22 February 2018
EMA/64964/2018
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report on extension of marketing authorisation grouped with a variation

Lynparza

International non-proprietary name: olaparib

Procedure No. EMEA/H/C/003726/X/0016/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

Abbreviation or special term	Explanation
ACMG	American College of Medical Genetics and Genomics
ADR	Adverse drug reaction
AE(s)	Adverse event(s)
AESIs	Adverse events of special interest
AML	Acute myeloid leukaemia
AUC	Area under plasma concentration-time curve from zero to infinity (for HRQoL analyses, AUC is defined as “area under the curve”)
AUC_{ss}	Area under plasma concentration-time curve during any dosing interval at steady state
AZD2281	The generic name olaparib is generally used when referring to the drug substance known by the laboratory code AZD2281 or KU-0059436
BCRP	Breast Cancer Resistance Protein
bd	Twice daily
BICR	Blinded independent central review
BRCA	Breast cancer susceptibility gene (in accordance with scientific convention, gene and mutation is italicised whereas protein is not italicised)
Integrated BRAC*Analysis*®	The test consists of gene sequencing and large rearrangement analysis of the *BRCA1* and *BRCA2* genes performed by Myriad Genetics, Inc in their CLIA facility
BRACAnalysis CDx®	The test consists of gene sequencing and large rearrangement analysis of the *BRCA1* and *BRCA2* genes performed by Myriad Genetics, Inc in their Quality Systems Regulation (QSR) facility
BRCAm	*gBRCA* or *sBRCA* mutated
BRCAwt/VUS	*gBRCA* and *sBRCA* wild type/variant of uncertain significance
BUN	Blood urea nitrogen
CA-125	Cancer Antigen-125 (tumour biomarker)
CDx	Companion diagnostic
CE	Conformité Européene (European Conformity)
CHMP	Committee for Medicinal Products for Human Use, formerly known as the Committee for Proprietary Medicinal Products (CPMP)

Abbreviation or special term	Explanation
CI	Confidence interval
CLIA	Clinical Laboratory Improvement Amendments
C_{max} ($C_{max,ss}$)	Maximum plasma concentration (at steady state)
C_{min} ($C_{min,ss}$)	Minimum plasma concentration (at steady state)
CMML	Chronic myelomonocytic leukaemia
COMP	Committee for Orphan Medicinal Products
CR	Complete response
CrCL	Creatinine clearance
CRF	Case report form
CSR	Clinical study report
CTD	Common technical document
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DCO	Data cut-off
DDI	Drug-drug interactions
DFS	Disease-free survival
DMPK	Drug metabolism and pharmacokinetics
DVT	Deep vein thrombosis
EMA	European Medicines Agency
ESAs	Erythropoiesis-stimulating agents
EU	European Union
FACT	Functional of Cancer Therapy
FACT-O	Functional Assessment of Cancer Therapy - Ovarian
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIGO	Fédération Internationale de Gynécologie Obstétrique (International Federation of Gynaecology and Obstetrics)
FMEA	Failure Mode and Effects Analysis
FOSI	FACT/NCCN Ovarian Symptom Index
G-CSFs	Granulocyte colony stimulating factor

Abbreviation or special term	Explanation
gBRCA	Germline *BRCA*
gBRCAm	Germline *BRCA* mutated
gBRCAwt/VUS	Germline *BRCA* wild type/variant of uncertain significance
GCP	Good clinical practice
GI	Gastrointestinal
Gmean	Geometric mean
h	Hours
Hb	Haemoglobin
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HRD	Homologous recombination deficient/deficiency
HRQoL	Health-related quality of life
HRR	Homologous recombination repair
HRRm	Homologous recombination repair gene mutated/mutations
IC_{50}	Half maximal inhibitory concentration
IC_{90}	90% inhibitory concentration
ICH	International Conference on Harmonisation
IIV	Inter-individual variability
ILD	Interstitial lung disease
ISMP	Institute for Safe Medication Practices
ITT	Intention-to-treat
IVD	*In vitro* diagnostic
IVIVC	*in vitro-in vivo* correlation
Ka	Absorption rate constant
LOF	Loss-of-function
LOH	Loss of heterozygosity
MAA	Marketing Authorisation Application
MATE	Human Multi-Drug And Toxin Extrusion Transporter
MCV	Mean corpuscular volume
MDS	Myelodysplastic syndrome

Abbreviation or special term	Explanation
MedDRA	Medical Dictionary for Regulatory Activities
MRP2	Multi-drug resistance protein 2
MTP	Multiple testing procedure
NCCN	National Comprehensive Cancer Network
NDA	New Drug Application
OAT	Organic anion transporter
OATP	Organic anion-transporting polypeptide
OCT	Organic cation-transporter
ORR	Objective response rate
OS	Overall survival
PARP	Polyadenosine 5'diphosphoribose polymerase
PBPK	Physiologically-based pharmacokinetic
PBRER	Periodic benefit-risk evaluation report
PD	Pharmacodynamic
PFS	Progression-free survival
PFS2	Time from start of randomisation to second progression or death
P-gp	P-glycoprotein
PK	Pharmacokinetic
PR	Partial response
PRO	Patient reported outcomes
PSR	Platinum-sensitive relapsed
PT	Preferred term
QC	Quality control
qd	Once daily
QSR	Quality Systems Regulation
QT	ECG interval measured from the beginning of the QRS complex to the end of the T wave
QTcF	QT interval corrected for heart rate using Fridericia correction
QTcI	QT interval corrected for heart rate using individual-specific correction
RECIST	Response Evaluation Criteria in Solid Tumours

Abbreviation or special term	Explanation
SAE	Serious adverse event
SAP	Statistical analysis plan
sBRCA	Somatic *BRCA* (*BRCA* variant found in the tumour but not in the germline)
sBRCAm	Somatic *BRCA* mutated
sBRCA VUS	Somatic *BRCA* variant of uncertain significance
sd	Standard deviation
SGO	Society for Gynecologic Oncology
SmPC	Summary of Product Characteristics
SOC	System organ class
$t_{1/2}$	Half life
t-AML	Therapy-related acute myeloid leukaemia
tBRCA	Tumour *BRCA* (mutations detected in the tumour)
tBRCAm	Tumour *BRCA* mutated
tBRCAwt/VUS	Tumour *BRCA* wild type/variant of uncertain significance
TCP	Temporal change parameter
TDT	Time to discontinuation of treatment or death (defined as time from randomisation to discontinuation of study treatment or death)
TFST	Time to first subsequent therapy or death (defined as time from randomisation to start of first subsequent therapy or death [ie, following discontinuation of randomised study treatment])
TCGA	The Cancer Genome Atlas
TIM-1	TNO Intestinal Model
t_{max}	Time to reach maximum concentration
TOI	Trial outcome index
TSST	Time to second subsequent therapy or death (defined as time from randomisation to the start of second subsequent therapy or death)
UGT	UDP-glucuronosyltransferase
ULN	Upper limit of normal
US (USA)	United States (of America)
VEGF	Vascular endothelial growth factor
vs	Versus

Abbreviation or special term	Explanation
VUS	Variants of uncertain significance

1. Background information on the procedure

1.1. Submission of the dossier

AstraZeneca AB submitted on 6 April 2017 a group of variations consisting of extensions of the marketing authorisation and the following variation(s):

Variation(s) requested		Type
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II

Extension application to add a new pharmaceutical form associated with a new strength (100mg and 150 mg film-coated tablets) including an extension of the indication to treat patients with platinum-sensitive relapsed ovarian tumours (regardless of BRCA mutation status or histological type). The extension application is grouped with a type II variation to align the PI for the currently authorised capsule presentation with the safety updates proposed for the tablet formulation.

The legal basis for this application refers to:

Article 7(2) of Commission Regulation (EC) No 1234/2008 - Grouping of variations.

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) points (c) change or addition of a new strength/potency; (d) change or addition of a new pharmaceutical form - Extensions of marketing authorisations.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) CW/1/2011 on the granting of a class waiver.

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 submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific Advice / Protocol assistance

The MAH received protocol assistance from the CHMP on 19/02/2009. (EMEA/H/SA/1215/1/2008/PA/III) and 15/11/2012 (EMEA/H/SA/1215/1/FU/1/2011/PA/III).

The protocol assistance pertained to non-clinical and clinical aspects of the dossier.

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: Bart Van der Schueren

- The application was received by the EMA on 6 April 2017.
- The procedure started on 18 May 2017.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 4 August 2017. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 7 August 2017. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 11 August 2017.
- During the meeting on 1 September 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 14 September 2017, the CHMP agreed on the consolidated List of Questions to be sent to the MAH.
- The MAH submitted the responses to the CHMP consolidated List of Questions on 13 October 2017.
- The Rapporteur's Assessment Report was circulated on 21 November 2017.
- The PRAC Rapporteur's Assessment Report was circulated on 22 November 2017.
- The updated PRAC Rapporteur's Assessment Report was circulated 24 November 2017.
- During the PRAC meeting on 30 November 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- The updated Rapporteur's Assessment Report was circulated on 8 December 2017.
- During the CHMP meeting on 14 December 2017, the CHMP agreed on a list of outstanding issues to be sent to the MAH.
- MAH submitted the responses to the CHMP List of Outstanding Issues on 23 January 2018.
- The PRAC Rapporteur's Assessment Report was circulated on 31 January 2018.
- The updated PRAC Rapporteur's Assessment Report was circulated on 2 February 2018.
- The Rapporteur's Assessment Report was circulated on 8 February 2018.
- During the PRAC meeting on 8 February 2018, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- The updated Rapporteur's Assessment Report was circulated on 16 February 2018.
- During the meeting on 22 February 2018, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for an extension of the marketing authorisation for Lynparza on 22 February 2018.
- The CHMP adopted a report on similarity of Lynparza with Zejula and Yondelis on 22 February 2018. (Appendix 1)

2. Scientific discussion

2.1. Problem statement

The capsule formulation of olaparib was approved on 16 December 2014 by the European Commission for the following indication: “Lynparza is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed BRCA mutated (germline and/or somatic) high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy”. Platinum-sensitive is defined as disease progressing at least 6 months after completion of the penultimate platinum chemotherapy.This procedure concerns an extension application to add a new pharmaceutical form (film-coated tablets) associated with new strengths (100mg and 150mg).

The tablet formulation was developed to provide advantages over the capsule formulation in terms of bioavailability, pharmacokinetics, strength, pharmaceutical form and consequently potentially higher patient adherence to treatment (reduction from 16 capsules per day to 4 tablets per day).

In addition, the MAH applied for the following indication for the tablet formulation:

Olaparib is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.

The MAH also applied for amendments to the product information for the capsule formulation to ensure consistency between the product information of the two formulations. The previously approved indication for the capsule formulation was not amended.

2.1.1. Disease or condition

The requested indication concerns patients who are platinum sensitive, without restriction to the BRCA mutated status. The proposed indication also mentions ‘high grade’ cancer regardless of histological type and thus including high grade serous, high grade endometrioid and other types of ovarian, fallopian tube, or primary peritoneal cancer.

Data to support this application derive from two pivotal studies, the Phase III randomised, double-blind, placebo-controlled, multicentre study, SOLO2 (conducted with olaparib tablet formulation), and the Phase II randomised, double-blind, placebo-controlled, multicentre study, Study 19 (conducted with olaparib capsule formulation).

Both SOLO2 and Study 19 included ovarian cancer patients with platinum-sensitive relapsed disease who were in response (complete [CR] or partial [PR]) to their final platinum regimen and who had received at least two previous lines of platinum-based therapy.

2.1.2. Epidemiology

Ovarian cancer is the leading cause of death from gynaecological cancers in Europe and remains difficult to diagnose at an early curable stage. The disease presents an important public health issue in Europe. In 2012, ovarian cancer was estimated to be the fifth most common cause of cancer death (297,600 deaths) and the fifth most common newly diagnosed cancer (441,500 new cases) in the European Union (EU)-27

(Ferlay et al 2013). A total of 75% of patients present with advanced disease (Stage III or IV) (Hennessy et al 2009).

2.1.3. Biologic features

Epithelial ovarian cancer comprises the majority of malignant ovarian neoplasm (about 90%) (Chan JK et al 2006; Jelovac D et al. 2011). The World Health Organization (WHO) classification of surface epithelial ovarian tumours includes six major histotypes - serous, mucinous, endometrioid, clear cell, transitional cell and epithelial-stromal. The serous subtype of ovarian carcinoma accounts for approximately 60-80% of ovarian cancer cases and is the most aggressive type of ovarian cancer.

Grade is an additional prognostic determinant and a number of grading systems currently exist which are derived from reviewing the following tumour characteristics: architectural features, mitotic counts and nuclear atypia (ESMO Clinical Practice Guidelines). Low grade (grade 1, well differentiated) serous ovarian carcinoma is considered a distinct type of disease compared with high grade (grade 2 and 3 – moderately and poorly differentiated) serous carcinoma based on a number of clinical and molecular features, thus forming a 2 tier classification of low and high grade disease widely accepted and used in clinical practice (Levanon et al 2008; Vang et al 2009).

Despite the high sensitivity of ovarian cancer to initial treatment with platinum and taxane combination chemotherapy (following cytoreductive surgery), which is the standard of care in the front-line setting, the majority of women diagnosed with advanced-stage disease will have a recurrence of their cancer.

Recurrent disease is classified as platinum resistant or platinum sensitive, depending on whether the disease recurred less than or greater than 6 months following previous platinum therapy, and this classification is highly prognostic and is important in determining optimal chemotherapeutic treatment options.

Three subgroups of patients with relapsed ovarian cancer have been identified:

- patients with platinum-refractory disease who progress during platinum treatment,

- patients with platinum-resistant disease who develop recurrence <6 months from the completion of platinum chemotherapy,

- patients with platinum-sensitive disease: partially platinum-sensitive and platinum-sensitive recurrence are currently considered as separate sub-groups and are respectively defined by a relapse-free period of 6 to 12 months and >12 months following a response to the final dose of prior platinum treatment (NICE, technology Appraisal 91 May 2005; ESMO guidelines, Ledermann et al, 2013).

Platinum predominantly causes large-scale DNA intra-strand cross-links which require a competent homologous recombination pathway for effective repair. Given that platinum sensitivity and PARP inhibitor sensitivity may converge at the homologous recombination pathway, it was possible that platinum responsiveness may be also enrich for PARP inhibitor sensitivity [Mukhopadhyay et al 2010]. Clinical data support the hypothesis that platinum sensitive tumours are more sensitive to PARP inhibitors than platinum resistant tumours [Matulonis et al 2016]. Thus, while BRCA mutations and HRD might represent biological markers of sensitivity to PARP inhibitors, platinum responsiveness may be a clinical indicator of sensitivity to these compounds.

New emerging data suggest that PARP inhibitor sensitivity is broader than BRCA*1/2* and HRR deficiencies and may extend to non-HRR DNA damage response deficiencies and pathways as well [Postel-Vinay et al 2013, Cerrato et al, 2016, Murata et al, 2016, Lu et al 2017]. Moreover, it has been demonstrated that

51% of high-grade serous ovarian cancer have compromised homologous recombination-based repair (Cooke et al. 2011).

It is assumed that somatic BRCA and homologous repair deficiency (HRD) status refer to samples at time of diagnosis/primary surgery. Advanced tumours are normally heterogeneous and may be so also for somatic BRCA mutations/HRD. The selective pressure of platinum therapy is at least partly reflected in time to recurrence so that late recurrences may increase the likelihood of positive findings with respect to sBRCA/HRD. In addition reversion of gBRCA mutations is a well described mechanism associated with resistance development.

While Type I tumours are characterized by specific mutations in *KRAS*, *BRAF*, *ERBB2*, *PTEN* and *PIK3CA* but rarely *TP53* and are relatively genetically stable, Type II tumours are characterised by nearly universal *TP53*, which makes them genetically highly unstable (Cancer Genome Atlas Research Network 2011). Moreover, recent evidence suggests that serous and endometrioid carcinomas arise from the tubal fimbrae, suggesting similar biology and origin for the high grade epithelial histologies (Jayson et al 2014). Pennington et al reported in their study that contrary to the common belief of homologous recombination deficiencies being characteristic of high-grade serous ovarian cancer only, DNA repair deficiencies were found equally commonly in carcinomas with non-serous histology (Pennington et al 2014).

2.1.4. Clinical presentation, diagnosis and prognosis

Early stage ovarian cancer is often asymptomatic and therefore difficult to detect. For women who do experience symptoms in the early stages, ovarian cancer is sometimes misdiagnosed because the majority of symptoms are nonspecific. These symptoms may overlap those of gastrointestinal and other diseases, and as a result, many patients may be treated incorrectly for months or years.

The definitive diagnosis and staging of ovarian cancer is by surgery, and cytological or histological examination of tissue samples.

The Federation of Gynecology and Obstetrics (FIGO) surgical staging system is used for epithelial ovarian cancer and primary peritoneal adenocarcinoma. Because the disease tends to be asymptomatic in early stages, or associated with vague, non-specific symptoms, the majority of patients are diagnosed with advanced stage disease.

The advanced stage at which ovarian cancer is generally detected is reflected in the 5-year survival rates; 46% across all stages and 29% for advanced stages (Siegel et al 2017). Even though, over 80% of patients respond to initial platinum-based chemotherapy treatment, the majority subsequently relapse (Colombo et al 2010). Recurrent disease is incurable, and the challenge is to balance aggressive treatment in an effort to prolong disease-free time, while maintaining a tolerable side-effect profile and quality of life (Lancet 2009). Most patients will die within 3 to 4 years of diagnosis [Coleman et al 2013].

2.1.5. Management

Platinum-sensitive recurrence is defined clinically by a response to platinum-based therapy and a relapse-free period of ≥ 6 months after the final dose of prior platinum treatment (Colombo et al 2010; Pfisterer and Ledermann 2006). There are three primary treatment options for platinum-sensitive recurrent ovarian cancer patients who are in response (complete response or partial response) to platinum-based chemotherapy: observation (also referred to as surveillance), bevacizumab monotherapy maintenance after bevacizumab in combination with chemotherapy for platinum-sensitive recurrent

disease, or maintenance therapy following response to platinum-based chemotherapy followed by PARPi maintenance therapy. Olaparib capsules is currently approved in this setting in adult patients with platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer with a BRCA mutation (either germline or tumor) who are in response (complete response or partial response) to platinum-based chemotherapy, while niraparib is approved in the same setting but irrespective of the BRCA mutation status.

About the product

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

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

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

The capsule formulation of olaparib was approved on 16 December 2014 by the European Commission for the following indication: “Olaparib is indicated as monotherapy for the maintenance treatment of adult patients with platinum sensitive relapsed BRCA mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.

Platinum sensitive is defined as disease progressing at least 6 months after completion of the penultimate platinum chemotherapy.”

For the tablet formulation, the MAH applied for the following indication, which was agreed by CHMP:

Olaparib is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.

Treatment with olaparib should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

The drug product is supplied as 50 mg hard capsules and as 100 mg and 150 mg tablets for oral use.

The tablets and capsules are not to be substituted on a milligram-to-milligram basis due to differences in the dosing and bioavailability of each formulation. Therefore, the specific dosage recommendations for each formulation should be followed:

- Capsule formulation

Patients must have confirmation of a breast cancer susceptibility gene (BRCA) mutation (either germline or tumour) before olaparib treatment is initiated. BRCA mutation status should be determined by an experienced laboratory using a validated test method.

Genetic counselling for patients with BRCA mutations should be performed according to local regulations.

The recommended dose is 400 mg (eight 50 mg capsules) taken twice daily, equivalent to a total daily dose of 800 mg.

Patients should start treatment with olaparib no later than 8 weeks after completion of their final dose of the platinum containing regimen. It is recommended that treatment be continued until progression of the underlying disease.

The tablet formulation was developed to provide advantages over the capsule formulation in terms of bioavailability, pharmacokinetics, strength, pharmaceutical form and consequently potentially higher patient adherence to treatment (reduction from 16 capsules per day to 4 tablets per day).

- Tablet formulation

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

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

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

Type of Application and aspects on development

- Legal basis

The applicant AstraZenaca AB submitted on 6 April 2017, an extension application to the current marketing authorisation EU/1/14/959/001 to register two strengths (100mg and 150mg) of a tablet formulation for Lynparza in the following indication: “Monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy”.

The Applicant is grouping this application with a variation to align the capsule PI with the safety updates introduced for the tablet formulation.

- Significance of paediatric studies

The information relating to Paediatrics (Consolidated EMA decision on the list of paediatric class waivers (19 December 2011) and EMA PDCO Confirmation of applicability of class waiver - ovarian carcinoma (07 December 2012)) was previously submitted at the time of the initial MAA (EMEA/H/C/003726) in

sequence 0000 and is relevant to this application.

2.2. Quality aspects

2.2.1. Introduction

This application is a line extension to the existing marketing authorisations for Lynparza hard capsule 50 mg (EMEA/H/C/3726). Assessment of the active substance focused only on the main changes and reference to the already approved procedure was made in sections that are identical or essentially similar.

The finished product is presented as film coated tablets containing 100 mg or 150 mg of olaparib as the active substance.

Other ingredients in the tablet core are: copovidone, colloidal anhydrous silica, mannitol and sodium stearyl fumarate. Excipients in the coating are: hypromellose, Macrogol 400, titanium dioxide (E171), iron oxide yellow (E172) and iron oxide black (E172) (150 mg tablets only), as described in section 6.1 of the SmPC.

The product is available in Alu/Alu non-perforated blister, as described in section 6.5 of the SmPC.

2.2.2. Active Substance

The manufacturing process of olaparib for the tablet product is very similar to the current process used for capsule product starting from the same regulatory starting materials and using the same raw materials at each step (reagents, solvents and catalyst) within the same process parameters ranges.

The main differences between both processes are in the purification/seeding step and the removal of the micronisation step. Some further minor adjustments have been satisfactorily justified and can be accepted. The introduced changes are considered acceptable since the polymorphic form and particle size distribution of the active substance are not considered critical quality attributes for the tablet formulation since the active substance undergoes a hot melt extrusion process and is rendered amorphous during the finished product manufacturing process.

The current specifications for olaparib active substance are appropriate for the manufacture of the tablets. Olaparib for tablet formulation is routinely tested for appearance, identification by IR or NMR spectrometry, assay by LC, organic impurities by LC, residual solvents by NMR spectrometry or GC, water content by KF and sulfated ash (Ph. Eur.). Compared to the original capsule application, analytical methods and their validation remain unchanged except for the identification tests. Impurities detected in olaparib development batches remain unchanged, however given the reduction of the maximum daily dose (from 800 mg to 600 mg), the limits for specified impurities have been slightly increased in line with the ICH Q3A qualification threshold. The analytical methods for olaparib active substance have already been previously validated according to ICH Q2 (R1) requirements and assessed in the capsule application.

The packaging material for the active substance remains the same as the original submission i.e. double low-density polyethylene (LDPE) bags, within a rigid outer container/drum, which complies with EC regulation 10/2011 (as amended by EC regulation 1183/2012).

Stability data from three production scale batches stored in the proposed packaging under long term conditions for up to 36 months (25 °C / 60% RH) and under accelerated conditions (40 °C / 75% RH) for 6 months according to the ICH guidelines was provided.

The parameters assessed during stability studies are appearance, assay by HPLC, related substances by HPLC, water content by KF, polymorphic form by NIR method and particle size distribution by laser diffraction method. The specification limits and analytical procedures for parameters tested during stability are identical to those employed during release testing except for polymorphism and particle size distribution which are tested only for information. Details on laser diffraction method and NIR method have been provided along with validation data. The 36 month data show no significant change with regards to the description, assay, organic impurities, polymorphic form, water content or particles size distribution for the samples stored at 25 °C/60% RH, nor after 6 months at 40 °C/75% RH and 6 months at 50 °C/ambient humidity.

In addition, stability data under stress conditions under light has been provided. No significant change was observed for description, assay, organic impurities, polymorphic form or water content for the sample stored under ICH light conditions.

Based on the available stability data, the proposed retest period of 48 months for olaparib when stored in LDPE bags at or below 30°C was considered acceptable.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Olaparib film-coated tablets are intended for immediate release and are available in two strengths: 100 mg which is yellow to dark yellow film-coated tablets, oval, bi-convex, 14.5 x 7.25 mm, debossed with “OP100” on one side and plain on the reverse, and 150 mg is green-grey film-coated tablets, oval, bi-convex, 14.5 x 7.25 mm, debossed with “OP150” on one side and plain on the other side. The two dosage strengths are differentiated by colour and engraving.
Olaparib film-coated tablets are composed of milled olaparib extrudate blended with post-extrusion excipients. The final tablet strength is obtained using different compression weight of a common blend.

Olaparib is already authorised as a 50 mg capsule. However, since the posology of the capsule product is not ideal (8 size 0 capsules taken twice daily) in terms of convenience for the patient, an improved product is desirable to reduce the burden of a large number of dosage units for administration. The pharmaceutical form is adapted to the target population (adults) and to the posology: two 150mg tablets taken twice daily, equivalent to a total daily dose of 600 mg. The 100mg tablet is available for dose reduction. Both the 100 and 150 mg tablet strengths used the green film-coat during the early and pivotal clinical trials. The quality target product profile (QTPP) has been defined as shown in Table 1:

Table 1. Quality target product profile (QTPP) of Lynparza 100 mg and 150 mg film-coated tablets.

Quality attribute	Target
Maximum number of dosage units for the Phase III/ commercial dose	2 tablets taken twice daily
Appearance	Tablet conforming to size, shape and colour Sufficient mechanical robustness to withstand coating, packing and transport processes (hardness) Friability of cores - <1% weight loss to provide assurance that the product can be film coated robustly
Identity	Positive for olaparib
Assay	Shall comply with the relevant pharmacopoeial acceptance criteria
Degradation products	Individual unspecified degradation products: 0.2% maximum in line with ICH Q3B qualification threshold Individual specified degradation products: within toxicologically qualified limits
Uniformity of dosage units	Shall comply with the relevant pharmacopoeial acceptance criteria
Dissolution	Complete release <60 minutes to meet immediate release criteria
Stability of the product	Minimum 3 years product shelf life in moisture protective pack
Microbiological quality	Product free from microbial contamination. Shall comply with the relevant pharmacopoeial acceptance criteria

Attempts to develop a standard disintegrating tablet using crystalline olaparib were unsuccessful due to solubility-limited release from this type of dosage form, even when using micronised crystalline olaparib. Evaluation of alternative technologies was undertaken to deliver an acceptable oral solid dosage form that was capable of delivering a 300 to 400 mg dose in two dosage units per administration, enabling the maximum predicted daily clinical dose of up to 800 mg to be delivered in as few as four dosage units.

The results of the investigation with several different enhanced formulations demonstrate that the amorphous solid dispersions of olaparib by melt extrusion have significantly enhanced bioavailability over the other formulation types (i.e. using lauryl macrogol glycerides (LMG) capsule formulation.

Since olaparib has low solubility in aqueous media (≤0.1 mg/mL), the development of dosage forms has been directed towards solubility enhancing technologies. The capsule formulation was developed as a semi-solid surfactant-based formulation (LMG capsule formulation), which was demonstrated to enhance the solubility of the active substance in simple aqueous media. However this formulation was limited by low bioavailability.

Therefore a different approach has been taken for the tablet formulation. This was based on generating an amorphous solid dispersion of olaparib stabilised in a polymer carrier matrix, which allows an increase in the active substance loading possible in a single dosage unit, thus reducing the number of units required to deliver the required dose. Due to the solubility enhancement achieved with the amorphous solid dispersion, the bioavailability is also increased, leading to a lower required dose for the tablet compared to the capsule formulation.

The formulation development was realized in two stages: first to define the composition of the amorphous solid dispersion (extrudate), and then to determine the composition of the final compression blend.

Numerous extrudate formulations of olaparib containing different matrix polymers, surfactants and drug loadings were assessed against the following criteria: formation of degradation products of olaparib, drug

release profile. The data generated for this study led to definition of the optimal matrix polymer carrier. The impact of storage on product performance was then assessed. It was concluded that olaparib extrudate at relatively high drug loading in the lead formulation can be stored and that moisture does not impact physical stability, unless high temperatures and high relative humidity are encountered. The use of appropriate packaging materials for long-term storage mitigates the risk of exposure to such conditions.

During the hot melt extrusion process used to manufacture the tablet product, olaparib is converted to the amorphous form. The solubility of the amorphous form is significantly higher than that of the crystalline form, as it has been shown by the solubility data. Caco-2 permeability investigations have shown olaparib to be moderately permeable. Based on its solubility and permeability data olaparib drug substance is a BCS Class IV.

Small amounts of residual crystalline content have the potential to seed further recrystallization on storage. In order to further understand this risk and to evaluate the suitability of the formulation developed, a study was performed to assess the potential for the presence of residual crystalline content, in both extrudate and tablets, to seed additional crystalline material during the proposed shelf life of the product. Data presented showed no significant change in the crystalline content and no significant change in dissolution performance. This data demonstrates that the propensity for recrystallization in extrudate and tablets is very low, even when the initial residual crystalline content is high (a scenario which is excluded by the control strategy).

Potential direct compression tablet formulations were explored with dissolution properties evaluated as the decision criteria. Numerous different variants were processed (varying % extrudate, nature and % filler, nature and % lubricant, nature and % disintegrant).

Based on assessment of the dissolution, a post-extrusion tablet formulation with a good compressibility and with high extrudate loading has been defined. The dissolution performance of this variant gave the highest mean dissolution. In order to confirm that the *in vivo* performance of the chosen tablet gave an acceptable bioavailability increase, this formulation was dosed at 100 mg in a fasted beagle dog pharmacokinetic study. The data derived from this study were compared against the previously generated LMG capsule data and demonstrated that the melt extruded tablet prototype formulation delivered a significant enhancement in the bioavailability in dog compared to the clinically dosed LMG capsule.

For the tablet coating a standard non-functional film coat was selected based on known, standard commercially available hypromellose-based composition types. The tablet prototype formulation composition was subsequently developed into a range of tablet strengths for clinical use.

All excipients of the formulation are standard functional materials used in pharmaceutical direct compression tabletting processes and comply with Ph. Eur. or other relevant standards (e.g., food additives Regulation). Olaparib has been tested for compatibility with excipients in the formulation and no incompatibilities have been found. The largest single excipient by weight is the polymeric carrier for the extrudate. The use of matrix polymer is well established as a standard functional material in melt extrusion processes. The well-established function of this material enable melt extrusion processing and provide a medium in which olaparib is able to remain amorphous during storage and dissolution. The polymer is hygroscopic: in contact with humid air it can absorb water which has the potential to impair the physical stability. Therefore olaparib film-coated tablets and extrudate intermediate are stored in appropriately protective packs.

The development of the dissolution method has been described in sufficient detail taking into consideration the physicochemical properties of the active substance. The discriminatory power of the method has been investigated. Results obtained suggest that changes to the manufacturing process have little to no impact on product release characteristics both *in vitro* and *in vivo*. Overall the demonstration of discrimination power of the QC dissolution method is considered satisfactory.

Olaparib tablets do not disintegrate. The tablet erodes as the active substance and soluble excipients dissolve at the interface between tablet surface and the dissolution medium. As expected for a rapid erosion-based dissolution mechanism, the larger, higher strength, 150 mg tablet demonstrates a slightly slower rate of dissolution than the lower 100 mg strength tablet. As a consequence the dissolution specifications have been set accordingly.

Holding time studies were successfully finalized for for extrudate intermediate and based on the stability results a holding time of 12 months was established. Specifications for extrudate intermediate have been suitably justified. Olaparib extrudate intermediate is stored in a low-density polyethylene (LDPE) bag, within a rigid outer container/drum. It is stated that the primary packaging component is a food grade LDPE bag in compliance with EC regulation 10/2011 (as amended by EC regulation 1183/2012). A holding time of 24 months for bulk tablets has been also established and is supported by stability data on one batch of each strength.

Bulk olaparib film-coated tablets are packed in a sealed aluminium foil bag. The tablets may also be stored in a low-density polyethylene (LDPE) bag within the sealed aluminium foil bag. The bulk bag is stored within a rigid outer container/drum which provides physical protection. The polyethylene bags are food grade and comply with the Ph. Eur requirements.

Lynparza finished product 100 mg and 150 mg film-coated tablets are packaged in Alu/Alu non-perforated push-through type blister pack made from a base web of aluminium laminate, PVC, polyamide and sealed to a hard temper aluminium foil coated with heat seal lacquer. The packaging material in direct contact with the product complies with current legislation (EC 10/2011).

Manufacture of the product and process controls

The main steps of the olaparib 100 and 150 mg film-coated tablets manufacturing process are: mixing, hot melt extrusion, milling, compression, film coating and packing processes.]

The in-process controls (IPCs) during the manufacturing process have been presented and are adequately justified. The control strategy ensures that the manufacturing process consistently delivers a product that meets the defined criteria for all release specifications.

The manufacturing process for olaparib extrudate and the film-coated tablets has been validated on three commercial batches from each strength. Process validation data complies with set acceptance criteria.

In conclusion, it has been demonstrated that the manufacturing process is sufficiently robust to provide assurance that film-coated tablets of consistent quality, complying with the designated specification, are produced.

Product specification

The finished product release and shelf life specifications include appropriate tests and limits for description (visual), identification of olaparib (LC-UV), assay (LC), degradation products of olaparib (LC),

dissolution of olaparib (LC), uniformity of dosage units (Ph. Eur.), water content (KF) and microbiological quality (Ph. Eur.).

The finished product is released on the market based on the above release specifications, through traditional final product release testing. The analytical methods used have been adequately described and validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used in the routine analysis of finished product has been presented.

Batch analysis data from a large number (>140) of production scale batches, most of which have been entirely manufactured at the proposed site for commercial supply have been presented. All data is within specification except for description. The results show that the finished product can be manufactured with consistent quality and meeting its specifications.

Stability of the product

Three batches of each strength of Lynparza film-coated tablets (100 and 150 mg), manufactured at commercial scale in the commercial manufacturing facility, have been placed on stability under long-term (25 °C/60% RH), intermediate (30 °C/75% RH), accelerated (40 °C/75% RH), and 50°C/ambient according to the ICH guidelines. Results are available after 24 months of storage at 25 °C/60% RH and 30 °C/75% RH, 6 months of storage at 40 °C/75% RH and 3 months at 50°C. The stability batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, assay, degradation products, water content, dissolution, hardness and microbiological quality. The methods used for assay and degradation products were stability indicating. The specification limits and analytical procedures for parameters tested during stability are identical to those employed during release testing .

The results of stability batches show little change over time and a good physical and chemical stability at all conditions tested. The only trend at 50°C/ambient RH is a very slight increase in total degradation products observed for the 100 mg tablets.

A photostability study was carried out according to ICH Q1B Guideline. The result of the photostability testing indicates that olaparib film-coated tablets (100 and 150 mg) present little or no change for the tested parameters (description, assay, degradation products, dissolution, water content and hardness).

Forced degradation / stress studies were carried out on 100 and 150 mg olaparib film-coated tablets and excipient blends. Samples were subjected to stress conditions comprising thermal degradation, acid/base hydrolysis, oxidation and light. For each of these conditions low level degradation was observed and which indicates that olaparib film-coated tablets are extremely stable.

Based on the provided stability data, the proposed shelf life of 36 months stored in the original package in order to protect from moisture and without any special temperature storage condition, as stated in the SmPC (sections 6.3 and 6.4) is acceptable.

Adventitious agents

None of the materials used in the manufacture of olaparib tablets are derived from human or animal sources.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The applicant has applied QbD principles in the development of the active substance and finished product manufacturing processes. However, no design spaces were claimed for the manufacturing process of the active substance nor for the finished product. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

None.

2.3. Non-clinical aspects

2.3.1. Introduction

New non-clinical data were submitted to support this application, including two new toxicology studies, a non-GLP compliant 1 month repeat dose toxicity study in rats, and a GLP-compliant 3 months repeat-dose toxicity study also in rats, performed in compliance with GLP. Focus is hereby made on the data provided, not previously assessed as part of the initial MAA.

2.3.2. Pharmacology

Primary pharmacodynamic studies

New pharmacology data were provided as part of this application

- ***Activity of PARP inhibitors AZD2281 (olaparib) and AZD2461 against PARP-3:***

AZD2461 is a potent inhibitor of PARP-1 and PARP-2, developed as a follow-up to olaparib (AZD2281) that represented a poorer substrate for P-glycoprotein than olaparib. Published data (Rulten et al., 2011) demonstrated a role for PARP-3 in Non-Homologous End Joining (NHEJ) DNA double strand break (DSB) repair. As part of the characterization of AZD2461, PARP-3 activity was determined for both AZD2281 (olaparib) and AZD2461. These studies have demonstrated that while olaparib effectively inhibits PARP-3, AZD2461 does not. Together, the data demonstrating that AZD2461 is not an effective inhibitor of PARP-3 and NHEJ, while maintaining anti-tumour activity in BRCAm tumour models (Jaspers et al., 2013),

suggest that PARP-3 is not required for the synthetic lethality and anti-tumour activity of olaparib in BRCA deficient tumours.

- ***PK, PD and efficacy study using Different Olaparib Doses in the TNBC PDX in vivo model HBCx-10***

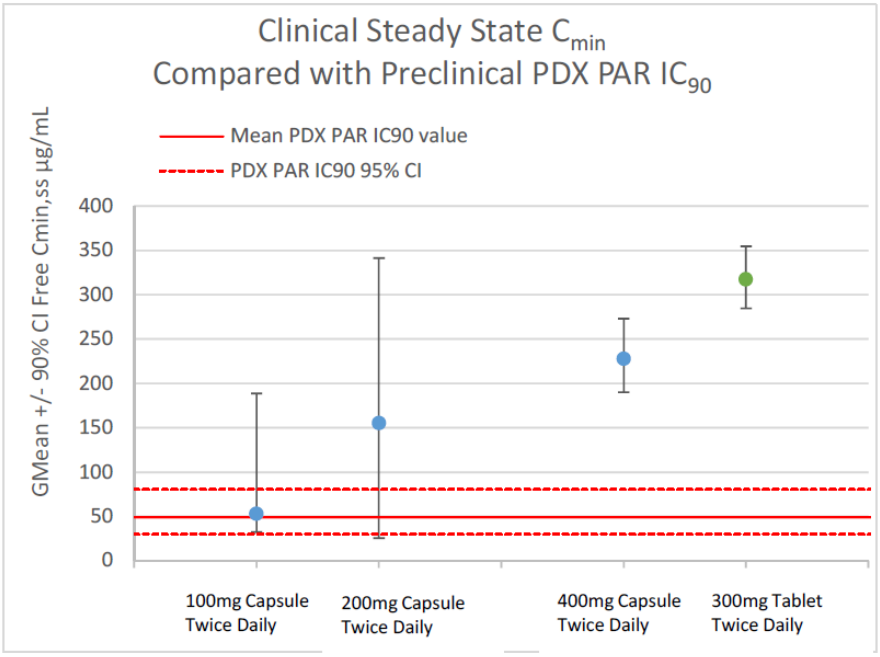
To build a preclinical PKPD/efficacy relationship model, an olaparib sensitive PDX model (HBCx-10) has been used. This model is derived from a triple negative breast cancer (TNBC) patient, carries a homozygous BRCA2 mutation and has been shown to respond to single agent olaparib given orally, once per day at 100 mg/kg. This model is also very sensitive to platinum treatment. A number of different continuous doses were tested in the HBCx-10 PDX model ranging from 2.5 mg/kg to 100 mg/kg. There was an initial period of tumour growth for both 50 mg/kg and 100 mg/kg treatments prior to tumour regression. This was consistent with the known mechanism of action for olaparib where cell death results from insupportable genomic instability that follows replication in a situation where both PARP-1 is inhibited and homologous recombination repair is deficient due to BRCA2 mutation (Farmer et al, 2005). For the 50 mg/kg dose treatment, the time taken to induce tumour regression was extended (from ~17 to ~28 days) compared to the 100 mg/ kg dose. In addition, the average Day 30 tumour volume for the 50mg/kg dose was 8.6% of the starting volume vs 1.4% with the 100 mg/kg dose. For doses below 50 mg/kg, no tumour regression was seen by Day 30.

Both tumour pharmacodynamics (PAR inhibition) and plasma pharmacokinetics were determined 1 hour after dosing on Days 7 and 14 of continuous dosing for both vehicle control and olaparib treated tumours. There was a clear correlation between dose of olaparib, free levels of olaparib in the plasma and the level of PAR inhibition in the tumour. Together, this information has been used to determine the predicted time above both the tumour PAR IC50 and IC90 for each of the doses tested and is shown in the table below.

Table 3 Time above IC_{50} and IC_{90} for different doses of olaparib in HBCx-10.

Dose mg/kg	Time above IC_{50} hours (56.5nM)	Time above IC_{90} hours (382nM)
2.5	1.9	0.7
10	7.1	1.1
25	10.5	3.4
50	13.1	6.0
100	15.6	8.5

Figure 9 **Relationship between clinical trough plasma exposures at different capsule and tablet doses of olaparib and the preclinical calculated IC_{90} value**



- ***Activity of olaparib metabolites in terms of PAR inhibition and anti-proliferation in sensitive cell line models***

Three olaparib metabolites (M15, M12 and M18) that each constitute approximately 10% of the total circulating drug-related material were tested for target (PAR) inhibition and antiproliferative potency against the BRCA mutant breast cancer cell line MDA-MB436 using clonogenic assays.

Olaparib was a more potent inhibitor of PARP-1 PARylation than the three olaparib metabolites, M15, M12 and M18 as determined by PAR ELISA with olaparib being approximately 7-fold more potent that M18 and 20-fold more potent than M12 and M15.

Olaparib was also more potent at inhibiting the growth of BRCA1 mutant cells (MDA-MB- 436) than the three olaparib metabolites, with approximately 4-fold greater potency than M18 and 30-fold greater potency than M12 and M15 and therefore are not considered to contribute significantly to efficacy.

2.3.3. Pharmacokinetics

No additional pharmacokinetic drug interactions and pharmacokinetic studies were conducted.

2.3.4. Toxicology

The full nonclinical safety profile of olaparib was previously assessed at time of the initial marketing authorisation application.

Single dose toxicity

No additional single dose toxicity studies were conducted. Previous studies showed that the highest non-lethal oral dose in rats was 240 mg/kg and that the highest non-lethal IV dose in mice and rats was 70 mg/kg.

Repeat dose toxicity

In the pivotal repeat dose rat studies reported in the original MAA, olaparib was formulated in DMSO diluted 1:10 with 10% hydroxylpropyl-β-cyclodextrin (HPβC) in phosphate buffer saline (PBS). In an attempt to explore higher dose levels for possible future carcinogenicity studies, two dose setting studies of 1 and 3 months duration in Han Wistar rats were conducted since the original MAA submission. A suspension formulation of milled olaparib in 0.5% hydroxylpropyl methyl cellulose (HPMC) and 0.1% Tween 80 was used in these dose setting studies.

Whilst not required to support this current advanced cancer indication, these studies were submitted by the MAH as the administered doses and exposures in these studies were higher than those achieved on the pivotal rat repeat dose studies.

In the pivotal repeat dose rat studies reported in the original MAA, olaparib was formulated in DMSO diluted 1:10 with 10% hydroxylpropyl-β-cyclodextrin (HPβC) in phosphate buffer saline (PBS). In an attempt to explore higher dose levels for possible future carcinogenicity studies, two dose setting studies of 1 and 3 months duration in Han Wistar rats were conducted since the original MAA submission. A suspension formulation of milled olaparib in 0.5% hydroxylpropyl methyl cellulose (HPMC) and 0.1% Tween 80 was used in these dose setting studies.

These studies are summarized in Table 1.

Table 1 Toxicology studies with olaparib completed since the original marketing application

Study type and duration	Route of administration	Species	Study number	GLP compliant
Repeat dose toxicity:				
1 month	Oral	Rat	8000589	No
3 month	Oral	Rat	526803	Yes

- **1 Month Oral (Gavage) Toxicity Study in the Rat (8000589)**

The objectives of this study were to determine the potential toxicity and toxicokinetic characteristics of AZD2281 (olaparib), when given by daily oral gavage for 1 month to rats, and to provide data to set a suitable high dose level for use in a subsequent 3 month oral toxicity study in rats.

Groups of 10 male and 10 female Wistar Hannover rats were dosed once daily with olaparib at dose levels of 0, 100, 250, 500 and 1000 mg/kg/day (males) or 0, 25, 50, 100 and 250 mg/kg/day (females) for one month. This study used suspensions of milled drug substance in 0.5% HPMC and 0.1% Tween 80.

After a single dose, exposure to olaparib increased in a less than proportional manner between the low and high doses, a trend more marked in males than females. Following repeat dosing, there was a trend to a decrease in exposure in males. In females, systemic exposure to olaparib was comparable with repeat dosing. Where both sexes received the same dose level, exposure was greater in females than in males. A summary of the TK data is provided in Table 2.

Table 2 **Toxicokinetics in male and female rats following single and multiple daily doses of olaparib**

Dose level (mg/kg/day)		C_{max} (µg/ml)				$AUC_{(0-t)}$ (µg.h/ml)			
		Day 1		Last day		Day 1		Last day	
Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
100	25	1.21	1.27	0.530	1.61	8.73	6.39	3.49	7.60
250	50	3.85	3.25	2.70	2.73	27.7	14.2	14.6	12.4
500	100	3.72	4.24	2.68	3.57	31.8	23.9	12.6	27.4
1000	250	6.52	8.60	3.12	6.13	45.6	51.3	17.5	53.4

Oral administration of olaparib at dose levels of up to 1000 mg/kg/day in males and 250 mg/kg/day in females was tolerated, with no compound-related deaths, but was associated with clinical signs in females at > 100 mg/kg/day, and reduced bodyweight gain, food consumption and decreased plasma alkaline phosphatase and/or triglycerides in both sexes at all dose levels. Haematological changes, including decreases in red blood cell parameters (red blood cell count, haemoglobin and haematocrit), leukocyte counts (lymphocytes, neutrophils, monocytes, eosinophils, basophils), reticulocytes and/or increases in platelets, were seen for males at ≥ 500 mg/kg/day and for females at ≥ 25 mg/kg/day.

Treatment-related histopathological findings were seen in the bone marrow, spleen, thymus, mesenteric lymph node and caecum. Decreased hematopoietic cellularity in the bone marrow and atrophy of the red pulp in the spleen was seen in males dosed at 1000 mg/kg/day and in females at > 100 mg/kg/day. Lymphoid depletion was seen in the thymus of males dosed at > 250 mg/kg/day and in females at > 50 mg/kg/day. There was an increased incidence of sinusal histiocytosis in the mesenteric lymph node in males at > 100 mg/kg/day and in females at 250 mg/kg/day. Epithelial erosion (characterised by a thinned, basophilic surface epithelium with occasional single epithelial cell necrosis, and with regenerative glandular epithelial hyperplasia and mucosal infiltrates of mixed inflammatory cells) was noted in the caecum in some males at > 100 mg/kg/day but was not present in females at any dose level.

The no observed adverse effect level (NOAEL) in this study was considered to be 500 mg/kg/day for males and 50 mg/kg/day for females.

- **3 Month Oral (Gavage) Toxicity Study in the Rat (526803)**

The objective of this study was to determine the potential toxicity of AZD2281 (olaparib) when given by oral gavage once daily for 3 months to rats. The dose response for toxicity was explored and a no-observed-adverse-effect level (NOAEL) was determined. Plasma samples were analysed in order to assess exposure to the test compound and to verify absence of test compound in control animals.

Groups of 10 male and 10 female Wistar Hannover rats were dosed once daily with olaparib at dose levels of 0, 100, 250 and 1000 mg/kg/day (males) or 0, 25, 50 and 100 mg/kg/day (females) for at least 91 days. This study used suspensions of milled drug substance in 0.5% HPMC and 0.1% Tween 80.

Systemic exposure to olaparib was demonstrated at all dose levels. In males systemic exposure to olaparib increased generally dose-proportionally between the low and mid doses and less than proportionally between mid and high doses. In females, Cmax increased in a generally dose-proportional manner between the low and mid doses and less than proportionally between the mid and high doses, with AUC(0-t) increasing generally proportionally across the dose range. Following repeat daily dosing, systemic exposure was comparable to that on Day 1 across the dose range in females, although an

appreciable decrease in exposure in males was noted at Week 13. Where both sexes received a comparable dose, systemic exposure to olaparib was consistently greater in females than in males.

A summary of toxicokinetic data is provided in Table 3.

Table 3 Toxicokinetics in male and female rats following single and multiple daily doses of olaparib

Dose level (mg/kg/day)		C_{max} (µg/ml)				$AUC_{(0-t)}$ (µg.h/ml)			
		Day 1		Last day		Day 1		Last day	
Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
100	25	1.85	1.97	0.55	2.37	7.78	8.34	2.93	10.5
250	50	3.84	4.69	1.40	3.59	22.4	17.1	6.65	17.8
1000	100	7.73	6.43	1.72	3.77	62.6	25.9	15.9	30.7

Oral administration of olaparib at dose levels of up to 1000 mg/kg/day in males and 100 mg/kg/day in females was tolerated, with no compound-related deaths. Throughout the dosing period, bodyweight gain and food consumption were reduced in both sexes at all dose levels.

Haematological changes, including decreases in red blood cell parameters (red blood cell count, haemoglobin and haematocrit), leukocyte counts (lymphocytes, neutrophils, monocytes, eosinophils and/or basophils), and reticulocytes, were seen for males at 1000 mg/kg/day and for females at 50 or 100 mg/kg/day. In addition increases in mean corpuscular volume, mean corpuscular haemoglobin, red blood cell distribution width and platelet count were seen for females at 100 mg/kg/day. Plasma chemistry changes, including decreases in creatinine, cholesterol and total protein levels in males at 250 and/or 1000 mg/kg/day and triglycerides and total protein in females at dose levels up to 100 mg/kg/day. Glucose levels were higher in both males and females at all dose levels.

Oral administration of olaparib to rats for 3 months was associated with findings in lympho-haemopoietic organs and small intestine. There were dose-related lower group mean thymus weights in females at ≥ 25 mg/kg/day and in males at 1000 mg/kg/day.

Treatment-related histopathological findings were present in the bone marrow (decreased haematopoietic cellularity), lymphoid organs (lymphoid depletion: thymus, GALT, mesenteric lymph node), spleen/ liver (increased extramedullary haematopoiesis, females only), spleen (decreased incidence of extramedullary haemopoiesis, males, only) and/or small intestine (epithelial degeneration in duodenum, jejunum, ileum, males only) for males at 1000 mg/kg/day and/or females at 50 or 100 mg/kg/day. Regenerative erythropoiesis was seen in the liver, spleen, and femoral and sternal bone marrow of females at 100 mg/kg/day, which was considered to be secondary to the anaemia seen in these animals.

Based on the effects on bodyweight gain, a no effect dose level (NOEL) was not determined. However, based on haematology and pathology findings, the no-adverse-effect dose level (NOAEL) for this study was considered to be 25 mg/kg/day for females and 250 mg/kg/day for males.

Summary of the submitted repeat-dose toxicity studies

Species **Gender and number per group** **Study ID** **GLP**	**Method of Administration** **Duration** **Doses** **(mg/kg/day)**	**Major findings – NOAEL (mg/kg/day)**
Rats		
Rat/CRL:WI (HAN) 10M and 10F 8000589 Yes	Oral, by gavage (Suspensions of milled drug substance in 0.5% HPMC and 0.1% Tween 80) 3 months Males: 0, 100, 250, 500, 1000 Females: 0, 25, 50, 100, 250	1000 mg/kg/day (males)/250 mg/kg/day (females): tolerated, reductions in body weight gain at all dose levels. Hematology changes (red and white blood cells, reticulocytes, platelets) were seen for males at >500 mg/kg/ day and for females at all dose levels. Histopathological findings in the bone marrow (decreased hematopoietic cellularity), thymus (lymphoid depletion), spleen (red pulp atrophy) and mesenteric lymph node (increased sinusal histiocytosis) in both sexes, and the cecum (epithelial erosion) in males. NOAEL M -500 F - 50
Rat / CRL:WI (HAN) 10M and 10F 526803 Yes	Oral, by gavage (Suspensions of milled drug substance in 0.5% HPMC and 0.1% Tween 80) 3 months Males: 0, 100, 250, 1000 Females: 0, 25, 50, 100	<u>1000 mg/kg/day (male)/100 mg/kg/day (females):</u> well tolerated, reduction in bodyweight (all doses), haematology changes (red and white blood cells, reticulocytes, platelets) sometimes starting at 50 mg/kg/day (female). Histopathological findings: bone marrow (decreased haematopoietic cellularity), lymphoid organs (lymphoid depletion: thymus, GALT, mesenteric lymph node), spleen/ liver (increased extramedullary haematopoiesis) and/or small intestine (epithelial degeneration in duodenum, jejunum, ileum) NOAEL M -250 F - 25

Genotoxicity

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

Carcinogenicity

No additional carcinogenicity studies were conducted.

Reproduction toxicity

No additional fertility, early embryonic and embryo-fœtal development studies were conducted.

As seen previously in a female fertility study, rats were dosed until implantation. Although extended oestrus was observed in some animals, mating performance and pregnancy rate was not affected. However, there was a slight reduction in embryofoetal survival. In previous rat embryofoetal development studies, and at dose levels that did not induce significant maternal toxicity, olaparib caused reduced embryofoetal survival, reduced foetal weight and foetal developmental abnormalities, including major eye malformations (e.g. anophthalmia, microphthalmia), vertebral/rib malformation, and visceral and skeletal abnormalities.

Other toxicity studies

No juvenile and prenatal or postnatal development studies were conducted nor required

Olaparib will be administered via the same oral route so no local tolerance studies are required.

2.3.5. Ecotoxicity / environmental risk assessment

This extension is not expected to change the usage of the product in such a way that a new environmental risk assessment is necessary. Since the environmental risk assessment was previously evaluated on the substance and not on the pharmaceutical form, no further studies were required.

2.3.6. Discussion on non-clinical aspects

Olaparib was first indicated as monotherapy for deleterious or suspected deleterious germline BRCA-mutated advanced ovarian cancer in patients who have been treated with ≥3 prior lines of chemotherapy. PARP inhibitor sensitivity is broader than BRCA and HRR deficiencies and may extend to non-HRR DNA damage response deficiencies and pathways as well (Postel-Vinay et al 2013, Cerrato et al, 2016, Murata et al, 2016, Lu et al 2017). Moreover, the extension to high-grade serous ovarian cancer is plausible because 51% of these cancers have compromised HRR and also that 5–7% of ovarian cancer cases will have somatic HRD (Cooke et al. 2011; Fray et al. 2017).

However, from a pharmacological perspective, high levels of continuous dosing of olaparib are still best in a maintenance setting and while intermittent breaks or reductions in dose are still capable of keeping the regressed tumours under control as long as the initial treatment resulted in little or no detectable (<2% in this tumour model) residual disease, there is an increase in likelihood of tumour progression on treatment with lower or intermittent dosing.

To build a preclinical PKPD/efficacy relationship model, an olaparib sensitive PDX model (HBCx-10) has been used. The data obtained suggest that for efficacy in the HBCx-10 preclinical model either the IC50 of PARP-1 (56.5 nM for tumour PAR) needs to be exceeded for more than 13 hours or the IC90 (382 nM for tumour PAR) for more than 6 hours.

Mechanistic modelling has been performed of the PKPD relationship and the binding kinetics of PARP-1, NAD, DNA single strand breaks (SSBs) and a PARP inhibitor (PARPi). This model has been used to gain insight into the relationship between tumour pharmacodynamics as measured by PAR concentration reduction and the resulting efficacy as measured by tumour growth inhibition in the HBCx-10 patient derived xenograft model. The results of the mechanistic model simulations suggest that as expected, there is an inverse relationship between PAR and SSB. However, importantly, there are only significant increases in SSB numbers when PAR is reduced by more than 90%. This model predicts that only by maintaining significant (>90%) inhibition of PAR levels can a large increase in SSB be generated that would translate into tumour cell death, for example those lacking homologous recombination repair (HRR) functionality.

Furthermore, the clinical activity of olaparib appears to be associated with doses that maintain the unbound steady state trough concentration above the IC90 for PARP inhibition. In previously published clinical trials with olaparib in breast and ovarian cancer patients carrying germ line BRCA mutations (Tutt et al, 2010; Audeh et al, 2010), an olaparib capsule dose of 400 mg bd was shown to be more clinically effective than a 100 mg bd capsule dose. The overlay of PK data from multiple clinical capsule doses of olaparib, where outcome data are available, support the idea that consistent inhibition of the target to achieve >90% inhibition of PAR in tumours is likely to be required for single agent monotherapy in sensitive tumour backgrounds. For the tablet formulation it can be seen that the 300 mg bd dose provides coverage well above this preclinical IC90 value.

Additional work using the HBCx-10 BRCAm PDX model provides preclinical evidence for olaparib maintenance treatment following initial tumour shrinkage (this time after 100 mg/kg continuous dosing for 35 days). The data demonstrate that in a maintenance setting, lower doses of continuous treatment (50 mg/kg od) dosing as well as high intermittent (100 mg/kg od1 week on/ 1 week off) dosing can maintain tumour regression if continued day 35 day. If tumours are left to progress after cessation of olaparib dosing at day 35, then high continuous dosing (100 mg/kg od) has the best chance to regress the tumours a second time.

The full non-clinical safety profile of olaparib was previously assessed at time of the initial marketing authorisation application. Additional non-pivotal dose setting toxicology studies of up to 3 months duration have been conducted in rats to support dose selection for future carcinogenicity studies in this species, to support earlier disease indications. Whilst not required to support this current advanced cancer indication, data from these studies were provided by the applicant because the administered doses and exposures in these studies were higher than those achieved on the pivotal rat repeat dose studies.

Systemic exposure to olaparib was demonstrated at all dose levels. In males systemic exposure to olaparib increased generally dose-proportionally between the low and mid doses and less than proportionally between mid and high doses. In females, Cmax increased in a generally dose-proportional manner between the low and mid doses and less than proportionally between the mid and high doses, with $AUC_{(0-t)}$ increasing generally proportionally across the dose range. Following repeat daily dosing, systemic exposure was comparable to that on Day 1 across the dose range in females, although an appreciable decrease in exposure in males was noted at Week 13. Where both sexes received a comparable dose, systemic exposure to olaparib was consistently greater in females than in males.

Olaparib toxicokinetics were also explored in male and female rats when the agent was formulated in 0.5% hydroxypropyl methylcellulose in 0.1% Tween 80 in water. These data are exemplified by studies 8000589 (28 days) and 526803 (13 weeks) (Table 7). In both studies, female rats were dosed at lower levels than male rats reflecting previous data that demonstrated higher clearance in male rats.

In both studies, on day 1 exposure (C_{max} and $AUC_{(0-t)}$) in male rats increased less than in proportion to dose over the dose range. Similar observations were made on the last day of dosing but exposures were markedly lower after multiple doses, which suggested either induction of clearance pathways or decrease absorption had occurred. On day 1, female animals also exhibited a less than proportional increase in exposure but this was much less pronounced than in male rats. There was no consistent evidence of decreased exposure in female rats after multiple doses.

Where male and female rats received the same dose, the exposure in male animals was much lower on the first day of dosing in both studies. This effect was more obvious on the last day of dosing.

No new target organs of toxicity were identified. These data confirm that the principal target organ for toxicity is the bone marrow, with associated changes in peripheral haematology parameters. Gastrointestinal toxicity has been observed in the new repeat-dose toxicity studies performed in rats (1 month non-GLP & 3 months GLP). Olaparib related histopathological findings were observed within the intestinal tract in male animals following 4 or 13 weeks daily oral dosing with the compound formulated in 0.5% hydroxylpropyl methyl cellulose and 0.1% Tween 80. Reversibility was not assessed in these studies. Olaparib is recognized as having an effect on bone marrow and peripheral blood, the mechanism of which may be related to the pharmacology and mechanism of action of olaparib as an inhibitor of PARP-1 and PARP-2. PARP-2 appears to play a key role in the survival of haematopoietic stem/progenitor cells under steady-state conditions and in response to stress (Farrés 2013). The degenerative changes observed within the intestines were characterised by the presence of scattered, shrunken, pyknotic nuclear cell debris located within the base of the intestinal crypts. This pattern of change is considered consistent with an effect on the proliferative tissue compartment and it is not unreasonable to assume that PARP-2 may similarly affect survival of intestinal stem/progenitor cells in this highly proliferative tissue. This finding was not accompanied by any inflammatory changes or concomitant downstream structural loss of integrity (e.g. villous atrophy). Given the minimal severity of the changes and the breadth of experience with other agents that induce similar degenerative changes in the crypt epithelium, the weight of evidence suggests that full recovery would occur upon cessation of dosing. These findings are now reflected in section 5.3 of the SmPC of both Lynparza capsule and tablet.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical data submitted are considered appropriate and supportive of the potential efficacy of the clinical dose for the 300mg tablet formulation and of the changes introduced to section 5.3 of the SmPC of capsule formulation.

2.4. Clinical aspects

2.4.1. Introduction

This application concerns the introduction of new 150 and 100 mg tablets with a claimed indication: “monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy”.

The claimed posology is reduced to 300 mg b.i.d comparatively to approved dose for capsules: 400 mg b.i.d in the BRCA mutated patients.

In addition, the MAH has applied for a modification of the product information of the capsule formulation in line with the proposed product information for the tablets.

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.

- Tabular overview of clinical studies

The claimed indication for olaparib is, as monotherapy, for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian cancer (including fallopian tube or primary peritoneal) who are in response (complete response or partial response) to platinum-based chemotherapy.

The indication claimed by this extension concerns olaparib tablet. SOLO2 study, which is limited to germline BRCA mutated patients, is the only clinical trial provided in support of this application with this formulation.

Study 19 was supportive for the initial Olaparib capsule application. Updated results are provided here to support extension in non BRCA mutated population. Additional PK studies are provided to support extrapolation of capsule data to tablet form.

Table 2 Summary of olaparib efficacy and safety studies in maintenance treatment of PSR ovarian cancer

Study number	Design	Patient population	Number of patients	Olaparib dose (maintenance treatment) and formulation	Efficacy endpoints	Nb of *BRCA*m ovarian patients	Study status
D0816C00002 (SOLO2)	Phase III double-blind, randomised, placebo-controlled, multicentre study	Advanced platinum-sensitive, *BRCA* mutated, high-grade serous or high-grade endometrioid ovarian cancer patients who had received 2 or more previous platinum-containing regimens	295 total (196 olaparib; 99 placebo)	300 mg bd (oral) tablet formulation	Primary: PFS Secondary: OS	295	In survival follow-up
D0810C00019 (Study 19)	Phase II double-blind, randomised, placebo-controlled, multicentre study	Advanced platinum-sensitive high-grade serous ovarian cancer patients who had received 2 or more previous platinum-containing regimens	265 total (136 olaparib; 129 placebo)	400 mg bd (oral) capsule formulation	Primary: PFS Secondary: OS	136	Completed

2.4.2. Pharmacokinetics

The olaparib clinical pharmacology programme was designed to characterise the PK and investigate the key factors that could potentially contribute to variability in exposure to olaparib in the target ovarian cancer population. The PK and PD of olaparib following dosing with the tablet formulation have been characterised in patients with advanced solid tumours and in the proposed target patient population.

The tablet formulation has been investigated and characterized in numerous formal PK studies (Studies 01, 04, 05, 06, 07, 08 and 024). These studies were part of the initial submission and have been assessed in the context of the initial application of the capsules. In general, appropriate and validated bioanalytical methods were used to determine concentrations of olaparib.

The pivotal phase 3 Efficacy/Safety study (SOLO2) submitted as a support to this extension application investigated only the tablet formulation. In this study, sparse samples were collected in a sub-group of patients in order to characterize the PKs of the tablets and identify the covariates influencing it in the target population using a population PK approach (PPK). In addition, the comparability of systemic exposure to olaparib with both modalities of treatment (capsules 400 mg b.i.d versus Tablets 300 mg bid) was reviewed in order to elicit the findings of the phase 2 study to the claimed tablets.

Absorption

Comparative systemic exposure: Tablets versus capsules

Relevant data could be obtained from formal study 024 already reviewed but also from studies D0810C00001 and D081BC00001 conducted in Japanese patients (Study D0810C00001 investigated olaparib PK of capsules while study D081BC00001 investigated the tablets). For clarity purpose the findings of these studies are compiled and presented below in a tabulated format:

Relative Bioavailability Tablet versus capsule formulation Study 024		
Parameters	Tablet 300 mg/ Capsule 400 mg	Tablet 400 mg/ Capsule 400 mg
Day 1: First dose		
AUC12 (µg.h/mL)	1.92	2.65
Cmax (µg/mL)	1.82	2.15
Day 29: Steady-State		
AUC0-12 (µg.h/mL)	1.41	1.75
Cmax (µg/mL)	1.47	1.89

Relative Bioavailability Tablet versus capsule formulation Studies D0810C00001 & D081BC00001		
Parameters	Tablet 300 mg/ Capsule 400 mg	Tablet 400 mg/ Capsule 400 mg
Day 1: First dose		
AUC12 (µg.h/mL)	1.27	---
Cmax (µg/mL)	1.61	----
Day 1: Steady-State		
AUC0-12 (µg.h/mL)	1.49	---
Cmax (µg/mL)	1.43	----

Following oral administration of olaparib via the tablet formulation (2 x 150 mg), absorption is rapid with median peak plasma concentrations typically achieved 1.5 hours after dosing.

Food effect

Table 3: Relative bioavailability of olaparib 300 mg tablet dose in fed and fasted states

Comparison	Parameter	Geometric least square mean ratio	90% CI
High fat meal vs fasted state	C_{max} (µg/mL)	0.79	0.72, 0.86
	$AUC_{(0-t)}$ (µg.h/mL)	1.08	1.01, 1.16
	AUC (µg.h/mL)	1.08	1.01, 1.16

AUC area under the plasma concentration-time curve from zero to infinity; $AUC_{(0-t)}$ area under the plasma concentration-time curve from time zero to time t (the last measurable concentration); CI confidence interval; C_{max} maximum plasma concentration.
Data source: Table 15 of the Study 04 CSR Module 5.3.1.1.

Co-administration with food slowed the rate (t_{max} delayed by 2.5 hours and C_{max} reduced by approximately 21%) but did not significantly affect the extent of absorption of olaparib (AUC increased 8%). Consequently, Lynparza may be taken without regard to food.

Distribution

As requested in the original procedure, a new study, Study BS001884-14, has been carried out to determine the in vitro binding of olaparib metabolites (AZ14102299, AZ14102296 and AZ14102567) to plasma proteins in the mouse and human.

The objective of this study was to determine the plasma protein binding of olaparib metabolites (AZ14102299, AZ14102296 and AZ14102567) in the male mouse and mixed human plasma. The animal species chosen reflects the species to be used in the pharmacological and safety assessment of AZ14102299, AZ14102296 and AZ14102567 during the pharmaceutical development of the compound.

The *in vitro* binding of AZ14102299, AZ14102296 and AZ14102567 to plasma protein from the male mouse and mixed human has been measured over a concentration range of 0.1 to 100 µmol/L AZ14102299, AZ14102296 and AZ14102567.

Table 4: Plasma protein binding results (% Free) of AZ14102299 (mean ± SD) following in vitro dialysis of mouse and human plasma at 37°C for 18 hours at 0.1 to 100 µmol/L AZ14102299 (n=3)

AZ14102299 concentration (µmol/L)	Free %	
	Mouse	Human
0.1	44.0 ± 1.74	6.82 ± 0.628
1	42.3 ± 0.865	6.74 ± 0.270
10	40.0 ± 1.14	10.8 ± 0.299
100	45.0 ± 0.467	47.1 ± 1.14

Table 5: Plasma protein binding results (% Free) of AZ14102296 (mean ± SD) following in vitro dialysis of mouse and human plasma at 37°C for 18 hours at 0.1 to 100 µmol/L AZ14102296 (n=3)

AZ14102296 concentration (µmol/L)	Free %	
	Mouse	Human
0.1	60.1 ± 0.501	56.8 ± 4.48
1	58.2 ± 1.68	55.0 ± 1.23
10	55.1 ± 1.41	57.4 ± 0.321
100	57.1 ± 1.77	60.3 ± 2.83

Table 6: Plasma protein binding results (% Free) of AZ14102567 (mean ± SD) following in vitro dialysis of mouse and human plasma at 37°C for 18 hours at 0.1 to 100 µmol/L AZ14102567 (n=3)

AZ14102567 concentration (µmol/L)	Free %	
	Mouse	Human
0.1	24.6 ± 1.11	11.6 ± 0.295
1	24.0 ± 1.08	12.0 ± 0.174
10	28.7 ± 1.76	14.4 ± 0.898
100	31.5 ± 1.17	23.4 ± 0.652

For AZ14102299, the percentage unbound was not concentration dependent in the mouse over the range 0. 1 to 100 µmol/L, and the percentage unbound was ranging from 44.0 % at 0.1 µmol/L to 45.0 % at 100 µmol/L. There was a trend for higher percentage unbound at higher AZ14102299 concentrations in the human, and the percentage unbound was concentration dependent ranging from 6.82 % at 0.1 µmol/L to 47.1 % at 100 µmol/L.

For AZ14102296, the percentage unbound was not concentration dependent in the mouse and human over the range 0. 1 to 100 µmol/L. The percentage unbound was ranging from 60.1 % at 0.1 µmol/L to 57.1 % at 100 µmol/L in the mouse and ranging from 56.8 % at 0.1 µmol/L to 60.3 % at 100 µmol/L in the human.

For AZ14102567, there was a trend for higher percentage unbound at higher AZ14102567 concentrations in the mouse and human. The percentage unbound was concentration dependent ranging from 24.6 % at 0.1 µmol/L to 31.5 % at 100 µmol/L in the mouse and ranging from 11.6 % at 0.1 µmol/L to 23.4 % at 100 µmol/L in the human

Metabolism and elimination

The metabolism of olaparib is extensive and the data from Studies KMX009 and KMX041 submitted in the original dossier indicated that the metabolism of olaparib was predominantly via CYP3A4.

The 3 main metabolites were M12 (ring-open hydroxyl-cyclopropyl: 12.3%), M15 (monooxygenated: 9.4%) and M18 (dehydrogenated piperazine: 7.9%).

The following new studies were conducted to further characterise these metabolites:

Study BE000726-40

The objectives of this study were to structurally characterise M12 and M18 and confirm the identity of M12, M15 and M18 using authentic reference standards where possible. In study BE001071-20, M15 could be unambiguously identified as the 4- fluorophenol (hydroxy)methyl metabolite, whilst M18 was only detected as the chemical decomposition product, the dehydrogenated piperizine, and M12 could only be confirmed as a+H2O metabolite having the aromatic signals intact.

This study has enabled the structural characterisation of Codexis generated metabolite M12 as the ring open piperazin-3-ol. M18 could not be fully characterized by 1H NMR spectroscopy or 2D 1H-13C NMR experiments, however in combination with mass spectrometry and semicarbazide trapping it was possible to infer the structure to be a monooxygeneated piperazine (piperazin-ol) metabolite in either the 2 or 3 position. It is proposed that M12 was derived from the corresponding Piperazin-ol. Further analysis the H-ADME plasma samples with the synthetic standards of M12 (M12a and M12b) and M15 by co-chromatography and MS confirmed that M12b was the M12 metabolite reported in the H-ADME study (KMX032) as the ring open piperazin-3-ol, the M12a metabolite/isomer as the ring open piperazin-2-ol and M15 as the 4-fluorophenol (hydroxy)methyl metabolite.

Study BE001071-20

The objectives of this study were to characterise the three major metabolites (M12, M15 and M18) of AZD2281 in human plasma from the human ADME metabolite identification study (KMX032) using UHPLC-UV-MS mass

spectrometry and NMR. The samples used in this study were from the single oral dose to man study (D0816C00006). Cross-subject pooled urine and plasma samples were analysed spanning 0-24 h. UHPLC-UV-MS was used for the detection and identification of M12, M15 and M18 from study D0816C00006. LC fractionation of these metabolites followed by 1H NMR analysis was used to define their structures.

The three major metabolites identified from study D0816C00006, M12, M15 and M18 were isolated using fraction collection and analysed by 1H NMR spectroscopy. These metabolites were identified as M12 (a +H2O metabolite, structure as yet unidentified by 1H NMR spectroscopy), M15 [4-fluorophenol(hydroxy)methyl] and M18 (+O metabolite) that degraded to a single -H2O product prior to NMR analysis.

Pharmacokinetics in target population

The PK of olaparib following dosing with the tablet formulation have been characterised in patients with advanced solid tumours and in the proposed target patient population. In addition to the information collected in phase I studies, PK data are available from study SOLO2 and a population PK analysis has been performed:

Study D0816C00002 (SOLO 2)

This study is a Phase III Randomised, Double Blind, Placebo Controlled, Multicentre Study of Olaparib Maintenance Monotherapy in Platinum Sensitive Relapsed BRCA Mutated Ovarian Cancer Patients who are in Complete or Partial Response Following Platinum based Chemotherapy

The PK analysis set (93 patients) comprised all patients who received study treatment as per protocol, did not violate or deviate from the protocol in ways that would significantly affect the PK analyses and had valid PK data. The majority of the patients who were excluded from the PK analysis set were not included due to having no analysable PK data (no PK sample was collected).

The plasma concentration-time data were analysed by nonlinear mixed effects modelling using NONMEM software in order to characterise the PK and exposure-response of olaparib for relevant efficacy and safety endpoints (see population PK analysis below).

Population PK analysis

Two separate reports were submitted for tablet formulation in addition to the report submitted for capsule formulation, reflecting the sequential approach taken by the applicant during the modelling exercise.

A. Pooled population PKPD analysis of olaparib tablet (olaparib-MS-02)

The objectives of the analysis were to: 1) develop a population PK model that could describe the time course of olaparib in cancer patients including exploring the impact of covariates on relevant PK parameters, and further, to generate individual PK parameter estimates for each individual included in the analysis; and 2) develop an exposure/safety response model(s) if they are supported by exploratory analyses.

A population PK model was developed using plasma concentration data obtained after single and multiple doses of olaparib tablet (ranging from 100 to 450 mg) in 5 Phase I studies in patients with solid tumours (D081BC00001[01], D0816C00004 [04], D0816C00007 [07], D0816C00008 [08], D0816C00024 [24]). In total, 7020 observations from a total of 296 patients were included in the population PK model development. Of

296 patients, the majority were female (85%), and Caucasian (90%) or Asian (7.8%). The mean (range) of age, and body weight were 57 (19 to 85) years and 72 (34 to 147) kg, respectively.

Olaparib tablet plasma concentration-time data were analysed using a nonlinear mixed effects modelling approach. After identification of the base model, covariates were evaluated using a stepwise covariate model (SCM) search process The final population PK structure model was described by a linear 2- compartment model with sequential zero- and first-order absorption rates (Ka) and first-order elimination. The olaparib elimination was described by 2 distinct clearances (CL) between single and multiple dose administrations. The predicted population mean estimates of CL are 6.2 L/h and 5.0 L/h, for single and multiple dose administrations, respectively. The population mean estimates for volume of distribution of the central compartment (V2), intercompartment clearance (Q), volume of distribution of the peripheral compartment (V3), duration of the zero-order absorption (D1), and Ka were 4.4 L, 1.49 L/h, 23.6 L, 0.432 hours and 0.211 1/h respectively. The estimated inter-individual variability (IIV) (coefficient of variation, CV%) for CL at steady-state, V2, Q, V3, D1 and Ka were 45%, 70%,57%, 73%, 88%, and 27%, respectively. Covariates including age, body weight, gender, race, tablet strength, hepatic and renal function markers were evaluated in the population analysis, and the only significant covariate impacting olaparib PK in the final model was the olaparib tablet strength, which affected Ka.

Final model parameters, goodness of fit plots and visual predictive check plots are displayed below.

Table 7: parameters estimates for the final model and bootstrap results

Table 8 Parameter estimates for the final model and bootstrap results

		Final model			Bootstrap		
Parameter	**Description**	**Estimate**	**RSE (%)**	**Shrinkage (%)**	**Median**	**2.5%**	**97.5%**
θ3	Clearance for single dose, CL (L/h)	6.19	3.89		6.19	5.68	6.69
θ4	Volume of distribution of central compartment for single dose, V_2 (L)	4.37	5.40		4.35	3.85	5.05
θ5	Volume of distribution of peripheral compartment, V_3 (L)	23.6	5.57		23.5	20.7	27.0
θ6	Inter-compartmental clearance, Q (L/h)	1.49	6.45		1.49 1	1.29	1.73
θ7	Absorption rate constant, Ka (h^{-1})	0.211	4.48		0.211	0.192	0.234
θ8	Duration of zero-order absorption, D_1 (h)	0.432	4.90		0.435	0.381	0.479

Table 8 Parameter estimates for the final model and bootstrap results

		Final model			Bootstrap		
Parameter	**Description**	**Estimate**	**RSE (%)**	**Shrinkage (%)**	**Median**	**2.5%**	**97.5%**
θ9	Clearance for repeat doses, CL (L/h)	5.04	2.81		5.04	4.76	5.34
θ10	Strength (100 mg) on Ka, Ka*(1+θ10)	0.743	11.4		0.743	0.597	0.916
θ11	Strength (100, 200, 300, 125, 225 mg) on Ka, Ka*(1+θ11)	0.269	21.6		0.266	0.155	0.400
Inter-individual variability							
ω1	IIV in CL for single dose (CV%)	66.2	9.81	4.84	66.0	59.6	72.4
ω(1,2)	Correlation IIV CL and IIV V2	0.418	22.8[a]		0.437	0.316	0.529
ω2	IIV in V_2 for single dose (CV%)	70.1	13.6	20.4	69.6	58.9	79.9
ω3	IIV in V_3 (CV%)	73.3	16.4	21.7	73.0	61.7	87.0
ω(3,4)	Correlation IIV Q and IIV V_3	0.796	16.8[a]		0.804	0.769	0.808
ω4	IIV in Q (CV%)	56.5	16.4	27.2	56.0	45.9	66.6
ω5	IIV in Ka (CV%)	26.6	19.6	19.1	26.4	20.3	31.5
ω6	IIV in D_1 (CV%)	87.7	12.1	18.8	87.1	75.7	100.0
ω7	IIV in CL for repeat dose (CV%)	44.9	8.68	10.6	44.8	41.2	48.2
Residual variability							
θ1	Proportional error	0.313	2.32	9.88	0.313	0.299	0.328
θ2	Additive error (μg/mL)	0.000508	16.0	9.88	0.00049	0.000	0.0010

[a] The RSE (%) for correlation parameters were based on the estimates of the covariance

θ Typical parameter estimate; ω Omega*100=IIV in CV%; CL Clearance; CV% Coefficient of variation; D_1 Duration of zero-order absorption; IIV Inter-individual variability; IOV Inter-occasion variability; OFV Objective function value; Q Inter-compartmental clearance; RSE Relative standard error from NONMEM output.

Data source: \\usuwphdevcanda1\PM_1\Olaparib 2\hxu\popPK\model\run303\run303.lst

Figure 7 **Diagnostic plots for the final olaparib PK model**

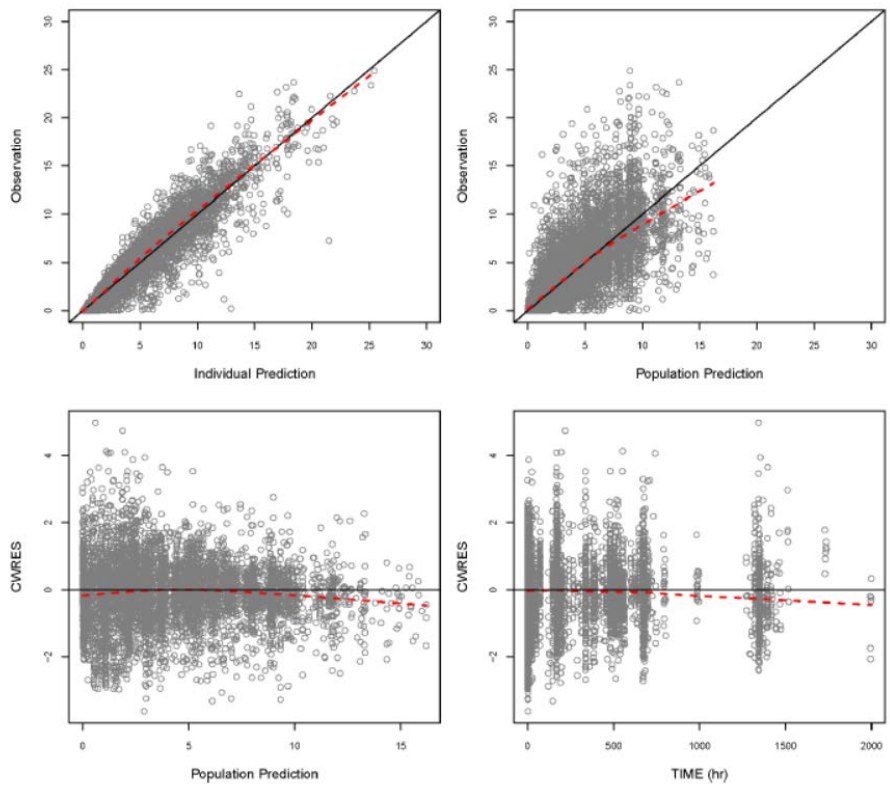


Figure 1: Diagnostic plots for the final olaparib PK model

Figure 8 **Visual predictive check for the final olaparib PK model**

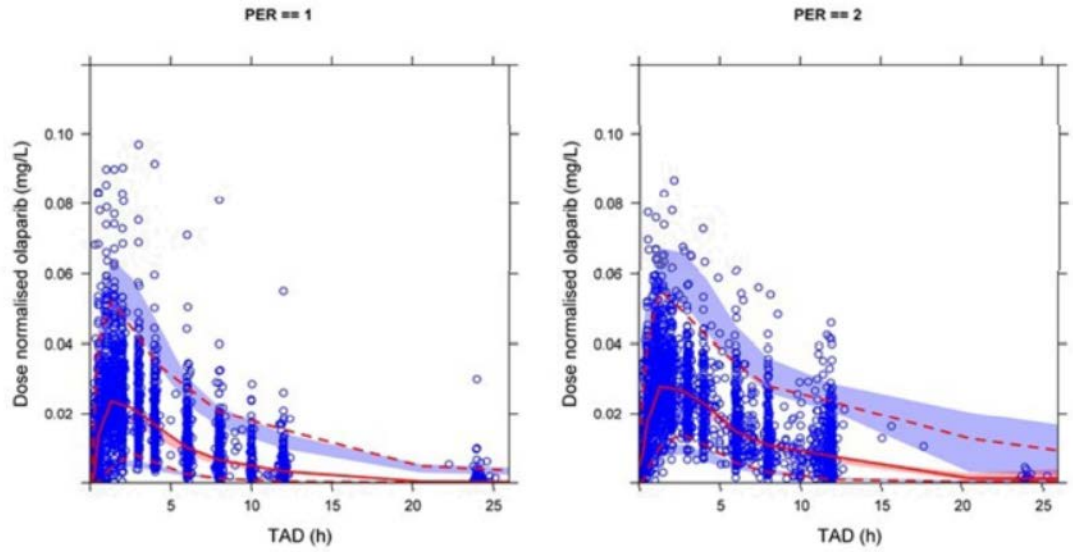


Figure 2: Visual predictive check for the final olaparib PK model

Olaparib Ka increased by 74% with a 100 mg strength tablet compared to a 150 mg strength tablet. However, the model predicted olaparib area under the plasma concentration-time curve at steady state (AUCss) was similar, and the maximum plasma concentration at steady state (Cmax,ss) was slightly higher for the 300 mg dose twice daily (bd) given as 3x100 mg tablets compared with 2x150 mg tablets bd; the geometric mean ratios of 3x300 mg tablet strength over 2x150 mg tablet strength were 0.98 and 1.28 for AUCss and Cmax,ss, respectively. The primary tablet strength used in clinical studies was 150 mg, while 100 mg tablet strength was available for dose reduction.

The final population PK model was used to obtain individual empirical Bayes estimates of PK parameters and exposure estimates of area under the plasma concentration-time curve from zero to infinity after single dose administration (AUC) or AUCss (referred as AUC for both subsequently), maximum plasma concentration after single olaparib dose administration (Cmax) or Cmax,ss (referred as Cmax for both subsequently), and minimum plasma concentration at state-state (Cmin,ss) for patients included in the final dataset for the population PK analysis. The estimated geometric mean AUCss, Cmax,ss and Cmin,ss for the proposed therapeutic dose, 300 mg dose bd were 59.7 (50 CV%) µg.h/mL, 9.1 (39 CV%) µg/mL, and 1.95 (87 CV%) µg/mL, respectively.

The relationships between exposure and adverse events (AEs) were analysed by graphical exploratory analysis first and subsequently modelled if an apparent relationship was supported by the exploratory analysis. The exposure and response analysis was focused on the assessment of the impact of olaparib tablet exposure on typical safety events that occurred within the longest time period of olaparib treatment observed in the data (85 days). The safety analyses used data from the patient Studies 01, 04, 07 and 08. A total of 151 patients were included in the safety analysis dataset. Most patients (82%) were treated with 300 mg, bd, during the multiple dosing period. There was no evidence to suggest that measures of exposure were predictive of anaemia, nausea, vomiting, fatigue, dyspepsia, upper abdominal pain, dysgeusia, constipation, headache, diarrhoea, neutrophil and platelet count, or decreased appetite. A trend was observed for decreased haemoglobin with increasing olaparib exposure. Therefore, exposure response modelling was conducted for AUC and haemoglobin measurements to quantify the potential relationship. An indirect response model with olaparib AUC inhibiting the haemoglobin synthesis rate in a linear relationship adequately described the relationship between olaparib exposure in AUC and haemoglobin response. The model estimated a mean slope to olaparib AUC of 0.002 (g/dL)/(µg.h/mL). For a baseline haemoglobin concentration of 10 g/dL, the predicted mean haemoglobin concentrations on Day 85 were 8.7, 8.4 and 8 g/dL, respectively, for the predicted geometric mean AUCss (59.7 µg.h/mL) after olaparib 300 mg bd (GMAUCss,300mgbd), 1.5x GMAUCss,300mgbd, and 2x GMAUCss,300mgbd. For a baseline haemoglobin concentration of 14 g/dL, the predictions were 12.3, 11.6 and 10.8 g/dL, respectively.

B. Population analysis of SOLO2 (Olaparib-MS-03)

This report describes the data, methods and results for the analysis of olaparib population pharmacokinetics (PopPK), exposure measured as average concentration during a dosing interval (Cav) or area under the concentration vs. time curve (AUC), maximum concentration (Cmax) and minimum concentration (Cmin), exploratory analysis or simulation for safety and efficacy response to olaparib exposure for the SOLO2 study.

Variations of these metrics were calculated to represent patients' overall exposure given their actual dosing history and the multiple dose nature of the study (e.g. average cumulative which took the average of the metrics over time for each patient, and a daily version which took the average within each day considering olaparib's twice-daily dosing regimen). The objectives of this analysis were:

- To evaluate predictability of the previously-developed olaparib PopPK model to olaparib pharmacokinetics (PK) from the SOLO2 study, and to develop a PopPK model for olaparib for study SOLO2 if needed.

- To obtain individual empirical Bayes estimates (EBE) of olaparib compartment PK parameters and exposure measured by Cav and AUC (both daily and average cumulative throughout treatment); Cmax; and Cmin in SOLO2 study for subjects with plasma concentrations available.

- To explore and model (if feasible) the relationship between olaparib plasma exposure (as represented by a metric such as Cav) and selected efficacy and safety variables.

When applying the previously developed Phase I Tablet Analysis PopPK model with all the parameters fixed, to SOLO2 data the model showed an overall over-prediction of the data. Hence, the previously developed model was refined and most parameters were re-estimated. The random effects model was refined to include inter individual variability (IIV) on CL/F, apparent central volume of distribution (Vc/F) and duration of zero order absorption (D1) only and the additive residual variability was removed. Due to only one PK sample per patient on Day 1 the single dose CL/F was restrained to the ratio of single dose to multiple dose CL/F from the previous model. In addition, the e
effect of tablet strength on absorption rate constant (ka) for 100 mg and the combination of 100 mg and 150 mg tablet was fixed to the value estimated from the previous model. Of the primary covariates including WT, age, race (white vs Asian), creatinine clearance (CLcr), albumin, and hepatic impairment based on the NCI criteria (HINC) none were found to be statistically significant. The population mean estimates for multiple dose CL/F, Vc/F and ka for the 150 mg tablet were 7.40 L/h (relative standard error (RSE): 4.21 %), 7.92 L (RSE: 14.6 %) and 3.22 h□1 (RSE: 20.6 %), respectively. IIV for CL/F, Vc/F and D1 were estimated to 36.5 coefficient of variation (CV)% (RSE: 17.6 %), 39.2 CV% (RSE: 38.5 %) and 84.1 CV% (RSE: 37.1 %), respectively.

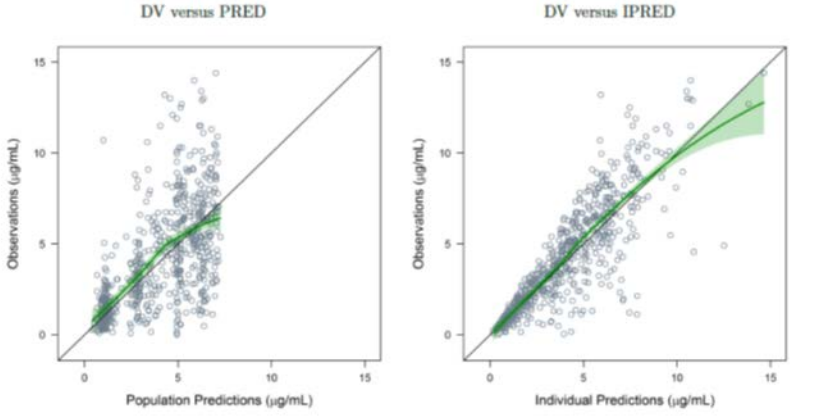
Final model parameters, goodness of fit plots and visual predictive check plots are displayed below.

Table 8: parameters estimates of the final olaparib POPPK model.

Table 6: Parameter Estimates of the Final Olaparib PopPK Model

Parameter	Alias	Estimate	Relative SE (%)	95% CI
θ_1	Proportional residual variability	0.349	4.3	(0.32 - 0.379)
θ_3	CL/F single dose ratio	1.23	.....	NC
θ_4	V_c/F (L)	7.92	14.6	(5.65 - 10.2)
θ_5	V_p/F (L)	34.5	33.3	(12 - 56.9)
θ_6	k_a 150 mg (h^{-1})	3.22	20.6	(1.92 - 4.53)
θ_7	Q/F ($L{\cdot}h^{-1}$)	0.350	10	(0.282 - 0.419)
θ_8	D1 (h)	0.527	13.6	(0.386 - 0.668)
θ_9	CL/F multiple dose ($L{\cdot}h^{-1}$)	7.40	4.2	(6.79 - 8.01)
θ_{10}	Dose strength (100 mg) on k_a, $k_a*(1+\theta_{10})$	0.743	.....	NC
θ_{11}	Dose strength (Other) on k_a, $k_a*(1+\theta_{11})$	0.269	.....	NC
$\omega_{1.1}$	$\omega^2_{CL/F}$	0.134	17.6	(0.0874 - 0.18)
$\omega_{2.2}$	$\omega^2_{Vc/F}$	0.154	38.5	(0.0376 - 0.27)
$\omega_{6.6}$	ω^2_{D1}	0.707	37.1	(0.193 - 1.22)

Parameter values for the final PopPK model. NC: Not Calculated. k_a: absorption rate. CL/F: Apparent systemic clearance. V_c/F: Apparent volume of distribution for central compartment . V_p/F: Apparent volume of distribution for peripheral compartment. Q/F: Apparent intercompartment clearance. ω^2_X: Variance of the IIV of parameter X, IIV is derived from variance according to $\sqrt{\omega^2_X} \cdot 100$.



Green line is a simple fit of the local data (loess smooth) and green area is its 95% CI. These are used to help analysts see if there are undesired trends in the data.

Figure 3: olaparib observations (DV) versus population (PRED) and individual (IPRED) predictions – Final olaparib POPPK model

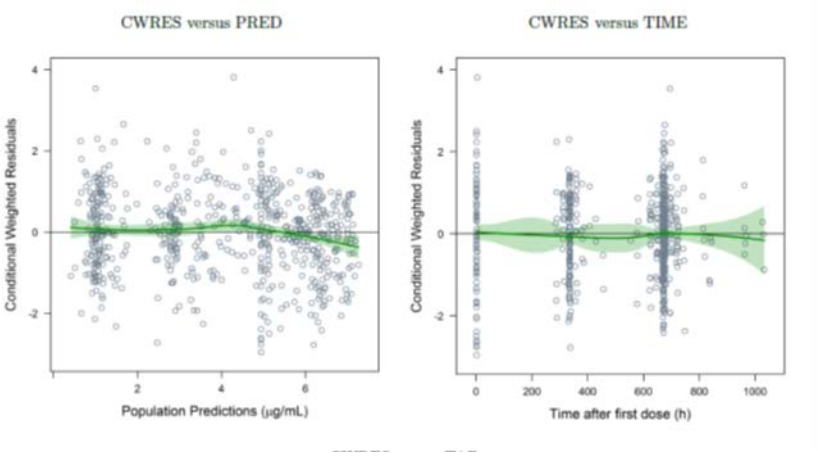


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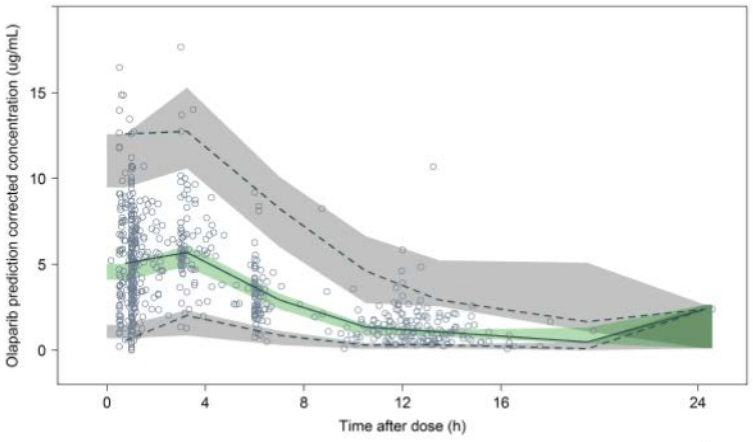
Figure 4: Conditional Weighted residuals (CWRES) versus predictions (PRED), time after first dose (TIME) and time after dose (TAD) – final olaparib POPPK model



Circles: Observations, **Solid Black Line**: Median of the observed olaparib concentrations, **Dashed Lines**: 2.5^{th} and 97.5^{th} percentiles of the observed olaparib concentrations, **Shaded Area**: The shaded areas indicate the 95% CI around the prediction-corrected median (green area), and 2.5^{th} and 97.5^{th} percentiles (grey areas). All observations and predictions are adjusted using prediction correction as described in Bergstrand et al.[2].

Figure 5: Visual predictive check – final olaparib PoPK model

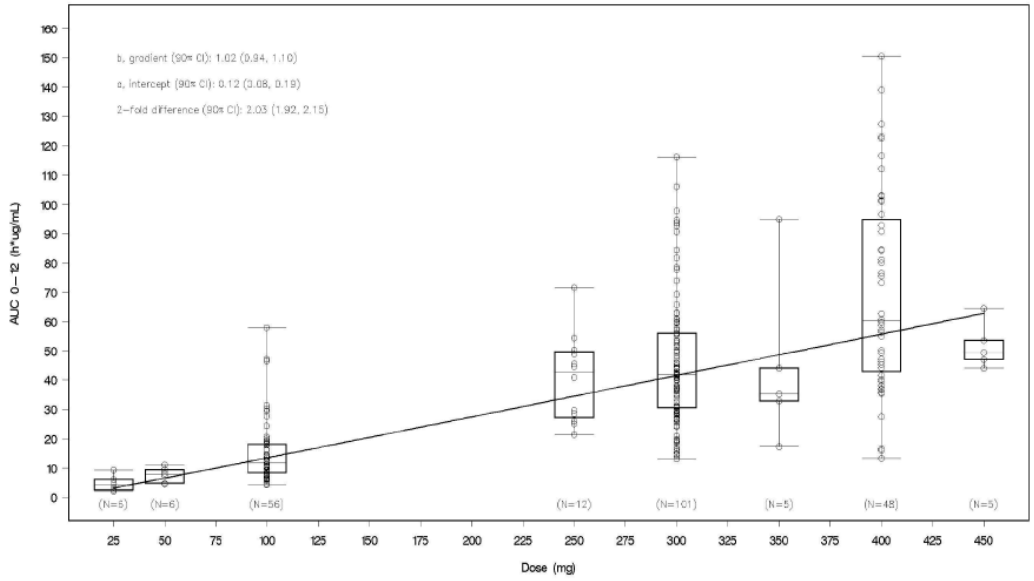
The estimate of the multiple dose CL/F in this analysis was somewhat higher as compared to the Phase I Tablet Analysis where the multiple dose CL/F was estimated to 5.04 L/h. This corresponds to an estimated geometric mean area under the concentration vs. time curve at steady-state (AUCss) of 40.7 µg*h/mL compared to 59.7 µg*h/mL following multiple dosing of 300 mg bid for SOLO2 and Phase I Tablet Analysis respectively, suggesting approximately 30% lower exposure in SOLO2 as compared to previous Phase I Tablet Analysis. This was not due to differences in the patient population datasets used for the analyses. The patient population datasets included in the Phase I Tablet Analysis and the SOLO2 had similar renal and hepatic function and demographic data. Age, WT and ethnicity were not significant covariates in the Phase I Tablet Analysis nor the current analysis and are therefore unlikely to have affected exposure to olaparib.

Dose proportionality and time dependencies

- Single dose

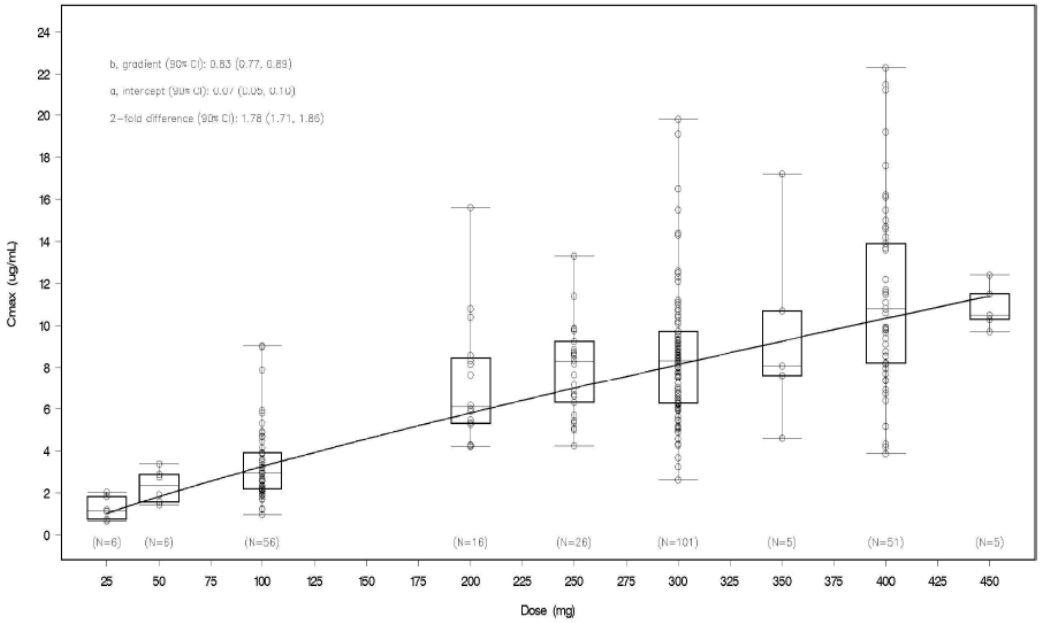
The exposure data (C_{max} and AUC_{0-12}) for Study 04 (300 mg), Study 07 (100 mg), Study 08 (300 mg) and Study 24 (25 mg to 450 mg) have been combined and analysed using a power model. The graphical results show that for AUC_{0-12} a 100% increase in dose would be predicted to give a 103% increase in AUC_{0-12} and 90% CI 92%, 115% and for C_{max} a 100% increase in dose would be predicted to give a 78% increase in Cmax, 90% CI 71%, 86%. Therefore, exposure appears to increase proportionally with dose for AUC_{0-12} and slightly less than proportionally with dose for C_{max}, a doubling in dose is predicted to give an 80% increase in C_{max}.

Table 9: Olaparib tablet dose proportionality: single dose AUC(0-12) in Studies 04 (300 mg), 07 (100 mg), 08 (300 mg) and 24 (25 mg to 450 mg)



$AUC_{(0-12)}$ area under plasma concentration-time curve from zero to 12 hours; CI confidence interval.
Circle denotes observed values, the line denotes the fitted prediction regression line based on the power model.
Data source: Figure 2.7.1.1.1 Module 5.3.5.3. $AUC_{(0-12)}$ for Cohorts 1-3 Study 24 Table 2.7.1.1.3 Module 5.3.5.3.

Table 10: Olaparib tablet dose proportionality: single dose C_{max} in Studies 04 (300 mg), 07 (100 mg), 08 (300 mg) and 24 (25 mg to 450 mg)



C_{max} maximum plasma concentration; CI confidence interval.
Circle denotes observed values, the line denotes the fitted prediction regression line based on the power model.
Data source: Figure 2.7.1.1.2 Module 5.3.5.3.

- Multiple dose

Similarly, the population PK analysis Olaparib-MS-02 did not show any deviation from dose proportionality based on the dose-adjusted observations after single dose or multiple doses. Following the dosing of the tablet formulation, the AUC for the tablet formulation was shown to increase proportionally with dose for the dose range 25 to 450 mg.

- Time dependency

Based on its single dose half-life, it would be expected that steady state exposure would be achieved within 3 days after commencing dosing with olaparib. Study 04 has shown that for the olaparib tablet formulation time-dependent PK was observed. In study 2, with the capsule formulation, comparison of the Day 14 AUC_{0-24} with the Day 1 AUC for the patients, showed that for 8 of the 12 patients where the comparison was possible, the Day 14 AUC_{0-24} was within 30% of the Day 1 AUC value, suggesting there was no marked time dependency in the pharmacokinetics of olaparib.

Special populations

Investigation of olaparib PK in subjects with renal insufficiency has been requested by the CHMP during the initial evaluation of the MA for the capsule formulation and was due by the MAH as a post-authorisation measure.

Study D0816C00006 was a 2-part, Phase I, multicentre study in patients with advanced solid tumours. Part A was an open-label, parallel group, single dose study comparing the PK of olaparib in patients with moderate or mild renal impairment to patients with normal renal function. Each patient received a single oral dose of olaparib (300 mg) given via the tablet formulation on Day 1. In Part B, patients were allowed continued access to olaparib

(300 mg bd) for 12 months. During and after Part B, patients could continue to take olaparib, if they and the investigator deemed it appropriate, until such time as their disease progressed, the investigator believed they were no longer deriving clinical benefit, or they stopped taking olaparib for any other reason

A total of 44 patients (15 patients with normal renal function, 15 patients with mild renal impairment and 14 patients with moderate impairment) were assigned to Part A treatment and received 1 dose of olaparib. The majority of patients assigned to treatment completed Part A of the study (43 patients [97.7%]), with 1 patient being discontinued from the study due to an AE. All of the remaining 43 (97.7%) patients continued to Part B of the study. The population was half female (19 males and 25 females), aged between 32 and 76 years and the most common primary tumour locations were ovary, renal and breast. All patients had an ECOG performance status ≤1.

In patients with mild renal impairment (creatinine clearance [CrCL] 51 to 80 mL/min), there was a small increase in mean olaparib exposure, 15% for Cmax and 24% for AUC. This was not considered to be clinically relevant and no olaparib dose adjustment is warranted in patients with mild renal impairment. In patients with moderate renal impairment (CrCL 31 to 50 mL/min), Cmax and AUC increased 26% and 44% compared to patients with normal renal function. Patients with moderate renal impairment are recommended to take a starting dose of olaparib of 200 mg bd (equivalent to a total daily dose of 400 mg) and olaparib is not recommended for patients with severe renal impairment or end-stage renal disease (CrCL ≤30 mL/min) since there are no data in such patients.

Table 11: Treatment ratio of mild renal impairment to normal renal function of olaparib

PK parameter	Normal renal function		Mild renal function		Moderate renal function		Point estimate (90% CI) of GLSmean ratio mild to normal	Point estimate (90% CI) of GLSmean ratio moderate to normal
	N	GLSmean	N	GLSmean	N	GLSmean		
C_{max} (µg/mL)	12	8.30	13	9.52	13	10.42	1.15 (1.04, 1.27)	1.26 (1.06, 1.48)
AUC (µg.h/mL)	12	57.55	13	71.61	13	82.85	1.24 (1.06, 1.47)	1.44 (1.10, 1.89)
AUC_{0-t} (µg.h/mL)	12	51.99	13	64.60	13	74.66	1.24 (1.06, 1.45)	1.44 (1.11, 1.86)

AUC Area under the plasma concentration-time curve; AUC_{0-t} Area under the plasma concentration-time curve from zero to the last measurable time point; CI Confidence interval; C_{max} Maximum observed plasma concentrations; GLS Geometric least squares; PK Pharmacokinetic
Data Source: Table 11.2.1.3 and Table 11.2.1.4 from D0816C00006 CSR in Module 5.3.3.3

Sections 4.2 and 5.2 were updated with the recommendations for patients with renal impairment based on the results of the study D0816C00006 (MEA 006).

The study D0816C00005 in hepatic impaired patients has been completed. In the study, 52 patients were enrolled and 31 patients (13 patients with normal hepatic function, 10 patients with mild hepatic impairment and 8 patients with moderate hepatic impairment) were assigned to treatment. All patients assigned to treatment completed Part A (PK assessment) of the study and all continued to Part B (continued access and safety monitoring) of the study (31 patients). All 31 (100%) patients discontinued treatment during Part B of the study.

Table 12: Treatment ratio of mild and moderate hepatic impairment compared to normal

PK parameter	Mild hepatic impairment		Normal hepatic function		Point estimate of GLSmean ratio of mild to normal	90% CI of GLS Mean ratio of mild to normal
	N	GLSmean	N	GLSmean		
C_{max} (µg/mL)	9	8.25	13	7.32	1.13	0.82, 1.55
AUC (µg.h/mL)	9	60.25	13	52.33	1.15	0.77, 1.73
AUC_{0-t} (µg.h/mL)	9	59.64	13	51.82	1.15	0.77, 1.72
CL/F (L/hr)	9	4.98	13	5.73	0.87	0.58, 1.31

AUC Area under the plasma concentration-time curve; $AUC_{(0-t)}$ Area under the plasma concentration-time curve from zero to the last measurable time point; CI Confidence interval; CL/F Apparent plasma clearance; C_{max} Maximum observed plasma concentration; GLS Geometric least squares; PK Pharmacokinetic.
Patient E2357008 (Mild) is excluded as underwent a cephalic duodenopancreatectomy surgery prior to study which may affect olaparib absorption.
Data Source: Table 11.2.1.3 from D0816C00005 CSR in Module 5.3.3.3

Results from Part A of the study for patients with normal hepatic function and for patients with mild hepatic impairments were provided as part of this extension application. The results were used to support dosing recommendation for patients with mild hepatic impairment in the prescribing information for the capsule formulation. In this extension application were provided the results from the moderate hepatic impairment cohort in Part A and all patients in Part B.

From the results obtained in study D0816C00005 Part B, a slight 13% decrease in Cmax (mean ratio 0.87; 90% CI: 0.63, 1.22) and a slight 8% increase in AUC (mean ratio 1.08; 90% CI: 0.66, 1.73) were observed in patients with moderate hepatic impairment compared to patients with normal hepatic function. No additional safety signals were identified in patients with moderate hepatic impairment. In this context, it can be concluded that no dose-adjustment is needed in this subpopulation.

The population PK analysis in Olaparib-MS-002 report did not identify body weight, age and gender as having a significant impact on olaparib PK after a single dose or at steady state. There are insufficient data to evaluate the potential effect of race on olaparib pharmacokinetics as clinical experience is mainly collected in Whites (94% of patients were Caucasian). In the limited data available, there was no evidence of any marked ethnic difference in the PK of olaparib between Japanese and Caucasian patients. In the same way, the population PK analysis did not identify race as having an impact on olaparib PK.

Interactions

The effects of olaparib on the main CYP450 enzymes and on the main efflux/uptake transporters, as a substrate, inhibitor and/or inducer, have been investigated and previously assessed in previous applications. New data were provided as part of this extension application: an UGT in vitro study and PBPK modelling and simulations.

In vitro data showed that olaparib may have the potential to cause CYP3A reversible inhibition, CYP3A time dependent inhibition, CYP3A induction as well as UDP-glucuronosyltransferase (UGT)1A1 inhibition. The effect of olaparib on a sensitive CYP3A or UGT1A1 substrate has not been tested in clinical studies but PBPK simulations predicted olaparib to be a weak CYP3A inhibitor *in vivo* and predicted no effect on UGT1A1.

Study 8305966

In this study, the inhibitory potential of AZD2281 on UGT1A1 and UGT2B7 was determined *in vitro* by using pooled human hepatic microsomes and selective substrates.

AZD2281 showed concentration-dependent inhibition of UGT1A1 at 30 and 100 µM, but not at lower concentrations (0.243, 0.81, 2.7, and 9 µM). At 30 and 100 µM of AZD2281, the mean activity remaining was 81.3 and 48.1% of the vehicle control, corresponding to 18.7 and 51.9% inhibition, respectively. The IC50 value of UGT1A1 inhibition was calculated to be 96.7 µM. Under the same experimental conditions, troglitazone (a known inhibitor of UGT1A1) at 25 µM demonstrated significant inhibition of UGT1A1 (74.7%).

Inhibition of UGT2B7 by AZD2281 was also conducted and the data are presented (up to 100 µM) showed no inhibition of UGT2B7. The mean activity remaining was ≥87.3% of the vehicle control. Under the same experimental conditions, mefenamic acid (a known inhibitor of UGT2B7) at 50 µM demonstrated potent inhibition of UGT2B7 (91.2%).

Induction of CYP1A2 and 2B6 has been shown *in vitro*, with CYP2B6 being the most likely to be induced to a clinically relevant extent. Even if the importance of the effect on CYP2B6 was lower that elicited by the positive control phenobarbital, small but notable increases in bupropion hydroxylation in hepatocytes treated with olaparib at 30 µM were observed as specified by the applicant. The applicant states that it is unlikely that administration of olaparib *in vivo* would result in a clinically significant induction effect. Based on evaluation using enzyme activity, olaparib was not considered an inducer of CYP2C9 and 2C19.

In vitro, olaparib has been shown to be an inhibitor of OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K.

PBPK modeling and simulations

New simulations have been provided assessing the effect of olaparib as a victim and perpetrator. PBPK simulations and modeling is qualified only for enzyme inhibitions (CYP, UGT) and if the input parameters are reliable and sensitive analysis performed. The assessment of this study was limited to CYP and UGT inhibition.

2.4.3. Pharmacodynamics

Mechanism of action

Olaparib is an inhibitor of human poly (ADP-ribose) polymerase enzymes (PARP-1, PARP-2 and PARP-3), which are multifunctional proteins involved in multiple cellular processes (Gibson and Kraus, 2012).

Besides inhibiting enzymatic activity, cytotoxicity of PARP inhibitors is due to PARP trapping at DNA and leading to obstructed replication folk, but could also interfere in the PARP function in replication folk protection and restart (Bryant et al, 2009; Schlacher et al, 2011).

The recent profiling of PARP inhibitors revealed that olaparib is a potent inhibitor of PARP1 but is less selective. It inhibited full length PARP1 with 10-fold higher potency than its catalytic fragment and full length PARP2 with 20-fold higher potency than its catalytic fragment (Thorsell et al, 2017).

Primary and Secondary pharmacology

Primary pharmacology

Inhibition of PARP-1 activity has been explored as a pharmacodynamic endpoint in tumour and surrogate tissue (peripheral blood mononuclear cells - PBMCs) collected primarily from the patients dosed in Studies 02 and 07. These studies were assessed as part of this initial marketing authorisation application.

Study 24

The secondary objective of this study described in the PK part was to compare the extent of PARP inhibition achieved in PBMCs following dosing of both the Melt-extrusion (tablet) formulation and existing Gelucire 44/14 (capsule) formulation.

To compare the extent of PARP inhibition achieved in PBMCs following dosing of both the tablet and capsule formulation, PBMC samples were obtained from the 18 patients dosed in the PKP phase, prior to and at 3, 10 and 24 hours after single dosing with the capsule and the tablet formulation. The PARP inhibition data obtained are summarised in the tale below:

Table 5 Mean % inhibition of PARP-1 from baseline (± SE) in PBMC samples following administration of single oral doses of the tablet or capsule formulation (n=6 per cohort)

	Tablet formulation			Capsule formulation		
Time after dose (h)	25 mg dose	50 mg dose	250 mg dose	50 mg dose	100 mg dose	400 mg dose
3	49.4 ± 43.5	58.2 ± 22.0	22.4 ± 43.0	42.8 ± 282	66.9 ± 167	50.5 ± 274
10	69.9 ± 31.0	74.9 ± 55.0	89.4 ± 63.0	66.9 ± 331	55.7 ± 47.0	83.7 ± 28.0
24	39.0 ± 45.0	41.5 ± 174	46.2 ± 215	16.7 ± 402	83.6 ± 100	54.4 ± 256

SE: Standard error.

The PARP inhibition data showed high variability and an average extent of inhibition from baseline which generally fell between 20 and 80%.

Genetic differences in PD response

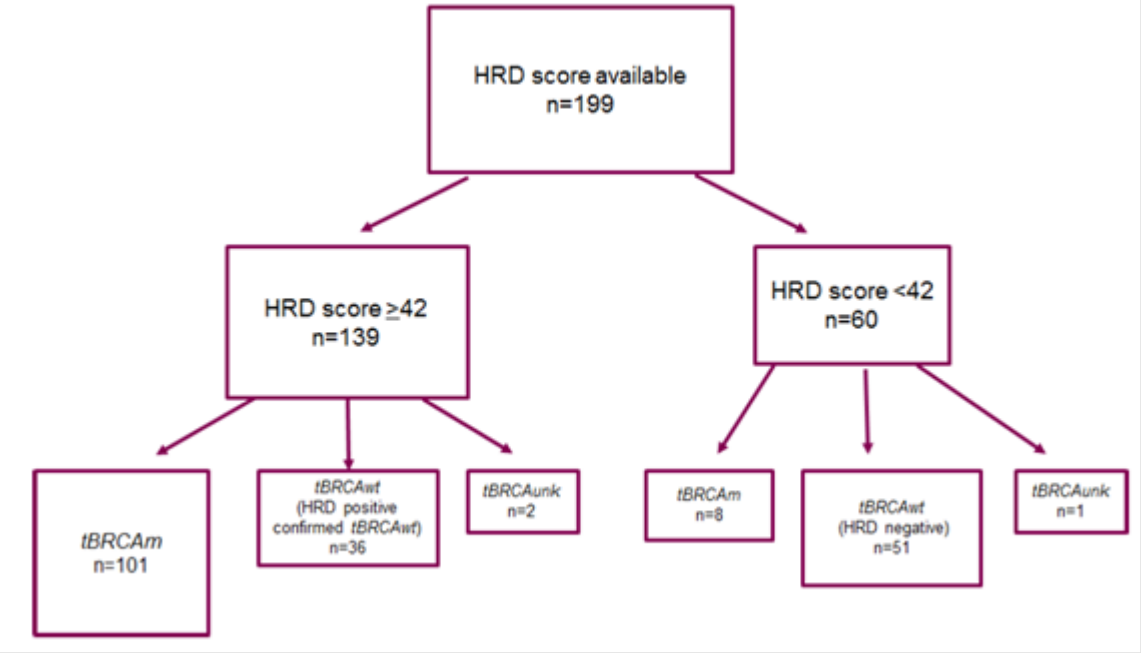
Based on the main mechanism of action, HRD tumours would be the most sensitive to PARP inhibitors and to platinum agents. Therefore, biomarkers of HRD would be predictive of response to both classes of agents.

In addition to initially provided genomic analysis data from the Study 19 using germline testing in blood (via a local test or the Myriad CLIA Integrated BRACAnalysis® test) or from testing a tumour sample (using a test performed by Foundation Medicine), exploratory diagnostic testing and retrospective analysis were conducted based on tumour samples with an aim to further explore homologous recombination deficiency biomarkers. Analyses were performed on archival tumour samples (blocks or sections) for which provision was mandatory for participation in Study 19.

Two types of tests have been used for analysis: Myriad myChoice HRD scores test and Foundation Medicine test (FMI) for detection tBRCA1/2 mutations and mutations in HRR genes.

The results in different subgroups are provided below.

1) Myriad myChoice HRD scores were determined using an assay that calculates whole genome tumour loss-of-heterozygosity (LOH), telomeric allelic imbalance and large-scale state transition scores (Timms et al 2014). The HRD score is the sum of the three scores and a threshold of ≥ 42 is considered positive. Analyses were performed blind to previous gBRCAm and tBRCAm data.



The overview of efficacy data in subgroups per HRD score is provided below:

- tBRCAwt and HRD score 42 and more

Endpoint	Group	N	Number (%) of events	Median [a] Median	95% CI	Treatment effect [b] Hazard ratio	95% CI	2-sided p-value
PFS (Investigator)	Olaparib 400 mg bd	16	8 (50.0)	6.3	(5.5, NC)	0.48	(0.18, 1.27)	0.13919
	Placebo	20	11 (55.0)	5.3	(2.6, NC)			
PFS (BICR)	Olaparib 400 mg bd	16	7 (43.8)	NC	(2.8, NC)	0.80	(0.26, 2.35)	0.67874
	Placebo	20	9 (45.0)	10.6	(2.8, NC)			
TDT	Olaparib 400 mg bd	16	14 (87.5)	7.0	(5.5, 11.7)	0.55	(0.26, 1.14)	0.11140
	Placebo	20	20 (100)	5.7	(3.4, 8.3)			
TFST	Olaparib 400 mg bd	16	12 (75.0)	7.7	(5.9, 15.7)	0.61	(0.27, 1.31)	0.20958
	Placebo	20	20 (100)	9.4	(7.0, 14.3)			
TSST	Olaparib 400 mg bd	16	12 (75.0)	13.0	(10.9, 21.1)	1.04	(0.46, 2.23)	0.92692
	Placebo	20	20 (100)	19.7	(12.9, 21.6)			
OS	Olaparib 400 mg bd	16	12 (75.0)	23.6	(19.8, 35.7)	0.94	(0.43, 1.99)	0.87231
	Placebo	20	19 (95.0)	27.7	(21.2, 35.8)			

- tBRCAwt and HRD score less than 42

Endpoint	Group	N	Number(%) of events	Median [a] Median	95% CI	Treatment effect [b] Hazard ratio	95% CI	2-sided p-value
PFS (Investigator)	Olaparib 400 mg bd	26	18 (69.2)	5.5	(5.3, 10.0)	0.60	(0.31, 1.17)	0.12610
	Placebo	25	21 (84.0)	4.2	(2.7, 5.5)			
PFS (BICR)	Olaparib 400 mg bd	24	14 (58.3)	5.6	(5.3, 8.4)	0.45	(0.21, 0.90)	0.02472
	Placebo	25	20 (80.0)	3.1	(2.6, 5.5)			
TDT	Olaparib 400 mg bd	26	25 (96.2)	7.5	(5.5, 11.5)	0.41	(0.23, 0.75)	0.00389
	Placebo	25	25 (100)	4.3	(2.8, 5.5)			
TFST	Olaparib 400 mg bd	26	22 (84.6)	12.9	(7.4, 15.8)	0.45	(0.24, 0.82)	0.00973
	Placebo	25	25 (100)	6.2	(3.5, 9.3)			
TSST	Olaparib 400 mg bd	26	22 (84.6)	17.1	(15.2, 19.4)	0.60	(0.32, 1.09)	0.09467
	Placebo	25	25 (100)	14.3	(10.1, 15.5)			
OS	Olaparib 400 mg bd	26	22 (84.6)	21.9	(17.7, 29.7)	1.04	(0.57, 1.88)	0.90422
	Placebo	25	25 (100)	24.9	(14.8, 32.5)			

By Myriad HRD testing from the SOLO2 trial (246/295 patients) of the 219 samples evaluable for the HRD score (89% pass), the majority (209 samples) had HRD scores of 42 or more and 10 samples had a score <42 (4.6%; 5 were BRCA2; 4 were BRCA1 and 1 was classed by Myriad as a VUS [BRCA2 c.517-2A>G]). The only patient in SOLO2 for whom gene specific loss of heterozygosity (LOH) was called as absent (E4102507) had an HRD score of 53.

The results of the both Study 19 and SOLO-2 point to the higher potential for HR deficiency in patients with BRCA mutations than in tBRCAwt patients, as expected. By Myriad HRD test in the Study 19, among 139 patients with higher HRD score (42 or more), 101 patients had tBRCA mutations, while among 60 patients with lower HRD score (<42), 51 patients were tBRCAwt.

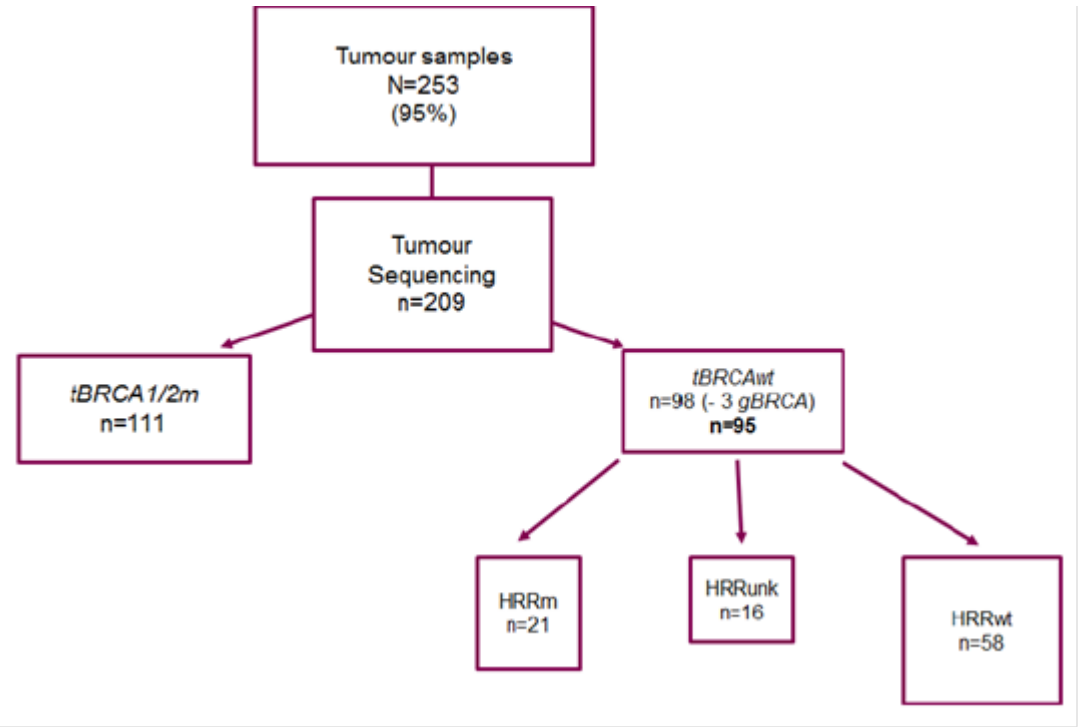
2) Tumour mutation status in BRCA1, BRCA2 and other key HRR related genes (HRRm) status was established using massively parallel DNA sequencing analysis at Foundation Medicine (Frampton et al 2013). Tumour analysis was performed on coded tumour samples, and results were returned blind to previous gBRCAm and tBRCAm data. The classification of variants was based on the American College of Medical Genetics recommendations (Richards et al 2008, Richards et al 2015). A total of 95 patients were classified as having tBRCAwt tumours.

Patients in the tBRCAwt group were further subdivided into three groups:

- HRRm: 21 patients (22%) whose tumours had at least one LOF mutation in a high confidence HRR gene with the HRR mutations identified as: BRIP1, CDK12, RAD54L, RAD51B, RAD54L rearr, ATM rearr, FANCA rearr, FANCD2, FANCI rearr, FANCL, RAD51C, RAD52 del, and XRCC3 rearr.

- HRRunk: 16 patients with a potential LOF mutation in any gene associated with DNA repair (eg, MSH2, MUTYH), or in genes where a postulated role in DNA repair has been the subject of significant controversy (eg, EMSY)

- HRRwt: 58 patients (61%) with no potential LOF mutations in any of the 13 genes tested that are involved in DNA repair.



The overview of data in these subgroups is provided below:

PFS

Endpoint	Group	N	Number(%) of events	Median [a] Median	95% CI	Treatment effect [b] Hazard ratio	95% CI	2-sided p-value
tBRCAwt/HRRm	Olaparib 400 mg bd	12	7 (58.3)	7.4	(4.5, NC)	0.21	(0.04, 0.86)	0.03056
	Placebo	9	6 (66.7)	3.1	(2.7, NC)			
tBRCAwt/HRRwt	Olaparib 400 mg bd	25	17 (68.0)	5.5	(5.1, 7.5)	0.71	(0.37, 1.35)	0.30310
	Placebo	33	23 (69.7)	5.5	(2.8, 5.5)			

TFST

Endpoint	Group	N	Number(%) of events	Median [a] Median	95% CI	Treatment effect [b] Hazard ratio	95% CI	2-sided p-value
tBRCAwt/HRRm	Olaparib 400 mg bd	12	11 (91.7)	13.5	(7.2, 29.0)	0.54	(0.18, 1.60)	0.26280
	Placebo	9	9 (100.0)	6.7	(3.6, 17.0)			
tBRCAwt/HRRwt	Olaparib 400 mg bd	25	21 (84.0)	8.0	(5.7, 13.1)	0.65	(0.36, 1.13)	0.12733
	Placebo	33	32 (97.0)	7.4	(5.6, 10.4)			

OS

Endpoint	Group	N	Number(%) of events	Median [a] Median	95% CI	Treatment effect [b] Hazard ratio	95% CI	2-sided p-value
tBRCAwt/HRRm	Olaparib 400 mg bd	12	11 (91.7)	33.4	(21.5, 49.3)	0.77	(0.28, 2.28)	0.63168
	Placebo	9	8 (88.9)	19.5	(16.8, 35.4)			
tBRCAwt/HRRwt	Olaparib 400 mg bd	25	21 (84.0)	20.0	(15.8, 30.8)	1.19	(0.66, 2.10)	0.55016
	Placebo	33	32 (97.0)	29.3	(24.0, 35.8)			

Somatic BRCA1/2 mutations

Further re-analysis of samples in Study 19 determined that 10% (20/209) of tumour sequenced patients have sBRCAm (Dougherty et al 2017). Ten patients were treated with olaparib and 10 with placebo. Data are consistent with gBRCAm patients in this smaller group of patients identified as sBRCAm in Study 19 (PFS HR 0.23 95% CI [0.04 to 1.12])

Analysis by TP53 disruptive vs non-disruptive status

The MAH provided an analysis of Study 19 based on the sub-classification of TP53 mutations according to their functional effects "TP53 disruptive vs non-disruptive status". This analysis was exploratory and performed post-hoc in a subgroup of the full analysis set for patients that were able to be assigned a TP53 status (209/265, 78.9%). Patients with TP53 disruptive mutations in the BRCA wild-type group treated with olaparib demonstrated median OS of 35.0 months compared to 25.5 months for similar patients on placebo (n=47, HR 0.80 [95% CI 0.40, 1.52]). The mutational subgroup of 40 patients with BRCA wild-type and TP53 non-disruptive mutation did not derive benefit from olaparib treatment, HR 1.58 (95% CI 0.77, 3.35).

Large genomic rearrangements in BRCA1/2 genes

Large rearrangements in the BRCA1/2 genes were detected in 4.7% (14/295) and in 7.4% (10/136) of the randomised patients in SOLO2 and Study 19, respectively.

Genetic analysis in patients with long-term non-progressive disease

Among patients with long-term non-progressive disease, 15 patients have received olaparib for more than 6 years, 9 of which have been reported to have a BRCA mutation (5 in BRCA2, 3 in BRCA1 and 1 in both BRCA2 and BRCA1) in their tumour or blood sample, with 3/9 being a somatic mutation. One of the remaining 6 patients was not evaluable for tBRCA status testing at either Myriad or Foundation Medicine; hence 5/15 patients treated with olaparib for more than 6 years had no detectable BRCA mutation. Three out of these 5 patients had Myriad HRD scores available (2 were HRD positive and 1 was HRD negative) and 5 out of these 5 patients had HRRm status available (1 was HRRm, 2 were HRR uncertain and 2 were HRRwt). Of the 2 HRRwt tumours, 1 was Myriad HRD negative and the other was Myriad HRD status unknown.

Relationship between plasma concentration and effect

As part of a modelling exercise using data from Phase I studies conducted with the tablet formulation, the relationships between exposure and adverse events (AEs) were analysed by graphical exploratory analysis first and subsequently modelled if an apparent relationship was supported by the exploratory analysis. In this analysis, data from studies 01, 04, 07 and 08 were used. A total of 151 patients were therefore included in the safety analysis dataset.

The exposure and response analysis was focused on the assessment of the impact of PK exposure of tablet formulation on typical safety events that occurred within the longest time period of olaparib treatment observed in the data (85 days). There was no evidence to suggest that measures of exposure were predictive of anaemia, nausea, vomiting, fatigue, dyspepsia, upper abdominal pain, dysgeusia, constipation, headache, diarrhoea, neutrophil and platelet count, or decreased appetite. A trend was observed for decreased haemoglobin with

increasing olaparib exposure. Therefore, exposure response modelling was only conducted for AUC and haemoglobin measurements to quantify the potential relationship. An indirect response model with olaparib AUC inhibiting the haemoglobin synthesis rate in a linear relationship adequately described the relationship between olaparib exposure in AUC and haemoglobin response. The model estimated a mean slope to olaparib AUC of 0.002 (g/dL)/(µg.h/mL).

The GOF and VPC displayed acceptable fitting as shown below for VPC.

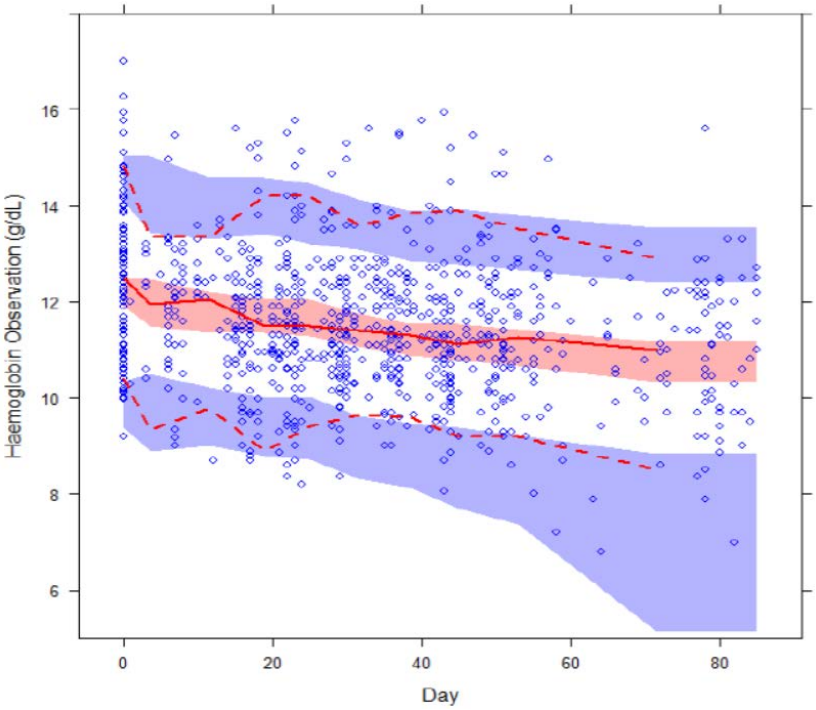


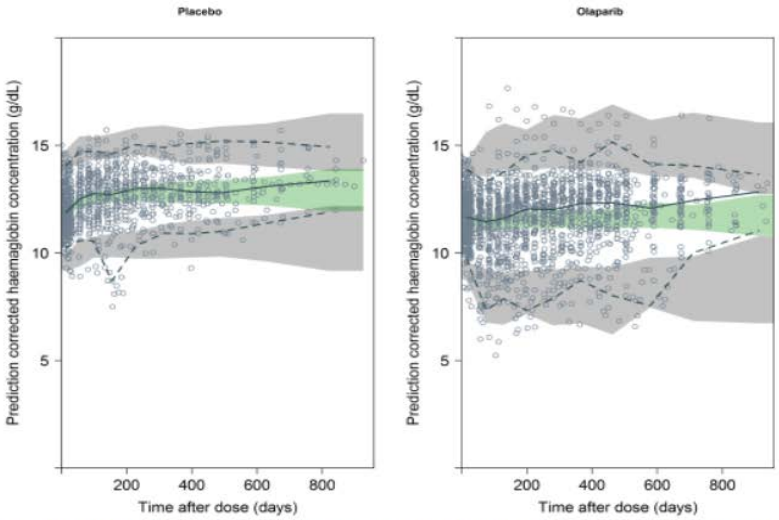
Figure 6: Visual predictive check of haemoglobin model

For a baseline haemoglobin concentration of 10 g/dL, the predicted mean haemoglobin concentrations on Day 85 were 8.7, 8.4 and 8 g/dL, respectively, for the predicted geometric mean AUCss (59.7 µg.h/mL) after olaparib 300 mg bd (GMAUCss,300mgbd), 1.5x GMAUCss, 300mgbd, and 2x GMAUCss,300mgbd. For a baseline haemoglobin concentration of 14 g/dL, the predictions were 12.3, 11.6 and 10.8 g/dL, respectively.

In addition to this, data from SOLO2 study were separately used to develop PK/PD models for both efficacy and safety endpoints using the same approach as described below.

For efficacy, the graphical exploration of PFS, PFS2 and OS indicated no signs of potential ER. Kaplan Meier plots stratifying the results by tertiles of exposure (average cumulative Cav; and daily C_{max} and C_{min}; all at time of progression) showed no pattern that would suggest exposure-response relationship at the exposures analyzed in this study. Additionally, stratification based on baseline disease status as measured by Eastern cooperative oncology group (ECOG) yielded no clear ER, perhaps limited by low sample sizes in some strata. Thus, no modeling of ER for efficacy was performed.

For safety, haemoglobin was modelled based on previous finding of a significant ER relationship in the Phase I Tablet Analysis. Haemoglobin levels appeared to change over time in placebo patients, and thus time dependent models were evaluated. This resulted in a placebo model that considered how this effect appeared to saturate over time and was described by an Emax type of relationship. An indirect response model with olaparib average cumulative AUC inhibiting the production of haemoglobin adequately described the relationship of olaparib exposure and haemoglobin response. Baseline haemoglobin at start of treatment was estimated to 11.6 g/dL (RSE: 11.7 %). The time to reach half of maximum level in haemoglobin levels in placebo was estimated as 42.4 days, and its Emax was estimated as 1.39 g/dL. The model estimated a linear effect of olaparib average cumulative AUC on the rate of synthesis of haemoglobin with a mean slope of 0.00287 (g/dL/h)/(µg*h/mL) (RSE: 11.7 %). At a baseline haemoglobin concentration of 11.6 g/dL, haemoglobin is predicted to decrease to 10.3 g/dL (95% CI: 9.98-10.6 g/dL) at predicted steady-state median olaparib exposure (assuming 300 mg bid dosing), while if the exposure is doubled, haemoglobin is predicted to decrease to 8.93 g/dL (95% CI: 8.33-9.52 g/dL). Final model displayed acceptable fitting as shown by VPC below.



Circles: Observations, **Solid Black Line**: Median of the observed concentrations, **Dashed Lines**: 2.5^{th} and 97.5^{th} percentiles of the observed concentrations, **Shaded Area**: The shaded areas indicate the 95% CI around the prediction-corrected median (green area), and 2.5^{th} and 97.5^{th} percentiles (grey areas). All observations and predictions are adjusted using prediction correction as described in Bergstrand et al. [2].

Figure 7: VPC of haemoglobin concentration

The latter results were consistent with the Phase I Tablet Analysis model which predict haemoglobin concentrations to decrease on average to 8.7 and 9.3 g/dL for baseline haemoglobin concentrations of 11.0 and 12.0 g/dL, respectively, when AUC is doubled.

The graphical exploration of safety indicated an ER for fatigue and this endpoint was further explored by modeling. Fatigue was modelled using daily observations of graded fatigue events. A significant ER was found between olaparib daily Cav and the probability of observing higher grade fatigue. However, this relationship was relatively weak as the increased probability of fatigue when olaparib exposure is increased, are minor.

2.4.4. Discussion on clinical pharmacology

The proposed tablet formulation is clearly beneficial to the patients and represents a clear advantage over the capsules. The tablet formulation is designed to deliver the therapeutic dose of olaparib in fewer and smaller dose units, to improve bioavailability, to reduce PK variability and to have food-independent exposure. Given that the capsules are not bioequivalent to the tablets with respect to rate and extent of absorption, and given that dose adjustment could not lead to similar exposure, the two formulations should not be substituted on a milligram-to-milligram basis.

ADME properties have been extensively described and have been adequately reflected in the SmPC. Olaparib is rapidly absorbed following oral dosing in fasting conditions, with peak plasma concentrations observed typically after 1.5 hours post-dose. Olaparib tablets may be taken without regard to meals. The pooled population PK analysis characterised the absorption phase of olaparib as a sequential zero and first-order absorption and showed a significant impact of olaparib tablet strength on the absorption rate constant.

The in vitro plasma protein binding is approximately 82%. The pharmacokinetics of olaparib at the 300 mg tablet dose are characterised by an apparent volume of distribution of ~158 L.

CYP3A4/5 were shown to be the enzymes primarily responsible for the metabolism of olaparib. Following a single dose of 14C-olaparib, ~86% of the dosed radioactivity was recovered within a 7-day collection period, ~44% via the urine and ~42% via the faeces. Majority of the material was excreted as metabolites. Olaparib at the 300 mg tablet dose is characterised by an apparent plasma clearance of ~7 L/h and a terminal half-life of 15 hours.

Patients with moderate renal impairment are recommended to take a starting dose of olaparib of 200 mg bd (equivalent to a total daily dose of 400 mg). Olaparib is not recommended for patients with severe renal impairment or end-stage renal disease (CrCL $\leq$ 30 mL/min) since there are no data in such patients.

Additional information was provided on the completion of study D0816C00005. In this context, the SmPC recommendations in section 4.2 concerning the moderate hepatic impaired patients and the PK properties in section 5.2 have been updated taking the results obtained in study D0816C00005 part B: a slight 13% decrease in Cmax (mean ratio 0.87; 90% CI: 0.63, 1.22) and a slight 8% increase in AUC (mean ratio 1.08; 90% CI: 0.66, 1.73) are observed in patients with moderate hepatic impairment compared to patients with normal hepatic function. No additional safety signals were identified in patients with moderate hepatic impairment. In this context, it can be concluded that no dose-adjustment is needed in this subpopulation.

The population PK analysis in Olaparib-MS-002 report did not identify body weight, age and gender as having a significant impact on olaparib PK after a single dose or at steady state. The population PK analysis did not identify race as having an impact on olaparib PK and in the limited data available, there was no evidence of any marked ethnic difference in the PK of olaparib between Japanese and Caucasian patients.

The MAH provided several exploratory post-hoc analyses based on genetic analysis of tumour samples from the Study 19. In SOLO2 study, patients with germline BRCA1/2 mutations were identified either from germline testing in blood via a local test or the Myriad CLIA Integrated BRACAnalysis® test or from testing a tumour sample using a local test. In addition, initial exploratory analysis of data from the SOLO2 for HR deficiency based on Myriad myChoice HRD scores has been provided. The final analysis of Myriad HRD scores testing of tumour samples from the SOLO2 trial will be submitted in Q1 2018.

The results of the both Study 19 and SOLO-2 point to the higher potential for HR deficiency in patients with BRCA1/2 mutations than in tBRCAwt patients, as expected. It is noted that there is no clear overlap between patients considered as having HRDneg tumours and patients with tumours not harbouring mutations in HRD-related genes. Other mechanisms than genetic alteration would result in functional HR deficiency. A substantial proportion of patients harbours tumours that are HRDneg and do not harbour mutations in HR-related genes. The magnitude of benefit is such patients needs further investigation. In the OPINION study requested to be conducted post-approval, Myriad myChoice HRD test will be used. With the aim to define the subgroup of patients that would not benefit from olaparib maintenance treatment, the MAH is encouraged to pursue testing for the TP53 mutational status.

Accumulating evidence starts to dissect the differential implications of BRCA1 versus BRCA2 mutations with regard to sensitivity to PARPi and anti-tumour response to olaparib may be different in patients harbouring germline BRCA1 versus BRCA2 mutations (Liu et al, 2012; Hollis et al, 2017). Clinical evidence supporting differential effect in patients with BRCA1 or BRCA2 mutations starts to accumulates as well (see efficacy part).

Nevertheless, less is known about the implications of the exact mutation site within each of the two genes and differential impact for different BRCA1 and BRCA2 mutations has been recently reviewed (Hollis et al, 2017). An analysis in a limited number of patients from Study 19 and SOLO2 that harboured mutations in exon 11 or RING domain did not allow to make definitive conclusions on differential effect.

While the majority of germline inactivating mutations in BRCA1/2 are small-scale mutations, BRCA genes are prone to large rearrangements. The prevalence of large genomic rearrangements (LGRs) observed in 'BRCA mutated' group of patients (4.7% and 7.4% of BRCAm cases in SOLO2 and Study 19 respectively), is in line with reported prevalence. Numerous types of LGRs have been found in different populations, with variable frequencies (approximately 0–27% of all pathogenic variants) probably due to both ethnic diversity and technical approach employed (Minucci et al, 2017). Among pathogenic variants that are reported on ClinVar database, at least 81 BRCA1 and 17 BRCA2 variants (accounting for 8%–27% and 0%–11% of all BRCA1 and BRCA2 mutations, respectively) are LGRs, which account for at least 10% of the mutations in BRCA1 and 5% of BRCA2 mutations in outbred hereditary breast and ovarian cancer (HBOC) families. High prevalence of LGRs in BRCA1 have been demonstrated in several European populations. The identification of LGRs has increased the number of informative patients who could benefit from molecular screening and associated targeted therapy with PARPi. Such patients would also benefit from olaparib treatment and the available data are consistent with data in overall population. Since BRCA1/2 genes rearrangements are representing substantial proportion of 'BRCA mutations', information on the proportion of patients enrolled in studies was included in section 5.1 of the SmPC.

2.4.5. Conclusions on clinical pharmacology

Overall, the pharmacokinetics of olaparib tablets were appropriately investigated.

The pharmacodynamics of olaparib was investigated in studies with the capsule formulation and some additional data is available from studies conducted with the tablet formulation. Exploratory genetic analysis of tumour samples from the study 19 was provided and biomarkers of HRD will be further studied in planned and ongoing studies, including the requested OPINION study and ongoing ORZORA and LIGHT study. Further, the MAH is recommended to submit the final analysis of Myriad HRD testing of tumour samples from the SOLO2 in Q1 2018.

2.5. Clinical efficacy

This application of olaparib 300 mg bd tablet formulation is based on two pivotal studies, the Phase III randomised, double blind, placebo controlled, multicentre study, SOLO2 (conducted with the olaparib tablet formulation) and the Phase II randomised, double-blind, placebo-controlled, multicentre study, Study 19 (conducted with olaparib capsule formulation).

The claimed indication for the tablet formulation of olaparib is as monotherapy for the maintenance treatment of adult patients with platinum sensitive relapsed (PSR) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.

The recommended dose for the tablet formulation of olaparib maintenance monotherapy in patient platinum-sensitive relapsed ovarian cancer is 300 mg (two 150 mg tablets) taken twice daily, equivalent to a total daily dose of 600 mg.

The tablet formulation of olaparib has been developed to deliver a clinically therapeutic dose of olaparib in fewer dose units than that required for the capsule formulation.

2.5.1. Dose response study

The clinical dose taken into the pivotal Phase III SOLO2 study was determined **in Study 24.**

Study 24 was originally intended to establish the comparative bioavailability of the olaparib tablet to the olaparib capsule. The PK Phase of the study was designed as a randomised, two-period, two-sequence, cross-over single-dose study under fasting conditions in cancer patients with advances solid tumours. Even if this study was not powered as a bioequivalence study, data showed that the 200 mg bd tablet dose failed to meet the criteria to be considered similar to 400 mg bd capsule based on one-sided 80% upper CI above the predefined 20% threshold for non-inferiority. Therefore, it was concluded that 200 mg bd tablet was inferior to 400 mg bd capsule.

Next to the initial PK phase, the study comprised successive phases (continued supply expansion, dose-escalation and two final randomised expansion) in order to identify a tablet dose which provided comparable clinical activity to the 400 mg capsule dose and was well-tolerated.

The 300 mg bd tablet dose and the 400 mg bd capsule dose resulted in a similar decrease in tumour size with a LS mean treatment difference of 1.8% and the one-sided 80% UCL of the difference was less than 15% indicating that the 300 mg bd dose had similar efficacy to the 400 mg bd capsule dose. The percentage change in tumour size for the 400 mg bd tablet dose was observed to be numerically greater than the 400 mg bd capsule dose, however, the tolerability profile was less favourable with higher level of myelotoxicity. Additionally, PK data showed that steady state exposure with olaparib tablet dose of 300 mg or higher matched or exceeded that of olaparib 400 mg bd capsule.

Radiological objective response rate at the 300 mg bd and 400 mg bd tablet dose was similar to 400 mg bd capsule dose and higher as compared to 200 mg bd tablet dose in ovarian cancer *gBRCAm* patients.

The incidence of anaemia as Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher was 22% at the 300 mg bd tablet dose level and 400 mg bd capsule dose level and 29% at the 400 mg bd tablet dose level (Group 6). The incidence of anaemia as CTCAE Grade 3 for the 200 mg bd tablet cohort in Group 1 (n=13) was 0%. However the efficacy of the 200 mg bd tablet dose was deemed not equivalent to the 400 mg bd capsule dose cohort in the same group (Group 1).

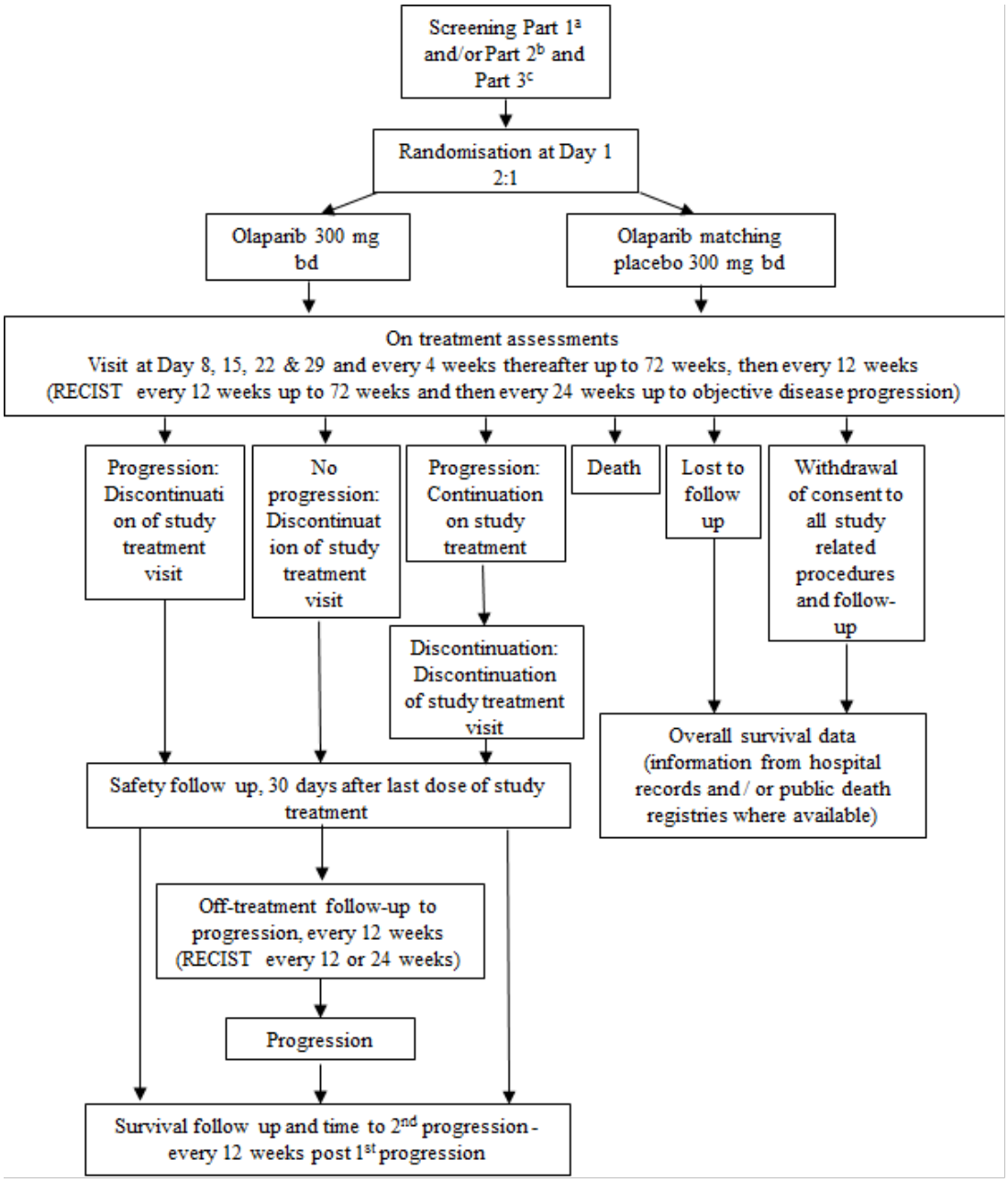
Overall based on PK, efficacy and safety data from Study 24, the 300 mg bd tablet dose was chosen as the recommended dose for the entire olaparib Phase III clinical development programme (over 7 confirmatory clinical trials) across multiple tumour type including ovarian, breast, prostate, and pancreatic.

2.5.2. Main studies

Study SOLO2 (D0816C00002) (tablet formulation)

This study was a phase 3 randomised, double-blind study of maintenance therapy with olaparib or placebo in platinum sensitive relapsed *BRCA* mutated ovarian cancer patients who are in complete or partial response following platinum containing chemotherapy.

Figure 8: Flow chart of study design (study SOLO2)



a Screening Part 1 (Post Cycle 3 of ongoing chemotherapy to –28 days): applicable to those patients who did not know their *gBRCA* or *tBRCA* mutation status prior to entry into the study. Screening Part 1 was conducted to determine if the patient was considered eligible to undergo the *BRCA* status blood test. The *BRCA* blood test was only performed once the patient was deemed eligible. Once Part 1 was successfully completed these patients continued to Part 2.

b Screening Part 2 (-28 days to –1 day): applicable to those patients whose *BRCA* mutation status was already known and had a deleterious or suspected deleterious mutation. These patients had a confirmatory Myriad test post randomisation. Screening Part 2 was also applicable to those patients who had a confirmed mutation after completing screening Part 1.

c Screening Part 3 (-7 days to -1 day): applicable to: all patients who were still deemed eligible to continue with screening after completing Part 1 and/or Part 2.

Methods

Study Participants

Patients were randomised at 119 centres, in 16 countries worldwide, including: Australia, Belgium, Brazil, Canada, France, Germany, Israel, Italy, Japan, Netherlands, Poland, Russia, Spain, South Korea, United Kingdom (UK) and the United States of America (US).

Main Inclusion Criteria:

- Patients must have been ≥18 years of age
- Female patients with histologically diagnosed relapsed HGSOC (includes primary peritoneal and/or fallopian tube cancer) or high-grade endometrioid cancer
- Documented mutation in *BRCA*1 or *BRCA*2 that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function)
- Patients who have received at least 2 previous lines of platinum-containing therapy prior to randomisation

<u>For the penultimate platinum-based chemotherapy course prior to enrolment on the study:</u>

- Treatment must have contained a platinum agent (eg, carboplatin or cisplatin per standard clinical practice; there are no other specific requirements)
- Patients defined as platinum sensitive after this treatment; defined as disease progression greater than 6 months after completion of their last dose of platinum chemotherapy
- Maintenance treatment was allowed at the end of the penultimate platinum regimen, including bevacizumab

<u>For the last chemotherapy course immediately prior to randomisation on the study:</u>

- Patients must be considered, in the opinion of the investigator, to be in response (PR or CR), or may have no evidence of disease (if optimal cytoreductive surgery was conducted prior to chemotherapy), and no evidence of a rising CA-125, as defined below, following completion of this chemotherapy course
- Patients had to have received a platinum-based chemotherapy regimen (carboplatin or cisplatin) and have received at least 4 cycles of treatment
- Patients must not have received bevacizumab during this course of treatment
- Patients must not have received any investigational agent during this course of treatment
- Patients must be randomised within 8 weeks of their last dose of chemotherapy (last dose is the day of the last infusion)
- Chemotherapy course must have consisted of a minimum of 4 treatment cycles

- Pre-treatment CA-125 within the upper limit of normal (ULN)

- Patients must have had normal organ and bone marrow function measured within 28 days of randomisation
- ECOG PS 0 to 1
- A life expectancy of ≥16 weeks

Main exclusion criteria

- BRCA1 and/or BRCA2 mutations that are considered to be non-detrimental
- Patients who had drainage of their ascites during the final 2 cycles of their last chemotherapy regimen prior to enrolment on the study
- Participation in another clinical study with an investigational product during the chemotherapy course immediately prior to randomisation
- Any previous treatment with PARPi, including olaparib
- Patients with a known hypersensitivity to olaparib or any of the excipients of the product
- Patients with another malignancy, except: adequately treated non-melanoma skin cancer; curatively treated in situ cancer of the cervix; ductal carcinoma in situ (DCIS); stage 1, grade 1 endometrial carcinoma; or other solid tumours including lymphomas (without bone marrow involvement) curatively treated with no evidence of disease for ≥5 years. Patients with a history of primary breast cancer may be eligible provided they completed their definitive anticancer treatment more than 3 years ago and they remain breast cancer disease free prior to start of study treatment.
- Patients receiving any systemic chemotherapy or radiotherapy (except for palliative reasons) within 3 weeks prior to study treatment (or a longer period depending on the defined characteristics of the agents used).
- Patients with symptomatic uncontrolled brain metastases. A scan to confirm the absence of brain metastases is not required. The patient can receive a stable dose of corticosteroids before and during the study as long as these were started at least 4 weeks prior to treatment. Patients with spinal cord compression unless considered to have received definitive treatment for this and evidence of clinically stable disease for 28 days
- Major surgery within 2 weeks of starting study treatment and patients must have recovered from any effects of any major surgery

Treatments

Patients were randomised in a 2:1 ratio to received olaparib (experimental arm) or placebo (control arm) as maintenance therapy at a dose of 300 mg twice daily.

There is no maximum duration for taking study treatment. Patients should continue to receive study treatment until objective radiological disease progression as per RECIST as assessed by the investigator or as long as in the investigator's opinion they are benefiting from treatment.

Objectives, Outcomes/endpoints

Table 13: Study objectives and variables

OBJECTIVE			VARIABLE
Priority	Type	Description	
Primary	Efficacy	To determine the efficacy by PFS (investigator-recorded assessments according to modified RECIST v1.1) of olaparib maintenance monotherapy compared to placebo in *BRCAm* relapsed ovarian cancer patients who were in complete or partial response following platinum based chemotherapy.	**PFS**: the time from randomisation until the date of objective radiological disease progression according to modified RECIST 1.1 or death (by any cause in the absence of progression) regardless of whether the patient discontinued randomised therapy or received another anti-cancer therapy prior to progression.
Secondary	Efficacy	To determine the efficacy of olaparib maintenance monotherapy compared to placebo in *BRCAm* relapsed ovarian cancer patients who were in complete or partial response following platinum-based chemotherapy by assessment of OS, time to earliest progression by modified RECIST 1.1 or CA-125, or death, and PFS2	**OS**: the time from the date of randomisation until death due to any cause. **Time to earliest progression by modified RECIST 1.1 or CA-125 or death**: the time from randomisation to the earlier date of modified RECIST 1.1 or CA-125 progression or death by any cause. **PFS2**: the time from the date of randomisation to the earliest of the progression event subsequent to that used for the primary variable PFS or death.
	Efficacy	To obtain additional assessments of the anti-tumour activity of olaparib by evaluation of TFST, TSST and TDT	**TFST**: the time to first subsequent therapy or death **TSST**: the time to second subsequent therapy or death **TDT**: the time to study drug

			discontinuation or death
	Efficacy	To collect PRO data to explore disease-related symptoms and HRQoL as assessed by the TOI of the FACT-O	**FACT-O**: a questionnaire, which includes the following subscales: physical, social/family, emotional and functional well-being, as well as the additional concerns scale consisting of specific ovarian cancer symptoms. **TOI**: the trial outcome index derived from the FACT-O, which targets the most relevant symptoms together with functional and physical well-being and can be directly related to signs and symptoms and AEs.
	Efficacy	To assess 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 *BRCA* mutation assays (gene sequencing and large rearrangement analysis)	The following efficacy variables were reanalysed and reported in this CSR for patients whose *gBRCA*m status was confirmed by the Myriad Test: PFS, PFS2, OS, TDT, TFST and TSST.
	PK	To determine the patients' exposure to olaparib	Individual plasma concentration data. Where possible the following PK parameters were determined: $C_{max,ss}$, AUC_{ss} and $C_{min,ss}$; these data will be reported outside of this CSR.
Safety	Safety	To assess the safety and tolerability of olaparib maintenance monotherapy in *BRCAm* relapsed ovarian cancer patients who were in complete or partial response following platinum based chemotherapy	AEs, SAEs, DAEs, OAEs, laboratory vital signs and ECGs.
Exploratory	Efficacy	To explore the impact of treatment and disease on resource use	Resource use outcome variables include: length of hospital stay and reasons for hospitalisation, length of any time spent in the ICU.
	Efficacy	To explore the effects of olaparib	**FACT-O**: new patient-centric endpoints:

		maintenance monotherapy compared to placebo on HRQoL as assessed by the individual domains of the TOI of the FACT-O	disease-related symptoms, treatment-related toxicities, physical functioning and overall HRQoL.
	Other	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	*BRCA* mutation status by local, Myriad germline and Myriad tumour; deleterious and suspected deleterious mutation types in germline and tumour *BRCA* patients.

Sample size

In total 192 events were required to give sufficient precision of the HR. If a HR of 0.2 (similar to the Phase II study D0810C00019) was observed, the 95% Confidence Interval (CI) would be 0.15-0.27; if a HR of 0.3 was observed the 95% CI would be 0.22-0.40; if a HR of 0.4 was observed the 95% CI would be 0.30-0.54; and if a HR of 0.5 was observed the 95% CI would be 0.37-0.67.

Randomisation

Randomisation was stratified by:

- Response to last platinum chemotherapy (CR or PR)
- Time to disease progression in the penultimate platinum based chemotherapy prior to enrolment (>6 to ≤ 12 months and >12 months)

Blinding (masking)

Olaparib and placebo treatment were be blinded.

Statistical methods

PFS was analysed using a log-rank test stratified by response to previous platinum chemotherapy (CR or PR), and time to disease progression (>6 to 12 months and >12 months) in the penultimate platinum-based chemotherapy prior to enrolment and using the Breslow approach for handling ties. The HR and CI was estimated from a Cox Proportional Hazards model (with ties = Efron and the stratification variables as covariates) and the CI was calculated using a profile likelihood approach. The HR (olaparib vs placebo) together with its corresponding 95% CI and p-value was presented (an HR less than 1 represented the reduction in risk for those patients allocated olaparib). Kaplan-Meier (KM) plots of PFS were presented by treatment group. Where the observed p-value for treatment difference was <0.025 (1 sided), the result was regarded as statistically significant. As censoring rules in the primary analysis, PFS was defined as the time from

randomisation until the date of objective radiological disease progression according to RECIST or death (by any cause in the absence of progression) regardless of whether the patient discontinues randomised therapy or receives another anticancer therapy prior to progression (i.e. date of RECIST progression/death or censoring – date of randomisation + 1). Patients who have not progressed or died at the time of analysis, or who progress or die after two or more missed visits, are censored at the latest evaluable RECIST assessment, or day 1 if there are no evaluable visits. If the patient has no evaluable visits or does not have a baseline assessment they will be censored at day 1 unless they die within two visits of baseline (25 weeks allowing for visit window)

An initial analysis of PFS2 and OS was performed at the same time as the primary analysis of PFS, and the same methodology and model was used. As PFS2 reached statistical significance at the interim analyses, a further analysis of OS will be performed when the OS data are approximately 60% mature (177 OS events); this is anticipated to occur approximately 72 months (6 years) after the first patient was enrolled. A further analysis of PFS2 was to be performed at the time of the OS analysis if PFS2 was not statistically significant at the primary PFS analysis.

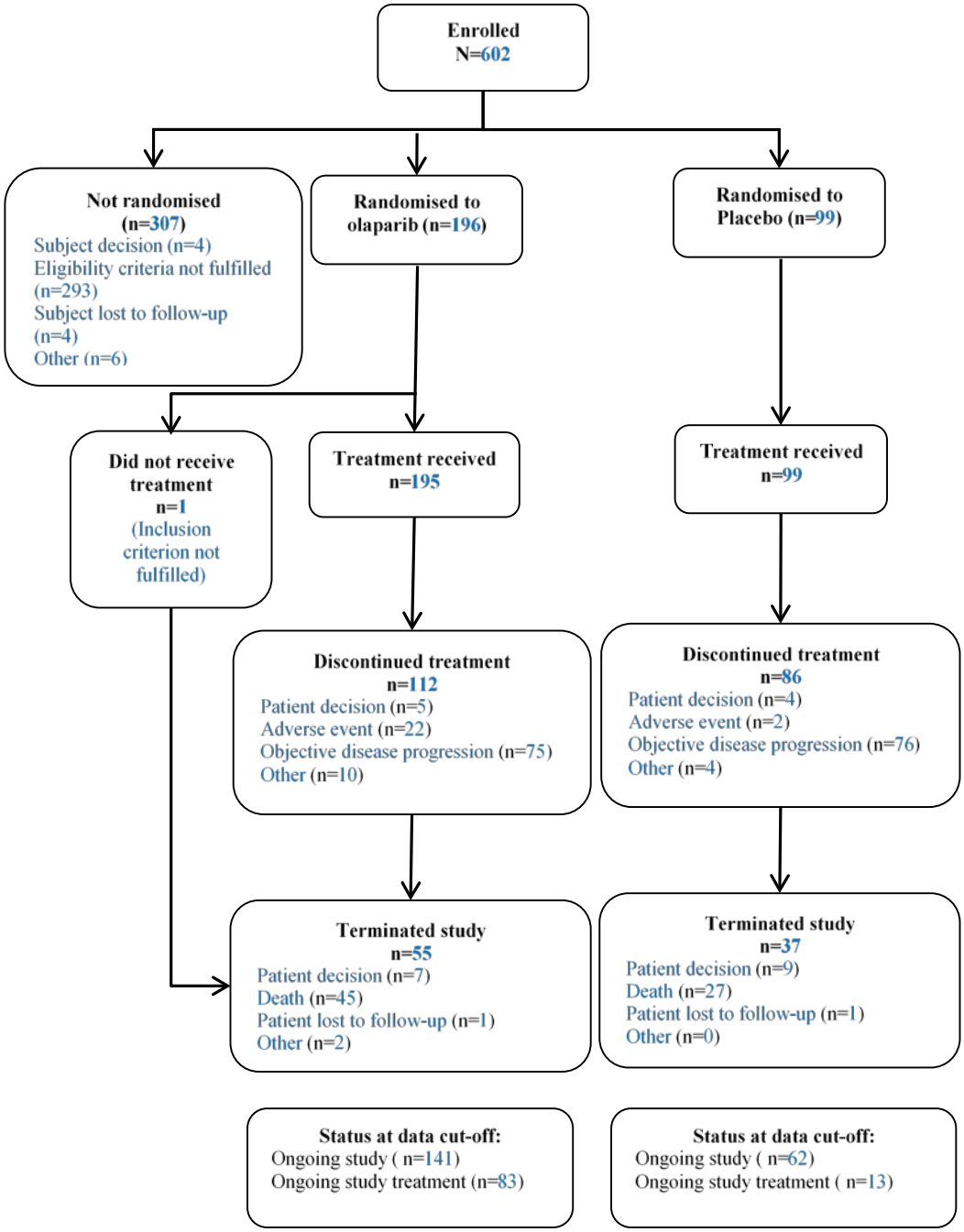
Results

Participant flow

Of the 602 subjects who enrolled for this study, 295 were randomized to receive maintenance treatment: 196 were allocated to olaparib and 99 to placebo.

The data cut-off for the primary analysis of PFS presented in this CSR (19 September 2016) took place when 187 progression events had occurred (~63.4% maturity), approximately 36 months after the first patient was enrolled. At this DCO, all efficacy, QoL and safety variables were analysed, as appropriate, based on the amount of data available at that time. The bioanalytical DCO was 27 May 2015 for PK samples received and all PK data were analysed, as appropriate.

Figure 9: Patient disposition (All patients)



Conduct of the study

Almost half of the patients enrolled in the study were not randomized, mainly because of the unfilled selection criteria (293 / 307 patients not randomised).

A notable number of patients in both olaparib (46 out of 195) and placebo (40 out of 99) groups were unblinded at the time of primary PFS analysis. The reason of unblinding of the patient was to determine the optimal subsequent therapy.

At the time of data cut-off for the analysis (19 September 2016), 96 patients were ongoing in the study (32.7%): 83 (42.6%) patients and 13 (13.1%) patients in the Olaparib arm and placebo arm, respectively.

A greater number of patients discontinued study treatment in the placebo group than in the olaparib group (86.9% versus 57.4%). However, more patients in olaparib arm stopped their treatment due to AEs than in the placebo arm (11.3% versus 2.0%).

- *Protocol deviations*

Table 14: Key protocol deviations (FAS)

	Number (%) of patients		
Key protocol deviation[a]	**Olaparib 300 mg bd (N=196)**	**Placebo (N=99)**	**Total (N=295)**
Number of patients with at least 1 key deviation	34 (17.3)	12 (12.1)	46 (15.6)
BRCA1 and/or *BRCA2* mutations considered non detrimental[b]	1 (0.5)	1 (1.0)	2 (0.7)
Baseline RECIST scan >28 days before study treatment is started	2 (1.0)	1 (1.0)	3 (1.0)
ECOG performance status 0-1	1 (0.5)	0	1 (0.3)
Missing or incomplete baseline RECIST 1.1 assessment on or before date of start of study treatment	3 (1.5)	1 (1.0)	4 (1.4)
Patients must have normal organ and bone marrow function measured within 28 days of randomisation	6 (3.1)	1 (1.0)	7 (2.4)
Patients receiving any systemic chemotherapy or radiotherapy (except for palliative reasons) within 3 weeks prior to study treat (or longer period depending on defined characteristics of agents used	5 (2.6)	2 (2.0)	7 (2.4)
Patients who have received at least 2 previous lines of platinum containing therapy prior to randomisation and met the further conditions of those therapies (as described in the protocol)	6 (3.1)	1 (1.0)	7 (2.4)

Key protocol deviation[a]	Number (%) of patients Olaparib 300 mg bd (N=196)	Placebo (N=99)	Total (N=295)
Pre-treatment CA-125 criterion:- 1st value within ULN, pt eligible for randomisation, 2nd sample not required.- 1st value > ULN then 2nd assessment performed ≥7 days after 1st. If ≥15% of 1st pt not eligible	10 (5.1)	2 (2.0)	12 (4.1)
RECIST scans outside of a scheduled visit window on >2 occasions	1 (0.5)	0	1 (0.3)
Resting ECG with QTc > 470 msec on 2 or more time points within a 24 hour period or family history of long QT syndrome	4 (2.0)	1 (1.0)	5 (1.7)
Severe non-compliance with treatment	5 (2.6)	3 (3.0)	8 (2.7)

a Key deviations before the start of treatment and during treatment.

b A patient had a deleterious *gBRCA* mutation identified using the Myriad CLIA test but was classified as *gBRCAwt* by the Myriad CDx test due to a technical issue. A patient was reported as *gBRCAwt* by both Myriad tests but reported as carrying a suspected deleterious mutation by local testing; subsequently, the local test has been confirmed as reporting a *gBRCA* VUS variant.

Note that the same patient may have had more than 1 key protocol deviation.

15.6% of patients had a protocol deviation, of which 17.3% were in olaparib arm and 12.1% in placebo arm. The most common key deviations were related to pre-treatment CA-125 levels. Key protocol deviations were generally balanced between the treatment groups.

Baseline data

- *Demographics*

Table 6: SOLO2 (tablet formulation): Summary of demographic and patient characteristics at baseline (FAS)

	Olaparib 300 mg bd (N=196)	Placebo (N=99)
Demographics		
Age (years)		
Mean (SD)	57.0 (9.20)	56.6 (8.90)
Median (range)	56.0 (28-83)	56.0 (39-78)
Age group (years), n (%)		
<50	38 (19.4)	25 (25.3)
≥50 to <65	118 (60.2)	52 (52.5)
≥65	40 (20.4)	22 (22.2)

	Olaparib 300 mg bd (N=196)	Placebo (N=99)
Race, n (%)		
White	173 (88.3)	91 (91.9)
Black/African American	1 (0.5)	0
Asian	22 (11.2)	7 (7.1)
Other	0	1 (1.0)
Ethnic group, n (%)		
Hispanic or Latino	10 (5.1)	1 (1.0)
Not Hispanic or Latino	186 (94.9)	98 (99.0)
Disease characteristics		
ECOG performance status, n (%)		
(0) Normal activity	162 (82.7)	77 (77.8)
(1) Restricted activity	32 (16.3)	22 (22.2)
(2) In bed ≤50% of the time	0	0
Unknown	2 (1.0)	0
Histology type, n (%)		
Serous	183 (93.4)	86 (86.9)
Endometroid	9 (4.6)	8 (8.1)
Mixed, epithelial	3 (1.5)	4 (4.0)
Other	0	1 (1.0)
Serous, papilliferum, endometrioid	0	1 (1.0)
Missing	1 (0.5)	0
Baseline CA-125 value, n (%)		
≤ULN	160 (81.6)	89 (89.9)
>ULN	34 (17.3)	10 (10.1)
Missing	2 (1.0)	0

Tumour characteristics		
Primary tumour location, n (%)		
Ovary	162 (82.7)	86 (86.9)
Fallopian tube	13 (6.6)	4 (4.0)
Primary peritoneal	18 (9.2)	9 (9.1)
Other	2 (1.0)	0
Missing	1 (0.5)	0
Patients with target lesions >2cm diameter at baseline, n (%)	30 (15.3)	18 (18.2)
Previous treatments		
Response to previous platinum chemotherapy (recorded at randomisation by IVRS)[a], n (%)		
PR	105 (53.6)	52 (52.5)
CR	91 (46.4)	47 (47.5)
Time to disease progression in the penultimate platinum-based chemotherapy prior to enrolment (recorded at randomisation by IVRS), n (%)		
>6 to ≤12 months	79 (40.3)	40 (40.4)
>12 months	117 (59.7)	59 (59.6)
Time from previous platinum chemotherapy to randomisation, n (%)		
≤8 weeks	187 (95.4)	97 (98.0)
>8 weeks	8 (4.1)	2 (2.0)
Missing	1 (0.5)	0
Prior use of bevacizumab, n (%)		
Yes	33 (16.8)	20 (20.2)
No	163 (83.2)	79 (79.8)

- *Prior therapy*

Table 15: SOLO2 (tablet formulation): Number of regimens of previous chemotherapy and previous platinum chemotherapy at baseline (FAS)

	Number (%) of patients	
	Olaparib 300mg bd (N=196)	Placebo (N=99)
Prior number of chemotherapy regimens		
0	0	0
1	0	0
2	108 (55.1)	60 (60.6)
3	54 (27.6)	21 (21.2)
4	23 (11.7)	12 (12.1)
5	6 (3.1)	2 (2.0)
6	2 (1.0)	3 (3.0)
7	2 (1.0)	0
13	0	1 (1.0)
Unknown	1 (0.5)	0
Mean (SD)	2.7 (0.98)	2.7 (1.43)
Median	2.0	2.0
Range	2-7	2-13
Prior number of platinum-based chemotherapy regimens		
0	0	0
1	0	0
2	110 (56.1)	62 (62.6)
3	60 (30.6)	20 (20.2)
≥4	26 (13.3)	17 (17.2)
Unknown	1 (0.5)	0

	Number (%) of patients	
	Olaparib 300mg bd (N=196)	Placebo (N=99)
Mean (SD)	2.6 (0.88)	2.6 (1.02)
Median	2.0	2.0
Range	2-7	2-7

- *BRCA mutation status*

Table 16: Summary of *BRCA* mutation status in SOLO2 by local germline and Myriad germline (FAS)

Treatment	Local germline status	Myriad CDx germline status Number (%) of patients			
		gBRCAm	*gBRCA* VUS	*gBRCAwt*	Missing
Olaparib (tablet) 300 mg bd (n=196)	*gBRCAm*	148 (75.5)	2 (1.0)	1 (0.5)	2 (1.0)
	Not performed	42 (21.4)	0	0	1 (0.5)
Placebo bd (n=99)	*gBRCAm*	80 (80.8)	2 (2.0)	1 (1.0)	0
	Not performed	16 (16.2)	0	0	0
Total (n=295)	*gBRCAm*	228 (77.3)	4 (1.4)	2 (0.7)	2 (0.7)
	Not performed	58 (19.7)	0	0	1 (0.3)

Of the 295 patients randomised, 5 patients were randomised with known t*BRCA*m. These 5 patients were subsequently confirmed to also have a g*BRCA* mutation by the Myriad CLIA Integrated BRACAnalysis test.

Table 17: SOLO2 (tablet formulation): Summary of patients by *BRCA1* and *BRCA2* status (DCO 19 September 2016)

	Local testing			Myriad CDx *gBRCAm*		
	Olaparib 300 mg bd (N=196)	Placebo (N=99)	Total (N=295)	Olaparib 300 mg bd (N=196)	Placebo (N=99)	Total (N=295)
***BRCA* gene name**						
BRCA1 (%)	103 (52.6)	55 (55.6)	158 (53.6)	132 (67.3)	61 (61.6)	193 (65.4)
BRCA2 (%)	50 (25.5)	28 (28.3)	78 (26.4)	58 (29.6)	35 (35.4)	93 (31.5)
Both (%)	0	0	0	0	0	0

	Local testing			Myriad CDx *gBRCAm*		
	Olaparib 300 mg bd (N=196)	Placebo (N=99)	Total (N=295)	Olaparib 300 mg bd (N=196)	Placebo (N=99)	Total (N=295)
***BRCA* gene name**						
Missing/non-*g BRCAm*	43 (21.9)	16 (16.2)	59 (20.0)	6 (3.1)	3 (3.0)	9 (3.1)

- *Subsequent therapies*

Table 18: SOLO2 (tablet formulation): Summary of subsequent therapies received in the FAS (DCO 19 September 2016)

FAS	Number of patients (%)		
	Olaparib 300 mg bd	Placebo	Total
N	196	99	295
Number of subsequent regimes			
0	23 (11.7)	9 (9.1)	32 (10.8)
1	43 (21.9)	34 (34.3)	77 (26.1)
2	24 (12.2)	26 (26.3)	50 (16.9)
3	15 (7.7)	16 (16.2)	31 (10.5)
4	4 (2.0)	0	4 (1.4)
5	3 (1.5)	1 (1.0)	4 (1.4)
Subsequently received a PARPi[a]	6 (3.1)	28 (28.3)	34 (11.5)

[a] One of the patients in the placebo group received olaparib as a subsequent therapy for ovarian cancer but was erroneously reported as receiving post-progression olaparib for breast cancer.

When considering only the patients who had disease progression, in both treatment groups, the majority of patients received a subsequent anticancer therapy (89/106 [84.0%] olaparib-treated patients vs 77/80 [96.3%] placebo-treated patients). A total of 31.6% [62/196] and 34.3% [34/99] of patients in the olaparib and placebo groups received a platinum containing regimen as a subsequent therapy and other chemotherapies (excluding platinum or bevacizumab) was received by 21.9% [43/196] and 40.4% [40/99] of patients in the olaparib and placebo groups, respectively (a platinum followed by olaparib maintenance was classified as a PARP regimen, even though it contained platinum).

Numbers analysed

The analysis sets and the number of patients in each analysis set are summarised in the below table.

Table 19: SOLO2: Analysis sets

	Number of patients (%)		
	Olaparib 300 mg bd (N=196)	**Placebo (N=99)**	**Total (N=295)**
Patients randomised	196	99	295
Patients included in FAS	196 (100)	99 (100)	295 (100)
Patients included in SAS	195 (99.5)	99 (100)	294 (99.7)
Patients excluded from SAS	1 (0.5)	0	1 (0.3)
Did not meet inclusion/exclusion criteria	1 (0.5)	0	1 (0.3)
Patients included in PK analysis set	94 (48.0)	0	94 (31.9)
Patients excluded from PK analysis set[a]	102 (52.0)	99 (100)	201 (68.1)
Patient has no analysable PK data	96 (49.0)	99 (100)	195 (66.1)
Patient has a history of GI surgery	6 (3.1)	0	6 (2.0)

[a] An individual patient could have been excluded for more than 1 reason.

Outcomes and estimation

Primary endpoint: PFS

The PFS analysis was conducted using data cut-off on 19 September 2016.

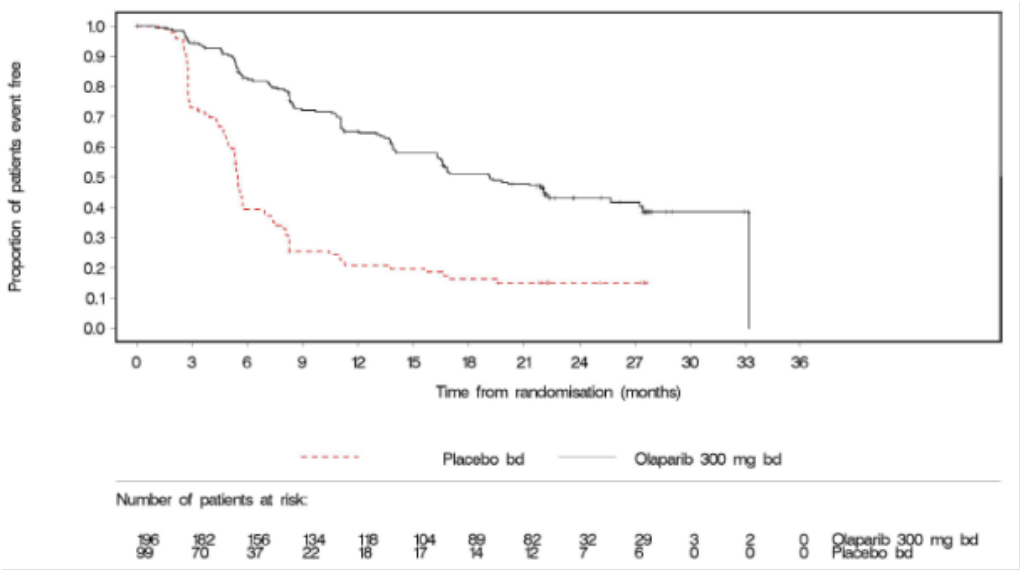
PFS investigator-assessed was statistically significant longer in the olaparib group than in the placebo group ((HR: 0.30; 95%CI 0.22-0.41; p<0.0001; median 19.1 vs 5.5 months). Analysis of PFS by BICR confirmed the robustness of the primary PFS result (HR: 0.25; 95% CI 0.18-0.35; p<0.0001).

Table 8: PFS results - SOLO2 (FAS, DCO 19 September 2016)

	Olaparib 300 mg bd	**Placebo**
PFS (investigator assessed, 63% maturity)		
Number of events: total number of patients (%)	107:196 (54.6)	80:99 (80.8)
Median PFS (months)	19.1 (16.3-25.7)	5.5 (5.2-5.8)
HR (95% CI)	0.30 (0.22-0.41)	
P-value (2-sided)	p<0.0001	
PFS (BICR assessed, 51% maturity)		

Number of events: total number of patients (%)	81:196 (41.3)	70:99 (70.7)
Median PFS (months)	30.2	5.5
HR (95% CI)	0.25 (0.18-0.35)	
P-value (2-sided)	p<0.0001	

Figure 10: SOLO2: Kaplan-Meier plot of PFS in the FAS (DCO 19 September 2016, by investigator assessment)



Sensitivity analyses for evaluation time bias (HR: 0.30; 95% CI0.23-0.41; p<0.0001) and attrition bias (HR: 0.28; 95% CI 0.21-0.38; p<0.0001) were all consistent with the primary analysis.

Secondary endpoints

Overall survival

At interim OS analysis (24% maturity), the results showed a non-statistically significant numerical advantage overall survival; the HR was 0.80 (95% CI 0.50-1.31; p=0.4267). Median OS was not reached in either treatment group.

Table 20: analysis of OS (DCO 19 September 2016)

	Full Analysis Set	
	Olaparib 300 mg bd	**Placebo**
Number of events: total number of patients (%)	45:196 (23.0)	27:99 (27.3)

	Full Analysis Set	
	Olaparib 300 mg bd	**Placebo**
Median follow-up for OS (months)	25.3	25.1
Median OS (months)	-	-
HR (95% CI)	0.80 (0.50-1.31)	
P-value (2-sided)	P=0.4267	

TDT, TFST, TSST and PFS2

Analyses of the intermediate clinical endpoints of TDT, TFST and TSST, each demonstrated a nominally statistically significant and clinically meaningful reduction in the risk of discontinuation of study treatment or death, delays in time until the first and the second subsequent therapies or death, respectively, in olaparib-treated patients compared to placebo-treated patients.

PFS2 met statistical significance (HR:0.50; 95% CI 0.34-0.72; p=0.0002; median not reached vs 18.4 months).

Table 8: SOLO2: Summary of key efficacy outcome variables (FAS, DCO 19 September 2016)

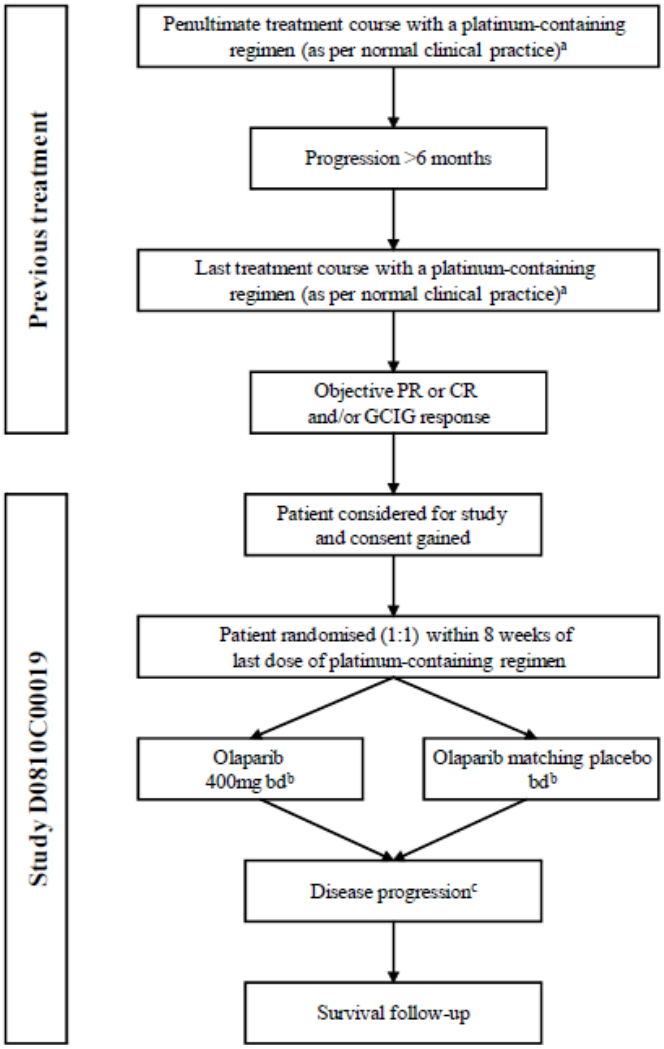
	Olaparib 300 mg bd	**Placebo**
PFS2 (40% maturity)		
Number of events: total number of patients (%)	70:196 (35.7)	49:99 (49.5)
Median PFS2 (months)	Not reached (24.1- NR)	18.4 (15.4-22.8)
HR (95% CI)	0.50 (0.34-0.72)	
P-value (2-sided)	p=0.0002	
TDT		
Number of events: total number of patients (%)	112:196 (57.1)	86:99 (86.9)
Median time (months)	19.4 (14.9-26.9)	5.6 (5.0-7.0)
HR (95% CI)	0.31 (0.23-0.42)	
Nominal P-value (2-sided)	p<0.0001	
TFST		

	Olaparib 300 mg bd	Placebo
Number of events: total number of patients (%)	92:196 (46.9)	79:99 (79.8)
Median time (months)	27.9 (22.6-NR)	7.1 (6.3-8.3)
HR (95% CI)	0.28 (0.21-0.38)	
Nominal P-value (2-sided)	p<0.0001	
TSST		
Number of events: total number of patients (%)	68:196 (34.7)	60:99 (60.6)
Median time (months)	Not reached (NR)	18.2 (15.0-20.5)
HR (95% CI)	0.37 (0.26-0.53)	
Nominal P-value (2-sided)	p<0.0001	

Study 19 (capsule formulation)

This study was a Phase II, randomised, double blind, multicentre placebo-controlled study to assess the efficacy of olaparib (capsule formulation) in the treatment of patients with platinum-sensitive (defined clinically as progression >6 months after previous platinum-based therapy) relapsed high-grade serous ovarian cancer, who had received ≥2 previous platinum regimens and were in partial response or complete response following their last platinum-containing regimen.

Figure 11: Study design



Methods

Study Participants

Patients were enrolled and randomised at 82 sites in 16 countries: Australia (7), Belgium (2), Czech Republic (1), Estonia (1), Germany (8), Israel (7), Canada (3), France (5), Netherlands (1), Poland (7), Romania (3), Russia (6), Spain (5), Ukraine (7), UK (8), and the US (11).

Main Inclusion Criteria:

✓ Patients must have been ≥18 years

- ✓ Female patients with histologically diagnosed serous ovarian cancer or recurrent serous ovarian cancer with a histology type of serous, or a serous component (including primary peritoneal and fallopian tube cancer)
    - Included patients who had developed recurrent ovarian cancer with macroscopic peritoneal metastases outside the pelvis or distant metastases
    - Patients with spinal cord compression could be considered if they have received definitive treatment for this and evidence of clinically stable disease for 28 days
- ✓ Patients had to have completed at least 2 previous courses of platinum-containing therapy
    - For the penultimate platinum-based chemotherapy course prior to enrolment on the study:
    - A patient had to have been defined as a platinum-sensitive after this treatment (defined as a disease progression greater than 6 months after completion of their last dose of platinum chemotherapy)
- ✓ For the last chemotherapy course prior to enrolment on the study:
    - Patients had to have received a platinum-containing regimen
    - Patients had to have demonstrated an objective stable maintained response (PR or CR) and this response needed to be maintained to permit entry into the study
    - Patients had to have been treated on the study within 8 weeks of completion of their final dose of the platinum-containing regiment
    - Chemotherapy course must have consisted of a minimum of 4 treatment cycles
- ✓ Pre-treatment CA-125 within the ULN
- ✓ ECOG PS ≤2
- ✓ A life expectancy of ≥16 weeks

Main exclusion criteria

- ✓ Low grade ovarian carcinoma (Grade 1)
- ✓ Patients who had drainage of their ascites during the final 2 cycles of their last chemotherapy regimen prior to enrolment on the study
- ✓ Previous treatment with PARPi including olaparib
- ✓ Patients with second primary cancer, except: adequately treated non-melanoma skin cancer, curatively treated in situ cancer of the cervix, DCIS, Stage 1, Grade 1 endometrial carcinoma, or other solid tumours including lymphomas (without bone marrow involvement) curatively treated with no evidence of disease for ≥5 years
- ✓ Patients with symptomatic uncontrolled brain metastases

Treatments

Patients were administered olaparib or matching placebo (capsule formulation) orally at 400 mg bd, continually throughout a 28 day cycle. Eight 50 mg olaparib or matching placebo capsules were to be taken at the same times each day, with approximately 240 mL of water.

Patients continued taking olaparib or matching placebo capsules until objective disease progression (determined by RECIST) provided that, in the Investigator's opinion, they were benefiting from treatment and they did not meet any other discontinuation criteria.

Objectives

Primary objective

- To determine the efficacy (assessed by PFS) of olaparib compared to placebo in the overall population.

Secondary objectives

- To determine the efficacy of olaparib compared to placebo by assessment of OS, best overall response, disease control rate, duration of response, change in tumour size, CA-125 response (Gynaecologic Cancer InterGroup [GCIG] criteria), time to progression by CA-125 (GCIG criteria), or RECIST.
- To determine the safety and tolerability of olaparib compared to placebo.
- To determine the effects of olaparib compared to placebo on disease related symptoms.
- To determine the quality of life of patients treated with olaparib compared to placebo.

Exploratory objectives

- To enable retrospective identification of tumours with increased sensitivity to olaparib by obtaining archival tumour samples for potential biomarker analyses.
- To obtain optional samples for biomarker analysis.
- To obtain an optional blood sample for DNA extraction for retrospective PGx analysis of the response to olaparib.

Outcomes/endpoints

The table below summarises the variables of this study, and shows how they relate to the study objectives.

Table 21: Main study objectives and variables

Objective			**Variable**
Priority	**Type**	**Description**	**Title and description**
Primary	Efficacy	To determine the efficacy (assessed by PFS) of	**Progression free survival**

		olaparib (capsule formulation) compared to placebo in the overall population	Defined as the time from randomisation to the earlier date of objective assessment of progression (per RECIST criteria) or death (by any cause in the absence of progression). At screening (within 28 days before first dose of study medication) and every 12 weeks after randomisation, up to 60 weeks then every 24 weeks until objective disease progression. *RECIST assessment by CT or MRI scans of abdomen and pelvis with other regions as clinically indicated.* *Scans were also reviewed by independent central review.*
Secondary	Efficacy	To determine the efficacy of olaparib (capsule formulation) compared to placebo by assessment of OS, best overall response and response rate (RECIST, CA-125, RECIST or CA-125), disease control rate, duration of response, change in tumour size at weeks 12 and 24, time to progression by CA-125 or RECIST.	**Overall survival** Defined as the time from randomisation to the date of death from any cause. **Best overall response** Best tumour response determined by RECIST (CR, PR, SD, PD, NE or NED). **Response rate** RECIST response, CA-125 response (GCIG criteria) and CA-125 (GCIG criteria) or RECIST response. **Disease control rate** Defined as the percentage of patients who had at least 1 confirmed visit response of CR or PR or demonstrated SD or NED for at least 23 weeks (i.e. 24 weeks ± 1 week) prior to any evidence of progression. **Duration of response** Measured from the time the measurement criteria for CR or PR were met (whichever was first recorded) until the patient progressed (per RECIST criteria). **Tumour size**

			Defined as the percentage change from baseline in tumour size at 12 weeks and 24 weeks. **Time to progression** Time to progression by CA-125 (GCIG criteria) or RECIST (Note: includes death as a progression event). *The tumour marker CA-125 was assessed locally from blood samples taken at the beginning of each cycle.*
Secondary	Safety	To determine the safety and tolerability of olaparib (capsule formulation) compared to placebo.	**Safety and tolerability** AEs, physical examination, vital signs including BP, pulse, ECG and laboratory findings including clinical chemistry, haematology and urinalysis.
Secondary	HRQL	To determine the quality of life of patients treated with olaparib (capsule formulation) compared to placebo. To determine the effects of olaparib (capsule formulation) compared to placebo on disease related symptoms.	**Health-related quality of life** Time to worsening and improvement/no change/worsening rates measured by TOI (primary HRQL endpoint; derived from FACT-O) and total FACT-O. **Disease related symptoms** Time to worsening and improvement/no change/worsening rates measured by FOSI (FACT/NCCN Ovarian Symptom Index), defined as the sum of 8 FACT-O items.
Exploratory	Efficacy	Intermediate clinical endpoints to evaluate whether PFS benefits are maintained with longer follow up, and to determine whether the PFS benefit is maintained beyond first progression (PFS2). These analyses were added at the time of the 58% interim OS analysis.	**Time to discontinuation of olaparib/placebo treatment (TDT)** The time from randomisation to discontinuation of olaparib/placebo treatment or death. **Time to first subsequent therapy or death (TFST)** The time from randomisation to the start date of the first cancer therapy received following the discontinuation of olaparib/placebo treatment or death. **Time to second subsequent therapy or death**

			(TSST; an approximation of PFS2) The time from randomisation to the start of a patient's second cancer therapy subsequent to the discontinuation of olaparib/placebo treatment or death.
Exploratory	Biomarker	To enable retrospective identification of tumours with increased sensitivity to olaparib by obtaining archival tumour samples for potential biomarker analyses [Excepting BRCA mutation status, not reported in CSR].	**Tumour biomarker data** Measurement of candidate biomarkers (including but not limited to ATM, MRE-11, MDC1, *BRCA)* status that may identify the HRD subset of tumours for correlation with benefit/risk of treatment with olaparib. **Circulating tumour biomarker data from blood** Measurement of candidate circulating predictive tumour biomarkers involved in response to olaparib.

Sample size

The study was planned on the basis that there would be 2 co-primary analysis populations: the first comprising all patients, the second comprising a subset of patients defined to be HRD.

However, the HRD status of patients could not be established at present due to the lack of diagnostic test to identify patients with HRD tumours. The analysis of efficacy in the HRD sub-population formed an exploratory objective of the study.

The following information refers to the HRD population in order to provide a clear understanding of the original sample size calculation.

The primary analysis was to be performed when a total of 137 PFS events had been observed in the overall population: this was reported in full in the CSR dated 26 July 2011 with 153 progression events. If the true HR was 0.75 (likely to correspond to a 33% increase in median PFS from 9 to 12 months) and the overall type I error rate was 20% (1-sided), there would be approximately 80% power to demonstrate a promising difference in favour of olaparib (ie, $p<0.2$, 1-sided).

The second co-primary analysis, in the HRD population, was to be performed at the time of the first co-primary analysis. If the true HR was equal to 0.62 (likely to correspond to a 61% increase in median PFS from 9 to 14 months) and the overall type I error rate was 20% (1-sided), there was approximately 80% power to demonstrate a promising difference in favour of olaparib ($p<0.2$, 1-sided) in the HRD group when 50 events were expected to have occurred.

The calculation for the overall population assumed that the HR for the non-HRD group was 0.9. Statistical significance at conventional levels, in favour of olaparib, was to be declared in the overall population for PFS if the observed p-value was <0.025 (1-sided).

It was prospectively defined to perform an initial analysis of OS at the time of the PFS DCO only if there were sufficient events (at least 20) to make it meaningful, with a final analysis of OS at a later point with more mature data. Statistical significance, in favour of olaparib, was to be declared in the overall population for OS if the observed p-value at the first OS analysis was <0.0125 (1-sided). The corresponding level of significance at the second OS analysis was to be calculated at the time of analysis. The overall Type I error rate for OS was to be controlled at the 2.5% level (1-sided) by accounting for the correlation between the 2 analyses.

It was intended that a total of 250 patients (125 patients in the olaparib group and 125 in the placebo group) would be randomised to the study. Assuming an HRD prevalence of 50% and a 25% attrition of samples, 94 patients would be included in the HRD group. If patients were recruited over 15 months according to a non-linear cumulative recruitment function of (t/15)2, and if the median PFS for the placebo group was 9 months, it was predicted that 137 PFS events overall (50 in the HRD group) would occur at 23 months after the first patient had entered the study.

- *Data and safety monitoring board*

An external IDMC was appointed to review key safety parameters when 100 patients had completed 2 cycles of treatment. The recommendation of the IDMC following this review was that the study should proceed unchanged.

Randomisation

Patients were to be randomised within 8 weeks after their last dose of the platinum containing regimen in a 1:1 ratio to one of 2 arms:

1. olaparib 400 mg bd
2. olaparib matching placebo bd

The randomisation scheme was stratified based on:

1. The time to disease progression from the completion of the penultimate platinum-containing therapy (last dose) prior to enrolment on the study(>6 to ≤12 months and >12 months).
2. Objective response to the last platinum-containing regimen prior to enrolment on the study (CR (defined as normal radiological findings and CA-125 within the normal range)/PR (defined as a RECIST PR and/or GCIG CA-125 response)
3. The ethnic descent of the patient (Jewish/Non Jewish)

Crossover to olaparib was not permitted within the design of the study, but patients were able to access PARP inhibitors outside of the study, and subsequent PARP inhibitor use was documented.

Blinding (masking)

Olaparib and placebo matched olaparib treatments were blinded. The active and placebo capsules were identical and presented in the same packaging to ensure blinding of the study medication.

Patients were not to be unblinded prior to the final PFS analysis, unless knowledge of the treatment assignment was necessary for the management of medical emergencies, or the patient was considered for enrolment into a study in which prior PARP therapy was not allowed.

Statistical methods

The study tested the hypothesis that olaparib 400 mg bd, given as maintenance therapy after a stable maintained objective response obtained upon completion of platinum-containing therapy, improves progression free survival (PFS) compared with placebo.

PFS was analysed using a Cox proportional hazards model adjusting for the following factors (using source-verified CRF data); ethnic descent, platinum sensitivity and response to final platinum therapy. All efficacy analyses were adjusted according to the true levels of the covariates, regardless of the levels declared at randomisation in the IVRS. The primary analysis of PFS did not censor patients who started subsequent therapy prior to progression. The effect of treatment was estimated by the adjusted HR together with its corresponding 80% and 95% CIs calculated using the profile likelihood approach. KM plots of PFS were presented by treatment group. If the observed p-value for the treatment difference was <0.025 (1 sided) then the result was regarded as statistically significant.

The analysis of OS used the same methodology and model as described for the primary analysis. Multiplicity adjustment for OS was pre-specified in the Study 19 CSP. Due to the interim analyses that were performed during the study, in order to declare statistical significance at the final OS analysis the observed p-value would need to have been <0.0095 (two-sided).

Interim Analysis

It was initially planned that the IDMC would conduct a single interim analysis of PFS when approximately 80 PFS events had occurred. The objective of this interim analysis was to determine whether there was sufficient efficacy to trigger a Phase III study in the overall population as per the IDMC charter. There was no intention to stop the study early on the basis of good efficacy results from the interim analysis. However, from emerging information in the ongoing olaparib programme, AstraZeneca determined in February 2010 that the interim analysis was not required to trigger Phase III studies and the interim analysis was not to be performed.

As only 1 analysis of PFS took place no adjustments were required to control the Type I error.

Consideration was to be given to formally analysing OS twice, depending on sufficient numbers of death events at the time of the primary analysis of PFS. If this was the case, the overall type I error for the OS analyses would be controlled at the 2.5% level (1-sided) by accounting for the correlation between the analyses. As part of CSP amendments, the AstraZeneca clinical project team added an interim analysis of OS, to be performed when there were approximately 100 deaths (~40% maturity) and then the final OS analysis was to be performed at approximately 85% maturity (~222 deaths).

Final analysis

The CSR addendum 3 presents descriptive results from the final analysis of OS at a DCO of 09 May 2016. Whilst p-values have been calculated, these are considered nominal only, with the multiple testing strategy only pre-specified for OS in the overall study population and not in the BRCA subgroup analyses.

Control of type I error for the exploratory endpoints of time to discontinuation of treatment or death (TDT), time to first subsequent therapy or death (TFST) and time to second subsequent therapy or death (TSST) were not defined in this Phase II study. Where p-values <0.05 are observed for these endpoints (meeting nominal significance), statistical significance is stated since they are interpreted in the context of a statistically significant improvement in PFS.

Multiplicity adjustment for OS was pre-specified in the Clinical Study Protocol. The testing strategy states that statistical significance, for OS in favour of olaparib, will be declared in the overall study population if the observed p-value is <0.001 (2-sided) at the first interim analysis, <0.03 (2-sided) at the second analysis with each subsequent analysis testing at half of the remaining alpha, unless it is the final analysis where all the remaining alpha will be spent. This allows the overall alpha to be controlled at 5% (2-sided).

This is the fourth and final analysis. The p-value required to declare statistical significance in the overall population is detailed below.

Table 22: Required p-values at each maturity analysis

Data cut-off	Analysis maturity	Alpha available	Test value (2 sided)	Remaining alpha % (2 sided)	Observed p-value in the Full Analysis Set
June 2010	7%	5	-	5	-
December 2011	38%	5	<0.001	4.9	0.75
November 2012	58%	4.9	<0.03	1.9	0.44
September 2015	77%	1.9	<0.0095	0.95	0.02483
Final	79%	0.95	<0.0095	0	0.02138

Determination of BRCA status

BRCA mutation testing was not mandatory for patients to participate in the study. However, *BRCA* mutation status data were obtained by three routes, as summarised below. Each route involved determination of gene sequence variants present within a patient's sample and classification of the sequence variant as to whether it could be regarded as causal of an increased risk of breast and ovarian cancer when inherited.

Route (i) for patients with pre-existing *BRCA* test results, the sequence variants (as determined on a blood sample) and local testing laboratory classification were captured in CRFs. This was pre-specified in the CSP.

Route (ii) blood samples from patients who consented to the optional genetic analysis were analysed and classified at Myriad in March 2012. This was retrospectively performed.

Route (iii) archival tumour samples in patients who consented to genetic analysis were analysed at Foundation Medicine for mutations in *BRCA*1 and *BRCA*2: the sequence variants were classified, by AstraZeneca Personnel, using the Breast Cancer Information Core (BIC) database on 6 December and 7 December 2012. This was retrospectively performed.

The MAH combined available data for germline *BRCA* mutation status and tumour *BRCA* mutation status provided from the various sources and re-classified the data into the categories listed below to define the subgroups for analysis. Data obtained via the CRF did not provide information on *BRCA* mutations variants of unknown significance (VUS) so no CRF data were reported for the "*BRCA* Unknown" category.

1. *BRCA* mutated

- patients with a deleterious or suspected deleterious mutation identified via germline testing (by Myriad and/or local test), or
- patients with a deleterious or suspected deleterious mutation identified in the tumour.

2. *BRCA* wildtype/*BRCA* unknown (variant of unknown significance; VUS): patients who were not *BRCA* mutated as defined above and at least one of the following:

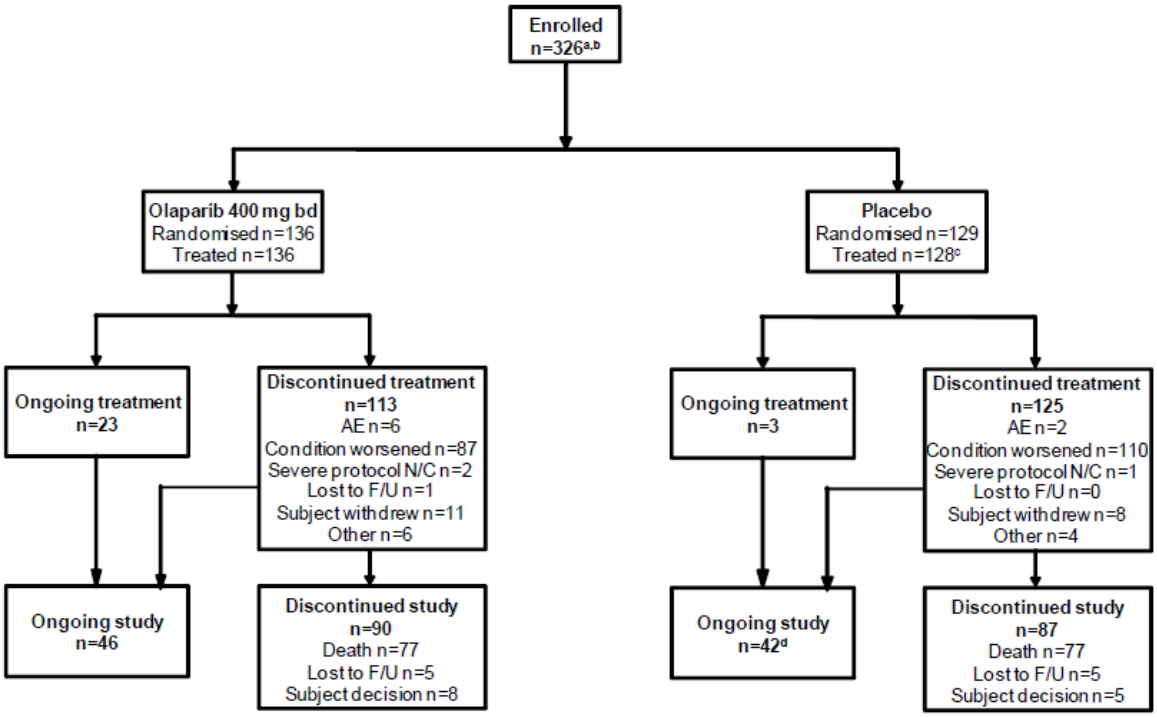
- Germline data from Myriad indicated a genetic variant of unknown significance, or
- patients who have undergone complete Myriad germline *BRCA* testing but with no deleterious or suspected deleterious mutation documented, or
- patients who have previously undergone testing at a local site and have no deleterious or suspected deleterious mutation documented, or
- tumour data showed either a *BRCA* variant of unknown significance or wild type.

3. *BRCA* missing

- patients who were not classified as BRCA mutated, BRCA wildtype/BRCA unknown (VUS) as defined above, and
- patients either did not have complete Myriad BRCA test reported and did not have BRCA result recorded from tumour analysis or a BRCA result recorded in the CRF.

Results

Participant flow



[a] Informed consent received.
[b] 61 patients were enrolled but not randomised as they were screen failures.
[c] One patient ([redacted]) was randomised to the placebo group but voluntarily withdrew her consent (and completely withdrew from the study) without receiving treatment.
[d] Patient [redacted] withdrew from the study on 25 August 2010, but at the time of database lock the necessary CRF pages were not available therefore this patient appears incorrectly as ongoing.

AE Adverse event; bd Twice daily; F/U Follow-up; N/C Non-compliance.
Data cut-off: 26 November 2012.

At the time of data cut-off for the final analysis (09 May 2016), 39 patients were ongoing in the study, of which 14 are still being treated by Olaparib and one by placebo.

The data cut-off (DCO) for the primary analysis was 30 June 2010 and the original CSR for the primary analysis was dated 26 July 2011. The CSR was revised to present data for the subpopulation of patients with breast cancer susceptibility gene (*BRCA*) mutation detected in blood (germline) and/or tumour samples as well as the overall population; this CSR was based on a DCO of 26 November 2012, and included interim overall survival (OS) analysis at 58% maturity; the CSR was dated 31 July 2013 and replaced the original CSR. Following the completion of this CSR, a number of data corrections were made and a CSR erratum was issued dated 27 September 2013. Subsequent to this, an addendum dated 25 November 2013, which was also based on the

DCO of 26 November 2012, presented results from a subgroup analysis based on classification of the patient population by the germline Myriad Clinical Laboratory Improvement Amendments (CLIA) accredited Integrated BRACAnalysis test.

An interim OS addendum was produced on 16 May 2016 at 77% data maturity, based on a DCO of 30 September 2015 and the addendum was issued. The current final addendum presents descriptive results from the final analysis of OS at 79% maturity with a DCO of 09 May 2016.

Table 23: Summary of patient disposition: Full Analysis Set

	Number (%) of patients		
	Olaparib 400 mg bd (n=136)	**Placebo (n=129)**	**Total (n=265)**
Patients randomised	136 (100)	129 (100)	265 (100)
Patients who received treatment	136 (100)	128 (99)	264 (100)
Patients ongoing study treatment at DCO[a]	14 (10)[b]	1 (1)	15 (6)
Patients who discontinued initial study treatment[a]	122 (90)	127 (99)	249 (94)
Adverse event	8 (6)	2 (2)	10 (4)
Condition under investigation worsened	94 (69)	116 (91)	210 (80)
Severe non-compliance to protocol	3 (2)	1 (1)	4 (2)
Patient lost to follow-up	1 (1)	0	1 (0.4)
Voluntary discontinuation by patient	14 (10)	8 (6)	22 (8)
Other	2 (2)	0	2 (1)
Patients completing the study	28 (21)	11 (9)	39 (15)
Patients who terminated study	136 (100)	129 (100)	265 (100)
Death	98 (72)	112 (87)	210 (79)
Patient lost to follow-up	2 (2)	3 (2)	5 (2)
Voluntary discontinuation of patient	7 (5)	3 (2)	10 (4)

[a] Percentages are calculated from number of patients who received treatment.
[b] Patient [redacted] discontinued treatment on 07 March 2016 due to disease progression. This date is however not reflected in the clinical database as it was not discovered until after database lock. This information is reflected in a footnote to the patient narrative (Module 5.3.5.3).
Patients who completed the study were ongoing at the time of the analysis DCO.
Data cut-off: 09 May 2016.

Recruitment

The first patient was enrolled on 28 August 2008 and the last patient was enrolled on 9 February 2010. The Clinical Study Report presents the 79% final overall survival data cut-off date, i.e. 09 May 2016.

Conduct of the study

Based on the detailed assessment of all deviations provided during the initial marketing authorization, the applicant considered that the important deviations reported in study 19 were unlikely to have influenced the overall study conclusions.

Baseline data

Demographic and Baseline characteristics

	FAS		*BRCAm*		*BRCAwt* / VUS	
	Olaparib (capsule) 400 mg bd (N=136)	Placebo (N=129)	Olaparib (capsule) 400 mg bd (N=74)	Placebo (N=62)	Olaparib (capsule) 400 mg bd (N=57)	Placebo (N=61)
Age (years)						
Mean (SD)	58.9 (10.95)	58.5 (9.89)	57.6 (10.37)	55.5 (10.53)	60.8 (11.69)	62.1 (7.82)
Median (range)	58.0 (21-89)	59.0 (33-84)	57.5 (38-89)	55.0 (33-84)	62.0 (21-80)	63.0 (49-79)
Age group (years), n (%)						
<50	30 (22.1)	20 (15.5)	19 (25.7)	16 (25.8)	10 (17.5)	1 (1.6)
≥50 to <65	61 (44.9)	74 (57.4)	38 (51.4)	35 (56.5)	20 (35.1)	37 (60.7)
≥65	45 (33.1)	35 (27.1)	17 (23.0)	11 (17.7)	27 (47.4)	23 (37.7)
Race, n (%)						
White	130 (95.6)	126 (97.7)	70 (94.6)	61 (98.4)	55 (96.5)	59 (96.7)
Black/African American	2 (1.5)	1 (0.8)	2 (2.7)	0	0	1 (1.6)
Asian	2 (1.5)	2 (1.6)	1 (1.4)	1 (1.6)	1 (1.8)	1 (1.6)
Other	2 (1.5)	0	1 (1.4)	0	1 (1.8)	0
Ethnic population, n (%)						
Jewish descent						
No	115 (84.6)	112 (86.8)	60 (81.1)	48 (77.4)	51 (89.5)	58 (95.1)
Yes	21 (15.4)	17 (13.2)	14 (18.9)	14 (22.6)	6 (10.5)	3 (4.9)

	FAS		*BRCAm*		*BRCAwt* / VUS	
	Olaparib (capsule) 400 mg bd (N=136)	**Placebo (N=129)**	**Olaparib (capsule) 400 mg bd (N=74)**	**Placebo (N=62)**	**Olaparib (capsule) 400 mg bd (N=57)**	**Placebo (N=61)**
Ashkenazi Jewish	17 (12.5)	12 (9.3)	12 (16.2)	10 (16.1)	5 (8.8)	2 (3.3)
Sephardic Jewish	1 (0.7)	1 (0.8)	1 (1.4)	1 (1.6)	0	0
Mizrahim Jewish	2 (1.5)	1 (0.8)	1 (1.4)	0	1 (1.8)	1 (1.6)
Other	0	3 (2.3)	0	3 (4.8)	0	0
Missing	1 (0.7)	0	0	0	0	0
ECOG performance status, n (%)						
- Normal activity	110 (80.9)	95 (73.6)	62 (83.8)	45 (72.6)	45 (78.9)	45 (73.8)
- Restricted activity	23 (16.9)	30 (23.3)	11 (14.9)	15 (24.2)	10 (17.5)	14 (23.0)
- In bed <50% of the time	1 (0.7)	2 (1.6)	0	1 (1.6)	1 (1.8)	1 (1.6)
Unknown	2 (1.5)	2 (1.6)	1 (1.4)	1 (1.6)	1 (1.8)	1 (1.6)
Primary tumour location, n (%)						
Ovary	119 (87.5)	109 (84.5)	65 (87.8)	54 (87.1)	50 (87.7)	49 (80.3)
Fallopian tube	3 (2.2)	3 (2.3)	1 (1.4)	2 (3.2)	2 (3.5)	1 (1.6)
Primary peritoneal	14 (10.3)	16 (12.4)	8 (10.8)	6 (9.7)	5 (8.8)	10 (16.4)
Other[a]	0	1 (0.8)[a]	0	0	0	1 (1.6)[a]

	FAS		*BRCAm*		*BRCAwt* / VUS	
	Olaparib (capsule) 400 mg bd (N=136)	Placebo (N=129)	Olaparib (capsule) 400 mg bd (N=74)	Placebo (N=62)	Olaparib (capsule) 400 mg bd (N=57)	Placebo (N=61)
Tumour grade, n (%)						
Well differentiated (G1)	0	0	0	0	0	0
Moderately differentiated (G2)	36 (26.5)	34 (26.4)	17 (23.0)	15 (24.2)	15 (26.3)	16 (26.2)
Poorly differentiated (G3)	97 (71.3)	89 (69.0)	55 (74.3)	46 (74.2)	41 (71.9)	41 (67.2)
Undifferentiated (G4)	2 (1.5)	4 (3.1)	1 (1.4)	0	1 (1.8)	4 (6.6)
Unassessable (GX)	1 (0.7)	2 (1.6)	1 (1.4)	1 (1.6)	0	0
Platinum sensitivity, n (%)						
>6 to ≤12 months	53 (39.0)	54 (41.9)	28 (37.8)	26 (41.9)	23 (40.4)	24 (39.3)
>12 months	83 (61.0)	75 (58.1)	46 (62.2)	36 (58.1)	34 (59.6)	37 (60.7)
Objective response, n (%)						
CR	57 (41.9)	63 (48.8)	36 (48.6)	34 (54.8)	20 (35.1)	25 (41.0)
PR	79 (58.1)	66 (51.2)	38 (51.4)	28 (45.2)	37 (64.9)	36 (59.0)

- *BRCA mutation status*

When the assessment of tBRCA mutation status was combined with the assessment of gBRCA mutation status, the BRCA mutation status was known for 254/265 patients (96% of the study population).

Table 24: Correlation between gBRCA and tBRCA mutation status: Full Analysis Set

Germline *BRCA* status	**Tumour *BRCA* status Number of patients (%)**				
	Mutant	Wild type	VUS	Missing	Total
Mutant	71 (26.8)*	3 (1.1)*	0	22 (8.3)*	**96 (36.2)**
Wild type	18 (6.8)*	65 (24.5)**	4 (1.5)**	23 (8.7)**	**110 (41.5)**
VUS	0	0	4 (1.5)**	0	**4 (1.5)**
Missing	22 (8.3)*	18 (6.8)**	4 (1.5)**	11 (4.2)	**55 (20.8)**
Total	**111 (41.9)**	**86 (32.5)**	**12 (4.5)**	**56 (21.1)**	**265 (100.0)**

g*BRCA* Germline breast cancer susceptibility gene; t*BRCA* Tumour breast cancer susceptibility gene;
a Variants of unknown significance.
**BRCAm*: defined as either tumour or germline mutation (n=136).
***BRCAwt*: or uncertain significance dataset: defined as wild type or variant of uncertain significance by either germline or tumour (and not *BRCAm*) (total n=118).

Knowledge of gBRCA mutation status was documented in 98/265 patients (37% of the study population); based on local laboratory testing. The tumour and/or gBRCA mutation status of all patients who had provided tumour and blood samples (prior to randomisation) with appropriate consent was determined, for germline BRCA mutations, using the Myriad Genetic Laboratories Inc diagnostic assay (Integrated BRACAnalysis) and by Foundation Medicine testing for tumour BRCA mutations. This resulted in the BRCAm status being known in 254/265 patients (96% of the study population) and the gBRCA mutation status being known for 210/265 patients (79% of the study population). In total, 136 patients had a BRCA mutation (either germline and/or tumour) and 118 were BRCAwt/VUS.

Overall, of the patients with a BRCA mutation, 68% of patients had a mutation in BRCA1 and 32% of patients had a mutation in BRCA2. These proportions are consistent with published literature (Alsop et al 2012a and Alsop et al 2012b).

Prior therapies

Table 25: Summary of time from most recent disease progression to randomisation / from completion of final platinum chemotherapy to randomisation: FAS

	Most recent progression to randomisation (days)	**Time from completion of final prior platinum chemotherapy to randomisation (days)**
Mean (standard deviation)	216.0 (113.43)	41.6 (32.46)
Median (range)	191.0 (56 to 1123)	40.0 (14 to 517)

The majority of patients in each treatment group were randomised to study treatment ≤8 weeks after completing their last platinum-containing therapy. Eight patients were not randomised within 8 weeks of completion of platinum (4 were randomised within 9 weeks).

Patients were randomised into the study a median of 40 days after completing their final platinum chemotherapy. They received an average of 3 previous chemotherapy regimens (range 2-11) and 2.6 previous platinum-containing chemotherapies (range 2-8).

Table 26: Summary of previous treatment modalities

	Number (%) of patients		
	Olaparib (N=136)	**Placebo (N=129)**	**Total (N=265)**
Chemotherapy	135* (99.3)	129 (100.0)	264 (99.6)
Radiotherapy	9 (6.6)	9 (7.0)	18 (6.8)
Immuno/hormonal therapy	21 (15.4)	14 (10.9)	35 (13.2)
Other systemic anticancer therapy	5 (3.7)	11 (8.5)	16 (6.0)

* 1 patient had received 2 previous lines of (platinum containing) chemotherapy but at the time of the last data cut-off these data had not been recorded on the database and hence were shown in the tables as 0.

A total of 8 patients in the olaparib group and 7 patients in the placebo group received bevacizumab treatment prior to the study.

Table 27: Summary of previous chemotherapy regimens at baseline: FAS

	Olaparib 400 mg bd n=136	Placebo n=129	Total n=265
Number of previous chemotherapy regimens			
2, n (%)	60 (44.1)[a]	63 (48.8)	122 (46.0)
3, n (%)	42 (30.9)	33 (25.6)	75 (28.3)
4, n (%)	19 (14.0)	20 (15.5)	39 (14.7)
5, n (%)	8 (5.9)	7 (5.4)	15 (5.7)
6, n (%)	2 (1.5)	3 (2.3)	5 (1.9)
7, n (%)	3 (2.2)	0	3 (1.1)
8, n (%)	1 (0.7)	3 (2.3)	4 (1.5)
11, n (%)	1 (0.7)	0	1 (0.4)
n	136	129	265
Mean (standard deviation)	3.0 (1.42)	3.0 (1.29)	3.0 (1.36)
Median	3	3	3
Number of previous platinum-containing chemotherapies			
2, n (%)	76 (55.9)[a]	84 (65.1)	159 (60.0)
3, n (%)	42 (30.9)	28 (21.7)	70 (26.4)
4, n (%)	13 (9.6)	12 (9.3)	25 (9.4)
5, n (%)	3 (2.2)	3 (2.3)	6 (2.3)
6, n (%)	1 (0.7)	1 (0.8)	2 (0.8)
7, n (%)	1 (0.7)	0	1 (0.4)
8, n (%)	0	1 (0.8)	1 (0.4)
n	136	129	265
Mean (standard deviation)	2.6 (0.92)	2.6 (0.95)	2.6 (0.93)
Median	2	2	2

bd Twice daily; FAS Full analysis set.
Data cut-off: 30 June 2010.

- *Subsequent therapies*

There was a high prevalence of subsequent therapy use following randomised treatment. Although crossover to olaparib was not permitted within the design of the study, patients were able to access PARP inhibitors outside of the study, through other clinical studies. Subsequent therapy use was reported by the investigators for patients ongoing in the study and so subsequent PARP inhibitor use was documented.

Of the 130 patients in the olaparib group of the FAS eligible to receive subsequent therapy (defined as having discontinued treatment without immediately terminating from the study [including death]), 91 (70%) received

≥1 subsequent therapy and 22 (17%) received ≥5 subsequent therapies. None went on to receive a PARP inhibitor

Of the 126 patients in the placebo group of the FAS eligible to receive subsequent therapy, 111 (88%) received ≥1 subsequent therapy and 24 (19%) received ≥5 subsequent therapies. Seventeen (14%) of these patients are known to have gone on to receive a PARP inhibitor (Table 11.2.6.6.1). No additional patients have received a PARP inhibitor since the 30 September 2015 DCO (1 additional patient had received a PARP inhibitor between the 26 November 2012 and 30 September 2015 DCOs).

Compared with the FAS, in the BRCA mutated subgroups the percentage of patients who received placebo and went on to receive a PARP inhibitor was higher: 14/61 (23%) patients in the BRCA mutated subgroup, 13/42 (31% patients in the gBRCA mutated subgroup, and 6/27 (22%) Myriad CLIA gBRCA mutated subgroup.

Table 28 Study 19 (capsule formulation): Summary of number of subsequent therapies and subsequent PARPi use by mutation status (DCO 09 May 2016)

	Number (%)		
	Olaparib 400 mg bd	**Placebo**	**Total**
Full Analysis Set			
N	136	129	265
N eligible to receive a subsequent therapy	130 (95.6)	126 (97.7)	256 (96.6)
N with ≥1 subsequent therapy	91 (66.9)	111 (86.0)	202 (76.2)
N with ≥2 subsequent therapy	65 (47.8)	86 (66.7)	151 (57.0)
N with ≥3 subsequent therapy	50 (36.8)	64 (49.6)	114 (43.0)
N with ≥4 subsequent therapy	32 (23.5)	43 (33.3)	75 (28.3)
N with ≥5 subsequent therapy	22 (16.9)	24 (18.6)	46 (17.4)
N who subsequently received a PARPi	0	17 (13.2)	17 (6.4)
BRCAm			
N	74	62	136
N eligible to receive a subsequent therapy	70 (94.6)	61 (98.4)	131 (96.3)
N with ≥1 subsequent therapy	47 (63.5)	55 (88.7)	102 (75.0)
N with ≥2 subsequent therapy	35 (47.3)	40 (64.5)	75 (55.1)
N with ≥3 subsequent therapy	28 (37.8)	30 (48.4)	58 (42.6)
N with ≥4 subsequent therapy	17 (23.0)	23 (37.1)	40 (29.4)
N with ≥5 subsequent therapy	13 (17.6)	11 (17.7)	24 (17.6)
N who subsequently received a PARPi	0	14 (22.6)	14 (10.3)

Numbers analysed

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

Table 29: Summary of analysis sets: All patients

	Number (%) of patients		
	Olaparib 400 mg bd n=136	Placebo n=129	Total n=265
Patients randomised	136	129	265
Full analysis set[a]	136	129	265
Patients included in safety analysis set[b,c]	136 (100.0)	128 (99.2)[d]	264 (99.6)
Evaluable for Response analysis set[e]	57 (41.9)	48 (37.2)	105 (39.6)
Evaluable for CA-125 analysis set[f]	8 (5.9)	9 (7.0)[e]	17 (6.4)
Evaluable for either CA-125 response or RECIST response set	61 (44.9)	53 (41.1)	114 (43.0)
HRQL analysis set - FOSI index[g]	117 (86.0)	115 (89.1)	232 (87.5)
HRQL analysis set – TOI[g] (TOI was the primary end point for HRQL analysis)	115 (84.6)	111 (86.0)	226 (85.3)
HRQL analysis set - Total FACT-O[g]	114 (83.8)	111 (86.0)	225 (84.9)

a All randomised patients analysed on an intent-to-treat (ITT) basis.
b All patients who received at least 1 dose of study treatment.
c Three patients received the incorrect study treatment for a short period due to a dispensing error. Patient [redacted] (olaparib group) received 1 bottle of placebo between Cycle 3 and Cycle 4 resulting in an olaparib dose interruption of approximately 1 week. No new AEs were reported for this patient between the Cycle 3 and Cycle 4. Patient [redacted] (olaparib group) received 2 bottles of placebo between Cycle 2 and Cycle 3 resulting in an olaparib dose interruption of approximately 2 weeks. Between Cycle 2 and Cycle 3, the patient had an SAE of Grade 3 syncope (Day 48) whilst potentially receiving placebo. This AE was counted in the olaparib safety analysis set. Patient [redacted] (placebo group) received 2 bottles of olaparib between Cycle 2 and Cycle 3 and, therefore, took the equivalent of olaparib 400 mg bd for approximately 2 weeks. Between Cycle 2 and Cycle 3, the patient had a non-serious AE of CTCAE Grade 3 fatigue (Day 56) while potentially receiving olaparib. This AE was counted in the placebo safety analysis set but the possibility that it was attributable to olaparib cannot be excluded.
d One patient (Patient [redacted]) was randomised to the placebo group but voluntarily withdrew her consent (and completely withdrew from the study) without receiving treatment.
e A subset of the full analysis set which includes patients with measurable disease at baseline.
f A subset of the full analysis set which includes patients evaluable for CA-125 response at baseline (CA-125 levels below the 2X ULN threshold at baseline).
g A subset of the full analysis set which includes patients who have Evaluable HRQL/Symptom Endpoints at baseline.

Outcomes and estimation

Primary variable: Progression free survival in the overall study population

The primary endpoint PFS was only analysed at the initial DCO (June 2010) and RECIST scans were not collected beyond this time point.

Table 30: Summary of progression status at time of primary PFS analysis: FAS

	Number (%) of patients	
	Olaparib 400 mg bd n=136	**Placebo n=129**
Progression, Total	60 (44.1)	94 (72.9)
RECIST progression	59 (43.4)	94 (72.9)
Death[a]	1 (0.7)	0
No progression, Total	76 (55.9)	35 (27.1)
Alive at time of analysis	70 (51.5)	31 (24.0)
Lost to follow-up	1 (0.7)	1 (0.8)
Withdrawn consent	5 (3.7)	3 (2.3)

bd Twice daily; FAS Full analysis set; PFS Progression free survival; RECIST Response Evaluation Criteria in Solid Tumours.

Note: This table presents data from the original analysis prior to a re-analysis of the PFS data (30 June 2010 data cut-off).

a Death in the absence of RECIST progression.

Data cut-off: 30 June 2010.

Table 31: Summary of primary analysis of PFS: FAS

	Olaparib 400 mg bd n=136	**Placebo n=129**
n (%) of events	60 (44.1)	94 (72.9)
Median PFS, months[a]	8.4	4.8
80% CI for median	8.1, 11.2	4.2, 5.3
95% CI for median	7.4, 11.5	4.0, 5.5
Treatment effect		
Hazard ratio	0.35	
80% CI	0.28, 0.43	
95% CI	0.25, 0.49	
2-sided p-value	<0.00001	

a Calculated using the Kaplan-Meier technique.

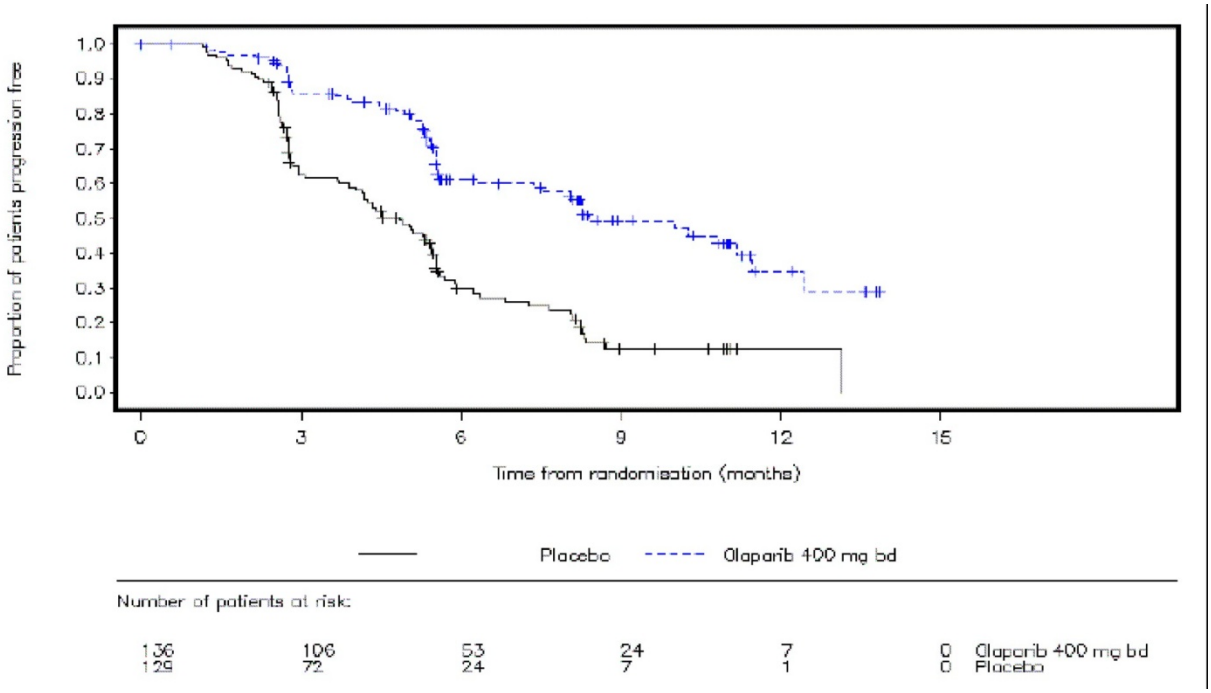
The analysis was performed using a Cox proportional hazards model with factors for treatment (olaparib vs. placebo), time to disease progression (>6-12 months and >12 months, in the penultimate platinum therapy prior to enrolment), objective response (CR or PR, in the last platinum therapy prior to enrolment), and Jewish descent (yes or no).

A hazard ratio < 1 favours olaparib.

bd Twice daily; CI Confidence interval; FAS Full analysis set; PFS Progression free survival.

Data cut-off: 30 June 2010.

Figure 3: Study 19: Kaplan-Meier plot of PFS in the Full Analysis Set (investigator assessment) DCO 30 June 2010



bd Twice daily; FAS Full analysis set.
Data cut-off: 30 June 2010.

Table 32: Supportive and sensitivity analyses of PFS: FAS

Analysis	Events:Patients	HR	80% CI	95% CI
Overall	Olaparib: 60:136 (44.1%) Placebo: 94:129 (72.9%)	0.35	0.28, 0.43	0.25, 0.49
Supportive analysis: Stratified log rank test	Olaparib: 60:136 (44.1%) Placebo: 94:129 (72.9%)	0.36	0.29, 0.44	0.25, 0.50
Sensitivity analysis: Evaluation time bias	Olaparib: 60:136 (44.1%) Placebo: 94:129 (72.9%)	0.39	0.31, 0.48	0.28, 0.54
Sensitivity analysis: Attrition bias	Olaparib: 60:136 (44.1%) Placebo: 93:129 (72.1%)	0.35	0.28, 0.44	0.25, 0.49
Sensitivity analysis: independent central review	Olaparib: 54:133 (40.6) Placebo: 81:127 (63.8)	0.39	0.31, 0.49	0.28, 0.56

CI Confidence interval; FAS Full analysis set; HR Hazard ratio; PFS Progression free survival.
Data cut-off: 30 June 2010.

Secondary variables

Table 33 Summary of key efficacy outcome secondary variables: Study 19 (capsule formulation)

	Full Analysis Set		***BRCAm***		***BRCAwt*/VUS**	
	N=265		**N=136**		**N= 118**	
	Olaparib 400 mg bd	**Placebo**	**Olaparib 400 mg bd**	**Placebo**	**Olaparib 400 mg bd**	**Placebo**
OS (79% maturity) – 09 May 2016 – Full Analysis Set						
Number of events: total number of patients (%)	98:136 (72)	112:129 (87)	49:74 (66)	50:62 (81)	45:57 (79)	57:61 (93)
Median time (months)	29.8 (26.9-35.7)	27.8 (24.9-33.7)	34.9 (29.2-54.6)	30.2 (23.1-40.7)	24.5 (19.8-35.0)	26.6 (23.1-32.5)
HR (95% CI)	0.73 (0.55-0.95)		0.62 (0.42-0.93)		0.84 (0.57-1.25)	

Table 33 Summary of key efficacy outcome secondary variables: Study 19 (capsule formulation)

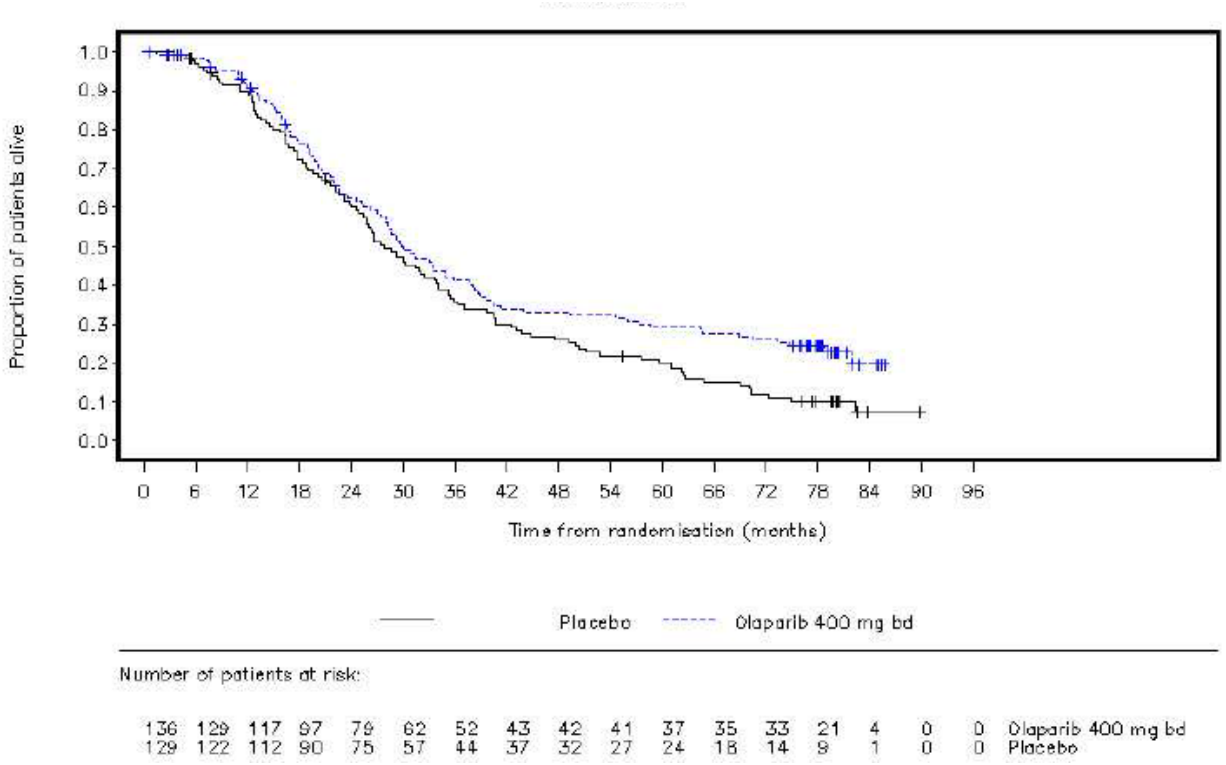
	Full Analysis Set		***BRCAm***		***BRCAwt*/VUS**	
	N=265		**N=136**		**N= 118**	
	Olaparib 400 mg bd	**Placebo**	**Olaparib 400 mg bd**	**Placebo**	**Olaparib 400 mg bd**	**Placebo**
Nominal P-value (2-sided)	p=0.02138		p=0.02140		p=0.39749	
TDT – DCO 09 May 2016 – Safety Analysis Set						
Number of events: total number of patients (%)	122:136 (90)	127:128 (99)	67:74 (91)	61:62 (98)	50:57 (88)	61:61 (100)
Median time (months)	8.6 (7.0-11.5)	4.6 (4.3-5.5)	11.0 (8.0-14.7)	4.6 (3.3-5.5)	7.5 (5.6-11.0)	4.9 (4.3-5.7)
HR (95% CI)	0.39 (0.30-0.51)		0.36 (0.25-0.52)		0.41 (0.27-0.61)	
Nominal P-value (2-sided)	p<0.00001		p<0.00001		p=0.00001	
TFST – DCO 09 May 2016 – Safety Analysis Set						
Number of events: total number of patients (%)	106:136 (78)	124:128 (97)	55:74 (74)	59:62 (95)	47:57 (83)	60:61 (98)
Median time (months)	13.3 (11.3-15.7)	6.7 (5.7-8.2)	15.6 (11.9-28.2)	6.2 (5.3-9.2)	12.9 (7.8-15.3)	6.9 (5.7-9.3)
HR (95% CI)	0.39 (0.30-0.52)		0.33 (0.22-0.49)		0.45 (0.30-0.66)	
Nominal P-value (2-sided)	p<0.00001		p<0.00001		p=0.00006	
TSST – DCO 09 May 2016 – Safety Analysis Set						
Number of events: total number of patients (%)	104:136 (77)	119:128 (93)	53:74 (72)	56:62 (90)	47:57 (83)	59:61 (97)
Median time (months)	19.1 (16.5-21.4)	14.8 (14.0-17.2)	21.4 (17.7-33.4)	15.3 (14.0-18.7)	17.0 (15.2-19.8)	14.7 (12.8-18.3)

Table 33 Summary of key efficacy outcome secondary variables: Study 19 (capsule formulation)

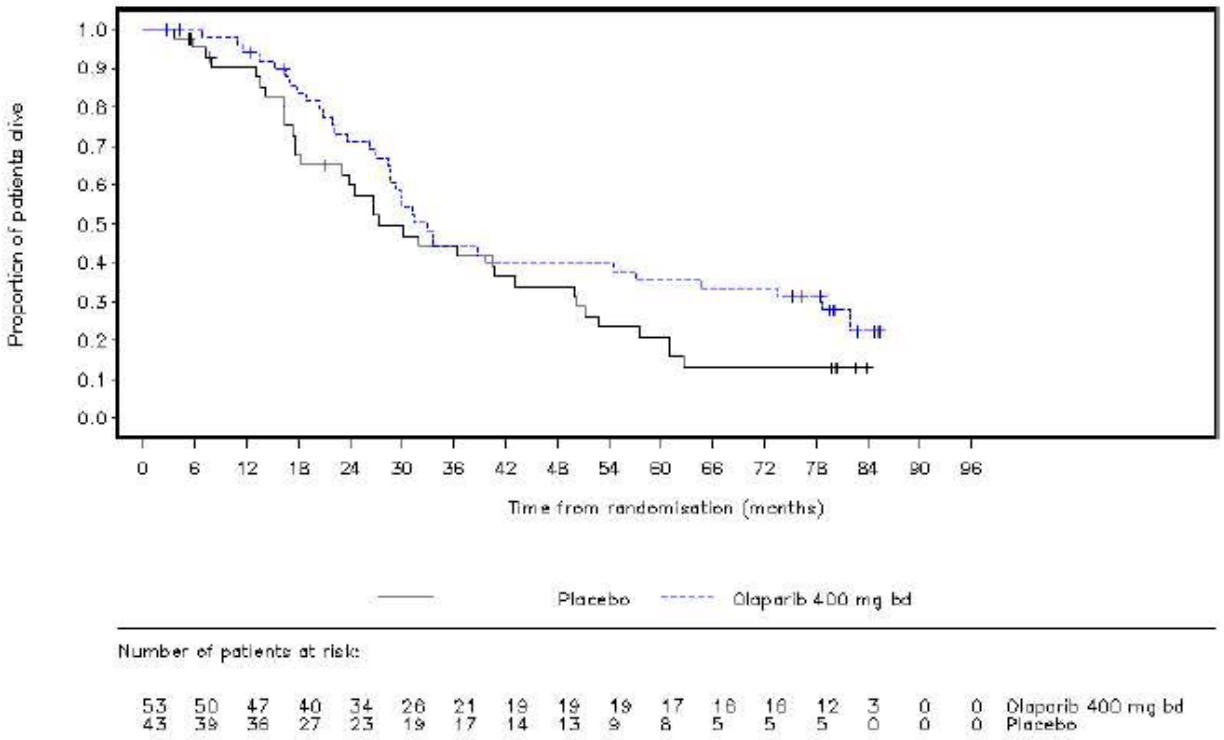
	Full Analysis Set N=265		*BRCAm* N=136		*BRCAwt*/VUS N= 118	
	Olaparib 400 mg bd	Placebo	Olaparib 400 mg bd	Placebo	Olaparib 400 mg bd	Placebo
HR (95% CI)	0.53 (0.40-0.69)		0.43 (0.29-0.64)		0.63 (0.43-0.94)	
Nominal P-value (2-sided)	p<0.00001		p=0.00003		p=0.02263	

Figure 5: Study 19: Kaplan-Meier plot of OS: overall population (A), gBRCAmt (B) and gBRCA wt/VUS (C) (FAS, DCO 09 May 2016)

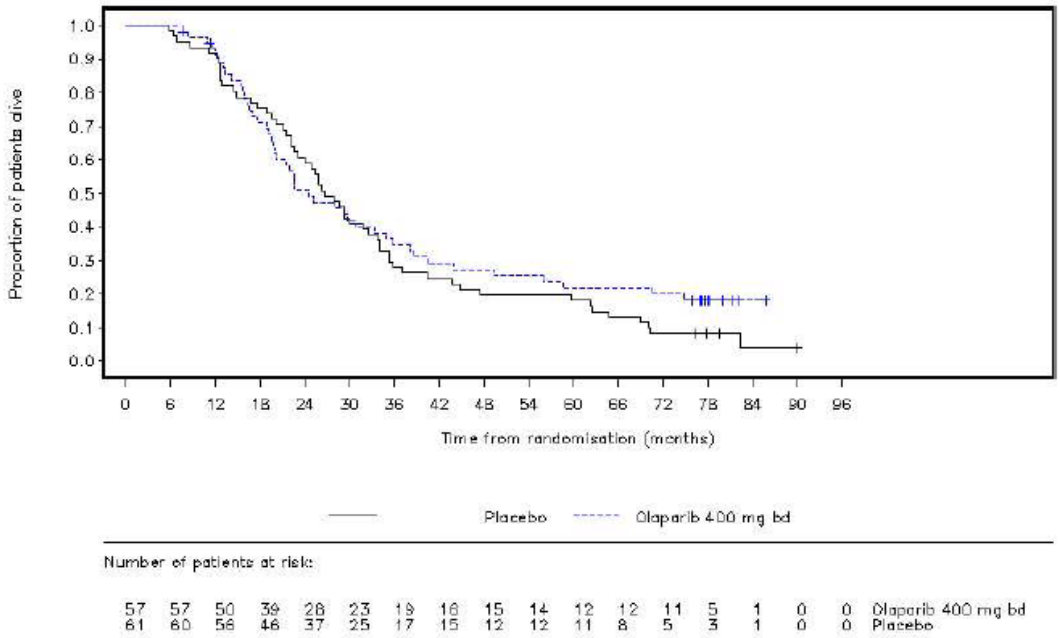
A



B



C



Data derived from: Figure 11.2.2.2, Study 19 CSR Addendum 3 (DCO 09 May 2016), Module 5.3.5.1.

Summary of main studies

The following tables summarise the efficacy results from the main studies 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 1034: Summary of efficacy for SOLO2 study

Title: A Phase III Randomised, Double Blind, Placebo Controlled, Multicentre Study of Olaparib Maintenance Monotherapy in Platinum Sensitive Relapsed BRCA Mutated Ovarian Cancer Patients who are in Complete or Partial Response Following Platinum based Chemotherapy			
Study identifier	D0816C00002		
Design	- Phase III - Randomized (2:1), double blind, multi-centre study - Placebo controlled		
	Duration of main phase:		First patient enrolled: 6 August 2013 Ongoing: primary PFS and interim OS analysis completed
Hypothesis	Superiority		
Treatments groups	Olaparib 300mg bd		n= 196
	Placebo		n= 99
Endpoints and definitions	Primary endpoint	PFS	Time from randomisation until the date of objective radiological disease progression according to modified RECIST 1.1 or death (by any cause in the absence of progression) regardless of whether the patient discontinued randomised therapy or received another anti-cancer therapy prior to progression
	Secondary endpoint	OS	Time from the date of randomisation until death due to any cause
		PFS2	Time from the date of randomisation to the earliest of the progression event subsequent to that used for the primary variable PFS or death.
		TFST	Time to first subsequent therapy or death
		TSST	Time to second subsequent therapy or death
		TDT	Time to study drug discontinuation or death
		Time to earliest progression of RECIST or CA-125	Time from randomisation to the earlier date of modified RECIST 1.1 or CA-125 progression or death by any cause
		HRQoL: Change from baseline in TOI score	TOI is composed of the following scales of the FACT-O: physical and functional well-being and additional concerns (ovarian cancer subscale)
Database lock	Data cut-off date: 19 September 2016		
Results and Analysis			
Analysis description	Primary Analysis		

Analysis population and time point description	Full analysis set (FAS) consisted of all randomized patients analyzed on an ITT basis		
Descriptive statistics and estimate variability	Treatment group	Olaparib	Placebo
	Number of subject	196	99
	PFS events, n (%)	107 (54.6)	80 (80.8)
	Median PFS, months	19.1 (16.3-25.7)	5.5 (5.2-5.8)
	PFS2 events, n (%)	70 (35.7)	49 (49.5)
	Median PFS2, months	NR (24.1- NR)	18.4 (15.4-22.8)
	n (%) of deaths	45 (23.0)	27 (27.3)
	Median OS, months	NR (NR)	NR (NR)
	n (%) of events	112 (57.1)	86 (86.9)
	Median TDT, months	19.4 (14.9-26.9)	5.6 (5.0-7.0)
	n (%) of events	92 (46.9)	79 (79.8)
	Median TFST, months	27.9 (22.6-NR)	7.1 (6.3-8.3)
	n (%) of events	68 (34.7)	60 (60.6)
	Median TSST, months	NR (NR)	18.2 (15.0-20.5)

Effect estimate per comparison	Primary endpoint PFS	Comparison groups	Olaparib - placebo
		HR	0.30
		95% CI	[0.22; 0.41]
		P-value	<0.0001
	Secondary endpoint PFS2	Comparison groups	Olaparib - placebo
		HR	0.50
		95% CI	[0.34; 0.72]
		P-value	0.0002
	Secondary endpoint OS	Comparison groups	Olaparib - placebo
		HR	0.80
		95% CI	[0.50; 1.31]
		P-value	0.4267
	Secondary	Comparison groups	Olaparib - placebo

	endpoint TDT	HR	0.31
		95% CI	[0.23. 0.42]
		P-value	<0.0001
	Secondary endpoint TFST	Comparison groups	Olaparib - placebo
		HR	0.28
		95% CI	[0.21; 0.38]
		P-value	<0.0001
	Secondary endpoint TSST	Comparison groups	Olaparib - placebo
		HR	0.37
		95% CI	[0.26; 0.53]
		P-value	<0.0001

Table 1135: Summary of efficacy for study 19

Phase II randomised, double blind, multicentre study to assess the efficacy of AZD2281 in the treatment of patients with platinum sensitive serous ovarian cancer following treatment with two or more platinum containing regimens		
Study identifier	D0810C00019	
Design	- randomised, double blind, multi-centre study - 2 arms - advanced platinum-sensitive serous ovarian cancer patients who had received 2 or more previous platinum-containing regimens	
	Duration of main phase:	Continually throughout a 28 day cycle until objective disease progression
	Duration of previous phase:	Completion of at least 2 previous courses of platinum-containing therapy: - disease progression greater than 6 months after completion of their last dose of penultimate platinum chemotherapy - treatment within 8 weeks of completion of the final dose of the last platinum-containing regimen (minimum of 4 treatment cycles) with a maintained PR or CR.
	Duration of follow-up phase:	Once discontinued from study medication, other treatment options at the discretion of the investigator. Follow-up for survival unless withdrawal of consent.
Hypothesis	Superiority	
Treatments groups	Olaparib 400mg bd	n=136
	placebo	n=129

Endpoints and definitions	Primary endpoint	PFS	In the original analysis, the primary variable of PFS was derived based on investigator assessments recorded on the CRFs. The study protocol required radiological examinations to be retained at the study sites in order to allow a blinded independent central review if required. A retrospective blinded independent central review of scans was performed as a sensitivity analysis to confirm the robustness of the original primary PFS analysis.
	Secondary endpoints		OS, best overall response and response rate (RECIST, CA-125, RECIST or CA-125), disease control rate, duration of response, change in tumour size at weeks 12 and 24, time to progression by CA-125 or RECIST. Safety
	Exploratory endpoints	TDT, TFST, TSST	Time to discontinuation of olaparib/placebo treatment, Time to first subsequent therapy or death, Time to second subsequent therapy or death
Database lock	Primary PFS analysis data cut-off: 30 June 2010 79% final overall survival data cut-off: 09 May 2016		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis population and time point description	Full analysis set (FAS) consisted of all randomized patients analyzed on an ITT basis Post-hoc analysis for BRCA subgroups		

Descriptive statistics and estimate variability	Treatment group	Olaparib 400mg bd	placebo
	Overall population (n=265)		
	Number of subjects	136	129
	Median PFS, months	8.4 (7.4-11.5)	4.8 (4.0-5.5)
	Median OS, months	29.8 (26.9-35.7)	27.8 (24.9-33.7)
	Exploratory analyses: TDT TFST TSST (Median time, months)	 8.6 (7.0-11.5) 13.3 (11.3-15.7) 19.1 (16.5-21.4)	 4.6 (4.3-5.5) 6.7 (5.7-8.2) 14.8 (14.0-17.2)
	BRCA mutant subgroup (n=136)		
	Number of subjects	74	62
	Median PFS, months	11.2 (8.3-NR)	4.3 (3.0-5.4)

	Median OS, months	34.9 (29.2-54.6)	30.2 (23.1-40.7)
	Exploratory analyses: TDT TFST TSST (Median time, months)	 11.0 (8.0-14.7) 15.6 (11.9-28.2) 21.4 (17.7-33.4)	 4.6 (3.3-5.5) 6.2 (5.3-9.2) 15.3 (14.0-18.7)
	BRCA WT/VUS subgroup (n=118)		
	Number of subjects	57	61
	Median PFS, months	7.4 (5.5-10.3)	5.5 (3.7-5.6)
	Median OS, months	24.5 (19.8-35.0)	26.6 (23.1-32.5)
	Exploratory analyses: TDT TFST TSST (Median time, months)	 7.5 (5.6-11.0) 12.9 (7.8-15.3) 17.0 (15.2-19.8)	 4.9 (4.3-5.7) 6.9 (5.7-9.3) 14.7 (12.8-18.3)
Effect estimate per comparison	Overall population		
	Primary endpoint (PFS)	Comparison groups	Olaparib - placebo
		HR	0.35
		95% CI for median	[0.25, 0.49]
		P-value	p<0.00001
	Secondary endpoint OS	Comparison groups	Olaparib - placebo
		HR	0.73
		95% CI for median	[0.55, 0.95]
		P-value	p=0.02138
	Exploratory analyses: TDT TFST TSST	Comparison groups	Olaparib - placebo
		HR	0.39 0.39 0.53
		95% CI for median	[0.30, 0.51] [0.30, 0.52] [0.40, 0.39]
		P-value	p<0.00001
	BRCA mutant subgroup		
	Primary endpoint (PFS)	Comparison groups	Olaparib - placebo
		HR	0.18

		95% CI for median	[0.10, 0.31]
		P-value	p<0.00001
	Secondary endpoint OS	Comparison groups	Olaparib - placebo
		HR	0.62
		95% CI for median	[0.42,0.93]
		P-value	p=0.02140
	Exploratory analyses: TDT TFST TSST	Comparison groups	Olaparib - placebo
		HR	0.36 0.33 0.43
		95% CI for median	[0.25, 0.52] [0.22, 0.49] [0.29, 0.64]
		P-value	p=<0.00001 p<0.00001 p= 0.00003
	BRCA WT/VUS subgroup		
	Primary endpoint (PFS)	Comparison groups	Olaparib - placebo
		HR	0.54
		95% CI for median	[0.34, 0.85]
		P-value	p=0.00745
	Secondary endpoint OS	Comparison groups	Olaparib - placebo
		HR	0.84
		95% CI for median	[0.57, 1.25]
		P-value	P= 0.39749
	Exploratory analyses: TDT TFST TSST	Comparison groups	Olaparib - placebo
		HR	0.41 0.45 0.63
		95% CI for median	[0.27, 0.61] [0.30, 0.66] [0.43, 0.94]
		P-value	p= 0.00049 p=0.00010 p=0.02263

2.5.3. Discussion on clinical efficacy

The MAH submitted an extension application to the current marketing authorisation to register the tablet formulation of olaparib (300 mg orally bd, tablets containing 150 mg, 4 tablets per day starting dose and 100mg strength to be used for dose reductions) which will progressively replace the capsule formulation (400 mg orally bd, capsules containing 50 mg of olaparib, 16 capsules per day).

The indication for capsule formulation remains the same, while indication for tablet formulation is as monotherapy for the maintenance treatment of adult patients with platinum sensitive relapsed (PSR) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.

The Phase III study 'SOLO2' and the updated analysis of the Phase II study 'Study 19' have been submitted to support this extension application. Given that only patients with germline BRCA mutations have been included in the pivotal Phase III SOLO-2 study with tablet formulation, the updated results of the Phase II Study 19 conducted with capsule formulation were provided to support an enlarged indication regardless of BRCA1/2 status.

The proposed indication also refers to high-grade ovarian cancer. The study population for SOLO2 was patients with PSR high-grade serous or high-grade endometrioid ovarian cancer, while for Study 19 the study population was patients with PSR high grade serous ovarian cancer.

Recent evidence suggests that serous and endometrioid carcinomas arise from the tubal fimbrae, suggesting similar biology and origin for the high grade epithelial histologies (Jayson et al 2014). Pennington et al reported in their study that contrary to the common belief of homologous recombination deficiencies being characteristic of high-grade serous ovarian cancer only, DNA repair deficiencies were found equally commonly in carcinomas with non-serous histology (Pennington et al 2014).

Design and conduct of clinical studies

Besides differences in the pharmaceutical formulation and the study population (selected vs unselected patients), SOLO2 and Study 19 were designed to be fundamentally alike in terms of outcome measures, conduct and geographical spread of patients.

The pivotal study SOLO2 of this application was a Phase III randomised, double-blind study of maintenance therapy with olaparib or placebo in platinum sensitive relapsed *BRCA* mutated ovarian cancer patients who are in complete or partial response following platinum containing chemotherapy. This study already started at the time of the initial marketing authorization approval of olaparib in both germline and somatic BRCAm patients in order to provide confirmatory efficacy and safety data. All patients were documented to have a deleterious/suspected deleterious BRCA1 or BRCA2 gene mutation prior to randomisation. Eligibility for randomisation was based on either local testing (germline or tumour) or Myriad CLIA testing. All patients were also subsequently tested using the Myriad CDx. Prior to receiving maintenance therapy, patients were required to have received at least 2 previous lines of platinum-containing therapy and completed their platinum-containing regimen as per normal clinical practice prior to enrolment, with a minimum of 4 cycles required. Patients could have received bevacizumab in conjunction with the penultimate but not during the chemotherapy course immediately prior to randomisation. Patients were randomised in a 2:1 ratio to received olaparib or placebo as maintenance therapy at a dose of 300 mg twice daily. The treatment was provided until progression. Two tablet strengths were available in order to manage dose reductions: tablet of 150 mg and 100 mg.

Study 19 conducted with the capsule form of Lynparza (400mg bd), was a Phase II, randomised, double-blind, multicentre placebo-controlled study to assess the efficacy of olaparib (capsule formulation) in the treatment of patients with platinum-sensitive (defined clinically as progression >6 months after previous platinum-based

therapy) relapsed high-grade serous ovarian cancer, who had received ≥2 previous platinum regimens and were in partial response or complete response following their last platinum-containing regimen. The population is solely targeted on patients with high-grade serous ovarian cancer whereas the proposed indication is extended to high grade ovarian cancer (deletion of "serous"). The study was performed in platinum-sensitive serous ovarian cancer patients who had received 2 or more previous platinum-containing regimens. The Study 19 protocol did not require the 2 prior platinum regimens determining eligibility to be sequential (eg, patients could have received a non-platinum regimen between the penultimate and the last platinum chemotherapy). Patients included in Study 19 were not selected for the presence of a BRCA mutation. Patients were administered olaparib or matching placebo (capsule formulation) orally at 400 mg bd, continually throughout a 28 day cycle.

Both trials were a placebo-controlled study. At the time these studies were commenced, there was no therapeutic option approved for the maintenance treatment of ovarian cancer after a response following a platinum-based chemotherapy. Therefore, the use of placebo as comparator was considered to be appropriate in order to determine the efficacy of olaparib as maintenance treatment of ovarian cancer after a response to platinum-containing regimens. In the study 'SOLO2' eligible patients must have a BRCA mutation.

In study 19, knowledge of the BRCA mutation status was not a requirement for entry but was documented at study entry in approximately one third of the study population based on local laboratory testing. Following this, retrospective BRCA mutation status testing was performed by Myriad Genetic Laboratories Inc using diagnostic assay 'Integrated BRACAnalysis' for germline BRCA mutations and by Foundation Medicine for tumour BRCA mutations. This resulted in the BRCA mutation status being known in 254 out of 265 patients (96% of the study population) and of which 136 patients had a BRCA mutation (either germline and/or tumour) and 118 were BRCAwt/VUS.

In both SOLO2 and Study 19, randomisation was stratified by response and sensitivity to platinum chemotherapy. In Study 19, ethnic descent of the patient was an additional stratification factor. However, a more global stratification based on the BRCA mutation in the overall population would have been more appropriate. The method for the random assignment of subjects to treatment groups in SOLO2 has not been reported.

Efficacy data and additional analyses

Dose-response studies

The selection of the Phase III olaparib tablet dose/regimen of 300 mg bd (as two 150 mg tablets two times per day [total daily dose 600 mg]) was based on data from the completed Phase I bioavailability study, Study 24.

In this study, higher exposures of olaparib were observed with the tablet formulation compared with the capsule formulation. However, based on data from PK/PD modelling it could not be concluded that higher exposure would result in higher efficacy. Based on the totality of data and intra-study comparability of PK, efficacy and safety data of Study 24, the tablet dose/schedule of 300 mg bd was considered to meet pre-defined efficacy criteria, demonstrating a similar magnitude of tumour shrinkage to the 400 mg bd capsule with a similar tolerability profile. Therefore, the proposed dose with the tablet formulation of 300 mg bd was considered acceptable.

Pivotal studies

In SOLO2, the efficacy endpoints and their priority were in line with recommendations from EMA 'Guideline on the evaluation of anticancer medicinal products in man' EMA/CHMP/205/95/Rev.5). The use of PFS as primary endpoint for maintenance therapy in ovarian cancer is supported if being statistically compelling with no detrimental effect on OS. In addition, secondary objectives are of interest in a maintenance setting and repeated platinum-based treatment in ovarian cancer patients (PFS2, TFST, TSST and TDT).

PFS assessment was initially by blinded independent central review (BICR) according to modified RECIST 1.1 criteria. Per protocol amendment 3 (issued April 2016) a change in the assessment of primary endpoint PFS from BICR to investigator assessment, with BICR assessment retained as a sensitivity analysis, was implemented. Although assessment by investigator might introduce bias, robustness of PFS assessment is ensured by the double-blind design and well balanced timing of radiologic assessments between treatment groups and minimisation of unscheduled radiological assessments. The change in the assessment of primary endpoint PFS from BICR to investigator assessment is acceptable.

FAS on an ITT basis was the main set used for the analysis of all efficacy endpoints. Adjustments were made for multiplicity introduced by analysing multiple endpoints (excluding TDT, TFST and TSST). A hierarchical testing strategy was employed where PFS was tested first using the full test mass (full test mass = alpha) and key secondary endpoints of PFS2 and OS were then tested using a multiple testing procedure (MTP) with a recycling strategy (ie, the MTP will recycle the test mass to the endpoint not yet rejected in the hierarchy). PFS2 (with the test mass split between interim and final PFS2 analyses) was tested at the time of the primary analyses of PFS because statistical significance was shown for PFS. At the interim analysis PFS2 was statistically significant, and so the full test mass (alpha) was carried forward to OS.

In Study 19, PFS by investigator assessment of scans according to RECIST 1.0 was the primary efficacy endpoint. Retrospective blinded independent central review of scans was performed as a sensitivity analysis to confirm the robustness of the original primary PFS analysis. OS, BoR (RECIST), ORR, DCR, DoR, change in tumour size, CA-125 response, time to progression by CA 125 or RECIST, and HRQoL were secondary efficacy endpoints. TDT, TFST and TSST were exploratory endpoints analysed retrospectively.

- *Study SOLO2*

In the pivotal study SOLO2, a total of 295 patients out of the 602 patients enrolled were randomly assigned to either the olaparib arm (196 patients) or matching placebo arm (99 patients). All except one olaparib patient (195) and all placebo patients (99) received study treatment.

At the time of the DCO, a total of 83 patients (43 and 40 patients in the olaparib and placebo groups, respectively) were un-blinded to randomised study treatment on the IVRS. Of the 43 patients unblinded to treatment in the olaparib group, 3 patients were unblinded prior to investigator-assessed modified RECIST 1.1 progression. Of the 40 patients un-blinded to treatment in the placebo group, 2 patients were un-blinded prior to investigator-assessed modified RECIST 1.1 progression. No cross over was planned in the protocol. However unblinding of patients could for example, occur in order to determine if olaparib or another PARP inhibitor may be administered as subsequent therapy.

In the overall population of SOLO2 study, demographic and baseline characteristics were generally well balanced between treatment groups.

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

In the FAS, 6 patients were identified as having a germline BRCA mutation by local testing in whom Myriad testing did not confirm a germline BRCA mutation. Furthermore, no patient with somatic BRCA1/2 mutation has been enrolled. For the 5 patients (among 295) randomized with a known somatic BRCA mutation, a gBRCA mutation was subsequently confirmed by the Myriad CLIA Integrated BRAC analysis test.

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

Overall, all analyses of PFS, including sensitivities (eg, evaluation time bias, attrition bias and deviation bias) demonstrated a consistent and favourable treatment benefit for olaparib in maintenance therapy for high grade serous ovarian cancer with germline BRCA mutation.

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

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

Subgroup analyses

Subgroup analysis of PFS across various particular subgroups did not reveal an obvious differential benefit across pre-defined subgroups compared with the overall population. The benefit of olaparib over placebo was maintained across all pre-defined subgroups, with different magnitude.

An assessment of PFS and OS (DCO 19 September 2016) in patients by gBRCA1m versus gBRCA2m status was performed. The results indicated that the treatment effect in patients with gBRCA1 mutation as well as with gBRCA2 mutation was consistent with that seen in the FAS population.

The results of the exploratory analysis of OS by gBRCA1m and gBRCA2m status suggest a potential differential survival benefit between gBRCA1 mutated patients and gBRCA2 mutated patients, with patients with gBRCA2

mutations appearing to benefit more. Further analyses and additional data from new studies may be more informative in this regard. A final OS analysis for SOLO2, scheduled to take place at ~60% maturity, is expected to provide more informative data on any differences in OS by BRCA1m and BRCA2m status as well as the rest of the planned subgroups. This report is to be provided by 2Q2020.

The results of homologous recombination deficiency (HRD) testing (using Myriad myChoice HRD scores) are now available and a preliminary review has been provided (see PD part). A full manuscript is currently in preparation and the MAH is recommended to submit it by 1Q2018.

- *Study 19*

Of the 265 patients randomised into the study, all patients randomised to olaparib (n=136) and 128 of the 129 patients randomised to placebo received study treatment. Of the 264 patients who received study treatment, 136 patients were classified as having a BRCA mutation (either germline and/or tumour; 74 received olaparib and 62 received placebo) and 118 patients were BRCAwt/VUS (57 received olaparib and 61 received placebo).

At the final DCO (09 May 2016) 39 patients were still in the study; of these, 14 were still receiving olaparib treatment (7 patients with BRCAm and 7 with BRCAwt/VUS) and 1 was still receiving placebo (BRCAm).

Of the 265 patients who enrolled for study 19, 62 (23.4%) were unblinded during the course of the study: 19 (14%) patients and 43 (33.3%) patients in the olaparib arm and placebo arm, respectively. The rate of patients unblinded prior progression is high (9.8%) but it is difficult to draw conclusions as the reasons for unblinding were not collected.

Study 19 data are presented according to the BRCA mutation status (BRCAm vs BRCAwt/VUS) whereas this stratification criterion was not initially pre-planned.

In the overall population of study 19, demographic and baseline characteristics were generally well balanced between treatment groups. The majority of patients were White (>94% in each arm), and no Jewish descent (>77% in each arm). The age distribution of the BRCA population was a little younger than the non-BRCA population, and consequently than the overall population (age <50 years: 25.7% versus 9.3% and 18.9%, BRCAm versus non-BRCAm and FAS, respectively).

Like in SOLO2 study, there was a slight imbalance between groups in the number of patients with ECOG PS 0 and 1, with mainly patients with an ECOG PS of 1 whatever the subgroup, and most patients had their primary tumour in the ovary, and it is stated in the study 19 that had in majority a poorly differentiated G3 tumour.

More than half of the patients had a >12 months progression-free interval since the penultimate platinum based chemotherapy, platinum free interval of more than 12 months and had a PR to the last chemotherapy regimen in the Study 19. Further, patients in this could have another treatment than platinum-containing therapy before the most recent platinum-containing treatment.

Due to the fact that study 19 protocol did not require the 2 prior platinum regimens determining eligibility to be sequential, the median number of prior platinum regimens was lower than the median number of prior chemotherapy regimens. Indeed, patients in each treatment group had received a median of 3 previous chemotherapy regimens (range: 2 to 11, and 2 to 8 regimens for olaparib and placebo, respectively) and a median of 2 prior platinum containing chemotherapies (range: 2 to 7, and 2 to 8 platinum-containing regimens for both olaparib and placebo respectively).

Study 19 patients received more treatment lines than SOLO2 study patients (median of 3 vs 2 previous chemotherapy regimens respectively).

The SmPC of the capsule formulation has been updated to reflect the analysis of the data of the mutated BRCA sub-group.

Retrospective analyses of samples have been conducted by the MAH. The mutational status of BRCA was known for 254 out of 265 patients. In total, 136 patients had a BRCA1/2 mutation (either germline and/or tumour), including 71 being mutated in both the germline and tumour. Of these 136 patients, 96 had a germline mutation of which 65 were determined by Myriad CLIA gBRCA test. The Applicant provided some explanations for discrepancies between germline and tumour status when only one of them was mutated.

In addition, 118 patients were defined as BRCAwt/variant of unknown significance. The pooling of these two subpopulations is questionable, even if out of these 118 patients defined as BRCA wild type or VUS, only 12 were defined by a BRCA mutation status unknown/VUS by either germline or tumour.

The PFS analysis was conducted using data cut-off on 30 June 2010. These data supported the initial marketing authorization for the capsule formulation, based on PFS results in the BRCA1/2 mutated population. In this application, the FAS efficacy data are supportive of the broad indication claimed by the MAH and long-term efficacy outcomes have been provided to support the initially observed PFS benefit in FAS population and in subgroups.

Study 19 met its primary objective of statistically significantly improved investigator-assessed PFS (by RECIST) in the overall population treated with olaparib compared with placebo (HR 0.35; 95% CI 0.25-0.49; p<0.00001; median 8.4 vs 4.8 months), which was confirmed by a blinded independent central radiological review (HR 0.39; 95% CI: 0.28, 0.56; p<0.00001).

As initially assessed, the main benefit in the mutated BRCA population was a prolongation of median PFS from 4.3 to 11.2 months (HR 0.18; CI 0.10-0.31, p<0.00001).

For the non-mutated BRCA population, 32 (56%) subjects in the olaparib arm and 44 (72%) in the placebo arm had a PFS event. The hazard ratio (HR) was 0.54 (95% confidence interval [CI], 0.34 to 0.85). The Kaplan-Meier (KM) median PFS from randomization was 7.4 months (95%CI 5.5, 10.3) in the olaparib arm and 5.5 months (95%CI 3.7, 5.6) in the placebo arm, resulting in an improvement of the median PFS of 1.9 months.

This PFS improvement in the overall population was clinically relevant and observed regardless the sub-groups (BRCAm and non-mutated BRCA population). All analyses of PFS, including sensitivities (eg, evaluation time bias, attrition bias, and those adjusted for ECOG PS) demonstrated a consistent and favourable treatment benefit for olaparib.

However, magnitude of PFS improvement was distinct depending on the BRCA mutation status (HR of 0.18 in BRCAm and HR of 0.54 in non-BRCAm). This difference explains why the HR of the overall population is pulled upward (HR 0.39; 95% CI: 0.28, 0.56; p<0.00001). In order to better estimate the magnitude of benefit in patients without germline BRCA1/2 mutations, the MAH should conduct and submit the results of the OPINION study, a phase IIIb single-arm, open-label, multicentre study of maintenance therapy in PSR non-germline BRCA mutated ovarian cancer patients who are in complete or partial response following platinum based chemotherapy.

The Study 19 was not powered and designed to show OS benefit. The descriptive final analysis (DCO: 09 May 2016) was performed at 79% maturity in the FAS (210 deaths out of 265 patients). Even if statistical significance was not reached, OS data were numerically in favour of the olaparib arm in terms of reduced risk of death (HR 0.73; 95% CI: 0.55, 0.95; p=0.02138).

In the BRCAwt/VUS group, the estimate for the median OS was 24.5 months in the olaparib arm and 26.6 months in the placebo arm, with 95%CI for HR exceeding 1 (HR 0.84 95%CI 0.57-1.25, p=0.3975), but as highlighted previously this patient population is highly heterogeneous and a larger sample size or analysis in specific subgroups would be more informative. Further analyses addressing subgroups by HRD status in gBRCAwt patients in a larger study are required as based on main mechanism of action, patients without HRD would not benefit from PARPi, and although platinum sensitivity would allow enriching patient population in HRD deficient tumours, this clinical marker will not optimally select the patient population. To identify patients who are likely to benefit to a greater extent, the MAH should investigate predictive biomarkers within this patient group in the context of the OPINION study.

Analysis of exploratory efficacy endpoints showed a reduction in the risk of discontinuation of study treatment or death, in the olaparib group, compared with the placebo group in overall population (FAS): HR of 0.39, 95% CI 0.30 to 0.51, p<0.00001, and a lengthening of time until the first subsequent anti-cancer therapy and the second subsequent therapy or death, compared with placebo: HR of 0.39, 95% CI 0.30 to 0.52, p<0.00001 and HR of 0.53, 95% CI 0.40 to 0.69, p<0.00001 for TFST and TSST respectively.

These exploratory efficacy outcomes support the PFS results, by showing that the treatment benefit of olaparib is maintained beyond the treatment period. This beneficial effect of maintenance therapy was found whatever the subgroup. However, it was more pronounced in BRCA mutated patients.

No PFS2 data has been reported for the Study 19 and TSST was used. Although the clinical relevance of TSST is acknowledged, PFS2 by independent review is a more unbiased measure of long-term term benefit.

Using descriptive statistics, there was no indication of impact on the quality of life, as measured by TOI and total FACT-O scores. However, the robustness of data is questioned and does not allow definitive conclusions to be made.

The MAH was asked to provide the efficacy outcomes in the subgroup of 20 patients defined as patients harbouring somatic BRCA mutations based on the most recent analysis of genomic data and to discuss current knowledge on the incidence of somatic BRCA 1/2 mutations and their predictive value for PARPi therapy. In Study 19, sBRCA mutations represented 18% of tBRCA cases with confirmed s/g status (20/114). In this smaller group of patients identified as sBRCAm in Study 19, a PFS HR = 0.23 (95% CI [0.04 to 1.12]), with a median PFS not reached in the olaparib group and of 4.7 months in the placebo group. No data in new patients are available to date.

Interpretation of the results in the overall population of the Study 19 should be done with caution given that the prevalence rate of BRCAm (germline and somatic) may not reflect the real world prevalence, since only about 10-15% of cases would occur in patients with germline BRCA mutation plus about 5-6% of patients with tumours harbouring somatic BRCA mutations. However, about half of patients in the Study 19 had BRCA mutations. To date, no larger prospective studies have been reported to allow a more precise estimation of the proportion of patients with BRCAwt tumours, but this patient population represents a majority of patients with HGSOC.

The Cancer Atlas Genome has shown that 96% of high-grade serous ovarian carcinoma have TP53 somatic mutations, thus suggesting that mutation of this gene is a virtually path gnomic, defining feature of this cancer. The histologic analysis of the few wild-type TP53 showed that the large majority of these tumours have morphologic features not typical of HGSOC or are not pure HGSOC; furthermore, the analysis of the molecular features indicate that these tumours are not HGS-OvCas (Testa et al, 2018). Therefore, the conclusion was that 100% of HGSOC are TP53-mutate. The large majority of these TP53 mutants exhibit a loss of- the function of normal TP53. The TP53 mutation is the first genetic somatic mutation occurring during HGS-OvCa development, as supported by the observation that TP53 mutations are observed in early tumor precursor lesions. Seagle and coworkers analyzed the impact of the location of TP53 mutation within the TP53 protein on overall survival: patients with missense mutations located in the minor groove of the DNA binding domain of TP53 have a clearly better OS than those with missense mutations at the level of the major groove of the DNA binding domain (Testa et al, 2018).

With the aim to define the subgroup of patients that would not benefit from olaparib maintenance treatment, the MAH committed to further characterise TP53 mutational status in ongoing and planned olaparib trials.

Finally, recent evidence suggests that serous and endometrioid carcinomas arise from the tubal fimbrae, suggesting similar biology and origin for the high grade epithelial histologies (Jayson et al 2014). Pennington et al reported in their study that contrary to the common belief of homologous recombination deficiencies being characteristic of high-grade serous ovarian cancer only, DNA repair deficiencies were found equally commonly in carcinomas with non-serous histology (Pennington et al 2014). This supports the extension of the indication to other histological types.

Study D0816C00020 ("OPINION")

The MAH proposed a single-arm study in 250 patients to investigate the efficacy and safety of olaparib in the non-gBRCA population with post-enrolment analysis of HRD status. To ensure that the study is truly representative of this population, prospective testing was not deemed appropriate by the MAH. Collection of tumour tissue is mandatory for all enrolled patients in order to conduct the Myriad HRD testing. As the HRD status of the subjects enrolled is mutually exclusive, the population will consist entirely of HRD scar positive and HRD scar negative patients. The natural prevalence would allow for a representation of both groups (54 to 59% HRD scar negative and 41 to 46% HRD scar positive). HRD testing will be conducted when approximately 25%, 50%, 75% and 100% of patients have been enrolled on to the study and the proportion of HRD scar positive and HRD scar negative patients be assessed at these timepoints. Should these numbers not align with the anticipated natural prevalence, steps will be taken to modify the protocol accordingly, to ensure an appropriate distribution between the two groups for conducting the analyses.

The MAH committed to revise the protocol and upgrade OS to a secondary endpoint. OS data will highly depend on the rate with which patients will be included in the study. Therefore, the collection of OS data should not be limited to a particular time point. This study is requested in accordance with the PAES delegated act c) (uncertainties with respect to the efficacy of a medicinal product in certain sub-populations that could not be resolved prior to marketing authorisation and require further clinical evidence). The MAH will submit the results by June 2021 (see Annex II).

2.5.4. Conclusions on the clinical efficacy

Extrapolation of efficacy results obtained with capsule formulation to tablet formulation is reasonably supported by PK data.

PFS benefit has been confirmed in patients with germline BRCA mutated high grade serious PSR ovarian cancer in the Study SOLO2 conducted with tablet formulation and further long-term data have been provided in patients with high grade serous PSR ovarian cancer regardless the BRCA mutation status in the Study 19 conducted with the capsule formulation. Study 19 data support the indication in patients including patients beyond gBRCA mutated tumours.

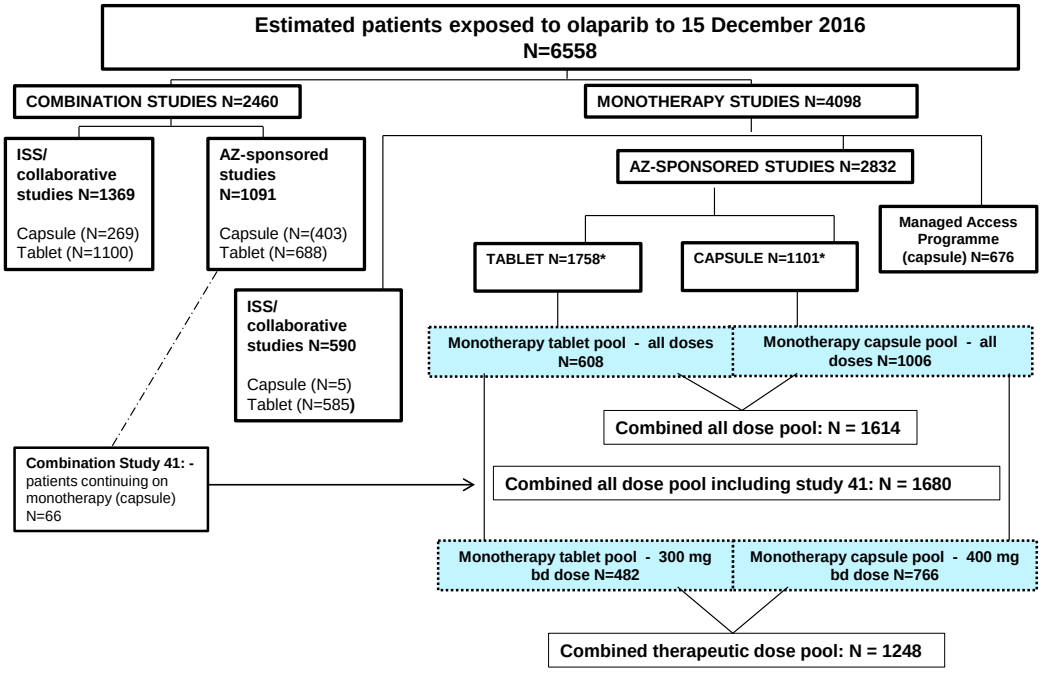
Efficacy in non-mutated BRCA patients has only been provided based on Study 19 results, for patients with high grade serous ovarian cancer. However, consistent results have been reported in the SOLO2 study for patients with high grade serous or endometrioid cancer. In addition, the mechanism of action of olaparib and recent evidence on the biologic features of high grade epithelial ovarian tumors support an extension of the indication from “serous” to other histological types.

Given an existing uncertainty in regard to magnitude of benefit in patients with gBRCAwt which should be balanced against known toxicity, and a potential for reduced benefit in subset of patients without HRD, the MAH should provide additional evidence specifically in this group of patients. Moreover, further investigation of biomarkers of HRD, such as TP53 disruptive status, that would allow to identify patients that benefit the most and optimise the target population. The OPINON study is expected to provide additional data (see Annex II).

2.6. Clinical safety

Across the entire clinical programme, as of 15 December 2016, an estimated 6558 patients with ovarian, breast, pancreatic, prostate, gastric or a variety of other solid tumours have received treatment with olaparib (tablet or capsule formulations) in AstraZeneca-sponsored studies.

Figure 12 Overview of the olaparib programme as of 15 December 2016



Note: The patient numbers in the shaded boxes are taken from the clinical database
*** 27 patients in study D0810C00024 received both the tablet and capsule formulations**

Main phase III study: SOLO2

The SOLO2 study provides the main safety data for the use of olaparib 300 mg bd tablet.

SOLO2 was a Phase III randomised, double-blind, placebo controlled, multicentre study of olaparib (300 mg bd tablet) as a maintenance treatment in PSR BRCA mutated ovarian cancer patients who were in complete or partial response following platinum-based chemotherapy. A total of 295 patients were randomised (196 were randomised to olaparib and 99 to placebo). The data cut off of safety data presented in this study is 19 September 2016. The SOLO2 data are supported by safety data from an additional 7 studies, with a total of 482 patients with advanced solid tumours 271 of whom were documented to have ovarian cancer.

The 300 mg bd tablet pool is made up of the SOLO2 study along with these 7 other supportive studies.

Supportive study: Study 19 (phase II)

Data from Study 19 provide a comparative dataset of the capsule formulation of olaparib in the PSR ovarian cancer maintenance treatment setting. Study 19 was a Phase II, randomised, double-blind, placebo-controlled, multicentre study designed to assess the efficacy and safety of olaparib 400 mg bd capsules as a maintenance treatment in patients with PSR ovarian cancer who were in response to platinum-based chemotherapy. A total

of 264 patients received treatment (136 received olaparib and 128 received placebo). The data cut off of safety data presented in this study is 09 may 2016.

An additional 11 studies provide supportive safety data for the use of olaparib 400 mg bd capsule, with a total of 766 patients with advanced solid tumours. The capsule pool includes 398 patients who were documented to have BRCAm ovarian cancer.

Patient exposure

- *SOLO2*

A total of 295 patients were randomised in SOLO2; 196 patients randomised to olaparib and 99 patients randomised to placebo received study treatment. All 295 patients had gBRCA mutations as this was a requirement for study entry. The data cut off of safety data presented in this study is 19 september 2016.

Duration of treatment

Table 36 Duration of treatment (SOLO2 [SAS])

Treatment duration (weeks)		**Olaparib 300 mg bd tablet N = 195 n (%)**	**Placebo bd N = 99 n (%)**
Total treatment duration (weeks)	Mean (sd)	75.6 (42.65)	39.0 (35.10)
	Median (range)	84.1 (1 - 151)	24.3 (4 – 137)
	Total treatment weeks	14733	3859
Actual treatment duration (weeks)	Mean (sd)	73.3 (42.15)	38.7 (34.99)
	Median (range)	81.3 (0 – 151)	24.3 (4 – 137)
	Total treatment weeks	14290	3828
Actual treatment duration at the assigned dose (weeks)	Mean (sd)	55.7 (42.73)	37.2 (34.23)
	Median (range)	39.0 (0 – 146)	23.9 (0 – 131)
	Total treatment weeks	10809	3682

Duration of treatment was collected in weeks.
Actual treatment duration is calculated as the number of days patients actually had treatment; it does not include days when they did not take dose.
Total treatment is the time from first to last dose, which does not take account of missed doses.
bd Twice daily; DCO Data cut-off; SAS Safety analysis set; sd Standard deviation.
Data derived from SOLO2 Table 11.3.1.1, Module 5.3.5.1. DCO for SOLO2 = 19 September 2016

The median total treatment duration was 84.1 weeks [19.4 months] in the olaparib group compared with 24.3 weeks [5.6 months] in the placebo group.

In the olaparib group, the median actual treatment duration was 81.3 weeks.

Table 37 Overall extent of exposure in SOLO2 (SAS)

Months	Olaparib 300 mg bd tablet N = 195 n (%)	Placebo bd N = 99 n (%)
>0	195 (100.0)	99 (100.0)
≥3 months	180 (92.3)	77 (77.8)
≥6 months	154 (79.0)	44 (44.4)
≥12 months	121 (62.1)	21 (21.2)
≥18 months	98 (50.3)	16 (16.2)
≥24 months	59 (30.3)	9 (9.1)

Duration of treatment was collected in days. An approximation of treatment duration in months was made by dividing the time points in days by 30.42 (based on 365 days/12 months) and selecting the one that was closest to (but not longer than) the treatment month.
Rows are cumulative and patients are included if they have taken treatment beyond the treatment day stated in the parenthesis
bd Twice daily; DCO Data cut-off; N number of patients; SAS Safety analysis set;.
Data derived from SOLO2 Table 11.3.1.4, Module 5.3.5.1. DCO for SOLO2 = 19 September 2016

Proportion of patient who continued to receive treatment at 2 years was 30% in the olaparib group and 9% in the placebo group.

Daily dose

Patients would be expected to receive a mean daily dose of 600 mg.

Table 38 Mean daily dose of olaparib by time period (SOLO2 [SAS])

	Number (%) of patients by time period				
Olaparib daily dose (mg)	Up to 3 months (N = 195)	>3 to ≤6 months (N = 184)	>6 to ≤9 months (N = 156)	>9 to ≤12 months (N = 140)	>12 months (N = 122)
>500 to ≤600	166 (85.1)	140 (76.1)	117 (75.0)	94 (67.1)	81 (66.4)
>400 to ≤500	18 (9.2)	27 (14.7)	27 (17.3)	28 (20.0)	29 (23.8)
≤400	11 (5.6)	17 (9.2)	12 (7.7)	18 (12.9)	12 (9.8)

bd Twice daily; DCO Data cut-off; SAS Safety analysis set.
Data derived from SOLO2 Table 11.3.1.5, Module 5.3.5.1. DCO for SOLO2 = 19 September 2016.

85.1% of patients received a mean daily dose of between 500 and 600mg during the first 3 months and 66.4% after 12 months.

Table 39 Summary of dose adherence and daily dose (SAS)

	Olaparib 300 mg bd (N=195)	Placebo (N=99)
Daily dose		
Mean daily dose (mg)	568.2	592.1
Range of mean daily doses (mg)	300.0 to 600.0	500.0 to 600.0

bd twice daily; SAS safety analysis set.
Data derived from Table 11.3.1.6

Mean daily dose was 568.2mg in the olaparib group and 592.1 mg in the placebo group.

Dose modifications

The number of patients with an interruption of the treatment was 54% in the olaparib group and 23% in the placebo group. The reason for interruption of the treatment is the occurrence of adverse event for 43.6% of patients in the olaparib group and 18.2% of patients in the placebo group.

The number of patients with dose reduction was 30% in the olaparib group and 6% in the placebo group. The reason for dose reduction is the occurrence of adverse event for 27% of patients in the olaparib group and 3% of patients in the placebo group.

Overall extent of exposure: Olaparib 300 mg bd tablet pool

Other than SOLO2, most of the additional exposure is in Phase I clinical pharmacology studies with intended short durations of exposure. Of the 482 patients, 231 (47.9%) had 6 months exposure and 145 (30.1%) had 12 months exposure. The number of patients in the tablet pool with olaparib exposure beyond 12 months was similar to that for SOLO2.

Table 40 Number (%) patients receiving treatment by years: Safety Analysis Set

	Olaparib 300mg bd Tablet Pool N = 482	SOLO2 N = 195
Treatment period	**Number (%)**	**Number (%)**
>0	482 (100.0)	195 (100,0)
>=1 week	476 (98.8)	

>=1 month	437 (90.7)	
>=3 months	315 (65.4)	180 (92.3)
>=6 months	231 (47.9)	154 (79.0)
>=12 months	145 (30.1)	121 (62.1)
>=18 months	102 (21.2)	98 (50.3)
>=24 months	61 (12.7)	59 (30.3)
>=30 months	15 (3.1)	

Source: table 2.7.4.1.9.2 of SCS outputs pg 451 and table 2 of add. to SCS

- *Study 19*

39.7% and 23.5% of patients remained on olaparib treatment after respectively 1 year and 2 years of treatment. Beyond this two years, the proportion of patients who remained on treatment was 17.6% (24/136), 14.7% (20/136) 13.2% (18/136), 11% (15/136) and 1.5% (2/136) during respectively, ≥ 3 years, ≥ 4 years, ≥ 5 years, ≥ 6 years and ≥ 7 years.

Long-term exposure to olaparib maintenance therapy was demonstrated in this study (table below).

Table 41 Overall extent of exposure (Study 19)

Treatment Day (approximate equivalent month)	**Olaparib 400 mg bd capsule SAS N = 136 n (%)**	**Placebo bd SAS N = 128 n (%)**
≥1 year	54 (39.7)	14 (10.9)
≥2 years	32 (23.5)	5 (3.9)
≥3 years	24 (17.6)	3 (2.3)
≥4 years	20 (14.7)	1 (0.8)
≥5 years	18 (13.2)	1 (0.8)
≥6 years	15 (11.0)	1 (0.8)
≥7 years	2 (1.5)	0

Duration of treatment was collected in days. An approximation of treatment duration in months was made by dividing the time points in days by 30.42 (based on 365 days/12 months) and selecting the one that was closest to (but not longer than) the treatment month.
Rows are cumulative and patients are included if they have taken treatment beyond the treatment day stated in the parenthesis. DCO Data cut-off; SAS Safety analysis set.
Data derived from Study 19 Table 11.1.26.1, Module 5.3.5.1. DCO for Study 19 = 09 May 2016. Source: table 6 of addendum to SCS.

Overall extent of exposure: Olaparib 400 mg bd capsule pool

Of the 766 patients, 325 (42.4%) had 6 months exposure and 140 (18.3%) had 12 months exposure. The number of patients in the capsule pool with olaparib exposure beyond 4 years was the same as that for Study 19.

Adverse events – Pooled dataset

Adverse events were analysed following the pooling strategy In SOLO2 study, the majority of patients (98.5%) had at least 1 AE reported with olaparib but also with placebo (97.8%). However, AE of CTCAE grade 3 or higher and SAE were more frequently reported with olaparib (respectively 37.9% and 17.9%), which is understood.

Serious and CTCAE Grade 3 or above adverse events did not always lead to treatment discontinuation (10.8%).

Proportion of patients with any AE, AE of CTCAE Grade 3 or higher and SAE are similar between SOLO2 study and the tablet pool and also between Study 19 and the capsule pool.

Proportion of patients with AE of CTCAE Grade 3 or higher and SAE are higher in the capsule pool than in the tablet pool (respectively 45.3% and 26.4% vs. 36.1% and 19.7%).

Table 42: Number (%) of patients who had at least 1 AE in any category (Olaparib treatment groups [SOLO2, Study 19, tablet pool and capsule pool])

AE category[a]	Olaparib 300 mg bd tablet		Olaparib 400 mg bd capsule	
	SOLO2 N = 195 n (%)	Tablet pool N = 482 n (%)	Study 19 N = 136 n (%)	Capsule pool N = 766 n (%)
Any AE	192 (98.5)	471 (97.7)	132 (97.1)	749 (97.8)
Any AE causally related to study drug[b]	180 (92.3)	418 (86.7)	122 (89.7)	666 (86.9)
Any AE of CTCAE Grade 3 or higher	72 (36.9)	174 (36.1)	59 (43.4)	347 (45.3)
Any AE with outcome = Death	1 (0.5)	1 (0.2)	2 (1.5)	14 (1.8)
Any SAE (including events with outcome = death)	35 (17.9)	95 (19.7)	31 (22.8)	202 (26.4)
Any AE leading to discontinuation of study treatment	21 (10.8)	36 (7.5)	8 (5.9)	45 (5.9)

[a] Other – Fimbria
ECOG PS Eastern Cooperative Oncology Group performance status; sd standard deviation

Data derived from Study 19 CSR, Table 11.1.4, and Table 11.1.15 (DCO 18 December 2013)

In SOLO2 study, the most common SOCs for reported AEs were: Gastrointestinal disorders (90.3% of patients in the olaparib group vs. 75.8% of patients in the placebo group), General disorders and administration site conditions (77.9% vs. 48.5%), Nervous system disorders (56.9% vs. 32.3%), Infections and infestations (54.9% vs. 40.4%), and Blood and lymphatic system disorders (48.7% vs. 12.1%). The most common AEs (reported by >30% patients) in the olaparib arm were nausea, anaemia, fatigue, vomiting, diarrhoea and asthenia.

Haematological toxicity was reported at an increased frequency with the tablet formulation, compared with the capsule formulation; however, anaemia remained manageable by interrupting or reducing the olaparib dose or giving blood transfusions, when indicated; treatment discontinuation was rarely required. Reports of neutropenia and thrombocytopenia remained at low frequency with the tablet formulation; these events were primarily low grade and rarely required treatment discontinuation.

In general, the onset of AEs by treatment period was similar for SOLO2 and Study 19. The majority of AEs occurred within the first 3 months of treatment

In SOLO2 study, there was a higher percentage of patients with AEs of CTCAE Grade ≥3 in the olaparib group (36.2%) compared with the placebo group (18.2%), which is understood. The most common AE of CTCAE Grade

≥3 reported on olaparib treatment was anaemia (19.5%). The overall percentage of CTCAE Grade ≥3 AEs for the other individual PTs, (ie, other than anaemia) was much lower (maximum of 3.1%).

Table 43 Number (%) of patients with the most common AEs of CTCAE Grade 3 or higher (reported in ≥2 patients in either group [all patients]) (Olaparib treatment groups [SOLO2, Study 19, tablet pool and capsule pool])

SOC and PT	Olaparib 300 mg bd tablet		Olaparib 400 mg bd capsule	
	SOLO2 N = 195 n (%)	Tablet pool N = 482 n (%)	Study 19 N = 136 n (%)	Capsule pool N = 766 n (%)
Any AE of CTCAE Grade ≥3	72 (36.9)	174 (36.1)	59 (43.4)	347 (45.3)
Blood and lymphatic disorders	**43 (22.1)**	**79 (16.4)**	**14 (10.3)**	**123 (16.1)**
Anaemia	38 (19.5)	68 (14.1)	8 (5.9)	88 (11.5)
Leukopenia	3 (1.5)	4 (0.8)	3 (2.2)	20 (2.6)
Neutropenia	5 (2.6)	13 (2.7)	5 (3.7)	22 (2.9)
Thrombocytopenia	0	4 (0.8)	1 (0.7)	17 (2.2)
Gastrointestinal disorders	**16 (8.2)**	**33 (6.8)**	**14 (10.3)**	**111 (14.5)**
Abdominal pain	5 (2.6)	8 (1.7)	3 (2.2)	25 (3.3)
Diarrhoea	2 (1.0)	5 (1.0)	3 (2.2)	13 (1.7)
Intestinal obstruction	2 (1.0)	2 (0.4)	1 (0.7)	15 (2.0)
Mouth ulceration	2 (1.0)	2 (0.4)	0	0
Nausea	5 (2.6)	8 (1.7)	3 (2.2)	21 (2.7)
Small intestinal obstruction	0	1 (0.2)	2 (1.5)	15 (2.0)
Stomatitis	2 (1.0)	3 (0.6)	0	3 (0.4)
Vomiting	5 (2.6)	11 (2.3)	3 (2.2)	25 (3.3)
General disorders and administration site conditions	**11 (5.6)**	**32 (6.6)**	**13 (9.6)**	**65 (8.5)**
Asthenia	6 (3.1)	8 (1.7)	1 (0.7)	5 (0.7)
Fatigue	2 (1.0)	16 (3.3)	11 (8.1)	53 (6.9)

SOC and PT	Olaparib 300 mg bd tablet		Olaparib 400 mg bd capsule	
	SOLO2 N = 195 n (%)	Tablet pool N = 482 n (%)	Study 19 N = 136 n (%)	Capsule pool N = 766 n (%)
Investigations	**9 (4.6)**	**22 (4.6)**	**9 (6.6)**	**44 (5.7)**
Haemoglobin decreased	0	0	2 (1.5)	17 (2.2)
Neutrophil count decreased	5 (2.6)	9 (1.9)	0	4 (0.5)
Platelet count decreased	2 (1.0)	3 (0.6)	0	1 (0.1)
White blood cell count decreased	2 (1.0)	5 (1.0)	0	2 (0.3)
Musculoskeletal and connective tissue disorders	**1 (0.5)**	**9 (1.9)**	**9 (6.6)**	**26 (3.4)**
Back pain	0	3 (0.6)	4 (2.9)	8 (1.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**5 (2.6)**	**10 (2.1)**	4 (2.9)	15 (2.0)
Gastric cancer	2 (1.0)	2 (0.4)	0	0
Respiratory, thoracic and mediastinal disorders	**3 (1.5)**	**12 (2.5)**	**3 (2.2)**	**33 (4.3)**
Dyspnoea	2 (1.0)	5 (1.0)	2 (1.5)	17 (2.2)
Vascular disorders	**2 (1.0)**	**5 (1.0)**	1 (0.7)	14 (1.8)
DVT	2 (1.0)	2 (0.4)	0	6 (0.8)

Tablet and capsule pools include data from SOLO2 and Study 19, respectively. Table ordered according to MedDRA classification.
Includes AEs with an onset date between the date of first dose and 30 days following the date of last dose of study 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; SOC System organ class.
DCOs for SOLO2 and Tablet pool = 19 September 2016 and Study 19 and Capsule pool = 09 May 2016.

In studies pool, the proportion of patients reporting events of CTCAE Grade ≥3 was lower for SOLO2 (36.9%) *versus* Study 19 (43.4%) and lower for the tablet pool (36.1%) compared with the capsule pool (45.3%).

The most commonly reported event of CTCAE Grade ≥3 was anaemia in all 4 populations; the proportion of patients with Grade ≥3 anaemia was higher in SOLO2 (19.5%) than in Study 19 (5.9%) but this proportion remained similar between the tablet pool (14.1%) and the capsule pool (11.5%).

Two cases of gastric cancer occurred among 1248 patients included in tablet and capsule pool studies. No relationship has been established between the occurrence of gastric cancer and the treatment with olaparib.

Serious adverse event/deaths/other significant events

- **Serious adverse event**

During SOLO2 study, a higher proportion of patients reported SAEs in the olaparib group (17.9%) compared with the placebo group (8.1%), either during treatment (median time in study was approximately 3 times longer in the olaparib group than in the placebo group) or in the 30-day follow-up period.

Table 44 Number (%) of patients reporting most common SAEs (≥2 olaparib-treated patients in either SOLO2 or Study 19 or ≥5 patients in the either the tablet pool or the capsule pool)

SOC and PT	Olaparib 300 mg bd tablet		Olaparib 400 mg bd capsule	
	SOLO2 N = 195 n (%)	Tablet pool N = 482 n (%)	Study 19 N = 136 n (%)	Capsule pool N = 766 n (%)
Any SAE	**35 (17.9)**	**95 (19.7)**	**31 (22.8)**	**202 (26.4)**
Blood and lymphatic system disorders	**9 (4.6)**	**26 (5.4)**	**6 (4.4)**	**33 (4.3)**
Anaemia	7 (3.6)	23 (4.8)	3 (2.2)	21 (2.7)
Thrombocytopenia	0	1 (0.2)	1 (0.7)	6 (0.8)
Gastrointestinal disorders	**8 (4.1)**	**20 (4.1)**	**9 (6.6)**	**75 (9.8)**
Abdominal pain	3 (1.5)	5 (1.0)	0	12 (1.6)
Intestinal obstruction	3 (1.5)	3 (0.6)	1 (0.7)	14 (1.8)
Nausea	1 (0.5)	2 (0.4)	1 (0.7)	9 (1.2)
Small intestinal obstruction	0	1 (0.2)	2 (1.5)	16 (2.1)
Vomiting	1 (0.5)	4 (0.8)	1 (0.7)	15 (2.0)
General disorders and administration site conditions	**4 (2.1)**	**10 (2.1)**	**3 (2.2)**	**12 (1.6)**
Pyrexia	1 (0.5)	2 (0.4)	1 (0.7)	5 (0.7)
Infections and infestations	**3 (1.5)**	**23 (4.8)**	**4 (2.9)**	**29 (3.8)**

Table 44 Number (%) of patients reporting most common SAEs (≥2 olaparib-treated patients in either SOLO2 or Study 19 or ≥5 patients in the either the tablet pool or the capsule pool)

SOC and PT	Olaparib 300 mg bd tablet		Olaparib 400 mg bd capsule	
	SOLO2 N = 195 n (%)	Tablet pool N = 482 n (%)	Study 19 N = 136 n (%)	Capsule pool N = 766 n (%)
Pneumonia	1 (0.5)	5 (1.0)	1 (0.7)	6 (0.8)
Urinary tract infection	1 (0.5)	6 (1.2)	1 (0.7)	5 (0.7)
Injury, poisoning and procedural complications	**1 (0.5)**	**2 (0.4)**	**3 (2.2)**	**16 (2.1)**
Femur fracture	0	0	2 (1.5)	3 (0.4)
Investigations	**2 (1.0)**	**2 (0.4)**	**0**	**11 (1.4)**
Haemoglobin decreased	0	0	0	7 (0.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**5 (2.6)**	**8 (1.7)**	**4 (2.9)**	**9 (1.2)**
Gastric cancer	2 (1.0)	2 (0.4)	0	0
Respiratory, thoracic and mediastinal disorders	**3 (1.5)**	**5 (1.0)**	**5 (3.7)**	**28 (3.7)**
Dyspnoea	1 (0.5)	1 (0.2)	2 (1.5)	10 (1.3)
Pleural effusion	0	1 (0.2)	0	6 (0.8)
Pulmonary embolism	0	0	1 (0.7)	7 (0.9)
Vascular disorders	**2 (1.0)**	**3 (0.6)**	**1 (0.7)**	**5 (0.7)**
Deep vein thrombosis	2 (1.0)	2 (0.4)	1 (0.7)	5 (0.7)

Tablet and capsule pools include data from SOLO2 and Study 19, respectively
Includes AEs with an onset date between the date of first dose and 30 days following the date of last dose of study treatment.
AE Adverse event; bd Twice daily; DCO Data cut-off.; N Total number of patients; PT Preferred term; SAE Serious adverse event; SOC System organ class.

Data derived from: Table 11.3.4.1.1.1, SOLO2 CSR, Module 5.3.5.1; Table 11.3.4.1.1.1, Study 19 CSR Addendum 3, Module 5.3.5.1; and Tables 2.7.4.1.3.1 and 2.7.4.2.3.1, Module 5.3.5.3. DCOs for SOLO2 and Tablet pool = 19 September 2016 and Study 19 and Capsule pool = 09 May 2016.

The most common SOCs for reported SAEs were blood and lymphatic system disorders and gastrointestinal disorders.

Most SAE PTs were reported in only one patient each. The most common SAE was anaemia; the only other SAEs reported in ≥2 patients in the olaparib treatment group were abdominal pain, deep vein thrombosis (DVT), gastric cancer and intestinal obstruction. A total of 52 SAEs were reported by patients in the olaparib group, with only SAEs of anaemia (12 SAEs in 7 patients), intestinal obstruction (4 SAEs in 3 patients) and peripheral oedema (2 SAEs in 1 patient) being reported more than once by any patient. SAEs reported in only 1 patient included an event of anaphylactic reaction and an event of hypersensitivity, both of which were reported to be related to administration of contrast media. In the olaparib group, a low proportion of patients (18 patients [9.2%]) had SAEs reported that were considered by the investigator to be causally related to study treatment; the only SAE considered treatment-related by the Investigators occurring in more than 1 patient was anaemia (6 patients [3.1%]). There were no SAEs in the placebo group that were considered to be causally related to study treatment.

In the olaparib arm, the majority of the 52 SAEs reported occurred whilst on treatment, with 10 SAEs having a date of onset during the safety follow-up. AEs of MDS/AML and new primary malignancies are collected beyond the 30-day follow-up period. Only 8 SAEs in the olaparib arm were not resolved/recovered at the cut-off date for this analysis (anaemia, abdominal pain, back pain, blood creatinine increased, DVT, MDS and muscular weakness); the majority had resolved with either no action taken or following a temporary dose interruption/dose change.

Deaths

In SOLO2 study, 72 patients (24.4%) died during the study; 45 (23.0%) and 27 (27.3%) in the olaparib and placebo groups, respectively. All patients had death related to the disease under investigation only, apart from one patient in the olaparib arm who developed AML and died 177 days after her last dose of olaparib and one patient in the placebo arm with subsequent olaparib exposure who developed AML and died 442 days after her last dose of placebo and approximately 3 months after her last dose of post-study olaparib treatment.

In all 4 datasets, the vast majority of deaths were due to disease under study, with few patients reporting AEs leading to death.

Other significant events

Myelodysplastic syndrome/acute myeloid leukaemia, pneumonitis and new primary malignancies have been classified in the Risk Management Plan as important potential risks.

Myelodysplastic syndrome (MDS) /acute myeloid leukaemia (AML)

The overall reporting incidence rate of MDS/AML in olaparib treated patients to date (data cut off 15 December 2016) across the programme is 0.49%, with 32 reports being received in 6558 patients treated with olaparib across the clinical programme. The 32 reports of MDS/AML comprise of the 21 reports from the olaparib monotherapy all doses pool. Seventeen of the 21 patients died (13 due to MDS/AML as either a primary or secondary cause of death and 4 due to other causes).

Where a placebo comparison is available, the incidence in the olaparib and placebo arms is similar, and when larger populations of olaparib treated patients are considered the incidence remains below 1.5%. The incidence rates calculated all remain within the range observed in the literature where reported incidence of secondary MDS/AML in ovarian cancer patients ranges from 0.15% to 1.8%. There was a similar broad range of time to

onset of MDS/AML in both the olaparib- and placebo-treated patients, with no obvious difference in the median time to onset of events.

A causal relationship between olaparib treatment and the development or acceleration of MDS/AML has not been established.

All patients had potential contributing factors for the development of MDS/AML. All patients had received previous chemotherapy with DNA damaging agents, with many patients having previous chemotherapy with multiple treatment regimens over multiple years including carboplatin, taxanes, anthracyclines, other alkylating and DNA damaging agents and radiotherapy.

Data provides in SOLO2 are reassuring since the incidence of MDS/AML in olaparib-treated patients is similar to that with placebo. However, the time of follow-up in this study is too short to bring any conclusion. Post-authorisation studies need to be conducted for a better assessment of this potential risks.

Other new primary malignancies

In SOLO2, the data show that where a placebo comparison is available, the incidence in the olaparib (0.51%) and placebo (1.01%) arms was similar.

In study 19 (DCO = 09 May 2016), the incidence was lower in the placebo-treated patients (0.78%) compared with olaparib-treated patients (2.94%). 4 patients developed a new primary malignancies on olaparib at the DCO 09 May 2016, whereas, it has occurred in only 2 patients at the DCO 26 November 2012.

When larger populations of olaparib treated patients are considered the incidence remains below 2%.

Patients enrolled into the olaparib clinical studies had already received prior chemotherapy with multiple cycles of platinum containing chemotherapy. Time from cancer diagnosis, onset of secondary cancers was generally several years and was overlapping with time when patients were receiving olaparib. Whilst it is not possible to exclude a contribution of olaparib, a causal relationship between olaparib treatment and the development of new primary malignancies has not been established.

Pneumonitis

Three pneumonitis (grade 1) occurred in the olaparib arm of SOLO2 (none in the placebo group) and one (also grade 1) in study 19. Overall 8 AEs occurred in the monotherapy group (0.48%) and 35 in the entire clinical program (0.53%). The frequency of pneumonitis events observed within the olaparib clinical trial programme continues to appear consistent with expected rates for cancer patients based on published data for patients with lung cancer.

Adverse drug reactions

SOLO2 study

92.3% of olaparib-treated patients and 62.6% placebo-treated patients had AEs were considered by the investigator to be causally-related to study treatment. Nausea and fatigue were the most frequently reported AEs considered by the investigator to be causally related to study treatment.

Most of the patients who had AEs considered causally-related to treatment had CTCAE Grade ≤2 events, with 29.7% olaparib-treated patients and 7.1% placebo-treated patients having related events of CTCAE Grade ≥3 severity. The most common high-grade, treatment-related event in the olaparib-treated group was anaemia (18.5% patients); asthenia, nausea and neutrophil count decreased each occurred in 2.6% olaparib-treated patients, neutropenia and vomiting each occurred in 2.1% patients and all other events occurred in ≤3 patients.

Table 45: Frequency of AEs in tablet pool, capsule pool and overall for events identified as ADRs associated with olaparib treatment

	Tablet monotherapy pool N=482		Capsule monotherapy pool N=766		Overall (tablet & capsule) N=1248			
System Organ Class/Preferred term	All CTCAE grades n (%)	CTCAE grades ≥3 n (%)	All CTCAE grades n (%)	CTCAE grades ≥3 n (%)	All CTCAE grades n (%)	Frequency descriptor	CTCAE grades ≥3 n (%)	Frequency descriptor
Blood and lymphatic system disorders								
Anaemia[a]	169 (35.1)	68 (14.1)	218 (28.5)	104 (13.6)	387 (31.0)	Very common	172 (13.8)	Very common
Neutropenia[a]	64 (13.3)	22 (4.6)	51 (6.7)	26 (3.4)	115 (9.2)	Common	48 (3.8)	Common
Thrombocytopenia[a]	42 (8.7)	7 (1.5)	53 (6.9)	18 (2.3)	95 (7.6)	Common	25 (2.0)	Common
Leukopenia[a]	41 (8.5)	9 (1.9)	44 (5.7)	21 (2.7)	85 (6.8)	Common	30 (2.4)	Common
Lymphopenia[a]	4 (0.8)	2 (0.4)	5 (0.7)	2 (0.3)	9 (0.7)	Uncommon	4 (0.3)	Uncommon
Metabolism and nutrition disorders								
Decreased appetite	127 (26.3)	3 (0.6)	171 (22.3)	5 (0.7)	298 (23.9)	Very common	8 (0.6)	Uncommon
Nervous system disorders								
Headache	87 (18.0)	1 (0.2)	134 (17.5)	2 (0.3)	221 (17.7)	Very common	3 (0.2)	Uncommon
Dysgeusia	94 (19.5)	0	107 (14.0)	0	201 (16.1)	Very common	0	-
Dizziness	51 (10.6)	1 (0.2)	103 (13.4)	3 (0.4)	154 (12.3)	Very common	4 (0.3)	Uncommon
Gastrointestinal disorders								
Nausea	297 (61.6)	8 (1.7)	477 (62.3)	21 (2.7)	774 (62.0)	Very common	29 (2.3)	Common
Vomiting	175 (36.3)	11 (2.3)	280 (36.6)	25 (3.3)	455 (36.5)	Very common	36 (2.9)	Common
Diarrhoea	138 (28.6)	5 (1.0)	185 (24.2)	13 (1.7)	323 (25.9)	Very common	18 (1.4)	Common
Dyspepsia	52 (10.8)	0	127 (16.6)	0	179 (14.3)	Very common	0	-
Upper abdominal pain	44 (9.1)	1 (0.2)	75 (9.8)	2 (0.3)	119 (9.5)	Common	3 (0.2)	Uncommon
Stomatitis	30 (6.2)	3 (0.6)	36 (4.7)	3 (0.4)	66 (5.3)	Common	6 (0.5)	Uncommon
General disorders and administration site conditions								
Fatigue (including asthenia)	283 (58.7)	24 (5.0)	471 (61.5)	57 (7.4)	754 (60.4)	Very common	81 (6.5)	Common
Investigations								
Increase in creatinine	26 (5.4)	0	43 (5.6)	2 (0.3)	69 (5.5)	Common	2 (0.2)	Uncommon
Mean corpuscular volume elevation	2 (0.4)	0	0	0	2 (0.2)	Uncommon	0	-

Laboratory findings

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

Safety in special populations

Age: A similar proportion of patients had AEs, AEs of CTCAE Grade ≥3 and SAEs in all age categories. A higher proportion of patients discontinued treatment due to AEs in the 75 to 84 years age category (10.7%), compared with <65 years (7.2%) and 65 to 74 years categories (7.5%). One AE (of AML) with an outcome of death (death occurring >30 days after last treatment dose) was reported in a patient in the 65 to 74 years age category.

Table 46 Number of patients reporting at least one adverse event by age group (Tablet pool, olaparib 300 mg bd)

MedDRA term	**Age <65 years N = 347 n (%)**	**Age 65–74 years N = 107 n (%)**	Age 75-84 years N = 28 n (%)	**Age ≥85 years N = 0**
Total AEs	340 (98.0)	104 (97.2)	27 (96.4)	0
Any AE CTCAE Grade ≥3	126 (36.3)	37 (34.6)	11 (39.3)	0
Serious AEs – total[a]	66 (19.0)	23 (21.5)	6 (21.4)	0
Fatal	0	1 (0.9)	0	0
Hospitalisation/prolong existing hospitalisation	64 (18.4)	20 (18.7)	6 (21.4)	0
Life-threatening	5 (1.4)	2 (1.9)	0	0
Other (disability incapacity)	3 (0.9)	0	0	0
Other (medically significant)	13 (3.7)	4 (3.7)	1 (3.6)	0
Death related to disease and an AE with outcome = death (death >30 days after last treatment dose)	0	1 (0.9)	0	0
AEs leading to treatment discontinuation	25 (7.2)	8 (7.5)	3 (10.7)	0

a. The total is not equal to the sum of the events across the seriousness criteria because investigators are asked to indicate each seriousness criterion valid for the event

Data derived from: Table 2.7.4.1.6.1.4 and 2.7.4.1.12.1; Module 5.3.5.3. DCO for SOLO2 = 19 September 2016.

There is no major difference in the safety profile of patients treated with olaparib aged <65 years versus ≥ 65 years, nor within the age categories of 65 to 74 years and 75 to 84 years. No patients were aged ≥ 85 years.

Race: Overall, there is no evidence of a difference in olaparib safety for White and non-White patients, but patient numbers are small in the non-White patient population.

Hepatic impairment: A formal study (D0816C00005) to evaluate the impact of hepatic impairment on olaparib PK has been initiated and completed for patients with mild hepatic impairment (Child-Pugh A). Olaparib is not recommended for use in patients with moderate or severe hepatic impairment; however, no olaparib dose adjustment is considered warranted for patients with mild hepatic impairment.

Renal impairment: A formal study (D0816C00006) was conducted to evaluate the impact of renal impairment on the overall clearance of olaparib with patients with mild renal impairment (CrCl 51 mL/min to 80 mL/min) and moderate renal impairment (CrCl 31 mL/min to 50 mL/min).

Olaparib is not recommended for use in patients with severe renal impairment; the dosage should be reduced to 200 mg bd in patients with moderate renal impairment, however, no olaparib dose adjustment is considered warranted for patients with mild renal impairment.

Effect of Food: Study D0816C00004 has evaluated the effect of food (a high fat meal) on the PK of the olaparib tablet formulation in 60 patients. Data show that food does not significantly affect the extent of exposure to olaparib. Olaparib may be taken with or without regard to meals.

Safety in long-term use

There are limited data available for patients treated with olaparib therapy beyond 2 years.

At the DCO of 19 September 2016, 62.1% of patients in SOLO2 have received olaparib treatment for ≥12 months and 30.3% of patients have received olaparib for ≥24 months. 23.5% of patients (32 patients) in Study 19 have received treatment beyond 2 years. Other completed studies with olaparib have treated later line patients with relapsed disease.

Safety related to drug-drug interactions and other interactions

Please refer to the section Pharmacokinetics.

Discontinuation due to adverse events

The below table summarises the number of AEs leading to discontinuations in the olaparib treatment groups in SOLO2, Study 19 and the tablet and capsule pools.

Table 47 Number (%) of patients reporting the most common AEs leading to discontinuation (≥2 olaparib-treated patients in any of the Olaparib treatment groups [SOLO2, Study 19, tablet pool and capsule pool])

SOC and PT	Olaparib 300 mg bd tablet		Olaparib 400 mg bd capsule	
	SOLO2 N = 195 n (%)	Tablet pool N = 482 n (%)	Study 19 N = 136 n (%)	Capsule pool N = 766 n (%)
Any AE leading to discontinuation	**21 (10.8)**	**36 (7.5)**	**8 (5.9)**	**45 (5.9)**
Blood and lymphatic disorders	**8 (4.1)**	**10 (2.1)**	**1 (0.7)[a]**	**9 (1.2)**
Anaemia	6 (3.1)	7 (1.5)	0	3 (0.4)
Neutropenia	2 (1.0)	3 (0.6)	0	3 (0.4)
Thrombocytopenia	1 (0.5)	1 (0.2)	0	3 (0.4)
Gastrointestinal disorders	**2 (1.0)**	**6 (1.2)**	**1 (0.7)**	**20 (2.6)**
Abdominal distension	0	0	0	2 (0.3)
Abdominal pain	1 (0.5)	1 (0.2)	0	3 (0.4)
Diarrhoea	0	0	0	3 (0.4)
Intestinal obstruction	0	0	0	3 (0.4)
Nausea	1 (0.5)	3 (0.6)	1 (0.7)	5 (0.7)
Small intestinal obstruction	0	0	0	2 (0.3)
Vomiting	0	3 (0.6)	0	4 (0.5)
General disorders and administration site conditions	**1 (0.5)**	**3 (0.6)**	**0**	**3 (0.4)**
Fatigue	0	2 (0.4)	0	1 (0.1)
Investigations	**2 (1.0)**	**5 (1.0)**	**0**	**1 (0.1)**
Neutrophil count decreased	1 (0.5)	2 (0.4)	0	0
Renal and urinary disorders	**0**	**0**	**0**	**2 (0.3)**
Acute kidney injury	0	0	0	2 (0.3)
Respiratory, thoracic and mediastinal disorders	**1 (0.5)**	**2 (0.4)**	**1 (0.7)**	**4 (0.5)**
Pleural effusion	0	0	0	2 (0.3)
Pneumonitis	1 (0.5)	2 (0.4)	0	1 (0.1)

[a]. The AE in this SOC was an AE of pancytopenia (CTCAE Grade 4)
Tablet and capsule pools include data from SOLO2 and Study 19, respectively
Includes AEs with an onset date between the date of first dose and 30 days following the date of last dose of study treatment.
AE Adverse event; bd Twice daily; CTCAE Common Terminology Criteria for Adverse Events; DAE Discontinuation adverse event; DCO Data cut-off.; N Total number of patients; PT Preferred term; SOC System organ class.

Post marketing experience

The capsule formulation of olaparib is currently approved in the 52 countries worldwide for the treatment of patients with ovarian cancer. As of 15 December 2016, a total of 676 patients have been dosed with olaparib capsules in the following Global Access Programmes: Named Patient Supply Scheme, French Authorisation of Temporary Use, Turkish Compassionate Use Programme, UK Early Access to Medicines Scheme, UK Compassionate Use Programme, German Compassionate Use Programme, Dutch Compassionate Use Programme, and USA early Access programme. In addition, there are a number of ongoing clinical studies in which patients have been dosed with either olaparib tablets or a blinded comparator agent.

No new or important safety information resulting in changes to the safety profile of olaparib has been identified from the ongoing studies or patient access programme.

2.6.1. Discussion on clinical safety

Safety results with olaparib 300 mg bd tablet are mainly coming from the phase III SOLO2 study. Pooled safety data from additional 7 studies in patients with advanced solid tumours (271 of whom were documented to have ovarian cancer) were also submitted by the MAH.

Data from the phase II Study 19 and an additional 11 studies provide a comparative dataset of the capsule formulation of olaparib in the PSR ovarian cancer maintenance treatment setting.

Overall, the safety profile is based on pooled data from 1248 patients treated with Lynparza monotherapy in clinical trials in the therapeutic indication at the 300mg bid and 400mg bid doses.

In SOLO2 study, the most common AEs (reported by >30% patients) in the olaparib arm were nausea, anaemia, fatigue, vomiting, diarrhoea and asthenia.

For a number of events reported at a higher (≥ 5%) frequency on olaparib compared with placebo, the exposure-adjusted event rates appear higher for placebo treated patients or similar between the arms (decreased appetite, diarrhoea, headache and pyrexia). This suggests that the difference in treatment duration between the arms may explain the differences in reporting frequencies observed in this study.

Reporting AEs in terms of exposure-adjusted event rates indicates that for many of the most common events reported at a higher (≥ 5%) frequency on olaparib compared with placebo, the rate remains higher for olaparib-treated patients when adjusted for exposure: anaemia; dizziness; dysgeusia; dyspnoea; fatigue; leukopenia; nausea; neutropenia and vomiting. Of these, anaemia, cough, dizziness, dysgeusia, fatigue, nausea, neutropenia and vomiting were considered as ADRs for olaparib by the MAH and reflected as such in section 4.8 of the SmPC. Based on these new data, leukopenia and cough was also considered as ADR and the SmPC was amended accordingly.

In studies pool, the most common AE was nausea, and this was consistently reported across SOLO2, Study 19, and the tablet and capsule pools. Other common events (≥ 30%) that were consistently reported (≤ 5% difference between SOLO2 and Study 19) were vomiting, diarrhoea and asthenia/fatigue.

Nausea was generally reported very early, with first onset within the first month of Lynparza treatment in the majority of patients. Vomiting was reported early, with first onset within the first two months of Lynparza

treatment in the majority of patients. Both nausea and vomiting were reported to be intermittent for the majority of patients and could be managed by dose interruption, dose reduction and/or antiemetic therapy. Antiemetic prophylaxis is not required.

In general, the onset of AEs by treatment period was similar for SOLO2 and Study 19. The majority of AEs occurred within the first 3 months of treatment. In the first 3 months of treatment, AEs of anaemia, asthenia, dysgeusia and hypomagnesaemia occurred at a higher frequency (≥ 5% difference) in SOLO2 compared with Study 19; whereas events of abdominal distension, dyspepsia and fatigue occurred at a higher frequency in Study 19.

Proportions of patients with AE of CTCAE Grade 3 or higher and SAE are lower in the tablet pool than in the capsule pool (respectively 45.3% and 26.4% vs. 36.1% and 19.7%).

The most commonly reported event of CTCAE Grade ≥3 was anaemia in all 4 populations; the proportion of patients with Grade ≥3 anaemia was higher in SOLO2 (19.5%) than in Study 19 (5.9%).However anaemia remained manageable by interrupting or reducing the olaparib dose or giving blood transfusions, when indicated and treatment discontinuation was rarely required.

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

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

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

The proportion of patients who permanently discontinued olaparib due to AEs was low. The only AE leading to discontinuation that occurred at ≥2% difference between any of the treatment groups was anaemia, which led to discontinuation in 3.1% patients in SOLO2 compared with no patients in Study 19. Discontinuations due to anaemia was also higher in the tablet pool than in the capsule pool but the difference was <2%.

A lower proportion of patients reported SAEs in tablet pool than in capsule pool. Most SAEs were reported as single PTs in SOLO2 and Study 19. The most common SAE was anaemia and the SOCs where SAEs were most commonly reported were gastrointestinal disorders and blood and lymphatic system disorders. Proportions of SAEs reported in blood and lymphatic system disorders SOC were similar between tablet pool and capsule pool whereas gastrointestinal disorders SOC were reported with higher frequency in the capsule pooled studies.

Although, the safety dataset contributing to long-term exposure to olaparib in SOLO2 study are limited, the long-term exposure was demonstrated in Study 19 with olaparib 400mg bd capsule. In this study, only two patients received olaparib 400mg tablets beyond 7 years of treatment is however limited.

In SOLO study, proportion of patients reported SAEs in the olaparib group was 17.9%. A total of 52 SAEs were reported in the olaparib group, with only SAEs of anaemia (12 SAEs in 7 patients), intestinal obstruction (4 SAEs in 3 patients) and peripheral oedema (2 SAEs in 1 patient) being reported more than once by any patient.

The overall reporting incidence rate of MDS/AML in olaparib treated patients to date across the programme is 0.49%, with 32 reports being received in 6558 patients treated with olaparib across the clinical programme. The 32 reports of MDS/AML comprise of the 21 reports from the olaparib monotherapy all doses pool. Seventeen of the 21 patients died (13 due to MDS/AML as either a primary or secondary cause of death and 4 due to other causes).

The causality relationship with prior olaparib exposure might not be dismissed in the occurrence of AML and death of one patient due to exposure of this patient, initially treated in the placebo group, to olaparib during 3 months in the post treatment phase at progression. This patient died 6 months after the first dose of olaparib. The time frame is compatible with this aggressive disease.

Where a placebo comparison was available, the incidence in the olaparib and placebo arms was similar, and when larger populations of olaparib treated patients were considered, the incidence remained below 1.5%. The incidence rates calculated remained within the range observed in the literature where reported incidence of secondary MDS/AML in ovarian cancer patients ranges from 0.15% to 1.8%.

There was a similar broad range of time to onset of MDS/AML in both the olaparib- and placebo-treated patients, with no obvious difference in the median time to onset of events. It is acknowledge that all patients had received previous chemotherapy with DNA damaging agents, with many patients having previous chemotherapy with multiple treatment regimens over multiple years including carboplatin, taxanes, anthracyclines, other alkylating and DNA damaging agents and radiotherapy.

Data provided in SOLO2 are reassuring since the incidence of MDS/AML in olaparib-treated patients is similar to that with placebo. However, because of the relatively short exposure and follow-up in this study no conclusion can be drawn. Periodic reviews via the collection and assessment of data emerging from the ongoing clinical program are foreseen in the RMP to further characterise these events (see RMP section).

In SOLO2, the data show that the incidence of other new primary malignancies in the olaparib (0.51%) and placebo (1.01%) arms was similar. In study 19, the incidence was lower in the placebo-treated patients (0.78%) compared with olaparib-treated patients (2.94%) as of 09 May 2016. When larger populations of olaparib treated patients are considered, the incidence remains below 2%.

Whilst it is not possible to exclude a contribution of olaparib, a causal relationship between olaparib treatment and the development of new primary malignancies has not been established. No routine risk minimisation measures are planned in the risk management plan to address this potential risk, which is considered acceptable.

Special populations

A similar proportion of patients had AEs, AEs of CTCAE Grade ≥3 and SAEs in all age categories. A slightly higher proportion of patients discontinued treatment due to AEs in the 75 to 84 years age category (10.7%), compared with <65 years (7.2%) and 65 to 74 years categories (7.5%). However, the safety data in patients aged 75 or over are limited.

There is no evidence of a difference in olaparib safety for White and non-White patients, but patient numbers are small in the non-White patient population.

Olaparib is not recommended for use in patients with moderate or severe hepatic impairment; however, no olaparib dose adjustment is considered warranted for patients with mild hepatic impairment.

Olaparib is not recommended for use in patients with severe renal impairment; the dosage should be reduced to 200 mg bd in patients with moderate renal impairment, however, no olaparib dose adjustment is considered warranted for patients with mild renal impairment.

Overdose

There is limited experience of overdose with olaparib. Data derived from 5 patients from the SOLO2 study who took a daily dose of up to 900 mg of olaparib tablets over two days reported no unexpected adverse reactions. Symptoms of overdose are not established and there is no specific treatment in the event of Lynparza overdose. In the event of an overdose, physicians should follow general supportive measures and should treat the patient symptomatically. This is reflected in the product information.

2.6.2. Conclusions on the clinical safety

Overall, the safety profile of both capsule and tablet formulations are comparable. From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the SmPC.

There is risk of medication error due to availability of capsule and tablet form on the market that cannot be substituted on a milligram-to-milligram basis. This could lead to possible overdoses if the capsule posology is used for the tablets and it was therefore agreed that a DHPC should be circulated at time of the launch of the tablet formulation in each Member State to raise awareness amongst healthcare professionals. In addition, separate SmPCs and PL for the capsule and the tablet formulations have been agreed, which all include clear statement informing that olaparib tablets and capsules are not to be substituted on a milligram-to-milligram basis due to differences in the dosing and bioavailability of each formulation. Distinct differences in the appearance of medication and packaging for tablets vs capsules (presentation, colour scheme, label design, and dosing statements on the packaging) have also been proposed and agreed. The CHMP considers that the measures adopted to minimise the risks of medication errors are satisfactory. It is important to minimise as much as possible the time where both the tablet and the capsule formulations will be available on the market and that the withdrawal of the capsules from the market is carefully managed.

2.6.3. PSUR cycle

The PSUR cycle remains unchanged.

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).

2.6.4. Direct healthcare professional communication

A Direct Healthcare Professional Communication (DHPC) is considered necessary in order to communicate that the tablet and capsule formulations cannot be substituted on a milligram-to-milligram basis due to differences in the dosing and bioavailability of each formulation, and the potential risk of medication errors associated with the availability of these two presentations on the market.

The DHPC is provided in Appendix 2 together with the communication plan.

The MAH should agree the translations and local specificities of the DHPC with national competent authorities. The DHPC should be sent at time of the launch of the tablet formulation in each Member State to oncologists who are prescribers or potential prescribers of olaparib and pharmacists involved in dispensing olaparib.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Anaemia Thrombocytopenia Neutropenia Raised creatinine levels Nausea including vomiting Drug-drug interactions with CYP3A strong/moderate inducers and strong/moderate inhibitors
Important potential risks	MDS/AML New primary malignancies Pneumonitis Potential for off-label use Potential for medication errors Effects on embryofoetal survival and development
Missing information	Drug-drug interactions with substrates of CYP3A enzymes and transporter proteins

Summary of safety concerns	
	Exposure in patients with severe hepatic impairment Exposure in patients with severe renal impairment and end-stage renal disease Exposure in elderly patients Exposure in ethnically diverse groups Long-term exposure to/potential toxicity to olaparib Use in patients with ECOG performance status >2 Potential inhibitory effect of olaparib on UGT1A4 and UGT1A9

Pharmacovigilance plan

On-going and planned additional pharmacovigilance studies/activities in the Pharmacovigilance Plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Periodic review (Category 3)	To further characterise the important potential risk of MDS/AML via the collection and assessment of data emerging from the ongoing clinical program.	MDS/AML	Started	To be provided concurrent with each PBRER

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Anaemia:	Wording in sections 4.2, 4.4 and 4.8 of the SmPC	None

Neutropenia:	Wording in sections 4.2, 4.4 and 4.8 of the SmPC	None
Thrombocytopenia	Wording in sections 4.2, 4.4 and 4.8 of the SmPC	None
Raised creatinine levels	Wording in section 4.8 of the SmPC	None
Nausea including vomiting	Appropriate wording in SmPC. Statement on management of AEs. Statement that antiemetic prophylaxis is not required.	None
Drug-drug Interactions with CYP3A strong/moderate inducers and strong/moderate inhibitors	Wording in sections 4.2, 4.4 and 4.5 of the SmPC	None
Important potential risks		
MDS/AML	Wording in section 4.4 of the SmPC	None
New primary malignancies	None	None
Pneumonitis	Wording in section 4.4 of the SmPC	None
Potential for off-label use	Wording in sections 4.1 and 4.2 of the SmPC	None
Potential for medication errors	Wording in section 4.2 of the SmPC Separate SmPCs and Package leaflets for the capsule and tablet formulations. SmPC and Package Leaflet contain a clear statement informing that olaparib is available as tablets and capsules which are not to be substituted on a milligram-to-milligram basis due to differences in the dosing and bioavailability of each formulation. Distinct differences in the appearance of medication and packaging for tablets vs capsules (presentation, colour scheme, label design, and dosing statements on the packaging). Warning on packaging of both tablets and capsules stating that patients should not switch between tablets and capsules.	Distribution of a DHPC at time of launch
Effects on embryofoetal survival and development	Wording in sections 4.4 and 4.6 of the SmPC	None

Missing information

Drug-drug interactions with substrates of CYP3A enymes and transporter proteins	Wording in section 4.5 of the SmPC	None
Exposure in patients with moderate / severe hepatic impairment	Wording in section 4.2 of the SmPC	None
Exposure in patients with severe renal impairment and end-stage renal disease	Wording in section 4.2 of the SmPC	None
Exposure in the elderly (>75 years)	Wording in section 4.2 of the SmPC	None
Exposure in ethnically diverse groups	Wording in section 4.2 of the SmPC	None
Long-term exposure to/potential toxicity to olaparib	None	None
Use in Patients with ECOG performance status >2	None	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 15.6 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

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. Product information

As a consequence of the line-extension, a new SmPC was agreed for the new 100mg and 150mg film-coated tablets based on the SmPC of the capsule formulation. Sections 4.1, 4.2, 4.4, 4.8, 4.9, 5.1 and 5.2 for the tablet formulation include information specific to the tablet formulation and relevant to the agreed indication and posology for Lynparza tablet which differ from the indication and posology of Lynparza capsule.

In addition, sections 4.2, 4.4, 4.5, 4.6, 4.7, 4.8, 5.1, 5.2 and 5.3 of the SmPC of Lynparza capsule have been aligned with the updates proposed for the tablet formulation, as appropriate.

A combined package leaflet has been agreed and updated accordingly.

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The initial authorization of the capsule formulation of Olaparib for the maintenance treatment of adult patients with platinum sensitive relapsed BRCA mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (CR or PR) to platinum based chemotherapy was granted on December 2014.

The proposed indication for tablet formulation of olaparib is, as monotherapy, the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian cancer (including fallopian tube or primary peritoneal) who are in response (CR or PR) to platinum-based chemotherapy (irrespective of the BRAC mutation and histological type).

3.1.2. Available therapies and unmet medical need

There are 3 primary treatment options for platinum-sensitive recurrent ovarian cancer patients:

Platinum-based Chemotherapy Followed by Observation Only

Following response to second-line chemotherapy, per NCCN and ESMO guidelines, one of the options for ovarian cancer patients is to monitor until disease progression while managing the patient's symptoms but not provide active anti-cancer treatment.

Bevacizumab in Combination with Chemotherapy Followed by Bevacizumab Maintenance

Bevacizumab is approved in Europe for use in patients with recurrent ovarian cancer in combination with platinum-based chemotherapy with continuation beyond chemotherapy in the maintenance setting; although this is not an option for patients who received bevacizumab in front line.

Maintenance Therapy following response to platinum-based chemotherapy

Olaparib (capsule formulation) is approved in Europe as monotherapy for the maintenance treatment of adult patients with platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer with a BRCA mutation (either germline or tumour) who are in response (CR or PR) to platinum-based chemotherapy.

On 14 September 2017, the CHMP adopted a positive opinion recommending the granting of a marketing authorisation for Zejula (niraparib) as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

3.1.3. Main clinical studies

Results are mainly coming from two clinical studies: Study SOLO2 (using the tablet formulation), and Study 19 (using the capsule formulation).

SOLO2 study was a phase 3 randomised, double-blind study of maintenance therapy with olaparib tablet or placebo in platinum sensitive relapsed *BRCA* mutated ovarian cancer patients who are in complete or partial response following platinum containing chemotherapy. The primary objective of the study was PFS or death regardless of whether the patient discontinued randomised therapy or received another anti-cancer therapy prior to progression. Secondary objectives notably included PFS2, TFST, TSST and TDT.

Study 19 was a phase II, randomised, double blind, multicentre placebo-controlled study to assess the efficacy of olaparib capsule in the treatment of patients with platinum-sensitive relapsed high-grade serous ovarian cancer, who had received ≥2 previous platinum regimens and were in partial response or complete response following their last platinum-containing regimen. The primary objective of this study was to evaluate PFS. Main secondary objectives were OS, best overall response, disease control rate, duration of response, or change in tumour size.

Long-term results have been provided in addition to those submitted for initial MAA with capsule formulation.

3.2. Favourable effects

At the time of study SOLO2 data cut-off, 107 (54.6%) subjects in the Olaparib arm and 80 (80.8%) in the placebo arm had a PFS event. The hazard ratio (HR) was 0.30 (95% confidence interval [CI], 0.22 to 0.41),

indicating a 70% reduction in the risk of disease progression or death for subjects in the Olaparib arm compared with those in the placebo arm. The median PFS from randomization was 19.1 months in the Olaparib arm and 5.5 months in the placebo arm. At 24 months, 43% of patients in the olaparib group remained progression-free *vs* 15% of placebo patients. This PFS improvement is clinically relevant.

PFS results were supported by other endpoints: Time to discontinuation of treatment or death (TDT), Time to first subsequent therapy or death (TFST, Time to second subsequent therapy or death (TSST).

Study 19 data supported the initial marketing authorization, based solely on efficacy results in the BRCA mutated population. Results confirmed that patients with wt/VUS BRCA might benefit from olaparib. Consequently, only the FAS efficacy data were supportive of the broad indication without any mutation status restriction. Study 19 met its primary objective of statistically significantly improved investigator-assessed PFS (by RECIST) in the overall population treated with olaparib compared with placebo (HR 0.35; 95% CI 0.25-0.49; p<0.00001; median 8.4 vs 4.8 months).

A descriptive OS final analysis was performed at 79% maturity in the FAS. Even if statistical significance was not reached at the time of the analysis, survival data were numerically in favour of the Olaparib arm in terms of reduced risk of death (HR 0.73; 95% CI: 0.55, 0.95; p=0.02138).

Exploratory efficacy endpoints (TDT, TFST, TSST) support the PFS results, by indicating that the treatment benefit of olaparib is maintained beyond the treatment period.

BRCAm subgroup

At the DCO of 30 June 2010, PFS outcomes were HR 0.18; 95% CI 0.10 to 0.31; median PFS 11.2 vs 4.3 months; p<0.00001. At the final analysis of OS (DCO 09 May 2016, 79% maturity), the HR for OS was 0.62 (95% CI 0.42 to 0.93; median OS 34.9 vs 30.2 months; p=0.02140). Exploratory analyses of the intermediate clinical endpoints of TDT, TFST and TSST are in line with primary analysis.

BRCA wt/VUS subgroup

At the DCO of 30 June 2010, PFS outcomes were HR 0.54; 95% CI 0.34 to 0.85; median PFS 7.4 vs 5.5 months; p=0.00745. At the final analysis of OS (DCO 09 May 2016, 79% maturity), the HR for OS was 0.84 (95% CI 0.57 to 1.25; median OS 24.5 vs 26.6 months; p=0.39749). Exploratory analyses of the intermediate clinical endpoints of TDT, TFST and TSST are in line with primary analysis.

The availability of the tablet formulation will also provide benefits in terms of fewer and smaller dose units and food-independent exposure.

3.3. Uncertainties and limitations about favourable effects

Uncertainties remain with regard to the magnitude of benefit of Lynparza in gBRCAwt patients due to the heterogeneity of this patient population and since data in this subgroup of patients are limited. In order to further define the efficacy of olaparib in patients with platinum sensitive relapsed (PSR) non-germline *BRCA* mutated high grade ovarian cancer in the maintenance setting and investigate predictive biomarkers within this patient group, the MAH should submit the results of study D0816C00020 (OPINION), a phase IIIb single-arm, open-label, multicentre study of maintenance therapy in PSR non-germline BRCA mutated ovarian cancer

patients who are in complete or partial response following platinum based chemotherapy (Annex II). In addition, as patients without HRD would not benefit from PARPi due to their mechanism of action, the MAH should investigate predictive biomarkers within this patient group in the context of the OPINION study, to identify patients who are more likely to benefit to a greater extent.

3.4. Unfavourable effects

Overall, the most common AEs reported for both tablet and capsule pool were nausea, asthenia/fatigue, vomiting, diarrhoea and anaemia. Proportions of patients with AE of CTCAE Grade 3 or higher and SAE were lower in the tablet pool than in the capsule pool (respectively 45.3% and 26.4% *vs*. 36.1% and 19.7%). Anaemia was reported at an increased frequency with the tablet formulation as compared to the capsule formulation. However, anaemia remained manageable by interrupting or reducing the olaparib dose or giving blood transfusions, when indicated; treatment discontinuation was rarely required.

Proportion of patients reporting events of CTCAE Grade ≥3 was lower in the tablet pool (36.1%) compared to the capsule pool (45.3%). The most commonly reported event of CTCAE Grade ≥3 was anaemia in all 4 populations; the proportion of patients with Grade ≥3 anaemia was higher in SOLO2 (19.5%) than in Study 19 (5.9%).

The incidence of AEs leading to discontinuation of olaparib was low. The only AE leading to discontinuation that occurred at ≥2% difference between any of the treatment groups was anaemia, which led to discontinuation in 3.1% patients in SOLO2 compared with no patients in Study 19. Discontinuations due to anaemia was also higher in the tablet pool than in the capsule pool, the difference was <2%).

There was a similar broad range of time to onset of MDS/AML in both the olaparib- and placebo-treated patients, with no obvious difference in the median time to onset of events.

Data from SOLO2 are reassuring since the incidence of MDS/AML in olaparib-treated patients is similar to that with placebo. Data also show that the incidence of other new primary malignancies in the olaparib (0.51%) and placebo (1.01%) arms was similar.

In study 19, the incidence was lower in the placebo-treated patients (0.78%) compared with olaparib-treated patients (2.94%) as the date of 09 May 2016. 4 patients developed new primary malignancies on olaparib.

In all 4 datasets, the vast majority of deaths were due to the disease under study, with few patients reporting AEs leading to death.

3.5. Uncertainties and limitations about unfavourable effects

In the SOLO2 study, grade ≥3 anaemia was reported at an increased frequency with the tablet formulation as compared to the capsule formulation used in study 19 (19.5% *versus* 5.9%, respectively). If, supposedly, this increased frequency could be linked to the tablet bioavailability that was shown to be approximately twice the capsule bioavailability, such a result was not observed for other events. Although anaemia remained usually manageable by interrupting or reducing olaparib dose, or giving blood transfusions when indicated, treatment discontinuation was nevertheless required in a minority of patients. Warning and recommendations have been included in the product information.

Data provided in SOLO2 are reassuring since the incidence of MDS/AML in olaparib-treated patients is similar to that with placebo. However, because of the relatively short exposure and follow-up in this study no firm conclusion can be drawn. To further characterise the potential risk of MDS/AML, the MAH will continue collecting data emerging from the ongoing clinical program.

It should be noted that the patient population was more fit in SOLO-2 than in Study 19 in later lines of therapy. Hence the extent of difference in terms of toxicity between the 2 formulations is difficult to establish. Further safety data with the tablet formulation will be collected in the planned and ongoing studies described above.

The posology and bioavailability for tablets and capsules are different and the two formulations should not be substituted on a milligram-to-milligram basis; there is a risk of overdose and increased adverse events if the capsule posology is used for the tablets or lack of efficacy if the tablet posology is used for the capsules. Relevant information is provided in the SmPC, labelling and package leaflet. In addition, a DHPC was agreed to raise awareness and minimise the risks associated with medication errors. The MAH also committed to minimise the time during which the two formulations will be available on the market. The CHMP considers that the agreed measures to minimise the risks of medication errors are satisfactory.

3.6. Effects Table

Table 48: Effects Table for Lynparza in the treatment of platinum-sensitive relapsed high-grade ovarian cancer who are in response (CR or PR) to platinum-based chemotherapy

Effect	Short Description	Unit	Olaparib	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects						
PFS (HR)	From randomisation to progression or death		0.30	1	Efficacy data based only on germline BRCA mutation	SOLO2
			0.35 (overall) 0.18 (BRCAm) 0.54 (BRCA WT/VUS)	1	Capsule formulation	Study19
PFS2 (HR)	From randomisation to the earliest of the progression event subsequent to that used for the primary variable PFS or death.	months	0.50	1		SOLO2
PFS2 (median)			NR	18.4	PFS2 data are immature	SOLO2
OS (HR)	From randomisation until death		0.80	1	P=0.4267 Not powered for OS and immature data	SOLO2

Effect	Short Description	Unit	Olaparib	Placebo	Uncertainties/ Strength of evidence	References
			0.73 (overall) 0.62 (BRCAm) 0.84 (BRCA WT/VUS)	1	NS, but no deleterious effect of the maintenance treatment on survival	Study19
OS (median)		months	NR	NR	OS data are immature	SOLO2
			29.8 34.9 24.5	27.8 30.2 26.6		Study19

Unfavourable Effects

Adverse Effect	Short Description	Unit	study SOLO 2		Pool	Uncertain-ties/ Strength of evidence (tablets)	References
			Placebo bd N = 99	Olaparib 300 mg tablets bd N = 195	Olaparib 300 mg tablets N = 482		
Blood and lymphatic disorders; All grades	anemia	% Pts	7.1% (7/99)	43.1% (84/195)	34.6% (167/482)	*Two times higher than in study19 (21.3%)*	*S2 CSR t36; A_SCS t23*
Gastrointes-tinal disorders; All grades	nausea	% Pts	33.3% (33/99)	75.9% (148/195)	61.6% (297/482)		"
	vomiting	% Pts	19.2% (19/99)	37.4% (73/195)	36.3% (175/482)		"

Effect	Short Description	Unit	Olaparib		Placebo	Uncertainties/ Strength of evidence	References
General disorders; All grades	fatigue	*% Pts*	15.2% (15/99)	37.9% (74/195)	44.8% (216/482)	*reverse order with asthenia than in study 19*	"
Blood and lymphatic disorders	AEs Grade 3 and 4	% Pts	5.1% (5/99)	22.1% (43/195)	16.4% (79/48)	*Two times higher than in study19 (10.3%)*	*S2 CSR t48; A_SCS t25*
	treatment discon-tinuations	% Pts	1.0% (1/99)	4.1% (8/195)	2,1% (10/482)		*S2 CSR t52; A_SCS t30*
Gastrointestinal disorders;	Grade 3 and 4	% Pts	6.1% (6/99)	8.2% (16/195)	6,8% (33/482)		*S2 CSR t48; A_SCS t25*
General disorders and administration site conditions	Grade 3 and 4	% Pts	3.0% (3/99)	5.6% (11/195)	6,6% (32/482)		"
	dose reduction	% Pts	0%	5.6% (11/195) *a	NA		S2 CSR t54
MDS/AML		% Pts	3.0% (3/99) *b	3.7% (7/195) *b	NA		S2 CSR t49

[a] the cumulative incidence of asthenia and fatigue that are both of 6 patients (3.1%) is expected to be limited to the incidence of grade ≥ 3 (cell above) of the SOC [b] olaparib causality of AML of patient E2307506 being assessed as plausible. Abbreviations for references; S2: SOLO2, CSR: Clinical study report, t36: table 36, A_SCS: addendum to summary of clinical safety

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Demonstration of olaparib capacity to delay disease progression in patients who are in response to platinum-based chemotherapy was mainly based on PFS results from two randomised studies in patients with platinum-sensitive tumours. The use of PFS as primary endpoint is supported provided that there is no detriment on OS. Whereas OS data from the SOLO2 study are still immature, newly provided data from the Study 19 do not indicate detrimental effect in overall 'all-comers' population regardless of the BRCA1/2 status. For patients with germline BRCA1/2 mutations, the magnitude of PFS benefit reported in SOLO2 and Study 19 is clinically relevant and supported by sensitivity analyses and secondary endpoints.

The key issue for this application was the extrapolation of the results obtained with the capsule formulation to the tablet formulation.

Overall, based on the available data, the safety and efficacy profile of both capsule and tablet formulations are comparable.

3.7.2. Balance of benefits and risks

Clinical data were provided in patients with BRCA germline mutated high grade PSR ovarian cancer for tablet formulation (SOLO2) and in patients with high grade serous PSR ovarian cancer irrespective of the BRCA mutation status (Study 19).

Efficacy in non-mutated BRCA patients has only been provided based on Study 19 results, for patients with high grade serous ovarian cancer. However, in view of (i) consistent results in the SOLO2 study for patients with high grade endometrioid cancer; (ii) the olaparib mechanism of action and biological rationale suggesting benefit in high grade tumours; (iii) and in order to provide treatment option for patients with rare conditions that would benefit from treatment, indication is not restricted to "serous" histological type.

Further data is requested to provide evidence of efficacy and better estimate the magnitude of benefit in BRCAwt subgroup, and to prospectively investigate biomarkers that would allow to define patients that benefit the most and optimise the target populations. This will be addressed in the OPINION study where post-enrolment analysis of HRD status will be done.

A potential higher incidence of hemato-toxicity (≥ 3 grade anaemia) observed with the tablet formulation is outweighed by the demonstrated benefits in this patient population.

3.8. Conclusions

The overall B/R of Lynparza is positive.

In order to further define the efficacy of olaparib in patients with platinum sensitive relapsed (PSR) non-germline *BRCA* mutated high grade ovarian cancer in the maintenance setting and investigate predictive biomarkers

within this patient group, the MAH should submit the results of study D0816C00020 (OPINION), a phase IIIb single-arm, open-label, multicentre study of maintenance therapy in PSR non-germline BRCA mutated ovarian cancer patients who are in complete or partial response following platinum based chemotherapy.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Lynparza is not similar to Yondelis and Zejula within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of, Lynparza 100 mg and 150 mg tablet is favourable in the following indication:

as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

The CHMP therefore recommends the extension of the marketing authorisation for Lynparza subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
PAES: In order to further define the efficacy of olaparib in patients with platinum sensitive relapsed (PSR) non-germline *BRCA* mutated high grade ovarian cancer in the maintenance setting and investigate predictive biomarkers within this patient group, the MAH should submit the results of study D0816C00020 (OPINION), a phase IIIb single-arm, open-label, multicentre study of maintenance therapy in PSR non-germline BRCA mutated ovarian cancer patients who are in complete or partial response following platinum based chemotherapy. The clinical study report should be submitted by:	June 2021

In addition, CHMP recommends the variation to the terms of the marketing authorisation, concerning the following change:

Variation(s) requested		**Type**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II

The extension application is grouped with a type II variation to align the PI for the currently authorised capsule presentation with the safety updates proposed for the tablet formulation.

Appendix

1. CHMP AR on similarity dated 22 February 2018.

2. DHPC and communication plan