bd (N=911)		**Placebo (N=904)**		
AE category [a]	**27 Mar 2020 DCO**	**12 Jul 2021 DCO**	**27 Mar 2020 DCO**	**12 Jul 2021 DCO**	**12 Jul 2021 DCO**
Any AE	216 (23.7)	217 (23.8)	35 (3.9)	35 (3.9)	1110 (35.2)
Any AE of CTCAE Grade ≥3	79 (8.7)	79 (8.7)	3 (0.3)	3 (0.3)	466 (14.8)
Any AE with outcome=death	0	0	0	0	0
Any SAE (including events with outcome=death)	15 (1.6)	15 (1.6)	1 (0.1)	1 (0.1)	142 (4.5)
Any AE leading to dose interruption of treatment	103 (11.3)	104 (11.4)	2 (0.2)	2 (0.2)	517 (16.4)
Any AE leading to dose reduction of treatment	73 (8.0)	77 (8.5)	2 (0.2)	2 (0.2)	354 (11.2)
Any AE leading to discontinuation of treatment	16 (1.8)	16 (1.8)	0	0	67 (2.1)

Neutropenia, Lymphopenia, Thrombocytopenia and Leukopenia

The incidence of other haematological effects associated with olaparib such as the grouped terms neutropenia, thrombocytopenia, leukopenia, and lymphopenia were low in OlympiA. These events are known ADRs for olaparib and were reported for a higher percentage of patients in the olaparib arm compared with the placebo arm. These events were predominantly Grade 1 or 2 in severity and rarely led to permanent discontinuation of treatment.

Table 49: OlympiA and the 300 mg bd Pool: Patients Who Had at least One AE of Neutropenia (Grouped Term) (SAS)

	Number (%) of patients				
	OlympiA SAS				Olaparib 300 mg bd pool (N=3155)
	Olaparib 300 mg bd (N=911)		Placebo (N=904)		
AE category [a]	27 Mar 2020 DCO	12 Jul 2021 DCO	27 Mar 2020 DCO	12 Jul 2021 DCO	12 Jul 2021 DCO
Any AE	149 (16.4)	150 (16.5)	60 (6.6)	60 (6.6)	536 (17.0)
Any AE of CTCAE Grade ≥3	47 (5.2)	48 (5.3)	7 (0.8)	7 (0.8)	183 (5.8)
Any AE with outcome=death	0	0	0	0	1 (0.0)
Any SAE (including events with outcome=death)	4 (0.4)	4 (0.4)	0	0	23 (0.7)
Any AE leading to dose interruption of treatment	55 (6.0)	55 (6.0)	6 (0.7)	6 (0.7)	211 (6.7)
Any AE leading to dose reduction of treatment	40 (4.4)	43 (4.7)	6 (0.7)	6 (0.7)	95 (3.0)
Any AE leading to discontinuation of treatment	10 (1.1)	10 (1.1)	1 (0.1)	1 (0.1)	22 (0.7)

[c] Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories.

Grouped term consisting of the PTs of agranulocytosis, febrile neutropenia, granulocyte count decreased, granulocytopenia, idiopathic neutropenia, neutropenia, neutropenic infection, neutropenic sepsis, and neutrophil count decreased.

Includes AEs with an onset date between the date of first dose of continuous treatment and 30 days following the date of last dose of continuous treatment.

AE = Adverse event; bd = Twice daily; CSR = Clinical study report; CTCAE = Common Terminology Criteria for Adverse Events; DCO = Data cut-off; N = Total number of patients; PT = Preferred term; SAE = Serious adverse event; SAS = Safety analysis set.

Source: Table 2.7.4.1.5.1 and Table 2.7.4.1.5.2.13b, Pooled Safety Outputs, Module 5.3.5.3 and Safety Update Table 2.7.4.1.5.2.13a, and Table 2.7.4.1.5.2.13b.

Table 50: OlympiA and the 300 mg bd Pool: Patients Who Had at Least One AE of Thrombocytopenia (Grouped Term) (SAS)

AE category [a]	Number (%) of patients				
	OlympiA SAS				Olaparib 300 mg bd pool (N=3155)
	Olaparib 300 mg bd (N=911)		Placebo (N=904)		
	27 Mar 2020 DCO	12 July 2021 DCO	27 Mar 2020 DCO	12 July 2021 DCO	12 July 2021 DCO
Any AE	38 (4.2)	38 (4.2)	11 (1.2)	12 (1.3)	299 (9.5)
Any AE of CTCAE Grade ≥3	2 (0.2)	2 (0.2)	1 (0.1)	1 (0.1)	66 (2.1)
Any AE with outcome=death	0	0	0	0	0
Any SAE (including events with outcome=death)	0	0	1 (0.1)	1 (0.1)	16 (0.5)
Any AE leading to dose interruption of treatment	6 (0.7)	6 (0.7)	1 (0.1)	1 (0.1)	85 (2.7)
Any AE leading to dose reduction of treatment	6 (0.7)	6 (0.7)	1 (0.1)	1 (0.1)	35 (1.1)
Any AE leading to discontinuation of treatment	2 (0.2)	2 (0.2)	0	0	23 (0.7)

[a] Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories.

Grouped term consisting of PTs of platelet count decreased, platelet production decreased, plateletcrit decreased, and thrombocytopenia.

Includes AEs with an onset date between the date of first dose of continuous treatment and 30 days following the date of last dose of continuous treatment.

AE = Adverse event; bd = Twice daily; CTCAE = Common Terminology Criteria for Adverse Events; DCO = Data cut-off; N = Total number of patients; PT = Preferred term; SAE = Serious adverse event; SAS = Safety analysis set.

Source: Table 2.7.4.1.5.1, Table 2.7.4.1.5.2.15a, and Table 2.7.4.1.5.2.15b, Pooled Safety Outputs, Module 5.3.5.3 and Safety Update Table 2.7.4.1.5.2.15a, and Table 2.7.4.1.5.2.15b.

Table 51: OlympiA and the 300 mg bd Pool: Patients Who Had at Least One AE of Lymphopenia (Grouped Term) (SAS)

AE category [a]	Number (%) of patients				
	OlympiA SAS				Olaparib 300 mg bd pool (N=3155)
	Olaparib 300 mg bd (N=911)		Placebo (N=904)		
	27 Mar 2020 DCO	12 Jul 2021 DCO	27 Mar 2020 DCO	12 Jul 2021 DCO	12 Jul 2021 DCO
Any AE	63 (6.9)	64 (7.0)	15 (1.7)	15 (1.7)	180 (5.7)
Any AE of CTCAE Grade ≥3	11 (1.2)	12 (1.3)	0	0	41 (1.3)
Any AE with outcome=death	0	0	0	0	0
Any SAE (including events with outcome=death)	0	0	0	0	0
Any AE leading to dose interruption of treatment	9 (1.0)	9 (1.0)	0	0	24 (0.8)
Any AE leading to dose reduction of treatment	2 (0.2)	2 (0.2)	0	0	6 (0.2)
Any AE leading to discontinuation of treatment	0	0	0	0	1 (0.0)

[a] Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories.

Grouped term consisting of the PTs of B-lymphocyte count decreased, lymphocyte count decreased, lymphopenia, and T-lymphocyte count decreased.

Includes AEs with an onset date between the date of first dose of continuous treatment and 30 days following the date of last dose of continuous treatment.

AE = Adverse event; bd = Twice daily; CTCAE = Common Terminology Criteria for Adverse Events; DCO = Data cut-off; N = Total number of patients; PT = Preferred term; SAE = Serious adverse event; SAS = Safety analysis set.

Source: Table 2.7.4.1.5.1, Table 2.7.4.1.5.2.14a, and Table 2.7.4.1.5.2.14b, Pooled Safety Outputs, Module 5.3.5.3 and Safety Update Table 2.7.4.1.5.2.14a, and Table 2.7.4.1.5.2.14b.

Table 52: OlympiA and the 300 mg bd Pool: Patients Who Had at Least One AE of Leukopenia (Grouped Term) (SAS)

AE category [a]	Number (%) of patients				
	OlympiA SAS				Olaparib 300 mg bd pool (N=3155)
	Olaparib 300 mg bd (N=911)		Placebo (N=904)		
	27 Mar 2020 DCO	12 Jul 2021 DCO	27 Mar 2020 DCO	12 Jul 2021 DCO	12 Jul 2021 DCO
Any AE	153 (16.8)	154 (16.9)	54 (6.0)	54 (6.0)	432 (13.7)
Any AE of CTCAE Grade ≥3	27 (3.0)	27 (3.0)	3 (0.3)	3 (0.3)	83 (2.6)
Any AE with outcome=death	0	0	0	0	0
Any SAE (including events with outcome=death)	0	0	0	0	4 (0.1)
Any AE leading to dose interruption of treatment	33 (3.6)	34 (3.7)	3 (0.3)	3 (0.3)	111 (3.5)
Any AE leading to dose reduction of treatment	16 (1.8)	17 (1.9)	3 (0.3)	3 (0.3)	44 (1.4)
Any AE leading to discontinuation of treatment	6 (0.7)	7 (0.8)	1 (0.1)	1 (0.1)	11 (0.3)

[a] Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories.

Grouped term consisting of the PTs of leukopenia and WBC count decreased.

Includes AEs with an onset date between the date of first dose of continuous treatment and 30 days following the date of last dose of continuous treatment.

AE = Adverse event; bd = Twice daily; CTCAE = Common Terminology Criteria for Adverse Events; DCO = Data cut-off; N = Total number of patients; PT = Preferred term; SAE = Serious adverse event; SAS = Safety analysis set; WBC = White blood cell.

Source: Table 2.7.4.1.5.1, Table 2.7.4.1.5.2.16a, and Table 2.7.4.1.5.2.16b, Pooled Safety Outputs, Module 5.3.5.3 and Safety Update Table 2.7.4.1.5.2.16a, and Table 2.7.4.1.5.2.16b.

Myelodysplastic Syndrome/Acute Myeloid Leukaemia

MDS/AML is considered an adverse event of special interest (AESI) and an important identified risk for olaparib and events are collected beyond the 30-day safety follow-up for the duration of the survival follow-up.

A summary of AEs of MDS/AML occurring in OlympiA together with cases in other pivotal studies, the larger olaparib monotherapy therapeutic dose pool, and across the clinical trial programme is shown in **Table 53**.

Following the marketing authorisation in December 2014 for olaparib capsules, and as of 15 June 2021, there have also been reports of MDS/AML from post-marketing surveillance, consistent with the characterisation of the events reported from monotherapy clinical studies.

Table 53 Summary of AEs of MDS/AML Occurring Across the Olaparib Programme

		Olaparib				Comparator [a]			
		Number of patients with AEs	Incidence [b]	Number of patients with AEs	Incidence [b]	Number of patients with AEs	Incidence [b]	Number of patients with AEs	Incidence [b]
		27 Mar 2020 DCO		12 Jul 2021 DCO		27 Mar 2020 DCO		12 Jul 2021 DCO	
OlympiA N=911 olaparib N=904 placebo	Breast cancer	2	0.2%	2	0.2%	3	0.3%	3	0.3%
POLO N=90 olaparib N=61 placebo	Pancreatic cancer, prior platinum	0	0	0	0	0	0	0	0
SOLO2 N=195 olaparib N=99 placebo	Ovarian	16	8.2%	16	8.2%	4 [c]	4.0%	4 [c]	4.0%
PAOLA-1 N=535 olaparib/bevacizumab N=267 placebo/bevacizumab	Ovarian	5	0.9%	5	0.9%	4	1.5%	4	1.5%
SOLO3 N=178 olaparib N=76 chemotherapy	Ovarian	4	2.2%	5	2.8%	3	3.9%	3	3.9%
SOLO1 N=260 olaparib N=130 placebo	Ovarian	3	1.2%	3	1.2%	0	0	0	0
Study 19 N=136 olaparib N=128 placebo	Ovarian	2	1.5%	2	1.5%	1	0.8%	1	0.8%
PROfound N=256 olaparib N=130 investigators choice of NHA	Prostate cancer	1	0.4%	1	0.4%	0	0	0	0
OlympiAD N=205 olaparib N=91 physician's choice	Breast cancer, prior platinum	0	0	0	0	0	0	0	0
VIOLETTE N=110 olaparib monotherapy (Patient Population E [Stratum A])	Breast cancer	NA	NA	0	0	NA	NA	NA	NA
Olaparib monotherapy, 300 mg bd tablet pool N=3155 olaparib		28	0.9%	28	0.9%	NA	NA	NA	NA

Olaparib monotherapy combined therapeutic dose pool N=4098 olaparib	34	0.9%	34	0.8%	NA	NA	NA	NA
Entire clinical programme pool [d] N=17923 olaparib	96	0.5%	96	0.5%	NA	NA	NA	NA

[i] The comparator was placebo in OlympiA, POLO, PAOLA-1, SOLO1, SOLO2, and Study 19. The comparator was physician's choice of chemotherapy in OlympiAD (which consisted of either capecitabine, eribulin, or vinorelbine) and SOLO3 (which consisted of either pegylated liposomal doxorubicin, paclitaxel, gemcitabine, or topotecan). The comparator was NHA (enzalutamide or abiraterone acetate with prednisone) in PROfound. There was no comparator in VIOLETTE.

[j] The percentage of patients experiencing any event of MDS/AML.

[k] One of the 4 placebo patients had received olaparib treatment 3 months prior to developing AML.

[l] As of 15 June 2021.

AE = Adverse event; AML = Acute myeloid leukaemia; bd = Twice daily; CSR = Clinical study report; DCO = Data cut-off; MDS = Myelodysplastic syndrome; N = Total number of patients; NA = Not applicable; NHA = New hormonal agent.
Source: Table 14.3.2.32.1 and Table 14.3.2.33, OlympiA CSR, Module 5.3.5.1 and Table 2.7.4.4.1.4, Pooled Safety Outputs, Module 5.3.5.3 (DCO 27 March 2020); Safety Update Table 2.7.4.4.1.4, Table 14.3.2.32.1 and Table 14.3.2.33 (DCO 12 July 2021); Table 11.3.2.3 and Table 11.3.2.7, POLO CSR Addendum 1, (DCO 21 July 2020); Table 14.3.2.2.1, Appendix 16.2.7.1.1, and Appendix 16.2.7.1.4, SOLO2 CSR Addendum, (DCO 03 February 2020); Table 14.3.2.12 and Appendix 16.2.7.1.1, PAOLA-1 CSR Addendum (DCO 22 March 2020); Table 11.3.4.2.1 and Table 11.3.2.9.4, SOLO3 CSR Addendum (DCO 10 January 2020); SOLO3 CSR Addendum 2 (DCO 16 April 2021); Table 11.3.2.3, SOLO1 CSR (DCO 17 May 2018); Appendix 12.2.7.1.b Study 19 CSR Addendum 3 (DCO 09 May 2016); Table 14.3.2.3.1, PROfound CSR Addendum (DCO 20 March 2020); Table 11.3.2.2 and Table 11.3.2.4, OlympiAD CSR (DCO 09 December 2016), Table 14.3.2.15e, VIOLETTE CSR (DCO 08 November 2019 and 13 November 2020).

Gastro-intestinal

Nausea and Vomiting

AEs of nausea and vomiting were reported for a higher percentage of patients in the olaparib arm compared with the placebo arm in OlympiA. These events were predominantly Grades 1 or 2 in severity and rarely led to permanent discontinuation of treatment in the olaparib arm. Of the 18 olaparib-treated patients with DAEs of nausea, 2 were CTCAE Grade 3 events, both of which recovered; 13 events were CTCAE Grade 2 and 3 were Grade 1.

Table 54 **OlympiA and the 300 mg bd Pool: Patients Who Had at Least One AE of Nausea or Vomiting Reported in Any Category (SAS)**

	Number (%) of patients									
	Nausea					Vomiting				
	OlympiA SAS				Olaparib 300 mg bd pool (N=3155)	OlympiA SAS				Olaparib 300 mg bd pool (N=3155)
	Olaparib 300 mg bd (N=911)		Placebo (N=904)			Olaparib 300 mg bd (N=911)		Placebo (N=904)		
AE category [a]	27 Mar 2020 DCO	12 Jul 2021 DCO	27 Mar 2020 DCO	12 Jul 2021 DCO	12 Jul 2021 DCO	27 Mar 2020 DCO	12 Jul 2021 DCO	27 Mar 2020 DCO	12 Jul 2021 DCO	12 Jul 2021 DCO
Any AE	519 (57.0)	519 (57.0)	211 (23.3)	212 (23.5)	1842 (58.4)	206 (22.6)	206 (22.6)	74 (8.2)	74 (8.2)	904 (28.7)
Any AE of CTCAE Grade ≥3	7 (0.8)	7 (0.8)	0	0	34 (1.1)	6 (0.7)	6 (0.7)	0	0	35 (1.1)
Any AE with outcome=death	0	0	0	0	0	0	0	0	0	0
Any SAE (including events with outcome=death)	1 (0.1)	1 (0.1)	0	0	10 (0.3)	2 (0.2)	2 (0.2)	0	0	17 (0.5)
Any AE leading to dose interruption of treatment	50 (5.5)	49 (5.4)	6 (0.7)	6 (0.7)	154 (4.9)	26 (2.9)	26 (2.9)	9 (1.0)	9 (1.0)	132 (4.2)
Any AE leading to dose reduction of treatment	43 (4.7)	43 (4.7)	2 (0.2)	2 (0.2)	93 (2.9)	14 (1.5)	15 (1.6)	2 (0.2)	2 (0.2)	37 (1.2)
Any AE leading to discontinuation of treatment	18 (2.0)	19 (2.1)	3 (0.3)	3 (0.3)	34 (1.1)	7 (0.8)	7 (0.8)	0	0	18 (0.6)

[a] Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories

Includes AEs with an onset date between the date of first dose of continuous treatment and 30 days following the date of last dose of continuous treatment.

AE = Adverse event; bd = Twice daily; CTCAE = Common Terminology Criteria for Adverse Events; DCO = Data cut-off; N = Total number of patients; SAE = Serious adverse event; SAS = Safety analysis set.

Source: Table 2.7.4.1.5.2.1a, Table 2.7.4.1.5.2.1b, Table 2.7.4.1.5.2.2a, and Table 2.7.4.1.5.2.2b, Pooled Safety Outputs, Module 5.3.5.3 and Safety Update Table 2.7.4.1.5.2.1a, Table 2.7.4.1.5.2.1b, Table 2.7.4.1.5.2.2a, and Table 2.7.4.1.5.2.2b.

Erythema Nodosum

The AE of erythema nodosum (single PT) has been added as an ADR for olaparib on the basis of data gathered in the post-marketing setting. There were no events of erythema nodosum in the olaparib arm of the OlympiA study.

Angioedema

The AE of angioedema (single PT) has been added as an ADR for olaparib on the basis of data gathered in the post-marketing setting. There were no events of angioedema in OlympiA or the 300 mg bd pool.

Important potential risks

New Primary Malignancies (NPM)

Excluding events of AML and leukaemia, non-melanoma skin cancers, and histologically-confirmed benign events there were 20 patients (2.2%) reporting 21 NPM events in the olaparib arm and 35 patients (3.9%) reporting 37 NPM events in the placebo arm occurring at any time on treatment or after the 30-day safety follow-up period.

Invasive and non-invasive contralateral breast cancers were reported as AESI when deemed to be new primary cancer by investigator's assessment.

Table 55: OlympiA: New Primary Malignancies (SAS)

	Number (%) of patients			
	Olaparib 300 mg bd (N=911)		Placebo (N=904)	
	27 Mar 2020 DCO	12 Jul 2021 DCO	27 Mar 2020 DCO	12 Jul 2021 DCO
Patients with new primary malignancies	**16 (1.8)**	**20 (2.2)**	**30 (3.3)**	**35 (3.9)**
AESI reported events (MedDRA preferred term)				
Breast cancer	4 (0.4)	7 (0.8)	6 (0.7)	7 (0.8)
Breast cancer female	0	0	3 (0.3)	4 (0.4)
Invasive breast carcinoma	0	0	1 (0.1)	2 (0.2)
Invasive ductal breast carcinoma	1 (0.1)	1 (0.1)	0	0
Intraductal proliferative breast lesion	0	2 (0.2)	0	1 (0.1)
Invasive lobular breast carcinoma	1 (0.1)	1 (0.1)	0	0
Lobular breast carcinoma in situ	0	1 (0.1)	0	0
Second primary malignancy	0	0	0	1 (0.1)
Triple negative breast cancer	1 (0.1)	1 (0.1)	0	0
Cervix carcinoma	0	0	1 (0.1)	1 (0.1)
Endometrial adenocarcinoma	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)
Fallopian tube cancer	0	1 (0.1)	2 (0.2)	3 (0.3)
Fallopian tube cancer Stage I	0	0	0	1 (0.1)
Female reproductive tract carcinoma in situ	0	0	0	1 (0.1)
Ovarian cancer	0	0	4 (0.4)	5 (0.6)
Serous cystadenocarcinoma ovary	0	0	0	1 (0.1)

	Number (%) of patients			
	Olaparib 300 mg bd (N=911)		Placebo (N=904)	
	27 Mar 2020 DCO	12 Jul 2021 DCO	27 Mar 2020 DCO	12 Jul 2021 DCO
Ovarian cancer recurrent	1 (0.1)	1 (0.1)	0	0
Lung adenocarcinoma	1 (0.1)	1 (0.1)	0	0
Lung neoplasm malignant	0	0	1 (0.1)	3 (0.3)
Colorectal cancer	1 (0.1)	1 (0.1)	0	0
Gastric Cancer	0	1 (0.1)	0	0
Pancreatic carcinoma [a]	0	0	1 (0.1)	1 (0.1)
Rectal cancer	0	0	1 (0.1)	1 (0.1)
Malignant melanoma	1 (0.1)	1 (0.1)	3 (0.4)	3 (0.3)
Meningioma [b]	1 (0.1)	1 (0.1)	0	0
Transitional cell carcinoma	0	0	1 (0.1)	1 (0.1)
Efficacy reported events (efficacy endpoint term) [c]				
Contralateral DCIS	2 (0.2)	0	1 (0.1)	0
Fallopian tube cancer	1 (0.1)	0	2 (0.2)	0
Ipsilateral DCIS	1 (0.1)	0	1 (0.1)	0
Serous tubular intraepithelial carcinoma in situ	0	0	1 (0.1)	0
New primary - lung	0	0	1 (0.1)	0

[b] One patient experienced the serious AE of pancreatic cancer >30 days after their last dose, which was incorrectly shown as non-serious in Listing 16.2.7.1, OlympiA CSR, Module 5.3.5.1 at DCO1 (27 March 2020). This was resolved at DCO2 (12 July 2021).

[c] Pathology report of meningotheliomatous meningioma with bone invasion.

[d] Events retrieved from the efficacy output, these were not coded to a MedDRA preferred term. Note: at DCO2 (12 July 2021), events previously reported as efficacy events are now reported as safety events.

Patients with multiple AEs were counted once for each preferred term.

Includes AEs with an onset date or that worsened from the first dose date to more than 30 days after date of last dose.

If the investigator considered the efficacy event to be a recurrence (eg, ipsilateral, contralateral breast cancer or DCIS) an AESI was not reported.

Adverse events sorted by frequency in the olaparib arm.

MedDRA Version 22.1 used for 27 March 2020 DCO and MedDRA Version 24.0 used for 12 July 2021 DCO.

AE = Adverse event; AESI = Adverse event of special interest; bd = Twice daily; DCIS = Ductal carcinoma in situ; DCO = Data cut-off; MedDRA = Medical Dictionary for Regulatory Activities; N = Total number of patients; SAS = Safety analysis set.

Source: Table 14.2.14, Table 14.3.2.32.1 and Table 14.3.2.33, OlympiA CSR, Module 5.3.5.1; Table 2832.3, Appendix 16.1.13, OlympiA CSR, Module 5.3.5.1; Safety Update Table 14.3.2.32.1, Table 14.3.2.33, and Listing 2970.3.1.

New primary malignancies were identified from safety and efficacy outputs. Adverse events of special interest in the SOC Neoplasms benign, malignant and unspecified (including cysts and polyps) with onset date ≤30 days following date of last study treatment were identified in 6 patients (0.7%) in the olaparib arm and 18 patients (2%) in the placebo arm and with onset >30 days after treatment end date in 19 patients (2.1%) in the olaparib arm and 27 patients (3%) in the placebo arm.

Table 56: Summary of AEs of New Primary Malignancies Occurring Across the Olaparib Programme

		Olaparib				Comparator [a]			
		Number of patients with AEs	Incidence [b]	Number of patients with AEs	Incidence [b]	Number of patients with AEs	Incidence [b]	Number of patients with AEs	Incidence [b]
		27 Mar 2020 DCO		12 Jul 2021 DCO		27 Mar 2020 DCO		12 Jul 2021 DCO	
OlympiA N=911 olaparib N=904 placebo	Breast cancer	16	1.8%	20	2.2%	30	3.3%	35	3.9%
POLO N=90 olaparib N=61 placebo	Pancreatic cancer, prior platinum	0	0	0	0	0 [c]	0	0 [c]	0
SOLO2 N=195 olaparib N=99 placebo	Ovarian	7	3.6%	7	3.6%	3	3.0%	3	3.0%
Study 19 N=136 olaparib N=128 placebo	Ovarian	4	2.9%	4	2.9%	1	0.8%	1	0.8%
SOLO3 N=178 olaparib N=76 chemotherapy	Ovarian	3	1.7%	4	2.2%	0	0	1	1.3%
SOLO1 N=260 olaparib N=130 placebo	Ovarian	5	1.9%	5	1.9%	3	2.3%	3	2.3%
PAOLA-1 N=535 olaparib/bevacizumab N=267 placebo/bevacizumab	Ovarian	13	2.4%	13	2.4%	5	1.9%	5	1.9%

		Olaparib				Comparator [a]			
		Number of patients with AEs	Incidence [b]	Number of patients with AEs	Incidence [b]	Number of patients with AEs	Incidence [b]	Number of patients with AEs	Incidence [b]
		27 Mar 2020 DCO		12 Jul 2021 DCO		27 Mar 2020 DCO		12 Jul 2021 DCO	
OlympiAD N=205 olaparib N=91 physician's choice	Breast cancer, prior platinum	1	0.5%	1	0.5%	0	0	0	0
PROfound N=256 olaparib N=130 investigators choice of NHA	Prostate cancer	1	0.4%	1	0.4%	2	1.5%	2	1.5%
VIOLETTE N=110 olaparib monotherapy (Patient Population E [Stratum A])	Breast cancer	NA	NA	0	0	NA	NA	NA	NA
Olaparib monotherapy combined therapeutic dose pool N=4098 olaparib		41	1.0%	46	1.1%	NA	NA	NA	NA
Entire clinical programme pool [d] N=17923 olaparib		115	0.6%	115	0.6%	NA	NA	NA	NA

[a] The comparator was placebo in OlympiA, POLO, PAOLA-1, SOLO1, SOLO2, and Study 19. The comparator was physician's choice of chemotherapy in OlympiAD (which consisted of either capecitabine, eribulin, or vinorelbine) and SOLO3 (which consisted of either pegylated liposomal doxorubicin, paclitaxel, gemcitabine, or topotecan). The comparator was NHA (enzalutamide or abiraterone acetate with prednisone) in PROfound.

[b] The percentage of patients experiencing any event of new primary malignancy.

[c] A review of AEs that started >30 days following the last dose of study treatment showed that 2 placebo-treated patients had AEs that were potential new primary malignancies (one patient had an AE of rectal cancer that was CTCAE Grade 2 and one patient was reported to have metastatic ovarian cancer as primary cause of death; both events occurred more than 300 days after the last dose of placebo treatment). These AEs are not included in the table as they were not actively solicited.

[d] As of 15 June 2021.

Note that events of tumour pain and benign malignancies were excluded from this analysis.

AE = Adverse event; CSR = Clinical study report; CTCAE = Common Terminology Criteria for Adverse Events; DCO = Data cut-off; N = Total number of patients; NA = Not applicable; NHA = New hormonal agent.

Source: Table 2832.3, Appendix 16.1.13, OlympiA CSR, Module 5.3.5.1 (DCO 27 March 2020); Table 11.3.2.3 and Table 11.3.2.7, POLO CSR Addendum 1 (DCO 21 July 2020); Table 14.3.2.2.1 and Table 14.3.2.3, SOLO2 CSR Addendum (DCO: 03 February 2020); Table 14.3.2.3, PAOLA-1 CSR Addendum (DCO 22 March 2020); Table 11.3.2.5 SOLO1 CSR (DCO 17 May 2018); Table 11.3.2.5.1 and Appendix 12.2.7.1.b Study 19 CSR Addendum 3 (DCO 09 May 2016); Appendix 12.2.5.1.1, Appendix 12.2.7.1.1, and Appendix 12.2.7.1.2, OlympiAD CSR, (DCO 09 December 2016); Table 11.3.2.9.4, SOLO3 CSR (DCO 10 October 2018); SOLO3 CSR Addendum 2 (DCO 16 April 2021); Table 14.3.2.3.1 PROfound CSR Addendum (DCO 20 March 2020); Table 14.3.2.15e, VIOLETTE CSR (DCO 08 November 2019 and 13 November 2020); Safety Update Listing 2970.3.1 (DCO 12 July 2021).

Information was drawn from a larger pool of olaparib studies (olaparib monotherapy combined therapeutic dose pool, n=3988) as well as from all patients exposed to olaparib during clinical development (ie, including data from ongoing studies, blinded studies, combination studies, ESRs, and the MAP) with data for 17923 patients (as of 15 June 2021). In this population, there have been 115 reports of NPMs out of a total of 17923 patients estimated to have received olaparib in the clinical study programme, giving an estimated cumulative incidence of 0.6%.

Pneumonitis

Adverse events of pneumonitis were routinely collected on-treatment and during the 30-day follow-up period only per protocol. Pneumonitis AEs were not actively solicited beyond the end of the 30-day follow-up period. At DCO2 (12 July 2021), 9 patients (1.0%) in the olaparib arm and 11 patients (1.2%) in the placebo arm had AEs of pneumonitis on treatment or during the safety follow-up period. One patient in the placebo arm had an AE of radiation pneumonitis after the 30-day follow up period.

Table 57: Summary of AEs of Pneumonitis Occurring Across the Olaparib Programme

		Olaparib				Comparator [a]			
		Number of patients with AEs	Incidence [b]	Number of patients with AEs	Incidence [b]	Number of patients with AEs	Incidence [b]	Number of patients with AEs	Incidence [b]
		27 Mar 2020 DCO		12 Jul 2021 DCO		27 Mar 2020 DCO		12 Jul 2021 DCO	
OlympiA N=911 olaparib N=904 placebo	Breast cancer	9	1.0%	9	1.0%	11	1.2%	11 [c]	1.2%
OlympiAD N=205 olaparib N=91 physician's choice	Breast cancer, prior platinum	0	0	0	0	0	0	0	0
SOLO2 N=195 olaparib N=99 placebo	Ovarian	3	1.5%	3	1.5%	0	0	0	0
Study 19 N=136 olaparib N=128 placebo	Ovarian	1	0.7%	1	0.7%	1	0.8%	1	0.8%
SOLO3 N=178 olaparib N=76 chemotherapy	Ovarian	0	0	0	0	0	0	0	0
SOLO1 N=260 olaparib N=130 placebo	Ovarian	5	1.9%	5	1.9%	0	0	0	0
PAOLA-1 N=535 olaparib/bevacizumab N=267 placebo/bevacizumab	Ovarian	6	1.1%	6	1.1%	0	0	0	0

		Olaparib				Comparator [a]			
		Number of patients with AEs	Incidence [b]	Number of patients with AEs	Incidence [b]	Number of patients with AEs	Incidence [b]	Number of patients with AEs	Incidence [b]
		27 Mar 2020 DCO		12 Jul 2021 DCO		27 Mar 2020 DCO		12 Jul 2021 DCO	
POLO N=90 olaparib N=61 placebo	Pancreatic cancer, prior platinum	2	2.2%	2	2.2%	0	0	0	0
PROfound N=256 olaparib N=130 investigators choice of NHA	Prostate cancer	5	2.0%	5	2.0%	2	1.5%	2	1.5%
VIOLETTE N=110 olaparib monotherapy (Patient Population E [Stratum A])	Breast cancer	NA	NA	1	0.9%	NA	NA	NA	NA
Olaparib monotherapy combined therapeutic dose pool [d] N=4098 olaparib		35	0.9%	37	0.9%	NA	NA	NA	NA

[a] The comparator was placebo in OlympiA, POLO, PAOLA-1, SOLO1, SOLO2, and Study 19. The comparator was physician's choice of chemotherapy in OlympiAD (which consisted of either capecitabine, eribulin, or vinorelbine) and SOLO3 (which consisted of either pegylated liposomal doxorubicin, paclitaxel, gemcitabine, or topotecan). The comparator was NHA (enzalutamide or abiraterone acetate with prednisone) in PROfound.

[b] The percentage of patients experiencing any event of pneumonitis.

[c] This table includes events that occurred up to the end of the 30-day follow up period. In OlympiA one additional patient in the placebo arm reported a pneumonitis event after the 30-day follow up period.

[d] As of 15 June 2021.

AE = Adverse event; CSR = Clinical study report; DCO = Data cut-off; N = Total number of patients; NA = Not applicable; NHA = New hormonal agent.
Source: Table 14.3.2.32.1 and Table 14.3.2.33, OlympiA CSR, Module 5.3.5.1 (DCO 27 March 2020); Safety Update Table 14.3.2.32.1 and Table 14.3.2.33 (DCO 12 July 2021); Table 11.3.2.3, POLO CSR Addendum 1, (DCO 21 July 2020); Table 14.3.2.2.1, SOLO2 CSR Addendum (DCO 03 February 2020); Table 14.3.2.3, PAOLA-1 CSR Addendum (DCO 22 March 2020); Table 11.3.2.5, SOLO1 CSR (DCO 17 May 2018); Table 11.3.2.5.1 and Appendix 12.2.7.1.b, Study 19 CSR Addendum 3 (DCO 09 May 2016); Appendix 12.2.5.1.1, Appendix 12.2.7.1.1, and Appendix 12.2.7.1.2, OlympiAD CSR (DCO 09 December 2016); Table 11.3.2.9.4, SOLO3 CSR (DCO 10 October 2018); Table 11.3.2.9.4, SOLO3 CSR Addendum 2 (DCO 16 April 2021); Table 14.3.2.3.1 PROfound CSR Addendum (DCO 20 March 2020); Table 14.3.2.15e, VIOLETTE CSR (DCO 08 November 2019 and 13 November 2020).

Laboratory findings

Haematology

Changes in the laboratory values for the haematology parameters of haemoglobin, neutrophils, platelets, and lymphocytes are considered ADRs for olaparib. The number and proportion of patients with maximum overall CTCAE Grade during treatment for selected haematology values are shown in the table below.

Table 58: OlympiA: Number (%) of Patients with Maximum Overall CTCAE Grade During Treatment for Key Haematology Parameters (SAS; DCO: 12 July 2021)

Parameter decease	Maximum overall CTCAE grade during treatment n/N (%) [a]				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Haemoglobin					
Olaparib 300 mg bd	315/899 (35.0)	410/899 (45.6)	102/899 (11.3)	72/899 (8.0)	0
Placebo	616/895 (68.8)	260/895 (29.1)	11/895 (1.2)	8/895 (0.9)	0
Lymphocytes					
Olaparib 300 mg bd	205/898 (22.8)	268/898 (29.8)	308/898 (34.3)	111/898 (12.4)	6/898 (0.7)
Placebo	364/893 (40.8)	310/893 (34.7)	186/893 (20.8)	31/893 (3.5)	2/893 (0.2)
Neutrophils					
Olaparib 300 mg bd	544/893 (60.9)	143/893 (16.0)	148/893 (16.6)	52/893 (5.8)	6/893 (0.7)
Placebo	656/894 (73.4)	130/894 (14.5)	98/894 (11.0)	9/894 (1.0)	1/894 (0.1)
Leukocytes					
Olaparib 300 mg bd	324/895 (36.2)	283/895 (31.6)	243/895 (27.2)	44/895 (4.9)	1/895 (0.1)
Placebo	520/890 (58.4)	265/890 (29.8)	99/890 (11.1)	5/890 (0.6)	1/890 (0.1)
Platelets					
Olaparib 300 mg bd	760/899 (84.5)	126/899 (14.0)	10/899 (1.1)	1/899 (0.1)	2/899 (0.2)
Placebo	828/895 (92.5)	60/895 (6.7)	4/895 (0.4)	2/895 (0.2)	1/895 (0.1)

[a] Derived from laboratory assessments between the start of treatment and up to and including 30 days following the date of last dose of study treatment.

N = total number of patients evaluable at baseline.

CTCAE Version 4.03. CTCAE grade: 1 = Mild AE; 2 = Moderate AE; 3 = Severe AE; 4 = Life-threatening or disabling AE; 5 = Death related to AE.

bd = Twice daily; CSR = Clinical study report; CTCAE = Common Terminology Criteria for Adverse Events; DCO = Data cut-off; N = Total number of patients; n = Number of patients at each grade; SAS = Safety analysis set.

Source: Safety Update Table 14.3.4.4.

Clinical Chemistry

A summary of maximum overall CTCAE grade during treatment for key clinical chemistry parameters (creatinine, bilirubin, ALT, AST, and ALP) is presented in **Table 59**. Changes in clinical chemistry parameters were generally mild or moderate and transient. In the majority of patients, the maximum CTCAE Grade was 0, 1, or 2 in both treatment arms. The proportion of patients with Grade 3 or 4 values was similar in the olaparib and placebo treatment arms.

Table 59: OlympiA: Number (%) of Patients with Maximum Overall CTCAE Grade During Treatment for Key Clinical Chemistry Parameters (SAS; DCO: 27 March 2020)

Parameter	Maximum overall CTCAE grade during treatment n/N (%) [a]				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Creatinine					
Olaparib 300 mg bd	742/898 (82.6)	150/898 (16.7)	6/898 (0.7)	0	0
Placebo	829/893 (92.8)	62/893 (6.9)	1/893 (0.1)	0	1/893 (0.1)
Bilirubin					
Olaparib 300 mg bd	845/896 (94.3)	39/896 (4.4)	10/896 (1.1)	2/896 (0.2)	0
Placebo	821/893 (91.9)	59/893 (6.6)	11/893 (1.2)	2/893 (0.2)	0
ALT					
Olaparib 300 mg bd	759/898 (84.5)	130/898 (14.5)	4/898 (0.4)	4/898 (0.4)	1/898 (0.1)
Placebo	670/893 (75.0)	210/893 (23.5)	8/893 (0.9)	5/893 (0.6)	0
AST					
Olaparib 300 mg bd	769/895 (85.9)	118/895 (13.2)	1/895 (0.1)	7/895 (0.8)	0
Placebo	704/891 (79.0)	172/891 (19.3)	8/891 (0.9)	6/891 (0.7)	1/891 (0.1)
ALP					
Olaparib 300 mg bd	718/898 (80.0)	177/898 (19.7)	3/898 (0.3)	0	0
Placebo	642/892 (72.0)	244/892 (27.4)	6/892 (0.7)	0	0

A summary of maximum overall CTCAE grade during treatment for key clinical chemistry parameters (creatinine, bilirubin, ALT, AST, and ALP) was not reproduced for the safety update with the DCO 12 July 2021.

Increases in creatinine

Mild elevations in creatinine have been observed with no apparent sequelae and with resolution on discontinuing olaparib, with no change in other renal function biochemistry tests (urea/blood urea nitrogen).

At the time of DCO1, No patients in the olaparib arm had CTCAE Grade 3 or 4 creatinine compared with 1 patient (0.1%) in the placebo arm who had CTCAE Grade 4 creatinine.

Three patients (0.3%) in the olaparib arm of the OlympiA study had a 2 grade increase from baseline in laboratory values for creatinine during the study, compared with 1 patient (0.1%) in the placebo arm; no patients in either arm had a 3 grade increase from baseline and no patients in the olaparib arm had a 4 grade increase from baseline compared with 1 patient (0.1%) in the placebo arm.

Laboratory values for creatinine showed an early increase: the median change in creatinine from baseline to Week 2 for patients in the olaparib arm was 8.8 µmol/L compared with no change for patients in the placebo arm.

Potential for Drug-induced Liver Injury

There were no confirmed or suspected Hy's Law cases. No patients in the olaparib arm of OlympiA had concurrent elevations of bilirubin and ALT/AST. Although 2 patients in the placebo arm had concurrent elevations of ALT or AST and bilirubin, there were alternative explanations for the elevated liver function test results in these patients.

Data for OlympiA and the 300 mg bd tablet pool have been summarised according to the following categories for ALT and AST: ⩽3×ULN, >3×ULN to ⩽5×ULN, >5×ULN to ⩽10×ULN, >10×ULN to ⩽20 ×ULN, and >20×ULN.

Table 60: OlympiA: Maximum value during continuous treatment for Aspartate Aminotransferase and Alanine Aminotransferase Safety Analysis Set (DCO: 27 March 2020)

		Maximum value during maintenance therapy							
		<=3x ULN		>3x ULN and <=5x ULN		>5x ULN and <=10x ULN		>10x ULN and <=20x ULN		>20x ULN	
Group	Parameter										
Olaparib 300mg bd Tablet(N=911)	Combined AST or ALT	887	(98.7)	4	(0.4)	6	(0.7)	1	(0.1)	1	(0.1)
	Alanine Aminotransferase	890	(99.0)	4	(0.4)	3	(0.3)	1	(0.1)	1	(0.1)
	Aspartate Aminotransferase	888	(98.8)	1	(0.1)	5	(0.6)	2	(0.2)	0	
Placebo 300mg bd Tablet(N=904)	Combined AST or ALT	873	(97.8)	11	(1.2)	7	(0.8)	1	(0.1)	1	(0.1)
	Alanine Aminotransferase	880	(98.5)	8	(0.9)	3	(0.3)	2	(0.2)	0	
	Aspartate Aminotransferase	878	(98.3)	8	(0.9)	6	(0.7)	0		1	(0.1)
Olaparib 300mg bd Tablet (N=3045)	Combined AST or ALT	2885	(95.6)	76	(2.5)	37	(1.2)	16	(0.5)	4	(0.1)
	Alanine Aminotransferase	2923	(96.9)	55	(1.8)	25	(0.8)	11	(0.4)	4	(0.1)
	Aspartate Aminotransferase	2920	(96.8)	45	(1.5)	35	(1.2)	12	(0.4)	0	

Safety in special populations

Effect of Race

The safety profile in the 300 mg bd pool for olaparib in White, Asian, and other non-White patients was generally similar. Safety data are presented for the 713 non-White patients who received the proposed dose of 300 mg bd as a monotherapy in the 300 mg bd pool (Table 61).

The most common (≥20% patients) AEs in the Asian patient population were nausea, anaemia, vomiting, fatigue, WBC count decreased, decreased appetite, and neutrophil count decreased. The most common (≥ 20% patients) AEs in the other non-White patient population were nausea, fatigue, anaemia, diarrhoea, constipation, decreased appetite, and vomiting.

Adverse events that occurred at a higher incidence in Asian patients (≥5 percentage points difference) compared with White patients were: ALT increased, anaemia, AST increased, decreased appetite, malaise, neutrophil count decreased, platelet count decreased, upper respiratory tract infection, and WBC count decreased. Adverse events that occurred at a lower incidence in Asian patients (≥5 % difference) compared with White patients were: abdominal pain, arthralgia, asthenia, back pain, constipation, diarrhoea, dyspnoea, fatigue, headache, and urinary tract infection.

Adverse events that occurred at a higher incidence in other non-White patients (≥5 percentage points difference) compared with White patients were anaemia, constipation, decreased appetite, hypertension, hypokalaemia, and oedema peripheral. Adverse events that occurred at a lower incidence in other non-White patients (≥5 percentage points difference) compared with White patients were asthenia, nausea, and vomiting.

Table 61: 300 mg bd Pool: Number (%) of Patients Who Had at Least One AE in Any Category by Race (White Patients, Asian Patients, and Other Non-White Patients)

AE category [a]	Number (%) of patients					
	White patients		Non-White patients [b]			
			Asian patients		Other patients	
	27 Mar 2020 DCO (N=2307)	12 Jul 2021 DCO (N=2385)	27 Mar 2020 DCO (N=620)	12 Jul 2021 DCO (N=633)	27 Mar 2020 DCO (N=93)	12 Jul 2021 DCO (N=100)
Any AE	2209 (95.8)	2284 (95.8)	596 (96.1)	608 (96.1)	89 (95.7)	96 (96.0)
Any AE of CTCAE Grade ≥3	822 (35.6)	856 (35.9)	240 (38.7)	241 (38.1)	40 (43.0)	42 (42.0)
Any AE with outcome=death	23 (1.0)	25 (1.0)	6 (1.0)	6 (0.9)	0	0
Any SAE (including events with outcome=death)	466 (20.2)	483 (20.3)	111 (17.9)	112 (17.7)	13 (14.0)	14 (14.0)
Any AE leading to dose interruption of study treatment	873 (37.8)	897 (37.6)	248 (40.0)	253 (40.0)	30 (32.3)	30 (30.0)
Any AE leading to dose reduction of study treatment	514 (22.3)	534 (22.4)	147 (23.7)	148 (23.4)	22 (23.7)	23 (23.0)
Any AE leading to discontinuation of study treatment	229 (9.9)	235 (9.9)	58 (9.4)	59 (9.3)	6 (6.5)	7 (7.0)

[a] Patients with multiple events reported in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories.

[b] As of DCO1 (27 March 2020), of the 713 non-White patients, 620 patients were Asian; 56 patients were Black or African American; 13 patients were American Indian or Alaska Native; 2 patients were Native Hawaiian or Other Pacific Islander; and 22 patients were 'other'. As of DCO2 (12 July 2021), of the 733 non-White patients, 633 patients were Asian; 58 patients were Black or African American; 13 patients were American Indian or Alaska Native; 2 patients were Native Hawaiian or Other Pacific Islander; and 27 patients were 'other'.

Includes AEs with an onset date between the date of first dose of continuous treatment and 30 days following the last dose of continuous treatment.

Twenty-five patients are not included in this table at DCO1 and 37 patients are not included in this table at DCO2 because race was not collected.

AE = Adverse event; bd = Twice daily; CSR = Clinical study report; CTCAE = Common Terminology Criteria for Adverse Events; DCO = Data cut-off; N = Total number of patients; SAE = Serious adverse event.

Source: Table 2.7.4.1.11.1 and Table 2.7.4.1.12.1, Pooled Safety Outputs, Module 5.3.5.3 and Safety Update Table 2.7.4.1.11.1 and Table 2.7.4.1.12.1.

Discontinuation due to adverse events

The incidence of AEs leading to discontinuation of study treatment is presented in **Table *62***. AE leading to treatment discontinuation were reported for 10.6% of patients in the olaparib arm and 4.6% of patients in the placebo arm. The most common AEs leading to discontinuation of olaparib (reported in ≥ 1.0% patients) were nausea, anaemia, fatigue, and neutrophil count decreased.

Table 62: Most Common AEs Leading to Discontinuation (Reported in ⩾3 Patients in the Olaparib Arm of OlympiA and/or Reported in ⩾2% of Patients in the 300 mg bd Pool; DCO: 12 July 2021)

System organ class / MedDRA preferred term	Number (%) of patients [a]		
	OlympiA SAS		
	Olaparib 300 mg bd (N=911)	Placebo (N=904)	Olaparib 300 mg bd pool (N=3155)
Patients with an AE leading to discontinuation [b]	**97 (10.6)**	**42 (4.6)**	**306 (9.7)**
Gastrointestinal disorders	**29 (3.2)**	**8 (0.9)**	**62 (2.0)**
Nausea	19 (2.1)	3 (0.3)	34 (1.1)
Vomiting	7 (0.8)	0	18 (0.6)
Diarrhoea	4 (0.4)	1 (0.)	5 (0.2)
Blood and lymphatic system disorders	**17 (1.9)**	**0**	**89 (2.8)**

System organ class / MedDRA preferred term	Number (%) of patients [a]		
	OlympiA SAS		
	Olaparib 300 mg bd (N=911)	Placebo (N=904)	Olaparib 300 mg bd pool (N=3155)
Anaemia	16 (1.8)	0	67 (2.1)
General disorders and administration site conditions	**17 (1.9)**	**4 (0.4)**	**42 (1.3)**
Fatigue	14 (1.5)	4 (0.4)	27 (0.9)
Nervous system disorders	**12 (1.3)**	**6 (0.7)**	**21 (0.7)**
Headache	7 (0.8)	2 (0.2)	7 (0.2)
Investigations	**12 (1.3)**	**4 (0.4)**	**28 (0.9)**
Neutrophil count decreased	9 (0.1)	1 (0.1)	12 (0.4)
WBC count decreased	7 (0.8)	1 (0.1)	9 (0.3)
Immune system disorders	**6 (0.7)**	**0**	**7 (0.2)**
Drug hypersensitivity	3 (0.3)	0	4 (0.1)
Metabolism and nutrition disorders	**3 (0.3)**	**2 (0.2)**	10 (0.3)
Decreased appetite	3 (0.3)	2 (0.2)	7 (0.2)

[e] Sorted by decreasing order of frequency for SOC and PT in the olaparib arm of OlympiA, and then by decreasing order of frequency in the placebo arm.

Adverse event action taken=olaparib/placebo permanently stopped.

Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories.

Includes AEs with an onset date between the date of first dose and 30 days following the date of last dose of study treatment.

MedDRA Version 24.0.

The majority (124 of 142 events) of the events that led to discontinuation of olaparib had resolved, or were resolving after study treatment was stopped. None of the events that led to discontinuation of olaparib were fatal; however, 16 AEs that led to permanent discontinuation of olaparib were considered by the investigator to be serious.

Seventy six of the 142 discontinuation events in the olaparib arm started within 30 days of the first dose of study treatment. For the majority (122 of 148 events) of events that led to discontinuation of olaparib, the investigator considered that the events were causally related to study treatment.

Dose Reductions/Interruptions Due to Adverse Events

Adverse events leading to dose reduction in study treatment (olaparib or placebo) in ≥2 patients in either treatment arm of OlympiA occurred in 22.5% of patients in the olaparib arm and 3.5% of patients in the placebo arm.

The most common AEs leading to dose reduction (≥3% of patients) in the olaparib arm were anaemia, nausea, neutrophil count decreased, and fatigue. The AEs that led to dose reduction in the olaparib arm were generally events known to be associated with olaparib or were associated with the disease under investigation.

The median time to first dose reduction of olaparib (for any reason) was 2.7 months (range 0 to 11 months). Once a patient was on a reduced dose, the dose could not be re-escalated.

Table 63 Adverse Events Leading to Dose Reduction Reported in ≥3 Patients in the Olaparib Arm of OlympiA or in ≥2% Patients in the 300 mg bd Pool (DCO: 12 July 2021)

MedDRA Preferred term	Number (%) of patients [a]		
	OlympiA SAS		
	Olaparib 300 mg bd (N=911)	Placebo (N=904)	Olaparib 300 mg bd pool (N=3155)
Patients with an AE leading to dose reduction of olaparib/placebo [b]	**213 (23.4)**	**33 (3.7)**	**711 (22.5)**
Anaemia	77 (8.5)	2 (0.2)	352 (11.2)
Nausea	43 (4.7)	2 (0.2)	93 (2.9)
Neutrophil count decreased	41 (4.5)	6 (0.7)	56 (1.8)
Fatigue	30 (3.3)	6 (0.7)	80 (2.5)
WBC count decreased	17 (1.9)	3 (0.3)	27 (0.9)
Vomiting	15 (1.6)	2 (0.2)	37 (1.2)
Diarrhoea	6 (0.7)	2 (0.2)	13 (0.4)
Platelet count decreased	6 (0.7)	1 (0.1)	16 (0.5)
Headache	4 (0.4)	3 (0.3)	6 (0.2)
Abdominal pain	5 (0.5)	0	7 (0.2)
Abdominal pain upper	3 (0.3)	0	4 (0.1)
Decreased appetite	3 (0.3)	0	14 (0.4)
Malaise	3 (0.3)	0	3 (0.1)

[f] Sorted by decreasing order of frequency for PT in the olaparib arm of OlympiA, and then by decreasing order of frequency in the placebo arm.

[g] Adverse event action taken=dose reduced.

Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories. Includes AEs with an onset date between the date of first dose and 30 days following the date of last dose of study treatment.

Includes AEs that led to dose reduction and did not lead to permanent discontinuation of study treatment.

MedDRA Version 24.0.

AE = Adverse event; bd = Twice daily; CSR = Clinical study report; DCO = Data cut-off; MedDRA = Medical Dictionary for Regulatory Activities; N = Total number of patients; PT = Preferred term; SAS = Safety analysis set; WBC = White blood cell.

Source: Safety Update Table 14.3.2.29.1 and Table 2.7.4.1.1.6.

Table 64: Adverse Events Leading to Treatment Interruption Reported in ≥5 Patients in the Olaparib Arm of OlympiA or in ≥2% Patients in the 300 mg bd Pool (DCO: 12 July 2021)

MedDRA Preferred term	Number (%) of patients [a]		
	OlympiA SAS		
	Olaparib 300 mg bd (N=911)	Placebo (N=904)	Olaparib 300 mg bd pool (N=3155)
Patients with an AE leading to dose interruption of olaparib/placebo [b]	**284 (31.2)**	**99 (11.0)**	**1191 (37.7)**
Anaemia	104 (11.4)	2 (0.2)	510 (16.2)
Neutrophil count decreased	54 (5.9)	6 (0.7)	101 (3.2)
Nausea	49 (5.4)	6 (0.7)	154 (4.9)
WBC count decreased	33 (3.6)	3 (0.3)	65 (2.1)
Fatigue	26 (2.9)	9 (1.0)	90 (2.9)
Vomiting	26 (2.9)	9 (1.0)	132 (4.2)
Diarrhoea	9 (1.0)	2 (0.2)	60 (1.9)
Dyspnoea	8 (0.9)	4 (0.4)	30 (1.0)
Abdominal pain	8 (0.9)	3 (0.3)	41 (1.3)
Lymphocyte count decreased	8 (0.9)	0	13 (0.4)
Platelet count decreased	6 (0.7)	1 (0.1)	35 (1.1)
Pyrexia	5 (0.5)	4 (0.4)	41 (1.3)
ALT increased	5 (0.5)	3 (0.3)	22 (0.7)
Neutropenia	0	0	110 (3.5)

[h] Sorted by decreasing order of frequency for PT in the olaparib arm of OlympiA, and then by decreasing order of frequency in the placebo arm.

[i] Adverse event action taken=drug interrupted.

Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories.

Includes AEs with an onset date between the date of first dose and 30 days following the date of last dose of study treatment.

Includes AEs that led to a dose interruption and did not lead to permanent discontinuation of study treatment.

MedDRA Version 24.0.

AE = Adverse event; ALT = Alanine aminotransferase; bd = Twice daily; CSR = Clinical study report; DCO = Data cut-off; MedDRA = Medical Dictionary for Regulatory Activities; N = Total number of patients; PT = Preferred term; SAS = Safety analysis set; WBC = White blood cell.

Source: Safety Update Table 14.3.2.30.1 and Table 2.7.4.1.1.7.

2.8.1. Discussion on clinical safety

The safety assessment is based on data collected from the phase III OlympiA study in which 911 patients received olaparib. The OlympiA data have been pooled with the data from patients receiving olaparib 300 mg bd tablet in additional monotherapy studies providing a pooled safety database of 3155 patients (1289 of whom had breast cancer).

Across the entire clinical programme, 17923 patients are estimated to have received treatment with olaparib as of 15 June 2021.

The majority of patients exposed to olaparib reported adverse events (AEs), which were generally mild to moderate in severity and did not lead to discontinuation. The toxicity of olaparib was often manageable by dose interruptions, dose reductions and standard supportive treatment as required. Overall, the safety findings in olaparib arm of OlympiA were reported at lower frequency than the 300 mg bd pool, except for AE leading to discontinuation of study treatment or to dose reduction which were reported with similar frequencies.

Exposure

The summary of clinical safety provided in support of the applied indication in early breast cancer (EBC) initially described the results of the interim analysis 2 of study OlympiA, with the data cut-off date of 12 July 2021 (DCO2). At the time of the DCO2, 1389 patients (75.7%) had completed study treatment per protocol and no patients remaned on study treatment. The planned duration of treatment was 12 months and most patients (76.1% in the olaparib arm and 81.7% in the placebo arm) received ≥11 months with most patients discontinuing treatment after 11.5 months.

Adverse events

The most common AEs in the olaparib arm were nausea (56.9%), fatigue (40.1%), anaemia (23.6%), vomiting (22.6%), headache (19.6%), diarrhoea (17.6%), neutropenia (16.4%), WBC decreased (15.8%), decreased appetite (13.1%), dysgeusia (11.7%), dizziness (11.4%).

The AE preferred terms (PTs) that were reported at a ⩾2% greater frequency in the olaparib 300 mg tablet bd arm compared with the placebo arm were: anaemia, decreased appetite, diarrhoea, dizziness, dysgeusia, fatigue, gastrooesophageal reflux disease, headache, lymphocyte count decreased, nausea, neutrophil count decreased, platelet count decreased, stomatitis, vomiting, and WBC count decreased.

Safety and tolerability findings were consistent between OlympiA and the tablet pool.

Grade ⩾3 AEs had a higher incidence in olaparib arm (24.5% of patients) than in the placebo arm (11.3%). Anaemia and neutropenia were the only AEs Grade ⩾3 reported in ⩾5% of patients in the olaparib arm (respectively 8.7% and 5.2% in the olaparib arm vs. 0.3% and 0.8% in the placebo arm). AEs of CTCAE Grade 3 or higher had overall lower frequencies in the olaparib arm of study OlympiA compared to the 300 mg bd olaparib pool (24.5% vs 36.6%).

SAEs were reported in a similar proportion of patients in the olaparib arm (8.7%) compared with the placebo arm (8.6%). The highest frequency of reported SAEs at the system organ class (SOC) level was blood and lymphatic system disorders (2% olaparib vs. 0.1% physician's choice of chemotherapy). The most common SAE in olaparib arm was anaemia (1.6% olaparib vs 0.1% placebo). A low proportion of patients had SAEs that were considered by the investigator to be causally related to study treatment (3.6% in the olaparib arm and 0.7% in the placebo arm). Anaemia (14 patients [1.5%] in the olaparib arm) was the only SAE reported in more than 2 patients. The majority of SAEs had resolved with either no action taken, or following a temporary dose interruption, delay/dose change or were recovering. SAEs were reported at a lower frequency in OlympiA than in the 300 mg bd pooled dataset (8.7% vs 19.5%).

The lower proportion of AEs, AEs of CTCAE Grade ≥3 and SAEs compared with the pooled data is likely reflective of the younger age, better ECOG performance status, no evidence of disease at randomisation, and capped duration of treatment in the OlympiA study.

Overall, the safety and tolerability data of olaparib in OlympiA was considered consistent with the known safety profile of olaparib treatment across the various indications studied.

Most of the deaths occurring on study were related to the disease under investigation (171 of 181 deaths [94.5%]; 70 patients in the olaparib arm and 101 patients in the placebo arm). Only one patient in the olaparib arm experienced an AE leading to death (cardiac arrest) which was not considered related to study treatment by the investigator. The frequency of deaths for any reason was lower for olaparib-treated patients than for patients in the placebo arm (6.5% vs. 9.5% respectively), mainly driven by death related to disease under investigation only. The frequency of deaths for any reason was lower for olaparib-treated patients (6.5%) in OlympiA compared to the 300 mg bd pool (28.8%), reflecting a population with an overall more favourable disease setting.

Three deaths in the olaparib arm and one in the placebo arm were reported under "other" (i.e. not reported as related to disease under investigation only, and not related to an AE). For one of them, cause of death was a pulmonary embolism for which relation to treatment could be excluded. For the second event, death occurred 113 days after last dose of study treatment (duration of exposure was 141 days) but information available was insufficient to conclude on relationship with olaparib. The last event reported as other was a case of AML. Although previous exposure to platinum based chemotherapy and taxanes constituted important confounding factors this case should have been counted as an AE leading to death (see discussion on the risk of new primary malignancies further below.

Dose interruptions or delay and dose reductions

Dose interruptions or delay and dose reductions were reported respectively in 57% and 25% patients on olaparib and respectively in 44.8% and 5.2% patients on placebo.

A numerically higher proportion of patients in the olaparib arm (36.2%) had a dose interruption due to an AE compared with the proportion of patients in the placebo arm (14.2%). In the olaparib arm, the median total intended treatment duration was similar to the actual treatment duration, which shows treatment interruptions did not have a significant impact on treatment duration. Similarly, a larger proportion of patients in the olaparib arm (24.4%) compared to the placebo arm (3.9%) had a dose reduction due to an AE.

The proportion of patients who reported AEs leading to discontinuation of treatment was higher in the olaparib arm than in the placebo arm (10.6% vs 4.6%). Nausea (2.1%), Anaemia (1.8%), fatigue (1.5%) and neutrophils count decreased (1%) were the only AEs leading to discontinuation of olaparib in one percent or more of the patients in the olaparib arm. A majority of discontinuation events (76/142) in the olaparib arm started within 30 days of the first dose of study treatment.

The frequency of treatment discontinuation due to AE in OlympiA study (10.6%) was higher than the one observed in OlympiAD (metastatic breast cancer; 4.9%). However, treatment duration was longer in study OlympiA (11.5 months) compared to study OlympiAD (8.2 months). Furthermore, the rate of treatment discontinuation observed in study OlympiA was similar to the one observed in the 300 mg pool (9.7%) in which treatment duration was similar 11.2 months.

Higher discontinuation rate in the adjuvant setting compared to the metastatic setting have been observed with several treatments against breast cancer. This might be related to different acceptability to drug toxicity from patients in an early curative intent setting.

ADR and AESI

No new adverse drug reaction has been identified based on the data provided. The adverse drug reactions (ADRs) identified for olaparib tablets are adequately described in section 4.8 of the SmPC. The frequency of several ADRs has been updated based on pooled data from 4098 patients with solid tumours treated with Lynparza monotherapy in clinical trials at the recommended dose (see SmPC section 4.8).

The adverse events of special interest (AESIs) for olaparib are pneumonitis, Myelodysplastic Syndrome/Acute Myeloid Leukaemia (MDS/AML) and new primary malignancies. Investigators in OlympiA were required to record new primary malignancies and MDS/AML events beyond 30 days after the last dose of olaparib at any point in OS follow-up. A causal relationship between olaparib treatment and the development or acceleration of new primary malignancies and pneumonitis has not been established.

In OlympiA, MDS/AML was reported in 0.2% (n=2) of olaparib-treated patients and 0.3% (n=3) of placebo-treated patients at DCO2 (12 July 2021). The incidence of MDS/AML in the olaparib arm of OlympiA (0.2%) was lower than the incidence reported for olaparib in PAOLA-1 (0.9%), SOLO 1 (1.2%), SOLO 2 (8.2%), SOLO 3 (2.2%), and Study 19 (1.5%), and the larger olaparib monotherapy combined therapeutic dose pool (0.9%). However, the follow-up period of OlympiA study was shorter than the monotherapy pool. Myelodysplastic syndrome/acute myeloid leukaemia are identified risk associated with Olaparib (see SmPC section 4.4 and 4.8) and will continue to be closely monitored (RMP).

In the OlympiA study, at DCO2 (12 July 2021) there were 20 patients (2.2%) reporting 21 new primary malignancies (NPM) events in the olaparib arm and 35 patients (3.9%) reporting 37 NPM events in the placebo arm occurring at any time on treatment or after the 30-day safety follow-up period. The incidence of new primary malignancies in the pool of patients who received olaparib in monotherapy studies (tablet and capsule formulations; all doses of olaparib) was 1% for olaparib (41 patients in a total of 3988 patients).

The risk of NPM is of particular concern in the adjuvant setting since patients have a longer life expectancy. The frequency of NPM was overall in line with previous experiences, even though slightly higher than the frequency reported in the general monotherapy pool and the total clinical trial population. Considering that the median follow-up time in OlympiA study was 3.5 years at DCO2, no final conclusion can be drawn on the potential increase in risk of NPM. This risk will continue to be monitored and follow up safety data will be provided in the PSUSA.

The causes for imbalance of NPM between olaparib and placebo arm remain difficult to assess. Considering the low absolute number of cases, a chance finding cannot be ruled out.

Considering the entire olaparib clinical programme 122 case reports have been received up to 15 June 2021 (crude incidence 122/17923; 0.7%). Overall, the majority of pneumonitis AEs reported in the olaparib monotherapy therapeutic dose pool were mild or moderate, non-serious, and resolved without treatment discontinuation.

The difference in exposure between study OlympiA and previous studies cannot fully explain the difference of pneumonitis incidence observed among studies. It is not possible to rule out a causal relation at this stage. However, considering that appropriate routine risk minimisation activities are implemented through the prescribing information, and that pharmacovigilance activities might not be able to provide further information on the issue, the MAH proposal to remove pneumonitis from the risk management plan is considered acceptable.

Laboratory parameters

Changes in the laboratory values for the haematology parameters of haemoglobin, platelets, leukocytes, neutrophils and lymphocytes are considered ADRs for olaparib. The changes in haematological parameters observed in study OlympiA were generally mild or moderate, manageable, and reversible.

Increases in creatinine have also been identified as an ADR with olaparib treatment. AEs of increased creatinine were predominantly Grade 1 in severity and none led to permanent discontinuation of treatment. The laboratory observations of elevated serum creatinine were not associated with renal impairment and had apparently no clinical sequelae. No hepatobiliary or renal safety concerns were identified from a review of laboratory and AE data.

Special populations

Assessment of the safety of olaparib in patient subgroups among the 300 mg bd pool showed an acceptable safety profile regardless of race, gender, or body weight. No dose adjustment is required on the basis of patient age, racial origin, gender or body weight. The study population from OlympiA study differed from the safety pool with an overall younger age.

It was considered that the safety in Hormone Receptor (HR) positive population should be evaluated separately as the patients received in a vast majority an endocrine therapy in parallel to the olaparib or placebo. A separated analysis of adverse events between HR positive patients with concomitant endocrine therapy and the safety analysis set (SAS) was provided (data not shown) and did not revealed differences in the safety profile of olaparib between the two populations.

The demographics and baseline characteristics of the Myriad gBRCAm subset (n=1539 patients) were broadly similar to the FAS (n=1836 patients) except for the different proportions of White (66.7% overall in the FAS versus 76.8% overall among Myriad gBRCAm subset) and Asian patients (28.9% overall in the FAS versus 18.3% overall among Myriad gBRCAm subset). This was expected given that the Myriad test was not performed in patients from China.

The MAH was requested to justify the proposed extrapolation of safety to patients with tumours harbouring somatic mutations in light of the claimed indication. In this respect, extrapolation was not considered justified due to limited clinical data available (see also discussion on clinical efficacy). From a safety perspective, clinical data with a longer follow-up to further assess the risk of AML/MS and new primary malignancies in this disease setting are lacking.

2.8.2. Conclusions on clinical safety

The safety profile of olaparib for patients in OlympiA study is generally consistent with the known safety profile of olaparib. It includes gastrointestinal AEs (nausea and vomiting), haematologic toxicity (anaemia) and general disorders (fatigue). No new safety signals were identified from patients with gBRCAm, HER2-negative, high risk early breast cancer. AEs associated with olaparib are generally mild or moderate, and manageable with dose modification or standard supportive treatment. Higher discontinuation rate due to AEs was observed in the EBC population compared the MBC Phase 3 study. Many discontinuations occurred relatively early during treatment. This might be due to a lower acceptance of AEs affecting daily life in a younger, often actively working patient population.

Regarding new primary malignancies, a causal relationship between olaparib treatment and these adverse events has not been established. Therefore, they are still considered as important potential risk for olaparib with ongoing surveillance activities detailed in the RMP.

2.8.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Risk management plan

The MAH submitted to submit an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 23.3 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 23.3 with the following content:

Safety concerns

Table 65: Summary of Safety Concerns

Important identified risks	Myelodysplastic syndrome/acute myeloid leukaemia
Important potential risks	New primary malignancies Medication errors associated with dual availability of capsules and tablets Effects on embryofoetal survival and abnormal development
Missing information	Long term exposure to/potential toxicity to olaparib

Pharmacovigilance plan

There are no ongoing or planned additional pharmacovigilance activities for Olaparib.

Risk minimisation measures

Table 66: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
MDS/AML	Routine risk minimisation measures: SmPC Section 4.4 and 4.8 PL Section 2 and 4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up targeted safety questionnaire Cumulative review (provided concurrent with each annual PBRER)
New primary malignancy	None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up targeted safety questionnaire
Medication errors associated with dual availability of capsules and tablets	Routine risk minimisation measures: SmPC Section 4.2 PL Section 3 **Additional risk minimisation measures:** Distribution of a DHPC to prescribers and pharmacists providing clear information on the 2 formulations.	Routine
Effects on embryofoetal survival and abnormal development	Routine risk minimisation measures: SmPC Sections 4.4, 4.6 PL Section 2	Routine
Long term exposure to/potential toxicity to olaparib	None	Routine

2.10. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 5.1 of the SmPC have been updated. Particularly, the warning with regard to women of childbearing potential/contraception in females has been modified to the product information. The SmPC of Lynparza capsule has been revised accordingly to reflect updated safety information. The Package Leaflet has been updated accordingly.

In addition, the list of local representatives in the PL has been revised.

2.10.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable because the changes are limited and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The indication is for the adjuvant treatment of adult patients with germline BRCA1/2-mutations who have HER2-negative, high risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy.

High risk early breast cancer patients were defined as follows:

- patients who received prior neoadjuvant chemotherapy: patients with either triple negative breast cancer (TNBC) or hormone receptor positive breast cancer must have had residual invasive cancer in the breast and/or the resected lymph nodes (non-pathologic complete response) at the time of surgery. Additionally, patients with hormone receptor positive breast cancer must have had a CPS&EG score of ≥3 based on pre-treatment clinical and post-treatment pathologic stage (CPS), estrogen receptor (ER) status and histologic grade as shown in Table 5.
- patients who have received prior adjuvant chemotherapy: triple negative breast cancer (TNBC) patients must have had node positive disease or node negative disease with a ≥2 cm primary tumour; HR positive, HER2-negative patients must have had ≥4 pathologically confirmed positive lymph nodes.

3.1.2. Available therapies and unmet medical need

The decision to treat patients with early breast cancer with neoadjuvant or adjuvant chemotherapy in addition to surgery/radiotherapy is driven by the consideration of clinical characteristics, tumour stage and pathology. Standard neo/adjuvant chemotherapy for HER2 negative early breast cancer is an anthracycline and taxane-based regimen. The clinical practice guidelines (ESMO 2019) recommend that a sequential anthracycline/taxane-based regimen be standard of care for the majority of patients.

Whilst platinum compounds are not routinely recommended, the addition of a platinum compound may be considered in high risk TNBC patients with deleterious BRCA1/2 mutations (ESMO 2019). In high risk TNBC patients not achieving pCR after standard neoadjuvant chemotherapy, the addition of adjuvant capecitabine post-operatively may be considered (NCCN Guidelines, ESMO 2019).

3.1.3. Main clinical studies

This application is based on the results from the pivotal Phase III, randomised, double-blind, parallel group, placebo-controlled, multi-centre study OlympiA (D081CC00006) in which patients with gBRCA1/2 mutations and triple negative or HR+/HER2- high-risk early breast cancer who had completed definitive local treatment and neoadjuvant or adjuvant chemotherapy were randomised 1:1 to receive either olaparib (300 mg bd, tablet formulation) (n=921) or matching placebo (n=915). Randomisation was stratified by hormone receptor status (HR positive/ HER2 negative versus TNBC), by prior neoadjuvant versus adjuvant chemotherapy, and by prior platinum use for current breast cancer (yes versus no). Treatment was continued for up to 1 year, or until disease recurrence, or unacceptable toxicity.

Patients with HR+ breast cancer were allowed to receive concurrent treatment with endocrine therapy as per local guidelines.

Central testing at Myriad or local g*BRCA* testing, if available, was used to establish study eligibility. Patients enrolled based on local g*BRCA* test results provided a sample for retrospective confirmatory testing. Out of 1836 patients enrolled into OlympiA, 1623 were confirmed as g*BRCA*m by central testing, either prospectively or retrospectively. There were no patients included in OlympiA tested for somatic BRCA-mutated tumours.

The primary endpoint was invasive disease free survival (IDFS) as determined by investigator assessment and defined as the time from randomisation to date of first recurrence, where recurrence was defined as invasive loco-regional, distant recurrence, contralateral invasive breast cancer, new cancer or death from any cause. Secondary objectives included OS and distant disease free survival (DDFS, defined as the time from randomisation until evidence of first distant recurrence of breast cancer). A hierarchical testing strategy was employed.

3.2. Favourable effects

A total of 1836 patients were randomised and 284 IDFS events were observed in the ITT population at the time of the efficacy interim analysis (DCO 27 March 2020). The median follow-up time was 2.3 years in olaparib arm and 2.5 years in placebo arm. OlympiA met its primary endpoint showing a statistically significant improvement in IDFS for olaparib-treated patients compared to placebo-treated patients. A reduction of the risk of recurrence of disease was observed at any given point in time by 42% in ITT population (HR 0.58; 99.5% CI: 0.41, 0.82; p=0.0000073). The difference in the percentage of patients invasive disease free at 3 years was 8.8% (95%CI, 4.5%-13.0%) between arms in favour of the olaparib arm. The observed IDFS improvement is considered clinically meaningful. Updated descriptive analyses of IDFS based on more mature data (with median follow-up of 3.5 years) conducted at the time of the pre-planned second OS interim analysis (DCO2: 12 July 2021) were consistent.

Results from the analyses of DDFS were consistent with the ITT analyses of IDFS showing a statistically significant 42.6% reduction in the risk of distant disease recurrence or death at any given point in time for olaparib vs placebo (HR=0.57; 99.5% CI: 0.39, 0.83; p=0.0000257]. The difference in the percentage of patients distant disease free at 3 year DDFS was 7.1% (95%CI, 3.0%-11.1%) and is considered clinically meaningful.

At the second planned analysis (DCO 12 July 2021), the OS results (10% maturity) showed a statistically significant reduction in the risk of death at any given point in time (HR 0.68, 98.5% CI: 0.47, 0.97, p=0.0091). At all-time points, a higher proportion of patients remained alive in the olaparib arm compared with the placebo arm (1 year [98.0%], 2 years [95.0%], 3 years [92.8%] and 4 years [89.8%] compared

with 96.9%, 92.8%, 89.1% and 86.4% respectively). The median duration of follow-up for OS was 3.5 years in the olaparib arm and 3.6 years in the placebo arm.

3.3. Uncertainties and limitations about favourable effects

There are no clinical data available on the responsiveness of breast tumours with sBRCA mutation to PARPi in the early setting (see section 3.7.3).

3.4. Unfavourable effects

The most common (reported by ≥20% of patients) adverse events reported in the olaparib arm were nausea (56.9%), fatigue (40.1%), anaemia (23.5%) and vomiting (22.6%). Grade ≥3 AEs had a higher incidence in the olaparib arm (24.3%) than in the placebo arm (11.3%).

At DCO2, adverse events of CTCAE Grade ≥3 occurred in 24.5% of patients in the olaparib arm and 11.3% of patients in the placebo arm. Anaemia was the only AEs Grade ≥3 reported in ≥5% of patients in the olaparib arm (reported in 8.7% of olaparib arm versus 0.3% of placebo arm).

SAEs were reported in 8.7% (79/911 patients) of the olaparib-arm compared with 8.4% (76/904) of the placebo arm. The most common reported SAE was anaemia (1.6% olaparib vs 0.1% placebo). The highest frequency of reported SAEs at the system organ class (SOC) level were blood and lymphatic system disorders (2.0% olaparib vs 0.1% placebo). For management of anaemia, 53 (5.8%) patients in the olaparib arm received transfusion and 8 (0.9%) in the placebo arm, with 16 patients (1.8%) and 2 patients (0.2%) receiving >1 transfusion in the olaparib and placebo arms.

The median total treatment duration to olaparib was similar to placebo (350 vs 358 days). Dose interruptions were reported respectively in 31.4% patients on olaparib and 11.4% placebo patients.

Five patients in the olaparib arm died from other cause than the disease under investigation, two of them qualify as AE leading to death. One was a cardiac arrest that happened 1 day after the last dose and was not found related to olaparib. The second was a case of AML with a date of onset 448 days after olaparib discontinuation, and death happening 295 after date of onset.

There were 2 (0.2%) cases of AML/MDS reported in the olaparib arm, including one with outcome of death and 3 (0.3%) with placebo.

The incidence of NPMs in the OlympiA trial was 2.2% and similar with the incidences seen in other trials (SOLO2 [3.6%], Study 19 [2.9%], SOLO1 [1.9%], PAOLA-1 [2.4%]).

It was reported that 9 (1%) patients in the olaparib arm and 11 (1.2%) patients in the placebo arm had an AE of pneumonitis on treatment and no patients had AEs of pneumonitis in the post-follow-up period.

3.5. Uncertainties and limitations about unfavourable effects

Uncertainties remain on potential risks of new primary malignancies (NPM) and pneumonitis.

Causal relationship between the exposure to olaparib and the occurrence of pneumonitis events could not be established based on available data. This risk will continue to be monitored as part of routine pharmacovigilance activities.

With regards to NPM, the causality of olaparib in occurrence of rare cases of new primary malignancies could not be firmly established in the context of previous courses of chemotherapy. NPM will continue to

be closely monitored in the post-marketing setting. This is of particular relevance in the adjuvant setting where patients have a long life-expectancy. Hence, continuous reporting of NPM occurring within the duration of OS follow up period in study OlympiA remains necessary.

3.6. Effects Table

Table 67: Effects Table for olaparib tablet formulation in BRCA1/2-mutated HER2-negative high risk early breast cancer (data cut-off: IDFS/DDFS: 27 March 2020; OS: 12 July 2021)

Effect	Short description	Unit	Olaparib N=921	Placebo N=915	Uncertainties / Strength of evidence	References
Favourable Effects						
IDFS	Invasive Disease Free Survival	N (%)	106/921 (12)	178/915 (20)	Efficacy data available only in patients with germline BRCA mutation.	OlympiA
		HR[a] (99.5 % CI)[b]	0.58 (0.41, 0.82) [c] p = 0.0000073[e]			
DDFS	Distant disease free survival	N (%)	89/921 (10)	152/915 (17)		
		HR[a] (99.5 % CI)[b,c]	0.57 (0.39, 0.83) p=0.0000257[e]			
OS	Overall survival	N (%)	75/921 (8.1)	109/915 (11.9)		
		HR[a] (99% CI) [b,c]	0.678 (0.503 – 0.907) p=0.0091[e]			
Unfavourable Effects						
AE of CTCAE Grade ⩾3	Related to study treatment according to investigator	N (%)	160 (17.6)	20 (2.2%)		OlympiA
AE with death outcome		N (%)	2 (0.2)	4 (0.4)		
Blood and lymphatic disorders	Anaemia All grades Grade 3-4 AE leading to treatment discontinuation		 215 (23.6) 79 (8.7) 16 (1.8)	 35 (3.9) 3 (0.3) 0		
General disorders;	Fatigue All grade Grade 3-4 AE leading to treatment discontinuation		 365 (40.1) 16 (1.8) 14 (1.5)	 246 (27.2) 6 (0.7) 4 (0.4)		
Gastrointestinal disorders;	Nausea All grade Grade ≥3 Vomiting	N(%)	519 (57%) 7 (0.8%) 19 (2.1) 206	212 (23.5%) 0 3 (0.3) 74 (8.2%)		

Effect	Short description	Unit	Olaparib N=921	Placebo N=915	Uncertainties / Strength of evidence	References
	All grade Grade ≥3		(22.6%) 6 (0.7%) 7 (0.8)	0 0		

a Estimate of the treatment HR was based on the stratified Cox's Proportional Hazards Model, <1 indicates a lower risk with olaparib compared with placebo arm. Stratification factors were the same as those used in the stratified log-rank test.

b The CI for the HR was estimated using the profile likelihood approach.

c Inferential, according to the alpha spending rules for the interim analysis.

d Exploratory, not inferential

e P-value from a stratified log-rank test. Stratification was by chemotherapy type (2 levels: adjuvant vs neoadjuvant), hormone receptor status (2 levels: ER and/or PgR positive, HER2 negative vs TNBC), and prior platinum therapy (2 levels: yes vs no). Stratification factors were based upon the categories used in the randomisation system and were chosen by the pooling strategy. Once the pooling strategy was applied, only the hormone receptor status stratification factor was selected.

F Percentages of patients were from the Kaplan-Meier estimates and the 95% CIs were calculated using Greenwood's formula.

CI = confidence interval; DDFS = distant disease free survival; FAS = full Analysis Set; HR = hazard ratio; IDFS = invasive disease free survival; N = total number of patients; OS = overall survival;

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In study OlympiA, a statistically significant improvement was observed in IDFS, DDFS and OS for olaparib-treated patients compared to placebo-treated patients. Treatment with olaparib was administered for up to 1 year and the results showed that there was a 41.9% reduction in the risk of invasive disease recurrence or death at any given point in time with olaparib arm compared to the placebo arm with 8.8% improvement in IDFS at 3 years. This is considered clinically meaningful.

The subgroup analyses of IDFS showed consistent effects with the primary analysis of IDFS in the ITT, with the treatment benefit of olaparib over placebo evidenced across all of the pre-defined subgroups.

Results of the analyses of DDFS were consistent with the analyses of IDFS, with a statistically significant benefit of olaparib vs placebo with a 42.6% reduction in the risk of distant disease recurrence or death at any given point in time. Between-group difference in 3 year DDFS was 7.1 percentage points (95%CI, 3.0-11.1) and is considered clinically meaningful.

Updated OS results from the second planned interim analysis (DCO2 12 July 2021), with a median duration of follow-up of 3.5 years in the olaparib arm and 3.6 years in the placebo arm showed a statistically 32.2% numerical reduction in the risk of death at any given point in time (HR 0.68, 98.5% CI: 0.47, 0.97, p=0.0091).

The safety profile of olaparib including patients from OlympiA is generally consistent with the known safety profile of olaparib. No new safety signals were identified from patients with gBRCAm HER2-negative early breast cancer of high risk of recurrence and safety findings in olaparib arm of OlympiA were consistent with the 300 mg tablet pool.

The toxicity of olaparib was most often manageable, including by dose interruptions, dose reductions and standard supportive treatment as required. A relatively higher frequency of treatment discontinuation was observed in the EBC compared with the MBC setting. The risk of new primary malignancy will continue to be closely monitored and is of particular importance in this earlier disease setting. The SmPC is considered to contain relevant safety information on the risks associated with olaparib and their management.

3.7.2. Balance of benefits and risks

Despite completion of standard surgery, radiation and neo/adjuvant chemotherapy disease recurrence will occur in a proportion of patients, generally with distant metastatic lesions, at which point their disease is incurable and will ultimately be fatal.

Study OlympiA evaluated the safety and efficacy of olaparib as adjuvant treatment in adult patients with germline BRCA1/2-mutations who have high risk early breast cancer and who have previously been treated with neoadjuvant or adjuvant chemotherapy. In this study, olaparib showed a statistically significant improvement in terms of IDFS, DDFS and OS compared to placebo. This benefit was shown for olaparib both in monotherapy and in association with endocrine therapy for the treatment of TNBC patients and HR+/HER2- patients respectively.

HR+/HER2- patients who have received prior neoadjuvant chemotherapy were partly selected based on the the CPS&EG scoring system to define high risk status. The MAH provided adequate clarification on the use of CPS&EG scoring system as a prognostic score following neoadjuvant chemotherapy in several retrospective studies including a large population of patients (Mittendorf et al 2011, Abdelsattar et al 2016, Marmé et al 2016). The CPS&EG scoring is considered adequately described in section 5.1 of the SmPC to inform prescribers.

The risks associated with olaparib are manageable and acceptable in the context of the meaningful treatment benefit observed with olaparib in patients with high risk early breast cancer treated in the proposed adjuvant setting.

3.7.3. Additional considerations on the benefit-risk balance

Clinical data in patients with somatic BRCA-mutated tumours are lacking as this population was not studied in OlympiA trial. The MAH submitted supportive efficacy data for olaparib and other PARP inhibitor treatments in gBRCAm, tBRCAm, and sBRCAm metastatic breast cancer patients. Overall available data support strong biological rationale and suggest antitumour activity in patients with sBRCA in the adjuvant treatment of EBC. However, the extrapolation of results from patients with germline BRCA mutations who developed early breast cancer to patients with sporadic breast cancers that harbour somatic BRCA mutations in their tumours is not considered justified for the time being considering the remaining uncertainties. Although the mechanistic rationale is acknowledged, the magnitude of the potential effect in the context of early breast cancer is uncertain and long-term safety data are lacking. The indication has therefore been restricted to gBRCAm patients only until clinical outcome data for sBRCAm patients become available.

3.8. Conclusions

The overall B/R of Lynparza is positive in the following indication: Lynparza is indicated as monotherapy or in combination with endocrine therapy for the adjuvant treatment of adult patients with germline BRCA1/2-mutations who have HER2-negative, high risk early breast cancer previously treated with

neoadjuvant or adjuvant chemotherapy (see SmPC sections 4.1, 4.2 and 5.1).

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		**Type**	**Annexes affected**
B.I.z	B.I.z - Quality change - Active substance - Other variation	Type IB	None
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

C.I.6.a - Extension of indication to include the use of Lynparza tablets as monotherapy or in combination with endocrine therapy for the adjuvant treatment of adult patients with germline BRCA1/2-mutations who have HER2-negative, high risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 5.1 of the SmPC are updated. The SmPC of Lynparza capsule has been revised accordingly to reflect updated safety information. The Package Leaflet is updated in accordance. In addition, the list of local representatives in the PL has been revised. Version 23.3 of the RMP is approved.

B.I.z – to reassess the control strategy for potentially mutagenic impurities in the active substance in view of the proposed extension of indication to an earlier line of cancer treatment.

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.

5. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Lynparza-H-C-3726-II-0051-G'

Attachments

1. Product information (changes highlighted) as adopted by the CHMP on 23 June 2022.

Reminders to the MAH

1. In accordance with Article 13(3) of Regulation (EC) No 726/2004 the Agency makes available a European Public Assessment Report (EPAR) on the medicinal product assessed by the Committee for Medicinal Products for Human Use. The EPAR is first published after the granting of the initial marketing authorisation (MA) and is continuously updated during the lifecycle of the medicinal product. In particular, following a major change to the MA, the Agency further publishes the assessment report of the CHMP and the reasons for its opinion in favour of granting the change to the authorisation, after deletion of any information of a commercially confidential nature.

   Should you consider that the CHMP assessment report contains commercially confidential information, **please provide the EMA Procedure Assistant your proposal for deletion of commercially confidential information** (CCI) in "track changes" and with detailed justification by 08 July 2022. The principles to be applied for the deletion of CCI are published on the EMA website at https://www.ema.europa.eu/en/documents/other/heads-medicines-agencies/european-medicines-agency-guidance-document-identification-commercially-confidential-information_en.pdf

   In addition, should you consider that the CHMP assessment report contains personal data, please provide the EMA Procedure Assistant your proposal for deletion of these data in "track changes" and with detailed justification by 08 July 2022. We would like to remind you that, according to Article 4(1) of Regulation (EU) 2016/679 (General Data Protection Regulation, "GDPR") 'personal data' means any information, relating to an identified or identifiable natural person (the 'data subject'). An identifiable natural person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person.

   It is important to clarify that pseudonymised data are also considered personal data. According to Article 4(5) of GDPR pseudonymisation means that personal data is processed in a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information (e.g. key-coded data).

   Accordingly, the name and the patient identification number are two examples of personal data which may relate to an identified or identifiable natural person. The definitions also encompass for instance: office e-mail address or phone number of a company, data concerning health, e.g. information in medical records, clinical reports or case narratives which relates to an identifiable individual."

2. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, if there will be one within 2 months from adoption of the CHMP Opinion, or prior to the next regulatory activity, whichever is first. If the Commission Decision will be adopted within 12 months from CHMP Opinion, the closing sequence should be submitted within 30 days after the Opinion. For additional guidance see chapter 4.1 of the Harmonised Technical Guidance for eCTD Submissions in the EU.

3. If the approved RMP is using Rev. 2 of the 'Guidance on the format of the RMP in the EU' and the RMP 'Part VI: Summary of the risk management plan' has been updated in the procedure, the MAH is reminded to provide to the EMA Procedure Assistant by Eudralink a PDF version of the 'Part VI: Summary of the risk management plan' as a standalone document, within 14 calendar days of the receipt of the CHMP Opinion. The PDF should contain only text and tables and be free of metadata, headers and footers.