EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 October 2014
EMA/CHMP/789139/2014
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Lynparza

International non-proprietary name: OLAPARIB

Procedure No.: EMEA/H/C/003726/0000

Note

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

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Administrative information

Name of the medicinal product:	Lynparza
Applicant:	AstraZeneca AB SE-151 85 Södertälje 15185 Södertälje SWEDEN
Active substance:	OLAPARIB
International Nonproprietary Name/Common Name:	OLAPARIB
Pharmaco-therapeutic group (ATC Code):	other antineoplastic agents (L01)
Therapeutic 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.
Pharmaceutical form:	Capsule, hard
Strength:	50 mg
Route of administration:	Oral use
Packaging:	Bottle (HDPE)
Package size:	448 (4 x 112 capsules) capsules

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List of abbreviations

ACMG	American College of Medical Genetics and Genomics
ADME	Absorption, distribution, metabolism and excretion
ADR	Adverse drug reaction
AE	Adverse event
AML	Acute myeloid leukaemia
ANSM	Agence nationale de sécurité du médicament et des produits de santé
ALT	Alanine transaminase
AST	Aspartate transaminase
AUC	Area under plasma concentration-time curve
BCRP	Breast cancer resistance protein
bd	Twice daily
BIC	Breast Cancer Information Core
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)
BRCAm	*gBRCA* and/or *tBRCA* mutated
BRCAwt/VUS	*gBRCA* and/or *tBRCA* wild type/variant of unknown significance
BUN	Blood urea nitrogen
CA-125	Cancer antigen (CA)-125 (tumour biomarker)
CAP	College of American Pathologists
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CLIA	Clinical Laboratory Improvement Amendments
Cmax	Maximum plasma concentration
CR	Complete response
CRF	Case report form
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria (CTC) for Adverse Events
CYP	Cytochrome P450
DCO	Data cut-off
DNA	Deoxyribonucleic acid
DSB	DNA double-strand breaks
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EMQN	European Molecular Genetics Quality Network
EU	European Union
FACT-O	Functional Assessment of Cancer Therapy – Ovarian
FAHMP	Federal Agency for Medicines and Health Products
FAS	Full analysis set (the overall study population, unselected for *BRCA* mutation status, equivalent to intent to treat [ITT] population)
FDA	Food and Drugs Administration
FFPE	Formalin fixed paraffin embedded
FTIM	First time in man
gBRCAm	Germline *BRCA* mutated
gBRCAwt/VUS	Germline *BRCA* wild type/variant of unknown significance
GCP	Good Clinical Practice
GCIG	Gynecological Cancer Intergroup
GFR	Glomerular filtration rate
hERG	Human ether-a-go-go-related gene
HR	Hazard ratio
HRD	Homologous recombination deficient/deficiency
HRQoL	Health-related quality of life
IC50	Half maximal inhibitory concentration
ICH	International Conference on Harmonisation
ILD	Interstitial lung disease
ITT	Intention to treat
IVRS	Interactive voice response system
LMG	Lauroyl macrogol-32 glycerides

LS	Least squares
MAA	Marketing Authorisation Application
MCV	Mean corpuscular volume
MDR1	Multi-drug resistance protein 1
MDS	Myelodysplastic syndrome
MEB	Medicines Evaluation Board
MedDRA	Medical Dictionary for Regulatory Activities
MLPA	Multiplex ligation-dependent probe amplification
MPA	Medical Products Agency
MRI	Magnetic resonance imaging
MRP2	Multi-drug resistance protein 2
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NGS	Next generation sequencing
NHEJ	Non-homologous end joining
OATP	Organic anion-transporting protein
OCT	Organic cation-transporter
ORR	Objective response rate
OS	Overall survival
PARP	Polyadenosine 5'diphosphoribose polymerase
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PFS	Progression-free survival
PFS2	Time from start of randomisation to second progression or death
PK	Pharmacokinetics
PLD	Pegylated liposomal doxorubicin
PR	Partial response
PSR	Platinum-sensitive relapsed
QC	Quality control
QT	ECG interval measured from the beginning of the QRS complex to the end of the T wave
QoL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumours
RMP	Risk Management Plan
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SSB	DNA single-strand breaks
stBRCAm	Somatic tumour *BRCA* mutated (mutations detected in the tumour but not in the germline)
stBRCAwt/VUS	Somatic tumour *BRCA* wild type/variant of unknown significance
t-AML	Therapy-related AML
tBRCAm	Tumour *BRCA* mutated
tBRCAwt/VUS	Tumour *BRCA* wild type/variant of unknown significance
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)
tmax	Time to reach maximum concentration
TOI	Trial outcome index
TSST	Time to second subsequent therapy, or death (defined s time from randomisation to the start of second subsequent therapy or death)
US	United States
USA	United States of America
ULN	Upper limit of normal
UTI	Urinary tract infection
VEGF	Vascular endothelial growth factor
VUS	Variants of unknown significance

1. Background information on the procedure

1.1. Submission of the dossier

The applicant AstraZeneca AB submitted on 3 September 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Lynparza, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 February 2013.

Lynparza was designated as an orphan medicinal product EU/3/07/501 on 6 December 2007. Lynparza was designated as an orphan medicinal product in the following indication: Treatment of ovarian cancer.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Lynparza as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find medicine/Rare disease designations

The applicant applied for the following indication:

"Lynparza is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed *BRCA*-mutated ovarian cancer (including fallopian tube or primary peritoneal) who are in response (complete response or partial response) to platinum-based chemotherapy. "

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that olaparib was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/1/2011 (EMEA-62-2012) 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 applicant submitted a critical report addressing the possible similarity with authorised orphan medicinal products in a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance olaparib contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice / Protocol Assistance

The applicant received Protocol Assistance from the CHMP on 19 February 2009 and 15 December 2011. The Protocol Assistance pertained to non-clinical and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer responsible for batch release

AstraZeneca UK Limited
Silk Road Business Park
Macclesfield
Cheshire, SK10 2NA
United Kingdom

1.3. Steps taken for the assessment of the product

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

Rapporteur: Pierre Demolis Co-Rapporteur: Bart Van der Schueren

- The application was received by the EMA on 3 September 2013.
- The procedure started on 25 September 2013.
- The CHMP adopted a report on similarity of Lynparza with Yondelis on 25 November 2013 The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 December 2013. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 17 December 2013.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 9 January2014.
- During the meeting on 23 January 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 January 2014.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 23 April 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 3 June 2014.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 12 June 2014.
- During the CHMP meeting on 26 June 2014, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 19 August 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the 1st List of Outstanding Issues on 5 September 2014

- During a meeting of SAG on 10 September 2014, experts were convened to address questions raised by the CHMP.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 11 September 2014
- The Rapporteurs circulated the updated Joint Assessment Report on the applicant's responses to the 1st List of Outstanding Issues on 18 September 2014
- During the CHMP meeting on 25 September 2014, the CHMP agreed on a 2nd list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 30 September 2014.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 9 October 2014
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the 2nd List of Questions to all CHMP members on 10 October 2014
- During the meeting on 23 October 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Lynparza.

2. Scientific discussion

2.1. Introduction

Problem statement

In 2012, ovarian cancer was estimated to be the fifth most common cause of cancer death (29,760 deaths) and the fifth most common newly diagnosed cancer (44,150 new cases) in females in the EU (Ferlay et al 2013). Ovarian cancer is generally detected at an advanced stage, with a 5-year survival rate of 44% across all stages and 27% for advanced stages (Siegel et al 2013).

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.

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).

The current most commonly used regimens in first relapse for patients with platinum-sensitive ovarian cancer are platinum-based combination chemotherapy regimens (e.g. doublets including carboplatin/paclitaxel, carboplatin/gemcitabine, and carboplatin/ pegylated liposomal doxorubicin).

Such regimens are associated with cumulative toxicities (including neurologic, renal and haematologic side effects) that generally limit the duration of treatment to 6 cycles for each line of therapy.

Bevacizumab (Avastin), a vascular endothelial growth factor inhibitor already indicated in combination with carboplatin and paclitaxel for the first-line advanced ovarian cancer, was approved in the EU for the treatment of first recurrence of platinum-sensitive relapsed ovarian cancer (in combination with carboplatin and gemcitabine). Additionally, trabectedin (Yondelis), an antineoplastic agent that binds to DNA and triggers a cascade of events affecting several transcription factors, DNA binding proteins, and DNA repair pathways, is indicated in combination with pegylated liposomal doxorubicin (PLD) for the treatment of patients with relapsed platinum-sensitive ovarian cancer.

Homologous recombination deficiency

Homologous recombination (HR) is a type of genetic recombination most widely used by cells to accurately repair harmful breaks that occur on both strands of DNA, known as double-strand breaks. About 50% of high grade serous ovarian carcinomas are estimated to have disruption of the HR pathway and thus might be sensitive to PARP inhibitors (The Cancer Genome atlas (TCGa), 2011).

DNA repair mechanisms rely on several DNA repair pathways that interact and compensate each other in order to ensure DNA integrity. In cancer cells, dysregulation of such mechanisms leads to genomic instability and make cells dependent on compensatory mechanisms of DNA repair that maintain cell viability.

Endogenous base damage is the most common DNA aberration in cells. The base excision repair (BER) pathway recognises the damaged bases and after excising them generates single-strand DNA breaks (SSBs). Up to 10,000-20,000 SSBs are predicted to occur every day in a metabolically active cell, with an even higher frequency in tumour cells.

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.

There are 17 known members of the PARP family of proteins (Hottiger et al. 2010), but mainly PARP-1, -2 and -3 are associated with the DNA repairvia different mechanisms and interactions. While PARP-1 is the main family member involved in the repair of DNA single-strand breaks, PARP-2 still has the ability to bind to DNA and compensate for PARP-1 activity in DNA single-strand breaks repair.

The loss of function in the BRCA1 or BRCA2 proteins due to genetic mutations (hereditary or acquired) is the most commonly recognised cause of tumour homologous recombination deficiency (HRD). However, other mechanisms may contribute to the loss or reduction of BRCA1/2 function, including epigenetic factors such as BRCA1 promoter hypermethylation, mutations in regulators of BRCA1 or BRCA2 (e.g., PALB2) or through loss of heterozygosity at the *BRCA1* or *BRCA2* loci.

Moreover, other components of HR and repair pathway could be affected.

Individuals inheriting germline BRCA1 and BRCA2 mutations are at increased risk of cancer development, mostly breast and ovarian cancers. Alsop et al. identified a germline BRCA1/2 mutation frequency of 16.6% in all women diagnosed with serous ovarian tumours (Alsop et al 2012). Women inheriting a mutated copy of BRCA1 or BRCA2 have a 39% and 11% risk, respectively, of developing ovarian cancer by the age of 70 (Antoniou et al 2003). The 5-year overall survival is 44% for BRCA1 carriers, 52% for BRCA2 carriers and 36% for noncarriers *(Bolton et al, 2012).* The prevalence of BRCA1/2 mutation carriers in the general population is around 0.2%; however, it can vary significantly between different European countries or some ethnic groups due to founder effect (Janavicius, 2010).

In vitro data showed an increased sensitivity to platinum-based drugs in BRCA1 mutant cells (Lafarge et al 2001, Quinn at al 2003). Platinum agents induce DNA DSBs that require homologous recombination for effective and accurate repair and homologous recombination deficiencies are thought to result in the high degree of platinum sensitivity seen in ovarian cancer (Bowtell 2010). In Europe, testing for germline BRCA mutations is routinely performed by multiple laboratories, in accordance with local clinical practice. Testing is offered routinely to ovarian and breast cancer patients where personal and family histories indicate that a patient might be at risk of harbouring a germline BRCA mutation.

In individuals inheriting a germline BRCA mutation, whilst the inherited mutation is present in all cells of the body, only one allele carries the mutation. The half-dosage of BRCA1 or BRCA2 protein could lead to initial genomic instability in certain types of tissues, like in ovary or breast. When both copies of the gene are altered or mutated cancer development might be promoted. Individuals with germline BRCA1 or BRCA2 mutations have also increased risk of other types of cancer (Moran et al, 2012).

Somatic BRCA mutations were less studied an were reported in 6-7% of patients without germline mutation (Alsop et al 2012; Hennessy et al, 2010). Nevertheless, some reports provide higher frequencies (Pennington et al, 2014).

About the product

Olaparib is an inhibitor of human poly (ADP-ribose) polymerase enzymes (PARP-1, PARP-2 and PARP-3).

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 (Helleday 2011; Murai et al. 2012). In replicating cells this leads to DNA double strand breaks (DSBs) when replication forks meet the PARP DNA adduct. In normal cells, homologous recombination repair (HRR), which requires functional BRCA1 and 2 genes, is effective at repairing these DNA double strand breaks.

In the absence of functional BRCA1 or 2, DNA DSBs cannot be repaired via HRR. Instead, alternative and error-prone pathways are activated, such as the 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 have a high DNA damage load relative to normal cells (see SmPC section 5.1).

Whilst olaparib does not potentiate the activity of platinum agents per se, the DNA damage effect caused by each individual agent is expected to be additive. Platinum agents in the clinic are routinely given at the maximum tolerated dose, require intermittent cyclical administration to allow for recovery of bone marrow toxicity and despite this can still only be administered for a limited number of cycles during each treatment course. Olaparib is proposed to be used in the maintenance therapy commencing after patients have already received the maximum benefit from platinum therapy.

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

The recommended indication for olaparib is 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 (see SmPC section 4.1).

Platinum sensitive is defined as disease progressing at least 6 months after completion of the penultimate platinum chemotherapy (see SmPC section 5.1).

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

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 (see SmPC section 4.2).

The drug product is supplied as 50 mg hard capsules for oral use (see SmPC section 2).

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 (see SmPC section 4.2).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as hard capsules containing 50 mg of olaparib as active substance.

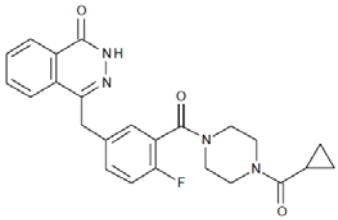
Other ingredients are: lauryl macrogolglycerides (LMG), for the capsule shell: hypromellose, titanium dioxide (E171), gellan gum, potassium acetate, for the capsule printing ink : shellac, iron oxide black (E172).

The product is available in HDPE plastic bottle with a child-resistant closure.

2.2.2. Active Substance

General information

The chemical name of olaparib is 4-[(3-{[4-(cyclopropylcarbonyl)piperazin-1-yl]carbonyl}-4-fluorophenyl)methyl]phthalazin-1(2H)-one and has the following structure:



Olaparib is a white to pale yellow non hygroscopic crystalline powder. The active substance is very slightly soluble in water, slightly soluble in acetonitrile and ethanol and sparingly soluble in methanol. Olaparib is classified as having low solubility and low permeability by the Biopharmaceutical Classification System (BCS Class 4). Olaparib has a non - chiral molecular structure. Polymorphism has been observed. Four polymorphic forms of olaparib were identified and one of them is consistently formed during the active substance manufacturing process and used in the manufacture of the finished product. This polymorphic form is kinetically favoured and is preferentially formed during the manufacturing process. One of the other potential polymorphic form that may be produced during the process is more thermodynamically stable at temperature below 60°C. The thermodynamic relationship between polymorphic form produced and the more thermodynamically stable polymorphic form has been satisfactorily discussed as well as the conditions necessary to produce other unwanted forms which are mostly precluded by Olaparib process.

The structure of olaparib has been confirmed using batch manufactured according to the synthetic route used during early development by elemental analysis, mass spectroscopy, ^{1}H, ^{19}F and ^{13}C-NMR, IR and single crystal XRD. Confirmation of the identity of the current reference standard of olaparib manufactured using the current route of synthesis has been confirmed using NMR spectroscopy, IR spectroscopy and X-ray diffractometry. Further characterisation of the current reference standard batch has also been performed: UV spectrum, GVS plot, DSC and TGA plots.

Manufacture, characterisation and process controls

Olaparib is synthesized in nine main steps using commercially available well defined starting materials with acceptable specifications. A major issue was initially raised around starting material selection and therefore it was proposed by the applicant to include the 2 stages preceding one of the originally proposed starting materials. Seven of the nine steps involve the making or breaking of covalent bonds, the eighth step comprises isolation of crude olaparib and the ninth step is micronization. The different steps of olaparib manufacture will be performed by three different sites.

The manufacturing process has been developed using a combination of conventional univariate studies and elements of QbD. Designs of Experiments (DoE) have been performed for six of the steps. Process parameters as proposed for all stages were generally defined on the basis of factorial experimental design (FED). For parameters not included in FEDs either additional data were provided in support of the proposed ranges or normal operating ranges were proposed. The critical steps whose variability has an impact on a critical quality attribute in the active substance were identified and critical process parameters (CPP) were provided.

Based on data submitted, the proposed ranges for process parameters are acceptable as they correspond to the ranges explored in the DoEs. Absence of details such as type of experimental design, list of design runs, statistical analysis, establishment of CPP and non-CPP status for each factor etc. is deemed acceptable as no Design Space has been claimed.

The specifications and control methods for intermediate products, starting materials and reagents have been presented. Validation data for the analytical methods used to control two of the intermediate products are missing and the CHMP recommended providing these data.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. Absence of routine control of impurities that may originate from starting materials or potential by-products has been justified. Considering the safety profile of olaparib (genotoxic and teratogenic), it has been agreed not to control the potential genotoxic imprurities to the threshold of toxicological concern (TTC) or to the staged TTC.

Batch data from 40 batches of micronised olaparib were presented. Six batches of the 40 were manufactured by proposed commercial synthetic route at the proposed manufacturing site. Five of the six batches were production scale batches. The results were within the specifications and consistent from batch to batch.

Specification

The active substance specifications are based on the active substance critical quality attributes (CQA). The active substance critical quality attributes (CQA) are provided and their control strategy is described (IPC, starting material, intermediate or active substance testing).

The active substance specification includes tests for: appearance, identification chemical and polymorphic (NIR), assay (HPLC), content of one of the other potential polymorphic form (NIR), impurities (HPLC), particle size (Laser diffraction), residual solvents (NMR spectroscopy or GC), water content (KF) and sulfated ash/residue on ignition (USP/Ph. Eur.). XRPD method has been added as a reference method in the scope of the NIR polymorphic identification method.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

NIR methods for identification (chemical and polymorphism) and quantification of one of the other potential polymorphic form have been appropriately described and validated in line with the note for

guidance “Guideline on the use of near infrared spectroscopy by the pharmaceutical industry and the data requirements to new submissions and variations”. Absence of a reference method for the quantification of one of the other potential polymorphic form was deemed acceptable considering the limitation of available alternative solid-state analysis methods sufficiently accurate. A detailed method maintenance protocol has been submitted together with a suitable Post Approval Change Management Protocol for both NIRS methods (Identification/Polymorphic Form and Quantification of one of the other potential polymorphic form). In addition, the CHMP recommended performing parallel testing by XRPD on 10 commercial batches in order to demonstrate additional validation of the NIR methods.

Batch data from 40 batches of micronised olaparib were presented. Six batches of the 40 were manufactured by proposed commercial synthetic route at the proposed manufacturing site. Five of the six batches were production scale batches. The results were within the specifications and consistent from batch to batch.

Stability

Stability data on 3 production scale batches of active substance manufactured via the proposed commercial synthetic route and stored in the intended commercial package for 48 months under long term conditions at 25 ºC / 60% RH and intermediate condition at 30 ºC / 65% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided.

The stability batches were not manufactured at the proposed manufacturing site. Commitment has been undertaken to carry out long-term (25°C/60 % RH) and accelerated (40°C/75% RH) stability studies on the three early commercial batches manufactured at the proposed manufacturing sites.

Photostability testing following the ICH guideline Q1B and thermal stress conditions (50°C/ambient humidity) were performed on one batch.

The following parameters were tested: description, assay, organic impurities, water, polymorphic form by XRD (except for thermal stress study), particle size distribution by laser diffraction (except for photostability study). Microbiological testing and content of one of the other potential polymorphic form by NIR were only tested at the 36 month time point for 3 stability batches for the 25°C/60% RH and 30°C/65% RH conditions.

The specification limits and analytical procedures for those parameters tested during stability are identical to those employed during release testing except for polymorphism and particle size distribution. Details on laser diffraction method and X-Ray Diffraction method have been provided along with validation data.

All parameters tested have remained within the limits of specification requirements for all samples. No trend of degradation is observed. No change in polymorphic form was observed after 36 months. Only a slight reduction is observed for the particle size at D(v,50).

Forced degradation studies of olaparib were also performed to assess the potential degradation pathway of the active substance in the solid state and on the active substance in organo-aqueous solutions. According to forced degradation studies results, Olaparib in the solid state is highly stable with respect to thermal, hydrolytic and photolytic degradation. Olaparib in solution is significantly degraded under basic and oxidative conditions. Only slight degradation occurs under acid and hydrolytic conditions. Olaparib is not light sensitive.

The stability results indicate that the active substance manufactured by the proposed supplier(s) is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

Comparability exercise for Active Substance

n/a

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The aim of the formulation work was to develop an immediate release dosage form allowing a maximised exposure of the poorly soluble active substance.

During early development stage, a tablet formulation and a capsule formulation using semi-solid Lauroyl macrogolglyceride (LMG) matrix were studied. Capsule formulation was selected for its better relative bioavailability found in a pre-clinical study in dogs.

Initial formulation development focussed on two enabling approaches to improve the bioavailability of this poorly soluble compound: a solution in capsule and a crystalline solid dispersion in capsule.

The range of materials evaluated for a liquid solution formulation included different hydrophilic, lipophilic and amphiphilic liquid vehicles. All of these solvents demonstrated too low solubilisation capacity and were thus discounted for this formulation type. A solution formulation was discounted based on greater potential problems with capsule leakage, stability and excipient/active substance interactions in comparison to the crystalline solid dispersion.

Other solid dispersion vehicles were screened in early development and the decision was made to develop the product based on LMG over the other solid dispersion types, based on the more appropriate processing temperatures combined with the reported bioavailability-enhancing effect of LMG.

Following selection of the LMG excipient, stability studies demonstrated that the product was stable and produced consistent dissolution performance throughout shelf life. Hypromellose capsules were chosen because leakage or embrittlement was observed upon storage with gelatine capsules. Olaparib capsules do not require additional components to prevent leakage or ensure stability.

The impact of drug loading on bioavailability was further investigated in dogs. As the drug loading increased, a decrease in exposure was observed due to a reduction in the drug: LMG ratio. Based upon this data the drug loading for the capsule formulation was fixed.

In order to maximise the exposure of the active substance, it was chosen to increase the surface area by micronisation since the phase 1 development studies.

Although drug loading has been optimized to the highest possible level within the selected dispersant excipient, the percentage of active substance in the finished product remains very low considering the recommended posology (daily intake of 16 capsules size 0). The retained formulation is considered by the applicant to be the best compromise between active substance solubilisation and drug loading. Olaparib 50 mg capsule has been administered to 801 patients across the 8-years clinical programme, using the maximum recommended posology for at least 1-year treatment with no evidence of compliance issues. The justifications provided by the applicant regarding concerns raised on long-term compliance were accepted considering the therapeutic indication and the medical need.

Transfer to commercial site and scale-up was done before the end of phase 1 clinical stage. No qualitative or quantitative changes were made since then to the olaparib capsule formulation, except for the addition of a black radial band printed on the body and cap of the capsule shell.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards or food additive standard. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The capsules are manufactured using conventional processes. It involves the formation of a suspension of active substance in molten excipient. The molten bulk material is filled into capsules.

Pharmaceutical development of the finished product contains QbD elements. The critical quality attributes identified were: description, assay, uniformity of dosage units, degradation products, dissolution.

The manufacturing development has been evaluated through the use of risk assessment and design of experiments to identify the critical product quality attributes and critical process parameters. A risk analysis was performed using the failure mode effect analysis (FMEA) method in order to define critical process steps and process parameters that may have an influence on the finished product quality attributes. No categorization of the effects has been done but the main variables have been considered in the experiments. The risk identification was based on the prior knowledge of products with similar formulations and manufacturing processes as well as on the experience from formulation development, process design and scale-up studies.

The critical process parameters have been identified.

It is noted that DoEs performed did not cover all the possible, and some final PARs have not been extensively tested. However taking into account that the manufacturing process consists in few unit operations with relatively few process parameters to handle and that potentially introduced variability in the process is further limited due to the fact that input materials (active substance and one excipient) have well defined specifications regarding functional attributes, it was considered that risk for interactions throughout the different unit operations is reduced. In that context, and as far as the investigated CQAs are concerned, it was acknowledged that a collection of multiple linear ranges of process parameters has been obtained without any significant interaction.

During clinical studies phase 1, the manufacturing process was transferred to the proposed commercial manufacturing site and scale. A comparative pharmacokinetic study was performed in dogs to demonstrate that the performance of the capsules manufactured at the commercial site is similar to the capsules from the development site. With the exception of minor changes made to the ink printing design on the capsule shells, no changes to the product or manufacturing process are planned between the pivotal clinical study and the to be marketed product. Development data generated on clinical batches manufactured at the commercial manufacturing site were considered to be fully representative of the commercial product, consequently, no clinical bioequivalence or formulation bridging studies were considered necessary to link the pivotal clinical study and the commercial product.

The discriminatory power of the dissolution method has been investigated. The proposed dissolution method for routine quality control has shown to be discriminant for active substance particle size and for drug loading. However, the method is not sensitive enough to discriminate the different polymorphic forms. Nevertheless, the overall control strategy was considered appropriate to compensate for this gap, a specific NIR method being in place for the monitoring of the polymorphic form in routine.

The primary packaging is a HDPE plastic bottle with a child-resistant closure. The material complies with EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of 5 main steps: melting of LMG, mixing of olaparib and LMG, capsule filling, capsule cooling and packaging. The process is considered to be a standard manufacturing process.

An evaluation of the process performance has been completed using data from clinical trial manufacture to provide further evidence of the acceptability and robustness of the proposed process. The data generated through the manufacture and testing of 30 clinical batches has been used to evaluate the capability of the proposed commercial manufacturing process. A formal validation will be completed prior to commercial launch, according to the provided validation scheme.

The maximum holding time and process duration is specified as validated on commercial clinical batches. The start of shelf-life is confirmed to be compliant with the Note for Guidance on the start of shelf-life of the finished dosage form CPMP/QWP/072/96. The CHMP recommended performing a formal bulk stability study on 2 commercial batches of olaparib capsules.

The impact of the manufacturing process on olaparib polymorphism was discussed. It was concluded that process parameters such as temperatures, mixing durations, holding times and cooling conditions do not have an impact on levels of the other potential polymorphic form in the finished product.

Proven acceptable ranges have been defined for the following steps of the medicinal product: preparation of bulk material, capsule filling. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form description (visual), identity (UV and UHPLC), assay (UHPLC), uniformity of dosage units (HPLC), dissolution (Ph. Eur., HPLC), microbial quality, degradation products (UHPLC). In addition, shelf-life specifications also include a test for the content of one of the other potential polymorphic form (NIR). The absence of a test for the content of one of the other potential polymorphic form in the release specifications was accepted considering that drug product manufacturing process provides adequate control of polymorph at time of release .

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

The in house analytical procedures are described and validated. Stress conditions studies including acidic, basic and oxidising conditions have been investigated showing that the assay method is stability indicating.

Batch analysis results are provided for 30 batches (29 are production scale batches) confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of 3 production batches of finished product stored under long term conditions for 36 months at 25 ºC / 60% RH, under intermediate (30°C/65% RH and 30°C/75% RH) and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided.

The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for description (visual), assay (LC), dissolution (Ph. Eur., HPLC), water content (Karl Fischer), microbial quality (Ph. Eur.) , degradation products (LC) .

Although the used methods of control for assay and degradation products are not those described in 3.2.P.5.2, the stability data can be considered as acceptable. The stability methods have been described and validation data have been provided. Comparative data with both methodologies have been generated on samples from the 36 month time point of the primary ICH stability studies. These results show no significant difference.

In addition commitment is undertaken to repeat the stability studies using the process validation batches to support the shelf life of 36 months when stored below 30°C with the approved methods.

Regarding the microbiological property of the drug product, the microbial enumeration was performed for the ICH primary study at release and at the end of shelf life for information only. A water activity test was conducted on each batch punctually. Results obtained indicate that the sample is unlikely to support microbial growth. This test has been described and validated.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Active Substances and Medicinal Products. The drug product was found not to be sensitive to light.

Additional in-use stability studies have been conducted on two batches of capsules previously stored 36 months at 30°C/75% RH to provide data to support the time after which the bottle may be opened and in use. The bottle contains a one week supply of capsules.

Samples of these batches were subsequently stored in conditions simulating the conditions the capsules may be exposed to once the bottle is opened.

Supporting stability study results were provided. One additional batch of capsules has been placed on stability within a HDPE bottle to support clinical studies. This batch was manufactured at commercial scale in the commercial manufacturing facility. They are stored at 5°C, 30°C/65% RH, 30°C/75% RH and 40°C/75% RH.

The duration of the stability study is 4 years and this study is complete.

In addition an open stress study (4 weeks at 40°C/75% RH) has been performed.

Bulk stability was studied. One batch of capsules, manufactured in the commercial manufacturing facility, has been placed on stability within a simulated bulk pack. Study conditions retained for storage time, storage temperature and bulk pack headspace simulate a worst case stress storage condition. Results support the proposed holding time.

The stability data of the ICH primary study and in-use stability study show there is no significant effect on the physical and chemical characteristics of capsules.

Regarding the investigation of one of the other potential polymorphic form, a large number of data was presented for several batches stored under non-ICH or uncontrolled conditions. The other potential polymorphic form was not detected in these batches tested at one time-point ranging from 1 to 39 months.

For 3 stability batches, the content of the other potential polymorphic form was evaluated by the NMR or NIR methods at one time-point and then after a period longer than the initial proposed shelf-life of 3 years. The results indicate that the other potential polymorphic form was not detected after 18 months whereas after 43 months, the level of the other potential polymorphic form is above the proposed limit.

On the basis of these results, showing out of specification results after 43 months, and given the fact that no stability results are available for the other potential polymorphic form in batches stored under ICH conditions and tested at regular intervals, only a shelf life of 2 years could be granted. The CHMP recommended performing on the process validation batches scheduled to be manufactured a full repeat

ICH stability study in which polymorphic form will be routinely monitored up to 36 months using the quantitative NIR method.

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

Comparability exercise for finished medicinal drug product

n/a

Adventitious agents

No excipients derived from animal or human origin have been used.

GMO

n/a

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 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.

A concern was raised during the procedure in view of the limited drug loading considering the recommended posology (daily intake of 16 capsules size 0). It was clarified that other formulations have been tested with even lower active substance solubilisation properties. The retained formulation is considered by the applicant to be the best compromise between active substance solubilisation and drug loading. Olaparib 50 mg capsule has been administered to 801 patients across the 8-years clinical programme, using the maximum recommended posology for at least 1-year treatment with no evidence of compliance issues. This justification is accepted considering the therapeutic indication and the medical need.

Major issues were initially raised in relation to the polymorphism. Another polymorph was detected, which is less soluble than the claimed polymorph used for the manufacture of the finished product. In response to the LoQ, the applicant provided a set of additional data to clarify the thermodynamic relationship between the main polymorph produced and the other polymorph. It was demonstrated that there is low risk for solid-solid transformation between the two forms. Further studies performed using wet dispersion laser diffraction show that the active substance remains in a crystallized state within the excipient. Considering the result of the characterization of the physical state of the active substance in the final product (crystallized solid dispersion of active substance within lauroyl macrogol glycerides), the likelihood for interconversion of the main polymorph produced to the other polymorph, in the drug product upon storage can be considered low as well.

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.

An analysis of the finished product process, focusing on process parameters having a potential impact on finished product CQAs, has been carried out. Main experiments details and results are presented in order to support the process settings in the description of the manufacturing process. According to the data, all

product CQAs investigated were within specifications with a great safety margin, without any significant impact of the process parameters within the ranges tested.

The outcome of the development studies identifies the critical process parameters. Data were provided to support the proposed process parameters settings in relation to their impact on polymorphism transformation using a quantitative NIR method to detect presence of one of the other polymorph in the drug product. All in-life tested samples showed no detectable level of the other polymorph whereas the other polymorph was detected in some out of life samples. Based on the provided data supported by a validated NIR method, and on the characterization of the physical state of the active substance within the drug product, the proposed ranges for the main operating parameters and operating conditions in the manufacturing process description (temperatures, mixing durations, holding times and cooling conditions) were considered satisfactory. No additional control of the other polymorph is proposed at release which is accepted. Furthermore, since the ability of polymorphic conversion to occur in the capsule product in aged out of life samples has been unexpectedly observed, an end of life specification limit for one of the other olaparib polymorph was proposed in the drug product specification at end of shelf life. This limit was supported by a biopharmaceutics evaluation. It was based on consideration for the impact of the level of olaparib other polymorph on safety and efficacy for the patient. The proposed limit for olaparib other polymorph is reasonable in view of the limit of quantitation of the NIR method. Overall the proposed specification limit was considered conservative.

2.2.1. 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.

2.2.2. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- performing parallel testing by XRPD on 10 commercial batches of olaparib in order to demonstrate additional validation of the NIR methods

- providing validation data for the analytical methods for 2 intermediates.

- performing a formal bulk stability study on 2 commercial batches of olaparib capsules

- performing on the process validation batches scheduled to be manufactured a full repeat ICH stability study in which polymorphic form will be routinely monitored up to 36 months using the quantitative NIR method

2.3. Non-clinical aspects

2.3.1. Introduction

All studies including Safety Pharmacology and pivotal Toxicology studies were performed in compliance with GLP. For the safety pharmacology study 0088/453 (KMD008), the Applicant refers to a non-GLP PK study for pharmacokinetic parameters.

Olaparib is also referred to as AZD2281, KU-0059436, KU0059436, COCE42, CO-CE42 and/or CO-CE000042 in some of these studies.

ERA studies were conducted in accordance with OECD Principles of Good Laboratory Practices.

Protocol assistance was given in relation to carcinogenicity, peri-and post-natal studies and duration of repeated dose toxicity studies. The CHMP agreed that the carcinogenicity and peri- and post-natal study were considered unnecessary in the context of treating patients with serious ovarian cancer as olaparib is already known to be embryolethal and teratogenic. Duration of 6 month of repeated dose toxicity studies in two species was also considered sufficient.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The Primary Pharmacodynamic effects of olaparib were evaluated in vitro and in vivo.

Table 1: Summary of *in vitro* primary pharmacodynamic studies

Study type / Study Number	Test system / Methods	Test conditions	Noteworthy findings
Activity of Olaparib across a panel of cancer cell lines *in vitro* KTS00101 and 24	The KuDOS cell line is a cross-tumour type panel consisting of 95 cancer cell lines. The panel comprises of colorectal, breast, ovarian, pancreatic, head and neck squamous cell carcinoma (HNSCC). This study was conducted to determine the growth inhibitory activity of olaparib across a broad range of cancer cell lines and tissue types. A comparison was also undertaken with the response of the breast cancer cell line panel of direct DNA damaging chemotherapy agents with different mechanisms of action. This included Carboplatin (a platinum salt DNA cross-linking agent), Camptothecin (a topoisomerase-Iinhibitor), Doxorubicin (a DNA intercalator/ Topoisomerase-II inhibitor) and Paclitaxel (a microtubule stabiliser).	0.018 µM through to >10 µM	A broad range, continuum of growth inhibitory (IC_{50}) activity for olaparib was observed across the cell line panel (ranging from 0.018 µM through to >10 µM). A strong, positive correlation was seen between olaparib and both carboplatin or camptothecin chemotherapeutic agents, a weak correlation observed for doxorubicin and no correlation with paclitaxel activity. Associations with enhanced olaparib sensitivity (IC_{50}<1µM) were observed in cell lines with known BRCA1 or BRCA2 mutations or low expression of HRR genes/proteins. Low expression of the target PARP1 gene or high expression of ABCB1 (P-gp) drug transporter gene were associated with less olaparib sensitivity or drug resistance. ⇒ While a broad range, continuum of growth inhibitory (IC_{50}) activity for olaparib was observed across the cell line panel (ranging from 0.018 µM through to >10 µM), associations with enhanced olaparib sensitivity (IC_{50} <1 µM) were observed in cell lines with known BRCA1 or BRCA2 mutations or low expression of HRR genes/proteins. These data are consistent with the proposed mechanism of action of PARP inhibitors, where deficiencies in HRR leads to an inability to repair DNA DSBs resulting from PARP inhibitor treatment.
Activity of Olaparib against purified PARP enzymes Menear *et al.*, 2008 Farmer *et al.*, 2005	The optimization of a series of 4-benzyl-2H-phthalazin-1-ones led to the identification of olaparib as described in Menear et al, 2008. Olaparib activity against PARP-1, PARP-2 and another PARP family member.		IC_{50} = 5 nM (for PARP-1 enzyme) and IC_{50} = 1 nM (for enzyme PARP-2 enzyme). IC_{50} for Tankyrase-1 is equal to 1500 nM.
Correlation of Olaparib and platinum response 22	Using long-term colony formation assays (CFA), a head-to-head comparative study of cancer cell line growth inhibition was conducted between olaparib and platinum-based chemotherapy agents (platinum and carboplatin). A strong, positive and statistically significant correlation was observed between olaparib and the platinum-based chemotherapeutic agents, carboplatin and cisplatin, across a panel of 12 breast, 11 head and neck squamous cell carcinoma (HNSCC), 10 non-small cell lung cancer (NSCLC) and 11 ovarian cancer cell lines.		A very strong and statistically significant correlation was observed between olaparib and platinum agent sensitivity across a panel of breast, HNSCC, NSCLC and ovarian cancer cell lines. Cisplatin and Carboplatin sensitivity were also strongly correlated with each other, as expected. The cell lines that were more sensitive to platinum agents showed sensitivity to olaparib (or vice versa), irrespective of tumour type.

Table 2: Summary of *in vivo* primary pharmacodynamic studies

Study type / Study Number	Test system / Species (strain) / Methods	Test conditions / ED_{50} (CI) mg/kg	Noteworthy findings
Anti-tumour efficacy of Olaparib in BRCA-deficient mouse tumour models Rottenberg *et al.* 2008	Mice carrying orthotopically transplanted BRCA1 -/- (p53-/-) tumours	50 mg of Olaparib per kg ip 28 or 100 days	BRCA1 deficient spontaneous mouse mammary tumours show an impressive and prolonged response to Olaparib. No dose-limiting toxicity is observed in tumour-bearing mice. Long-term treatment with AZD2281 in this model did result in the development of drug resistance, caused by up-regulation of Abcb1a/b genes encoding P-glycoprotein efflux pumps. This resistance to AZD2281 could be reversed by coadministration of the P-glycoprotein inhibitor tariquidar.
Cellular and *in vivo* efficacy and pharmacodynamic studies KTS00048, KTS00049 and 23	SW620 cancer cells A PTX model (HBCx-10) has been used: This model is derived from a triple negative breast cancer (TNBC) patient, carries a homozygous BRCA2 mutation.	IC_{50} = 6 nM 2.5 mg/kg, 10 mg/kg, 25 mg/kg, 50 mg/kg or 100 mg/kg	Study KTS00049: 3 independent experiments demonstrate maximal inhibition of PARP-1 activity occurs between 100 nM and 300 nM. Study KTS00049: The effective concentration for inhibiting cellular PARP activity in cancer cells by >90% is approximately 30 nM to 100 nM Olaparib in several tumour cell lines including ovarian A2780, breast MCF-7, and colorectal SW620. Study KTS00048: Maximal potentiation of an appropriate DNA SSB-inducing chemotoxic agent (methyl methanesulfonate, MMS) was also seen *in vitro* at 100 nM. Study 23: *use of PTX model (HBCx-10)* 2.5, 10 and 25 mg/kg: no effect 50 and 100 mg/kg: tumour regression Data suggest that for efficacy in the HBCx-10 preclinical model, either the PARP-1 IC_{50} = 120 nM needs to be exceeded for 10 to 12 hours or IC_{90} (576 nM) needs to be achieved for 4 to 7 hours.
Correlation of Olaparib and platinum response 22 24	Efficacy of single agent olaparib, cisplatin and the combination were assessed in both NSCLC and triple negative breast cancer (TNBC) *in vivo* patient-derived tumour (PTX) models in mice.	Efficacy was determined as inhibition of tumour growth in these PTX models.	A clear correlation was observed between olaparib and cisplatin sensitivity in both breast and lung PTX models. In platinum sensitive breast models, the addition of cisplatin to olaparib resulted in a prolongation of tumour regression.

Secondary pharmacodynamic studies

Olaparib was tested in a panel of 239 *in vitro* radioligand binding and enzyme assays, covering a diverse panel of molecular targets including enzymes, receptors, transporters and ion channels (Studies 0818SY, 8157 and 8234). In these studies, olaparib at a single concentration of 10 µM showed no significant activity (defined as >50% inhibition) against any of these targets. Olaparib was also tested *in vitro* in electrophysiological assays assessing 7 types of human recombinant voltage-gated cardiac ion channel and was shown to be inactive up to a maximum concentration of 31.6 µM (Study 0818SY).

Table 3: Summary of Secondary Pharmacodynamics studies performed with Olaparib

Study type / Study Number	Test system	Methods	Doses	Noteworthy findings
Receptor Binding Assays 8234	-	*In vitro*	10 µM	*In vitro* Olaparib receptor binding was tested on 50 receptor: A_1 (h), A_{2A} (h), A_3 (h), α_1, α_2, β_1 (h), AT_1 (h), BZD, B_2 (h), CCKA (h), D1 (h), D2S (h), ET_A (h), GABA, GAL2 (h), IL-8B (h), CCR1 (h), H_1 (h), H_2 (h), MC_4 (h), ML_1, M_1 (h), M_2 (h), M_3 (h), NK_2 (h), NK_3 (h), Y_1 (h), Y_2 (h), NT_1 (h), δ2 (h), κ, µ (h), ORL1 (h), 5-HT_{1A} (h), 5-HT_{1B}, 5-HT_{2A} (h), 5-HT_3 (h), 5-HT_{5A} (h), 5-HT_6 (h), 5-HT_7 (h), sst, VIP_1 (h), V_{1a} (h), Ca^{2+} channel, SK^+_{Ca} channel, K^+_V channel, Na^+ channel, Cl^- channel, NE transporter (h), DA transporter (h), Olaparib had no significant activity in 50 *in vitro* receptor binding assays at a concentration of 10 µM.
Selectivity Screening in radioligand binding, enzyme, and electrophysiological assays 0818SY	-	*In vitro*	10 µM 31.6 µM	AZD2281 was tested at a single concentration of 10 µM in 220 *in vitro* radioligand binding and enzyme assays. Olaparib had no significant (defined as >50% inhibition) activity in 220 *in vitro* radioligand binding and enzyme assays when tested at a concentration of 10 µM. AZD2281 was also tested in electrophysiological assays at 7 types of human recombinant voltage-gated cardiac ion channel: hNa_v1.5 (INa), hCa_v1.2 (ICaL), hCa_v3.2 (ICaT), hK_v1.5 (IKUR), hK_v4.3/hKChIP2.2 (ITO), hK_v7.1/hKCNE1 (IKS), and hCN4 (IF). Electrophysiological assays were all conducted in concentration-response mode. Olaparib was inactive in electrophysiological assays of 7 human recombinant voltage-gated cardiac ion channels when tested at a concentration of 31.6 µM.
In vitro Pharmacology: Phosphodiestrease Assays 8157	-	*In vitro*	10 µM	Olaparib had no significant activity in 6 *in vitro* phosphodiesterase binding assays at a concentration of 10 µM.

Safety pharmacology programme

Safety pharmacology studies were performed to investigate the effects of olaparib on cardiovascular, central nervous and respiratory system. Safety pharmacology of olaparib was evaluated by analysis of the effects on tail currents of the human ether-à-go-go related gene (hERG) channel *in vitro*, and on heart rate, blood pressure and electrocardiogram (ECG) *in vivo* in anaesthetised dogs. Additionally, effects of olaparib on Central Nervous System (CNS) in rats and respiratory function in dogs were evaluated.

Cardiovascular System and Respiratory System

Table 4: Summary of Cardiovascular System and Respiratory System studies with Olaparib

Study type / Study Number / GLP status	**Species / Strain**	**Route of administration**	**Doses**	**Gender and number per group**	**Noteworthy findings**
Cardiovascular (hERG inhibition) 0242SZ / Yes	CHO cells	*In vitro*	1, 3, 10, 30, 100 and 300 µM	-	hERG IC_{50} = 226 µM.
Cardiovascular and respiratory systems 2229/053 / Yes	Beagle Dog	*IV* infusion over 10 minutes	0, 1.5, 5, 15 mg/kg	2M + 2F	IV administration of Olaparib, at doses of 1.5 and 5 mg/kg had no noticeable effects on the cardiovascular or respiratory parameters of anaesthetised dogs when compared to the vehicle control group. A dose of 15 mg/kg elicited a slight increase in heart rate (123 bpm vs baseline of 88 bpm and dP/dtmax 5927 mmHg/s 10-min post dose vs baseline of 3925 mmHg/s), but this was not statistically significant compared with the vehicle treated group. A decrease is observed in the PR interval at 10 minutes after administration of the high dose.

Central Nervous System

Table 5: Summary of Central Nervous System studies with Olaparib

Study type / Study Number / GLP status	Species / Strain	Route of administration	Doses	Gender and Number / group	Noteworthy findings
CNS 2229/047 / Yes	Wistar Rat	Oral Gavage	0, 20, 115, 250 mg/kg	6M	Oral administration of Olaparib at dose levels of 20, 115 or 250 mg/kg produced no behavioural or physiological changes in rats when compared to vehicle-treated animals.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were conducted which was considered acceptable by CHMP.

2.3.3. Pharmacokinetics

The preclinical Absorption, Distribution, Metabolism and Excretion (ADME) studies were conducted in the same species and strains as used in the pharmacology and toxicology studies. The formulations used in the disposition studies were generally the same as those used in the pivotal toxicity studies; oral doses were administered by gavage. *In vitro* investigations were performed in isolated human tissue and in animal or insect derived tissue that expressed specific human drug metabolism and transport proteins (see table below).

Table 6: Overview of *in vitro* and *ex-vivo* studies contributing to PK characterisation of olaparib

Study ID	Study Description	Test System
Protein binding		
KPJ019	In vitro protein binding and blood cell/plasma partitioning	Mouse, rat, dog and human plasma/blood. Equilibrium dialysis
Metabolism		
KMX039	Metabolism of olaparib in human hepatocytes	Human hepatocytes
KMX032	Characterisation of metabolism in female patients and comparison to the rat	Human and rat plasma, urine and faeces
Drug-drug interactions		
Transporters		
KMX006	Investigation of olaparib as a substrate for human transport proteins MDR1 and BCRP	MDR1 & BCRP in MDCKII cells
KMN040	Investigation of the potential of olaparib to inhibit transport via MDR1 and BCRP	MDR1 & BCRP in MDCKII cells
KMX020	Investigation of olaparib as a substrate and/or inhibitor of MRP2	MRP2 in MDCKII cells
KMX042	Investigation of olaparib as a substrate and/or inhibitor of human hepatic uptake transporters	Human hepatocytes
KMN037	Investigation of olaparib as an inhibitor of OATP1B1	OATP1B1 in HEK293 cells
KMN046	Investigation of olaparib as an inhibitor of OATP1B1 mediated pravastatin uptake	OATP1B1 in HEK293 cells
Drug-drug interactions		
Metabolism		
KMX001	Assessment of olaparib as an inhibitor of CYP enzymes	Human liver microsomes
KMX002	Assessment of olaparib as a CYP inducer	Human hepatocytes
KMX009	Identification of the enzymes responsible for the metabolism of olaparib	Human liver microsomes
KMX041	Identification of the enzymes responsible for the metabolism of olaparib	Human liver microsomes

Absorption

Single doses

Table 7: Overview of single dose studies performed with olaparib

Study ID	**Species**	**Dose** mg/kg	**Route**	**Cmax** M/F µg/mL	**Tmax** M/F h	**AUC** M/F h.µg/mL	**Cl** M/F L/h/Kg	**Vd** M/F L/Kg
KPM035	Mouse 12M+ 12F	20 80	IV Oral	- 12.4/12.6	- 0.50/0.33	6.47/5.21 14.4/12.6	1.34/1.66 ND	0.356/0.428 ND
KKR007	Rat 9M+9F	1 5	IV Oral	1.08/1.34* 0.162/0.408*	0.5/0.25 1/2	0.590/2.52** 0.494/2.38**	ND ND	ND ND
KMD008	Beagle dog 3M	1 5	IV Oral	- 2.13	- 1	2.75 10.3	0.39 ND	0.93 ND
Pooled data£	Human	400mg bid	Oral	4.78 (1.47 to 14.5)	-	$AUC_{(0-12)}$ = 38.8 (6.83 to 149)		

*µg equiv/g
**h.µg equiv/g
£Human exposure data pooled from studies D0810C00002, D0810C00008, D0810C00009, D0810C00012 and D0810C00024
ND Not determined

Multiple dose toxicokinetics

After 14 daily doses, Cmax in male and female mice was much lower than on day 1 at all dose levels (in male mice, Cmax after 14 doses at 200 mg/kg/day was only 11.6% of value after a single dose and in female mice only 8.7% after 14 doses at 100 mg/kg/day). No clear relationship between Cmax and dose was observed. Exposure (AUC(0-24)) was also much lower in male and female mice after multiple doses (14.8% in male and 20.1% in female mice at 200 mg/kg/day) although a smaller than proportional increase in dose was observed. These data indicated either a change in oral absorption or induction of olaparib clearance may have occurred in animals of both sexes although this was not investigated.

In the rat study 2229/037, after 28 single daily oral doses, AUC(0-24) was unchanged in both sexes compared to day 1 at the low dose, approximately 20% lower in both sexes at the mid dose and 30% (male) and 45% (female) lower at the high dose; this may indicate increased drug transporter or metabolism mediated clearance at the mid and top doses after 1 months exposure.

In study T110012, after 26 weeks of daily dosing, Cmax data were similar to those after single doses at the low and mid doses. However, in this study Cmax was slightly higher at the top dose (1.3 and 1.2 fold higher in male and female rats respectively) after 26 weeks dosing in contrast to the moderate decrease observed after 28 days. In this study, exposure was reduced by ~30% in male rats after 6 months dosing at 30 mg/kg/day.

Olaparib exposures achieved in the rat embryofoetal development dose range-finding study (1555RR) and in the female rat fertility study (1557GR) were in line with those achieved in the 1 and 6-month studies and confirmed the tendency for exposure to increase more than proportionally with increasing dose.

In study 2229/038 and after 28 single daily oral doses, AUC(0-24) at the low dose was unchanged in male dogs and slightly higher in female dogs; this probably reflects minor variability in the data. At the mid and high dose the AUC(0-24) after multiple doses was similar to after single doses. Exposure increased less than in proportion to dose in male and female dogs after 28 doses; this may indicate saturated absorption at high doses.

In study T110011, after 26 weeks of daily dosing, Cmax data were similar to those after single doses and there was no convincing evidence of drug accumulation.

Distribution

Plasma protein binding

The *in vitro* plasma protein binding of [^{14}C]-olaparib was assessed in mouse, rat, dog and human plasma over the concentration range 0.010 to 10.0 µg/ml in study KPJ019.

Olaparib at 0.010 to 10.0 µg/ml (0.023 to 23.0 µM) demonstrated low binding to plasma proteins in *in vitro* studies. Binding was lowest in dog (38.1 to 45.3% unbound), followed by mouse (28.4 to 30.6% unbound), rat (26.5 to 27.3% unbound) and human (8.8 to 18.1% unbound). Protein binding was independent of olaparib concentration in mouse and rat plasma. In dog and human plasma, the unbound fraction was greater at 10.0 µg/ml than at lower concentrations.

The effect of LMG, a constituent of the olaparib clinical capsule formulation, on [^{14}C]-olaparib plasma protein binding was also investigated (KPJ043). Plasma was collected from naïve healthy male and female human volunteers (2 per cohort) and from the same volunteers after twice daily administration of LMG in capsules, for 4.5 days, at doses of either 1000 or 4000 mg (equivalent to 2000 mg/day or 8000 mg/day). The olaparib free fraction was similar in plasma collected after administration of either 2000 or 8000 mg/day LMG and in neither case was there a statistically significant difference in the free fraction compared to plasma collected from naïve volunteers. The proportion of olaparib bound to plasma proteins was similar to that measured previously in study KPJ019 and there was no evidence of a sex related difference in binding.

An additional study (Covance 829103) investigated [^{14}C]-olaparib protein binding in mouse, rat, dog and human plasma across an extended concentration range (0.1, 1, 10, 20, 40 µg/mL (0.23 to 92.1 µM)). Where the olaparib concentrations were similar to those used previously (KPJ019), the free fraction was consistent with the earlier study. In human plasma, the free faction was increased at the extended concentrations of 46 and 92.1 µM (both supra-therapeutic) although the increase in free fraction was less than proportional to the change in drug concentration.

Distribution in blood cells

In study KPJ019, the distribution of [^{14}C]-olaparib between blood cells and plasma, following *in vitro* incubation with whole blood from male mice, rats, dogs and human volunteers, was investigated. Association with blood cells was moderate at 25 and 24% in mouse and rat blood respectively; no concentration dependence was observed in these species. In contrast, [^{14}C]-olaparib had a greater association with dog blood cells and the interaction was concentration related with more drug binding to blood cells at higher than at lower concentrations (34% at 0.1 µg/ml and 44% at 10 µg/ml).

Following oral administration of [^{14}C]-olaparib to male and female rats in studies KMR017, KMR027 and KKR007, and to male dogs in study KMD008, the ratio of radioactivity in blood and plasma was assessed at pre-determined time points. In rat, the blood/plasma ratio was 0.65 to 0.75 shortly after dosing, indicating drug related material was mainly associated with plasma. The ratio changed at later times (0.82 to 0.84 at 12 hours) indicating a changed distribution of drug related material; this may reflect the presence of circulating metabolites. There was no marked sex difference in blood/plasma ratio in rats. In male dogs, the blood/plasma ratio data was similar to that in rat, with a minor change in distribution apparent at later times.

Tissue distribution studies

The distribution of radioactivity in rats was investigated by quantitative whole body autoradiography (QWBA) in studies KMR017 (male, albino rats) and KMR004 (male and female Lister hooded rats). The specific radioactivity was much higher in study KMR004 and this, coupled to the use of pigmented animals of both sexes made this a more informative study; concentrations of radioactivity from key tissues of male and female rats in study KMR004.

1h after administration of a single oral dose of [^{14}C]-olaparib to male Lister hooded rats (study KMR004, 15 mg/kg), radioactivity was widely distributed; maximal concentrations were measured in many tissues at this sample time. The highest concentrations of radioactivity were detected in a number of glandular tissues (*e.g.* adrenal, thyroid, Harderian, prostate and spleen) the mucosa of the upper and lower gastrointestinal (GI) tract, the liver, the bladder and the kidney. Distribution throughout the GI tract was typical of an oral drug. Radioactivity was below the limit of quantification in the brain and spinal cord and below the concentration in blood in many tissues. By 4h after dosing, concentrations of radioactivity had decreased in most tissue although the uveal tract (2.49 to 3.07), prostate (1.54 to 7.34) and seminal vesicles were notable exceptions; concentrations of radioactivity also increased in parts of the GI tract at this time although they decreased in liver (48.7 to 21.4) and kidney (10.2 to 4.2). By one day post dose, radioactivity was below the limit of quantification in the majority of tissues although it was still present at low levels in a small number of tissues including parts of the GI tract, excretory organs, pigmented skin and uveal tract. By 7 days after dosing, radioactivity was detectable by QWBA at low levels in only liver and uveal tract. Radioactivity was undetectable by QWBA in any tissues by 28 days after dosing although very low levels were detected in whole eye by LSC.

Any binding of drug related material to melanin rich tissues (*e.g.* the uveal tract, pigmented skin) appeared to be of relatively short duration with levels of radioactivity in these tissues at 3 days after dosing being similar to those in the excretory organs. The distribution of radioactivity was similar for male and female animals although higher concentrations of radioactivity were present in many tissues of female animals than in the tissues of male animals at equivalent times; this was consistent with the PK findings described previously.

The distribution of [^{14}C]-olaparib in male albino Sprague-Dawley rats following a single oral dose (15 mg/kg) was investigated by QWBA in study KMR017. The data were consistent with those from study KMR004 although the lower dose of radioactivity meant radioactivity was generally detected for a shorter period. A notable exception was in skin (non-pigmented) where levels of radioactivity slightly above the limit of quantification were measured at 48 hours.

The tissue distribution of [^{14}C]-olaparib in female BALB/c (albino) nude mice bearing HTC-116 human colorectal carcinoma tumours was investigated using QWBA (study KMM016). At six hours after dosing (first sampling point), the highest concentrations of radioactivity were associated with the liver and the organs and contents of the GI tract (not shown). Concentrations of radioactivity in many tissues were similar to those in blood although radioactivity was below the limit of quantification in brain, spinal cord and eye. Radioactivity was present at higher levels in tumour than blood. By 24 hours concentrations of radioactivity had fallen in most tissues; the highest concentrations continued to be associated with the liver and the organs and contents of the GI tract. In all tissues other than liver, tumour and GI tract, concentrations of radioactivity had fallen below the limit of quantification by 48 hours after dosing. Radioactivity was still measurable in liver, tumour and GI tract at 96 hours after dosing (final sampling point) resulting in estimated apparent tissue half-lives of 25.7 hours (liver) and 36.0 hours (tumour). Tissue/blood ratios showed that at 6 and 24 hours after dosing the concentrations of radioactivity in the tumour were 6 and 4 times higher than those in blood.

Metabolism

The metabolism of [^{14}C]-olaparib was investigated in rat, dog and human at doses representative of the toxicology programme or clinical use. Characterisation of olaparib metabolites was primarily focused on rat and human plasma and excreta while characterisation in dog was incomplete.

Following a single 100 mg oral dose of [^{14}C]-olaparib to female patients, olaparib and 3 additional components were quantifiable in plasma. Olaparib represented 70% and the additional components 9 to 14% of the plasma radioactivity. The additional components were identified as M12 (ring opened hydroxy-cyclopropyl), M15 (monooxygenated) and M18 (dehydrogenated piperazine); M18 was a positive ion MS source artifact from M39 (monooygenated) and it was M39 that was the plasma component. Each of M12, M15 and M18/M39 was also detected in male and female rat plasma, following single oral doses.

However, although these metabolites represented 8 to 12% of the radioactivity in plasma from male rats, they were insufficiently abundant to be quantified in female rat plasma. Up to 20 other metabolites were present in human plasma although none could be quantified by radio-HPLC; 14 of these were not detected in rat or dog plasma although 13 were present in rat excreta, which indicated exposure in a key toxicology species.

Following a single oral dose of [^{14}C]-olaparib to female patients, approximately 44% and 42% was eliminated in urine and faeces respectively and olaparib was extensively metabolised. Olaparib was the most abundant component in urine (10 to 19% of dose) but at least 37 drug related components were present in urine and 18 were quantifiable. The most abundant (M15, monooxygenated) accounted for 4 to 8% of the dose while the remainder each accounted for <2% of the dose. Olaparib was the most abundant component in faecal extract (<1 to 14% of dose) but at least 20 other drug-derived components were detected and 10 of these were quantifiable by radio-HPLC. As with urine, the most abundant was M15 (1 to 8% of the dose) while M9, M12, M23 and M25 each accounted for approximately 6% of the dose. While most components in human excreta were also present in rat excreta, four minor human metabolites were absent from rat excreta, however, in each matrix each of these metabolites accounted for <1% of the dose.

Following administration of single oral doses of [^{14}C]-olaparib to male and female rats, parent drug was the most abundant component in both faeces (20 and 38% from male and female) and urine (4 and 21% from male and female). However, a larger proportion of the dose was eliminated as metabolites in the excreta of male than female rats. A wider range of metabolites was also detected in the excreta of male rats. These data were consistent with the sex difference noted in rat plasma pharmacokinetics and excretion.

Following administration of single oral doses of [^{14}C]-olaparib to male dogs, parent drug was the most abundant component in both faeces (31% of dose) and urine (5% of dose). Four other components were quantified in faecal extract (4 to 7% of the dose) and 3 in urine (<2% of the dose) although these metabolites were not fully identified. In rat and human, most of the metabolites investigated were Phase I products; the main sites of metabolism were the piperazine carboxycyclopropyl ring structure and to a lesser extent the fluorophenyl and the phathalazinone ring systems. The major metabolic processes were oxidations and hydroxylations and many products were the result of multiple metabolic transformations. Some minor products resulted from Phase II metabolism of previously formed Phase I products.

Investigations in human *in vitro* systems indicated Phase I metabolism of olaparib was CYP mediated and that CYP3A4 and 3A5 were the dominant metabolic enzymes. As expression of CYPs 3A4 and 3A5 is highly variable in human and olaparib clearance in human was primarily metabolic, this may explain some of the variability observed in clinical pharmacokinetics.

Excretion

The recovery of [^{14}C]-olaparib related radioactivity following single IV or oral doses to rats and dogs:

Table 8: Recovery of radioactivity following single IV or oral doses of [^{14}C]-Olaparib to rats and dogs

Species (sex)	Study	Sample interval (h)	Dose route	Dose (mg/kg)	Radioactivity (% of dose)						
					Faeces	Urine	Bile	Carcass	Expired air	Cage wash	Total
Rat (M)	KKR007	48	IV	1	8.8	17.1	75.7	1.4	NS	2.2	105
Rat (F)	KKR007	48	IV	1	28.6	41.0	18.2	2.4	NS	10.6	101
Rat (M)	KMR017	120	Oral	15	87.0	11.5	NS	0.2	0.0	0.4	99.1
Rat (F)	KMR017	120	Oral	15	64.9	29.1	NS	0.3	0.0	1.4	95.7
Rat (M)	KMR027	120	Oral	15	88.7	7.8	NS	0.1	NS	0.6	97.1
Rat (F)	KMR027	120	Oral	5	72.8	23.2	NS	0.1	NS	2.0	98.2
Dog (M)	KMD008	168	IV	1	77.8	23.4	NS	NS	NS	1.9*	101
Dog (M)	KMD008	168	Oral	5	78.5	14.9	NS	NS	NS	1.8*	93.4

*: Includes cage debris and swabs.
NS : Not sampled.
In studies KKR007 and KMR027, Han Wistar rats were used.
In study KMR017 Sprague Dawley rats were used.
In study KMR008 Beagle dogs were used.

Following administration of single oral doses of [^{14}C]-olaparib to male and female rats, elimination was rapid (94% to 96% within 48h) and recovery was complete within 5 days. Faeces provided the major route of elimination of radioactivity in rats of both sex although a greater proportion of the dose was eliminated in the faeces of male rats. A corresponding sex difference in urinary elimination was observed with female rats eliminating a larger proportion of the dosed radioactivity by this route. Following single IV doses of [^{14}C]-olaparib to bile duct cannulated male and female rats, the sex difference in elimination route was confirmed with male rats eliminating a much greater proportion of the dose in the bile. These findings were consistent with the sex difference in metabolism of olaparib in rat.

After single oral and IV doses of [^{14}C]-olaparib to male dogs, elimination was again rapid (91% and 99% within 48 hours after oral and IV dosing) and recovery complete within 7 days. Faecal elimination provided the major route of elimination.

The main metabolite in human urine (M15) resulted from a single oxidation while the most abundant metabolites in human faeces (M12, M15, M23 and M25) resulted from single or dual oxidations/hydroxylations.

Following administration of single oral doses of [^{14}C]-olaparib to male and female rats, parent drug was the most abundant component in both faeces (20% and 38% from male and female) and urine (4% and 21% from male and female). However, a larger proportion of the dose was eliminated as metabolites in the excreta of male than female rats. A wider range of metabolites was also detected in the excreta of male rats. These data were consistent with the sex difference noted in rat plasma PK and excretion.

Following administration of single oral doses of [^{14}C]-olaparib to male dogs, parent drug was the most abundant component in both faeces (31% of dose) and urine (5% of dose). Four other components were quantified in faecal extract (4 to 7% of the dose) and 3 in urine (<2% of the dose) although these metabolites were not fully identified.

Following a single oral dose of [^{14}C]-olaparib to female patients, approximately 44% and 42% was eliminated in urine and faeces respectively. Olaparib was the most abundant component in urine (10 to 19% of dose) but at least 37 drug related components were present in urine and 18 were quantifiable. The most abundant (M15, mono-oxygenated) accounted for 4 to 8% of the dose while the remainder each accounted for <2% of the dose. Olaparib was the most abundant component in faecal extract (<1 to 14% of dose) but at least 20 other drug derived components were detected and 10 of these were quantifiable by radio-HPLC. As with urine, the most abundant was M15 (1 to 8% of the dose) while M9, M12, M23 and M25 each accounted for approximately 6% of the dose (see section 2.4.2, pharmacokinetics). While most

components in human excreta were also present in rat excreta, four human metabolites were not detected in rat excreta, however, in each matrix each of these metabolites accounted for <1% of the dose.

Pharmacokinetic drug interactions

Pharmacokinetics data from in vitro and ex vivo studies are presented and discussed in section 2.4.2 (pharmacokinetics) of this report.

Bioequivalence of Phase I development formulation and commercial site and scale batches

During Phase I a decision was taken to establish the olaparib capsule manufacturing process at the proposed commercial manufacturing site and scale. A pre-clinical dog study was undertaken to compare olaparib PK data from dogs dosed with capsules from the development and commercial manufacturing sites.

A comparison of the PK data using the t-test at 95% confidence limits, showed no significant difference between the batch from the commercial site and either of the batches from the development site for either Cmax (p values were 0.19 and 0.10 for BMR/07/429 and BMR/05/158 respectively) or AUC (p values were 0.15 and 0.08 for BMR/07/429 and BMR/05/158 respectively). These data indicated the performance of the material from the proposed commercial site is similar in dogs to olaparib capsules from the development site.

2.3.4. Toxicology

Single dose toxicity

Table 9: Summary of single-dose toxicity studies

Species Study ID GLP	Method of Administration Doses (mg/kg)	Major findings
Mice		
Mouse Crl:CD-1™ (ICR)BR 2229/035 Yes	Oral (gavage) *(DMSO in 10% HβCD in PBS)* Preliminary Phase (1M, 1F): 50, 100, 200, 300 Main test (5M, 5F): 300	*Preliminary and main phases*: **50, 100, 200, 300 mg/kg: no mortalities or adverse signs**. All mice gained weight over the course of the study. **300 mg/kg: no macroscopic abnormalities at necropsy** (on Day 8 or Day 15)
Mouse Crl:CD-1 (ICR)BR 2229/036 Yes	IV *(10% DMSO, 10% HβCD in PBS)* Preliminary Phase (1M, 1F): 25, 50, 70, 100, 140, 200 Main test (5M, 5F): 100, 140	*Preliminary phase*: **200 mg/kg: both animals died immediately post-dose**. **140 mg/kg:** male and female have prone posture within 2 minutes of dosing but recovered by 15 minutes post-dose. **100 and 70 mg:** only males have prone posture within 2 minutes of dosing but recovered by 15 minutes post-dose. No macroscopic changes seen in any animal at necropsy. *Main test*: **140 mg/kg:** 4M and 3F died immediately after dosing; prone posture and dyspnoea; ataxia, palpebral closure, hunched posture and/or ↓ activity with lethargy. **100 mg/kg:** 1M and 1F died 5 minutes after dosing; prone posture and dyspnoea; ataxia, palpebral closure, hunched posture and/or ↓ activity with lethargy. No macroscopic changes seen in any animal at necropsy.
Rats		
Rat Crl:WI(Glx/ BRL/Han) IGSBR 2229/033 Yes	Oral (gavage) *(10% DMSO, 10% HβCD in PBS)* Preliminary Phase (1M, 1F): 50, 100, 200, 240, 300 Main test (5M, 5F): 240	*Preliminary phase*: **300 mg/kg:** both animals found dead on Day 2 or 3. palpebral closure, ↓ activity, hypothermia, tremors, salivation, piloerection and lachrymation. **50, 100, 200, 240 mg/kg: well** tolerated, with no mortalities. No macroscopic changes related to treatment at necropsy. *Main test:* **240 mg/kg:** well tolerated, with no mortalities.

Species Study ID GLP	Method of Administration Doses (mg/kg)	Major findings
Rat Crl:WI(Glx/ BRL/Han) IGSBR 2229/044 Yes	Oral (gavage) *(10% DMSO, 10% HβCD in PBS)* Preliminary Phase (1M, 1F): 240, 300 Main test (5M, 5F): 240, 300	*Preliminary phase:* **300 mg/kg:** female dosed at 300 mg/kg found dead on Day 2. salivation, lachrymation, hypothermia, ↓ activity, hunched posture and palpebral closure. Macroscopic examination revealed severe darkening to all lobes of the lungs. in the male: well tolerated; adverse signs in animals included red extremities on Day 1 and/or 2. **240 mg/kg:** in both sexes: well tolerated; adverse signs in animals included red extremities on Day 1 and/or 2. *Main test*: **300 mg/kg:** 1M at 300 mg/kg found dead on Day 1; no macroscopic changes were seen at necropsy. salivation and red extremities on Day 1, with diarrhoea, discoloured faeces and anogenital soiling from Day 2.
Rat Crl:WI(Glx/ BRL/Han) IGSBR 2229/034 Yes	IV *(10% DMSO, 10% HβCD in PBS)* Preliminary Phase (1M, 1F): 25, 50, 70, 100 Main test (5M, 5F): 70	*Preliminary phase*: **100 mg/kg:** both animals died immediately post-dose. **70 mg/kg:** ↓ activity seen for both animals from approximately 15 minutes post-dosing, with recovery by 2 hours post-dose. No macroscopic changes at necropsy for animals that died on Day 1 or were killed on Day 8. *Main test:* **70 mg/kg:** well tolerated, with no mortalities. Clinical signs limited to palpebral closure, seen from approximately 15 minutes post-dosing on Day 1, with recovery by 2 hours post-dose. All animals gained weight during the observation period and there were no macroscopic changes at necropsy on Day 15.

Repeat dose toxicity

Table 10: Summary of repeat-dose toxicity studies

Species / Study ID / GLP	Method of Administration / Duration / Doses (mg/kg)	NOAEL (mg/kg/d)	Major findings
Rats			
Rat Crl:WI(GLX/ BRL/HAN) IGSBR 2229/040 Yes	Oral (gavage) **7 days + 21 days observation period** 0, 15, 100 and 200	M: 15 **F: NE**	**100 mg/kg/d and above:** Adverse signs and reduced body weight gain, food consumption and/or haematology parameters (red and white blood cells, reticulocytes, platelets, haemoglobin concentration) in one or both sexes during the dosing period. ↑ in myeloid:erythroid ratio in bone marrow. ↓ megakaryocytes in spleen (high dose) (only liver and spleen evaluated). **15 mg/kg/day:** Reduced body weight gain in females. All effects seen during the dosing period showed recovery by the end of the 21 day observation period.
Rat Crl:WI(Glx/ BRL/Han) IGSBR	Oral (gavage) **28 days** 0, 5, 15 and 40	**15**	**5, 15 and 40 mg/kg/d:** well tolerated. **40 mg/kg/d:** minor transient clinical signs, and with ↓ in food consumption and body weight gain (in males). Effects on the endothelial reticular system as expressed by changes in white cell populations, red blood cell parameters

Species / Study ID / GLP	Method of Administration / Duration / Doses (mg/kg)	NOAEL (mg/kg/d)	Major findings
2229/037 Yes			and the precursor haematopoietic cells in the bone marrow. At necropsy, ↑ spleen weight in females only, and histopathological findings in the bone marrow, spleen, liver and thymus in both sexes. The changes were more evident in the females, which correlated with a higher exposure to the drug in the females compared to males. All changes showed recovery following the cessation of treatment. **15 mg/kg/day:** minor changes in both sexes (↓ in food consumption in males and histopathological findings in the spleen and liver of females): considered not to be adverse.
Rat AlpkHsdRcc Han:WIST 1858KR Yes	Oral (gavage) **28 days** 0 and 40	**NE**	**The aim of the study was to qualify impurities in a new batch of Olaparib (batch C436/4) produced by a new route of synthesis. The study compared 2 batches of Olaparib at a single high dose level of 40 mg/kg/day.** **There were no noteworthy differences in exposure or toxicological findings between the 2 batches of olaparib administered to rats at a dose of 40 mg/kg/day for 28 days.** (*reductions in body weight gain and food consumption, changes in haematology affected red and white blood cells, platelets and reticulocytes, decreases in plasma protein and decreased thymus weight*).
Rat Crl:WI(Glx/ BRL/Han) IGSBR **Pivotal Study** TI10012 Yes	Oral (gavage) **26 weeks** Males: 0, 5, 15 and 30 Females: 0, 1, 5 and 15	**M: 30 F: 5**	Males: **30 mg/kg/d:** well tolerated. **5, 15 and 30 mg/kg/d:** haematological effects included ↓ red blood cell parameters Females: **15 mg/kg/d:** well tolerated. ↓ body weight gain and food consumption. ↓ red blood cell parameters, ↑ platelet counts and ↓ neutrophil counts in females at 5 and/or 15 mg/kg/day. The bone marrow smears of females showed ↑ in late myeloid cells and ↓ in early erythroid cells, with ↑ myeloid:erythroid ratio.
Dogs			
Dog Beagle 2229/039 Yes	Oral (gavage) MTD: 2-5 days Fixed dose: **7 days** MTD: 2.5, 5, 15, 30, 50 and 75 Fixed dose: 50	**N/A**	**MTD phase:** **75 mg/kg/day:** adverse signs, weight loss and inappetence. **50 mg/kg/day:** slight weight loss and ↓ food consumption. **30 mg/kg/day:** slightly ↓ food consumption but no effects on body weight. **5 mg/kg/day and above:** haematology changes (reduced red blood cell parameters, white blood cells, reticulocytes, platelets). Bone marrow atrophy was seen for both dogs. **Fixed Dose phase:** Adverse signs, weight loss and ↓ food consumption in 1 dog, which required this dog to be killed prematurely on Day 5. Haematology changes, similar to those seen in the MTD phase, and bone marrow atrophy were seen, with the greatest severity in the dog killed prematurely.
Dog	Oral (gavage)	**15**	**2.5, 5 and 15 mg/kg:** no premature deaths. no adverse

Species / Study ID / GLP	Method of Administration / Duration / Doses (mg/kg)	NOAEL (mg/kg/d)	Major findings
Beagle 2229/046 Yes	**7 days+ 21 days observation period** 2.5, 5 and 15		effects on body weight or food consumption. Minor haematology changes and small increases in plasma globulin, ALT and/or AST with no dose response relationship. All changes were small and, in the absence of any notable macroscopic and microscopic histopathology findings, were considered not to be toxicologically significant. **5 or 15 mg/kg/day:** mydriasis.
Dog Beagle 2229/038 Yes	Oral (gavage) **28 days** 0, 2.5, 5 and 15	**5**	**2.5, 5 and 15 mg/kg:** well tolerated. **5 and 15 mg/kg:** changes in haematology parameters, including ↓ in red blood cell parameters, and white blood cell, platelet and/or reticulocyte counts. At necropsy, bone marrow examination showed reductions in erythroid and ↑ in myeloid elements, with an ↑ in myeloid:erythroid ratio predominantly at 15 mg/kg/day. At histopathological examination, bone marrow atrophy was present in 1 male and 1 female dosed at 15 mg/kg/day. ↑ in prostate weight, with no histopathological correlate, were seen in several males dosed at 5 or 15 mg/kg/day at terminal kill. All changes showed reversibility following a 28 day recovery period.
Dog Beagle **Pivotal Study** TII0011 Yes	Oral (gavage) **26 weeks** 0, 1, 3 and 10	**3**	Males: **10 mg/kg/d:** well tolerated. Haematological changes, including ↓ in red blood cell parameters, white blood cell, platelet and reticulocyte counts in animals dosed at 10 mg/kg/day, with slightly ↓ white blood cell and platelet counts in males at 3 mg/kg/day. ↑ pigmentation in the liver, mainly in Kupffer cells. Females: **10 mg/kg/d:** well tolerated. a small ↓ in myeloid:erythroid ratio and a marginal ↑ in total erythroid cells in the bone marrow smear was seen. ↑ pigmentation in the liver, mainly in Kupffer cells.

Genotoxicity

The genotoxic potential of Olaparib was assessed *in vitro* in a bacterial mutation test and a mammalian cell cytogenetic test, both in the presence and absence of a metabolic activation system (S9), and *in vivo* in a rat bone marrow micronucleus study.

Table 11: Overview of Genotoxicity studies performed with Olaparib

Type of test / study ID / GLP status	Test system	Concentrations / Metabolising system	Results Positive / Negative / Equivocal
Gene mutations in bacteria TII0007 Yes	*S. typhimurium* (TA1535, TA1537, TA98, TA100) *E. coli* (WP2P, WP2PuvrA)	5000 µg/plate $S9^+/S9^-$	Negative
Mammalian Cell Cytogenetic Test TII0008 Yes	CHO	Assay 1, pulse treatment for 3h in the presence and absence of S9 followed by 15h recovery. Assay 2, pulse treatment for 3 hours in the presence of S9 followed by 15 and 39h recovery and continuous treatment for 18h in the absence of S9 with 0 and 24h	Increase in the frequency of chromosomal aberrations

		recovery.	
Micronucleus Assay 775498 Yes	5M/5F CD rats	100, 200 or 400 mg/kg/d (2 days)	Induction of micronuclei in bone marrow cells in rats

Carcinogenicity

No carcinogenicity studies were submitted.

Reproduction Toxicity

Reproductive and developmental toxicity studies assessing male and female fertility and embryofetal development were conducted in rats.

Table 12: Summary of Reproductive and Developmental studies with olaparib

Study type Species Study No.	**Route, doses (mg/kg/day), duration**	**Major findings**
Fertility		
Oral Fertility and Early Embryonic Development Study in the Female Rat 22 female AlpkHsdRccHan-WIST rats 1557GR Yes	Oral (gavage) 0, 0.05, 0.5 or 15 mg/kg/day, from 14d prior to pairing (with undosed males) and continuing up to Day 6 post-coitum inclusive.	**15 mg/kg/d:** showed slight toxicity including ↓ food consumption during gestation and ↓ body weight gain from the first week of dosing that continued throughout gestation for main test animals. Recovery animals dosed with 15 mg/kg/day also had ↓ weight gain during the dosing period and during the first 2 weeks of the recovery period, although during the latter part of the recovery period cumulative body weight gain was similar to that of recovery control animals. Maternal body weight gain for the recovery animals dosed with 15 mg/kg/day was also slightly higher than controls during the early part of gestation. ↑ incidence of females that had extended oestrus. None of the recovery animals dosed with 15 mg/kg/day had extended oestrus after a minimum of 14 days recovery. There was no effect of olaparib on mating performance or fertility (ovulation and pregnancy rates) at any dose level. ↓ embryofetal survival after dosing with 15 mg/kg/day for main test animals resulted in a slightly ↓ % of live foetuses per litter (90% *versus* 96% for controls). There was no effect on embryofetal survival after dosing with 0.05 or 0.5 mg/kg/day. After the recovery period, there was no decrement in embryofetal survival seen for animals previously dosed with olaparib at 15 mg/kg/day. There were no significant maternal in-life effects after dosing with 0.05 or 0.5 mg/kg/day. NOEL = 0.5 mg/kg/d.

Oral Fertility and Early Embryonic Development Study in the Male Rat 20 male AlpkHsdRccHan:WIST rats 1558GR Yes	Oral (gavage) 0, 5, 15 or 40 mg/kg/day for a minimum of 70 consecutive days prior to the start of the pairing period, and continuing until fertility	**15 or 40 mg/kg/day:** ↓ in body weight gain and food consumption, ↑ salivation and ↑ incidence of hair loss. **40 mg/kg/day:** slightly ↓ red blood cell counts. NOEL = 40 mg/kg/d.
Embryo-fetal Development		
Oral Dose **Range Finding** Embryofetal Development Study in the Rat 6 pre-mated female AlpkHsdRccHan-WIST rats 1555RR Yes	Oral (gavage) 0, 0.05, 0.1, 0.5, 5, 15 and 40 mg/kg/day Animals were dosed on Gestation Days 6 to 16	**5, 15 or 40 mg/kg/day:** reduced body weight gain and food consumption. ↓ in reticulocyte, white blood cell, neutrophil, monocyte and/or lymphocyte counts, indicating the bone marrow as a potential target organ. Embryofetal toxicity, resulting in no surviving foetuses. **15 or 40 mg/kg/day:** ↓ cumulative body weight gain was seen from Day 9 post-coitum, with reduced food consumption from Day 6 post-coitum. **5 mg/kg/day:** ↓ body weight gain and food consumption.
Oral Embryofetal Development Study in the Rat 22 pre-mated female AlpkHsdRccHan-WIST rats 1556TR Yes	Oral (gavage) 0, 0.05 and 0.5 mg/kg/day Animals were dosed on Gestation Days 6 to 16	**0.5 mg/kg/day:** ↓ body weight gain from Gestation Day 16 and increased food consumption prior to necropsy (between Day 18 to 21). There were no maternal effects after dosing with 0.05 mg/kg/day. Early embryofetal survival and weights of the surviving foetuses were reduced. Major eye (anophthalmia, microphthalmia) and vertebral/rib malformations occurred. There were ↑ incidences of several commonly occurring visceral observations (slightly non-uniform palate rugal pattern; additional liver lobe(s); left sided umbilical artery; slightly dilated ureter; kinked ureters). ↑ incidence of severely dilated ureters. ↑ incidences of several transient skeletal minor abnormalities and/or variants (affecting cervical, thoracic and caudal vertebra, sternebrae and hindlimb bones). Caudal displacement of the thoracolumbar border, indicated by the presence of 14th extra rib(s) or ossification centre, with associated shift in pelvic girdle positioning. **0.05 mg/kg/day:** no effect on embryofetal survival or weights noted for the foetuses from females. In addition, there was a single foetus with bilateral anophthalmia. ↑ incidence of severely dilated ureters. ↑ incidence of 14th extra rib(s).

Pre-natal and post-natal development studies were not submitted.

Toxicokinetic data

Comparative total steady state exposure data from animals in the repeat dose toxicity studies (AUC_{0-t}) and for humans ($AUC_{(0-12)}$ and estimated $AUC_{(0-24)}$) at the 400 mg bd clinical dose are presented in the following table.

Table 13: Comparative group mean total AUC in human, rat and dog (steady state)

Dose (mg/kg/day)	**Rat**		**Dog**	
	$AUC_{(0-t)}$ (µg.h/ml)	**[Study duration]**	**$AUC_{(0-t)}$ (µg.h/ml)**	**[Study duration]**
1	F **0.373**	[***6 months***] *Study: TII0012*	M **2.18, F 1.19**	[***6 months***] *Study: TII0011*
2.5	-	-	M 3.43, F 4.92	[*1 month*] *Study: 2229/038*
3	-	-	M **3.83, F 3.60**	[***6 months***] *Study: TII0011*
5	M 0.239*, F 1.64 M **0.227**, F **3.15**	[1 month] *Study: 2229/037* [***6 months***] *Study: TII0012*	M 5.60, F 6.52	[*1 month*] *Study: 2229/038*
10	-	-	M **15.6**, F **14.0**	[***6 months***] *Study: TII0011*
15	M 3.68*, F 6.26 M 1.06, F 6.27 M **1.64**, F **6.75**	[7 days] *Study: 2229/040* [1 month] *Study: 2229/037* [***6 months***] *Study: TII0012*	M 10.7, F 22.2	[1 month] *Study: 2229/038*
30	M 4.23	[***6 months***] *Study: TII0012*	-	-
40	M 5.75*, F 15.6	[1 month] *Study: 2229/037*	-	-
50	-	-	M 13.7, F 23.8, F 34.2	[7 days] *Study: 2229/039*
100	M 58.3, F 123	[7 days] *Study: 2229/040*	-	-
200	M 99.4, F 173	[7 days] *Study: 2229/040*	-	-
Human [a] 400 mg (bd)	**Mean $AUC_{(0-12)}$ = 38.8 µg.h/ml** [h] *Estimated Mean $AUC_{(0-24)}$ = 76.6 µg.h/ml* [h]			

$AUC_{(0-24)}$ is presented for rat and dog studies, except where indicated: * $AUC_{(0-8)}$.
Human dose of 400 mg twice daily (bd) = 800 mg/day, equivalent to 6.67 mg/kg bd (for 60 kg human).
[h] Human exposure data pooled from studies D0810C00002, D0810C00008, D0810C00009, D0810C00012 and D0810C00024. $AUC_{(0-12)}$ is calculated from samples taken over 12 hours post-dose; $AUC_{(0-24)}$ is estimated by doubling the $AUC_{(0-12)}$ values.

Estimated mean total steady state $AUC_{(0-24)}$ after dosing at 400 mg bd (~6.67 mg/kg bd) in humans (76.6 µg.h/ml) was approximately 5 to 13-fold higher than the mean total steady state exposure ($AUC_{(0-8)}$ for males and $AUC_{(0-24)}$ for females) achieved at the highest doses used on the pivotal rat 1 month repeat dose study (40 mg/kg/day) and approximately 11 to 18-fold higher than the mean total steady state AUC(0-24) at the highest doses used in the 6 month rat study (15/30 mg/kg/day). However, in the 7 day dose setting study in rats, mean total steady state $AUC_{(0-24)}$ at the high dose level (200 mg/kg/day) was approximately 1.3 to 2-fold higher than the estimated mean total steady state $AUC_{(0-24)}$ in humans at the clinical dose.

Local Tolerance

No studies have been submitted.

Other toxicity studies

Phototoxicity potential

Olaparib showed little absorbance within the UV range of 290 to 700 nm, with the peak of absorbance occurring at 276 nm. The molar extinction coefficient determined at 290 nm was 5926 L.mol-1.cm-1. Further nonclinical studies assessing phototoxic potential *in vitro* or *in vivo* were not conducted.

Myelotoxicity Studies with a Variety of Experimental Compounds

To explore potential effects of Olaparib on the bone marrow, *ex vivo* studies were conducted using human bone marrow cells obtained from donors. These studies consisted of a colonyforming unit/granulocyte/monocyte assay (CFU-GM), in which cells were continuously exposed to Olaparib for 14 days, and a bone marrow proliferation test, in which cells were continuously exposed to Olaparib for 3 days. Olaparib had an IC_{50} value of 3.9 µM in the CFU-GM assay (from a single donor) and a mean IC_{50} of 2.7 µM in the proliferation assay (n=4, range 1.05 to 4.6 µM). Olaparib was also tested for myelotoxicity in bone marrow cells obtained from Sprague-Dawley rats in the CFU-GM assay, in which cells were continuously exposed to olaparib for 14 days. In this study, Olaparib had an IC_{50} value of 0.33 µM.

14 Day Oral (Gavage) Tolerability and TK Study in the Mouse

A repeat dose study was conducted in mice to explore Toxicity and TK, as part of dose setting work to support possible future longer duration studies in this species. Oral dosing for up to 14 days at 400 mg/kg/day was not tolerated, with 1 animal killed prematurely on Day 11 following deterioration in its clinical condition. Whilst the cause of death for this animal was not established an association with treatment could not be discounted. Haematology changes, affecting reticulocytes, red blood cell parameters and leucocyte counts, were seen at 200 or 400 mg/kg/day. Systemic exposure in this study was markedly lower on Day 14, compared to Day 1.

2.3.5. Ecotoxicity/environmental risk assessment

Table 14: Summary of main study results

Substance (INN/Invented Name): olaparib			
CAS-number (if available): 763113-22-0			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	**OECD107 (study 06-0182/C)**	pH 7 log Kow = **1.55**	Not > 4.5: **not PBT**
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	If Fpen=0.01 4.0 (default) If Fpen=0.0001094 0.044 µg/L (refined)	µg/L	 < 0.01 µg/L
Other concerns (e.g. chemical class)			Clastogenic Embryotoxic Teratogenic
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	Modified OECD 106 (study 12-0285/A)	*High Organic Carbon (HOC) sediment mean* **K_d =111** **K_{oc} = 1986** *Low Organic Carbon (LOC) sediment* mean **K_d = 3.8**	*KFoc values indicated that [^{14}C]Olaparib was of* ***low mobility in the HOC sediment*** *(KFoc 500-2000), and* ***immobile in the LOC sediment***

		K_{oc} = 27487	*(KFoc>5000)*
Ready Biodegradability Test	OECD 301F (study 06-0182/J)	*Negligible biodegradation* (day 28: **<6%**)	*Not readily biodegradable*
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308 (study 08-0028/C)	$DT_{50,\ water}$ = **4.22 and 7.1** for high and low organic matter vessels respectively $DT_{50,\ sediment}$ = **not applicable**	*In both the high and low organic matter test vessels,* ***rapid dissipation of AZD2281 was observed****. In the sediments there was no evidence of any degradation and specific half-lives could not be calculated.*
Adsoprtion/desorption to sludge	OPPTS 835.1110 (study 08-0028/B)	$Kd_{sludge(ads)}$ = 25	*[^{14}C]AZD2281 did not show significant adsorption to sewage sludge and therefore, is not predicted to adsorb to bio-solids during wastewater treatment. A Kd value of 25 was calculated assuming a linear adsorption isotherm*
Hydrolysis	OECD 111 (study 06-0182/D)	<10 % (5 days) at pH 5, 7 and 9 Hydrolytically stable	*Hydrolytically stable (less than 10% hydrolysis over 120 hours at environmental relevant pHs)*

Phase IIa Effect studies

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

PNECmicroorganism = 10 000 µg/L
PNECsurfacewater = 32 µg/L
PECgroundwater = 0.011 µg/L and **PNECgroundwater** = 32 µg/L

PECsurfacewater/PNECmicroorganism = 4.4 × 10^{-6} (then <0.1): Olaparib is unlikely to present a risk to microorganisms
PECsurfacewater/PNECsurfacewater = 1.4 × 10^{-3} (then <1): Olaparib is unlikely to present a risk to organisms in surface water
PECgroundwater/PNECgroundwater = 3.4 × 10^{-4} (then <1): Olaparib is unlikely to present a risk to the groundwater environment

Phase IIb Studies

Toxicity to *Chironomus riparius*	**OECD 218 (study 08-0028/D)**	*28 d NOEC = 0.6 mg/kg dry sediment and; 28 d LOEC = 1.25 mg/kg dry sediment, based on development rate*

PECsediment , calculated in accordance with ECHA guidance (Equation R.16-35)
PECsediment =1.1 µg/kg

PNECsediment = NOEC from the chironomus test / 100
PNECsediment = 600 µg/kg / 100 = 6 µg/kg
PEC/PNECsediment = 0.18 (then <1): no further testing is required

Olaparib is not a PBT substance. Considering the above data, olaparib is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

Pharmacology

The principle for olaparib mode of action is synthetic lethality. Synthetic lethality is observed when defects in two genes individually have benign effects but when combined lead to lethality. For olaparib, the hypothesis is that inhibition of the PARP repair system (DNA single strand breaks repair) in Homologous recombination repair (HRR) deficient cells (i.e. BRCA 1 or 2 mutated) will lead to accumulation of unrepaired DSBs (or reparation by error prone system Non Homologous End-Joining = NHEJ pathway), unsustainable DNA damage burden and cell death.

In vitro results showed that Olaparib is a PARP-1/PARP-2/PARP-3 inhibitor. All three proteins were involved (although in different extent) in DNA repair response (Beck C et al, 2014).

Olaparib was shown to inhibit selected cell lines *in vitro* and, with a very good sensitivity, cell lines with BRCA mutant and low BRCA expression. An analysis of a panel of cancer cell lines treated with olaparib showed an enrichment of the most sensitive lines with those containing BRCA homozygous mutations, although activity was not limited to BRCA deficiencies, but also correlated with other DNA repair defects.

PARP inhibition with olaparib in term of clonogenic survival curves was selective for BRCA2 deficient (BRCA2-/-) at adequate doses and not for BRCA2 wild type and BRCA2 heterozygous (BRCA2+/-). Therefore, olaparib is expected to have significantly reduced effects on normal cells that are wild type or heterozygous for either BRCA1 or BRCA2.

Olaparib inhibited selected xenograft growth *in vivo* either as a stand-alone treatment (50 mg/kg ip per day) or in combination with established chemotherapies.

In vivo, BRCA1 and BRCA2-deficient models have also been able to confirm the single agent activity of olaparib with efficacious doses of 50 mg/kg qd and above.

An analysis of olaparib and platinum response was extended to additional tumour indications. A strong correlation was identified between platinum sensitivity and olaparib sensitivity in breast, HNSCC and NSCLC cancer cell.

Olaparib showed no significant activity *in vitro* in a panel of 239 radioligand binding and enzyme assays, covering a diverse panel of molecular targets including enzymes, receptors, transporters and ion channels, at a single concentration of 10 µM. Olaparib was also inactive in a panel of human recombinant voltage-gated cardiac ion channels *in vitro* at up to a maximum concentration of 31.6 µM. Overall, olaparib showed little potential for inducing significant off-target activity at clinically relevant concentrations (the human mean free C_{max} at the clinical dose of 400 mg bd = 1.99 µM).

Regarding safety pharmacology, olaparib had an IC50 of 226 µM in the hERG-encoded potassium channel, 113-fold higher than the human mean free C_{max} (0,865 µg/ml = 1.99 µM) at the clinical dose.

In the dog study (2229/053), there was no evidence for QT prolongation following IV dosing up to 15 mg/kg at clinically relevant exposures. At doses of 1.5 and 5 mg/kg olaparib had no effects on the cardiovascular of anaesthetised dogs when compared to the vehicle control group. However, a dose of 15 mg/kg elicited a slight increase in heart rate. Moreover, a decrease was observed in the PR interval at 10 minutes after administration of the high dose. Data from the 5-min timepoint in Study 2229/045, which was comparable to the data collected in the study 0088/453 (KMD008) showed that a 2.5 mg/kg intravenous dose to dogs in Study 2229/045 was associated with plasma exposures that were approximately 3-fold higher than those achieved at the 1 mg/kg dose in Study 0088/453, suggesting linearity. Moreover, these were approximately 2-fold above the revised mean total Cmax at the 400 mg BD clinical dose of 4690 ng/ml (range = 1180 to 14200 ng/ml). This entails that at the high dose level (15 mg/kg) tested in the intravenous cardiovascular safety pharmacology study in the anaesthetised dog (Study 2229/053), by linear extrapolation the 5-min C-max could amount to 25038 ng/mL which is 1.7-fold above the highest clinical exposure level measured following a clinical dose of 400 mg BD. As the Cmax levels measured immediately after dosing in Study 2229/045 were at least two fold higher it can be concluded that the non-clinical cardiovascular safety pharmacology in the anaesthetised dog did not demonstrate QT prolongation at plasma exposure levels at least 3-fold higher than human clinical exposure following a clinical dose of 400 mg BD.

Overall, the cardiovascular studies suggested no or a very little potential for QT prolongation in man. No effect was observed for the CNS and the respiratory system.

Pharmacodynamic drug interaction studies were not submitted as olaparib will not be co-administered with other agents in the maintenance setting in gBRCA ovarian cancer patients. This was considered acceptable by CHMP.

Pharmacokinetics

Absorption was rapid (C_{max} <2 hour in mice, rats and dogs) while bioavailability was 55 to 60% in male and female mice, <20% in male and female rats and 79% in male dogs. For male and female mice, exposure was generally similar in each sex. Exposure increased less than in proportion to dose in both sexes but more obviously in male mice. In male and female mice exposure was markedly lower at all dose levels after 14 daily oral doses. In rats, exposure was markedly higher in female animals (up to 5-fold the exposure in male rat) and exposure increased more than in proportion to dose in both sexes. The sex difference exposure between male and female rats was consistent with the frequently observed sexual dimorphism in rodent cytochrome P450 3A (CYP3A) enzyme expression. Following daily dosing for 1 and 6 months to rats of both sexes, exposure was largely unchanged at low doses but decreased by 25 to 45% at high doses. In male and female dogs, exposure was similar. Exposure increased in proportion to dose between the low and mid doses but less than proportionately between the mid and high dose in male dogs and proportionately in female dogs. In male and female dogs exposure was similar after single doses and daily dosing for 1 and 6 months.

The excipient Lauroyl Macrogol-32 Glycerides (LMG) present in the capsule formulation was absent from the product tested in the non-clinical program. Olaparib is mainly metabolized via CYP3A4/5. No clinical data is available yet concerning CYP inhibition/induction by LMG and the ongoing studies are being performed with the tablet formulation only. Adequate warnings are included in the SmPC recommending avoiding concomitant treatment with strong CYP3A4 inhibitors (see section on clinical pharmacokinetics). However, the situation concerning the excipient needs to be clarified and the CHMP recommends the Applicant to conduct an *in vitro* test assessing the potential CYP3A4 inhibition by LMG.

Olaparib demonstrated low binding to plasma proteins. Binding was lowest in dog (38 to 45% unbound), followed by mouse (28.4 to 30.6% unbound), rat (26.5 to 27.3% unbound) and human (8.8 to 18.1% unbound). Mean free fraction was 28.4%-30.6 in mouse and 26.5%-27.3% in rat. In dog plasma the free fraction (38.1%-45.3%) was higher than in mouse or rat. In human plasma, mean free fraction was low and varied between 8.8% at concentrations of 0.010 µg/ml and 18.1% at 10.0 µg/ml.

[^{14}C]-olaparib had a lower association with human blood cells and the interaction was again concentration related (12% at 0.1 µg/ml and 30% at 10 µg/ml). Following single oral doses of [14C]-olaparib to pigmented rats, radioactivity was widely distributed. With the exception of organs of the gastrointestinal (GI) tract and excretory organs, concentrations of radioactivity in many tissues were similar to whole blood; this was consistent with the low volume of distribution of olaparib. Radioactivity was not quantifiable in brain or spinal cord. A slightly prolonged association was noted with melanin containing tissues (uveal tract and pigmented skin) but this was of short duration. Generally, the tissues containing the highest concentrations of Olaparib included the liver, kidney and uveal tract. Distribution in male and female rats was similar but tissue concentrations were generally higher in females, which was consistent with the higher exposure noted previously.

Single oral doses of [^{14}C]-olaparib to female nude mice bearing HTC-116 human colorectal tumours produced a similar distribution of radioactivity to that in rat. However, radioactivity was present in tumour at higher concentrations than blood and was retained in tumour longer than in blood.

In rat and human, the metabolites formed heavily favoured Phase I products; the main sites of metabolism were the piperazine carboxycyclopropyl ring structure and to a lesser extent the fluorophenyl and the phathalazinone ring systems. The major metabolic processes were oxidations and hydroxylations and many products were the result of multiple metabolic transformations. Some minor products resulted from Phase II metabolism of previously formed Phase I products. Following a single 100 mg oral dose of [^{14}C]-olaparib to female patients, olaparib and 3 additional components were quantifiable in plasma. The 3 metabolites were M12 (ring-open hydroxy-cyclopropyl: 12.3%), M15 (monooxygenated: 9.4%) and M18 (dehydrogenated piperazine: 7.9%). Olaparib represented 70% and the additional components 9 - 14% of the plasma radioactivity. Each was also present in male and female rat plasma, following single oral doses. However, although these metabolites represented 8 to 12% of the radioactivity in plasma from male rats, they were insufficiently abundant to be quantified in female rat plasma. Up to 20 other metabolites were present in human plasma although none could be quantified by radio-HPLC; 14 of these were not detected in rat or dog plasma although 13 were present in rat excreta.

In humans and rats, many metabolites were present in very low quantities and were detectable by mass spectrometry but not quantifiable. Three metabolites were detected in human but not detected in rat plasma or excreta: M35 but also M10 (very low levels and in less than half of the analyzed samples) and M8 (0.5% of radioactivity in urine). Taking into account the low concentrations of these 3 metabolites, it is considered very unlikely that these would play a major role in the toxicity profile. The rats have thus been exposed to all main human metabolites in relevant amounts.

Following administration of single oral doses of [^{14}C]-olaparib to male and female rats, elimination was rapid (94% to 96% within 48h) and recovery was complete within 5 days. Faeces provided the major route of elimination of radioactivity in rats of both sex although a greater proportion of the dose was eliminated in the faeces of male rats. A corresponding sex difference in urinary elimination was observed with female rats eliminating a larger proportion of the dosed radioactivity by this route. Following single IV doses of [^{14}C]-olaparib to bile duct cannulated male and female rats, the sex difference in elimination route was confirmed with male rats eliminating a much greater proportion of the dose in the bile. These findings were consistent with the sex difference in metabolism of olaparib in rat.

After single oral and IV doses of [^{14}C]-olaparib to male dogs, elimination was again rapid (91% and 99% within 48 hours after oral and IV dosing) and recovery complete within 7 days. Faecal elimination provided the major route of elimination.

The main metabolite in human urine (M15) resulted from a single oxidation while the most abundant metabolites in human faeces (M12, M15, M23 and M25) resulted from single or dual oxidations/hydroxylations.

Toxicology

In mice, the acute minimum lethal oral dose was not established, as there were no deaths or adverse signs at 300 mg/kg. In rats, the acute minimum lethal oral dose of olaparib was 300 mg/kg, with some animals found dead on Days 1 to 3. The highest non-lethal oral dose in rats was 240 mg/kg. The acute minimum lethal intravenous dose of olaparib in mice and rats was 100 mg/kg, with animals dosed at 100 mg/kg and above dying immediately following dosing. The highest non-lethal IV dose in mice and rats was 70 mg/kg.

In repeat dose oral toxicity studies in rats, dosing olaparib for 7 days at dose levels of up to 200 mg/kg/day, for 1 month at up to 40 mg/kg/day and for 6 months at up to 15 mg/kg/day (females) or 30 mg/kg/day (males) was well tolerated, with no compound-related deaths nor reduced body weight. Reduced body weight gain, food consumption and effects on haematology parameters were observed at 40 mg/kg/d and higher. Reductions in body weight, body weight gain and/or food consumption were noted in these studies for females dosed at 15 mg/kg/day and above and for males at 40 mg/kg/day and above. The different high dose levels of 15 mg/kg/day (females) or 30 mg/kg/day (males) were selected for the 6 month rat study because of the higher plasma exposures in females compared to males.

In dogs, oral dosing for 3 or 7 days at 50 or 75 mg/kg/day resulted in body weight loss, inappetence and adverse signs, and as a result 1 dog dosed at 50 mg/kg/day was killed prematurely on Day 5. Lower dose levels of up to 15 mg/kg/day and up to 10 mg/kg/day were subsequently selected for the 1 and 6 month repeat dose dog studies, respectively, and were well tolerated, with no mortalities, nor effects on body weight or food consumption. Haematological changes were observed including decrease in red blood cell parameters, white blood cell, platelet and reticulocyte counts.

In both species, the principal target organ for toxicity following repeat dosing of olaparib for up to 1 or 6 months was the bone marrow, with associated changes in peripheral haematology parameters.

In rats, reductions in red blood cell parameters and white blood cell, neutrophil and/or lymphocyte counts, and increases and/or decreases in reticulocyte and platelet counts, were seen in one or both sexes dosed at 100 or 200 mg/kg/day for 7 days, at 40 mg/kg/day for 1 month or at 5, 15 or 30 mg/kg/day for 6 months. These changes were associated with increases in the erythropoietic and/or myelopoietic cell populations within the bone marrow, and with increases in splenic haemopoiesis, hepatocyte pigmentation and/or thymic atrophy.

The changes generally occurred at lower dose levels in female rats as a result of the higher systemic exposures in this sex, compared to males. Similar changes in red blood cell parameters and white blood cell, neutrophil lymphocyte, reticulocyte and/or and platelet counts, were seen following dosing dogs at 50 mg/kg/day for 7 days or 15 mg/kg/day for 1 month, and were associated with bone marrow atrophy and with an increase in the myeloid/erythroid (M:E) ratio in the bone marrow smear. Decreases in red and white blood cells and platelets, seen following dosing dogs at 3 or 10 mg/kg/day for 6 months, were not associated with any microscopic changes in the bone marrow. All changes seen in rats and dogs in the 1 month studies showed full or partial recovery following a 28 day recovery period.

It was noted that the mean total steady state $AUC_{(0-12)}$ in humans at the 400 mg bd clinical dose was approximately 5-fold higher than the mean steady state $AUC_{(0-24)}$ at the highest doses used in the dog 1 month (15 mg/kg/day) and 6 month (10 mg/kg/day) studies, respectively. Animals in the pivotal 6-month dog study were under-exposed compared to Human by a factor 3, whereas MTD (defined as a decrease in body weight gain of no more than 10%) was not reached. Given the limitations of the non-clinical general toxicology data, the limited amount of long-term exposure data for olaparib, the potential for long term toxicity on organ systems is unknown from a clinical perspective. Published clinical data on other PARP inhibitors to date has identified no additional toxicity concerns of importance. However, PARP inhibitors are a relatively new class of agents with limited published clinical information. Therefore, long-term exposure to/potential toxicity to olaparib have been included as missing information in the RMP and the MAH will assess the potential for any additional target organ toxicity following long-term dosing through pharmacovigilance activities.

Olaparib showed no mutagenic potential in the Ames bacterial mutation tests, but was clastogenic in an *in vitro* chromosome aberration test in mammalian cells and induced micronuclei in the bone marrow of rats following oral dosing for 2 days at dose levels of up to 400 mg/kg/day. This clastogenicity was consistent with the primary pharmacology of olaparib and indicated potential for genotoxicity in man (see SmPC section 5.3). No carcinogenicity studies were provided which is acceptable according to ICH S9 and in line with the protocol assistance received. Possible occurrence of new malignancies due to the pharmacological action of olaparib will be closely monitored in line with the RMP (see clinical safety).

In a female fertility and early embryonic development study, dosing olaparib to female rats from 14 days prior to pairing and continuing up to Day 6 post-coitum inclusive, produced no significant maternal toxicity or effects on mating performance or fertility (ovulation and pregnancy rates), but resulted in slight reduced embryofetal survival at the high dose of 15 mg/kg/day. Main test animals dosed with 15 mg/kg/day had markedly increased incidence of extended oestrus during dosing (9 affected animals versus 0 affected controls). This effect was no longer present after recovery. A recovery group was included in the study, with dosing for 19 days followed by a 4 week recovery period before pairing, and showed no decrement in embryofetal survival for animals previously dosed with olaparib at 15 mg/kg/day. In embryofoetal development studies, oral dosing of olaparib to pregnant rats during organogenesis caused complete embryofetal lethality at a dose of 5 mg/kg/day and above. At lower doses (e.g., 0.05 or 0.5 mg/kg/day), reduced foetal weight and increased incidences of major foetal developmental abnormalities (including visceral and skeletal abnormalities, and major eye (e.g. anophthalmia, micropthalmia) and vertebral/rib malformations) were seen. Overall, these data provide compelling evidence that olaparib can cause developmental toxicity at doses levels that did not induce significant maternal toxicity. Plasma exposures at the LOEL for teratogenicity were about 4500-fold lower than plasma exposures obtained in humans at the recommended dose of 400 mg b.i.d.

Assessment of placental transfer and distribution into milk has not been undertaken. It is unknown whether olaparib/or its metabolites are excreted in human milk. Olaparib is contraindicated during breast-feeding (see SmPC sections 4.4, 4.6 and 5.3).

In a male fertility study, dosing olaparib to male rats for at least 70 consecutive days prior to pairing with undosed females and until fertility was proven, produced no effects on mating performance, fertility, embryonic survival, sperm parameters or on testis and epididymal weights or histopathology, at doses of up to 40 mg/kg/day, although doses of 15 mg/kg/day and above were associated with signs of toxicity, notably reduced food consumptions and body weight gain.

Olaparib showed absorption in the UV visible spectrum and had a MEC of 5926 L.mol-1.cm-1 at 290 nm. In addition, olaparib distributed to the skin and eyes.

Olaparib was myelotoxic when assessed in ex vivo bone marrow proliferation and/or colony-forming unit granulocyte/macrophage assays, using human donor and rat bone marrow cells. This confirmed that olaparib is cytotoxic to human bone marrow cells (see SmPC section 5.3).

The Predicted Environmental Concentration (PEC) / Predicted No Effect Concentration (PNEC) ratios for ground water, surface water and sediment were below 1, and the PEC/PNEC for microorganisms was below 0.1. Olaparib is not predicted to present a significant risk to the environment. Any unused medicinal product or waste material should be disposed of in accordance with local requirements (see SmPC section 6.6).

2.3.7. Conclusion on the non-clinical aspects

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.

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.

In repeat dose toxicity studies of up to 6 months duration in rats and dogs, daily oral doses of olaparib were well tolerated. The major primary target organ for toxicity in both species was the bone marrow, with associated changes in peripheral haematology parameters. These findings occurred at exposures below those seen clinically and were largely reversible within 4 weeks of cessation of dosing. Ex vivo studies using human bone marrow cells also confirmed that olaparib is cytotoxic to human bone marrow cells.

Based on its mechanism of action (PARP inhibition), olaparib could cause foetal harm when administered to a pregnant woman. Non-clinical studies in rats have shown that olaparib causes adverse effects on embryofoetal survival and induces major foetal malformations at exposures below those expected at the recommended human dose of 400 mg twice daily (see discussion above). Therefore, olaparib should not be used during pregnancy and in women of childbearing potential not using reliable contraception during therapy and for 1 month after receiving the last dose of olaparib (see SmPC sections 4.4, 4.6 and 5.3). Given the pharmacologic property of the product, olaparib is also contraindicated during breast feeding and for 1 month after receiving the last dose.

Regarding the potential for any additional target organ toxicity following long-term dosing, the applicant will provide further information through pharmacovigilance activities as adequately reflected in the RMP.

The CHMP also recommends the applicant to conduct an *in vitro* test assessing the potential CYP3A4 inhibition by LMG.

2.4. Clinical aspects

2.4.1. Introduction

Olaparib capsules have been designed as an immediate release oral formulation, containing 50 mg of olaparib. The capsules consist of olaparib drug substance suspended in the semisolid excipient lauroyl macrogol-32 glycerides (LMG) within a white, opaque, hypromellose capsule shell. The same olaparib capsule formulation has been used in all Phase I and II studies included in the dossier and this is also the proposed commercial formulation. A 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. The tablet formulation is being used within the ongoing studies of olaparib.

The application relates to the capsule formulation of olaparib. Clinical data were provided from eight studies including in total 911 subjects with ovarian cancer relevant to the assessment of the efficacy of the capsule formulation of olaparib.

The Applicant received protocol assistance on the design of the clinical study and determination of BRCA mutations status in patients. The main points are summarised below:

- Since subsequent therapies are likely to confound OS data, PFS with clearly defined response criteria, independent response assessment and no cross over may be an acceptable endpoint if the effect is clinically relevant and robust, data on OS show no detrimental effects and toxicity of the substance is low (as reflected by absence of impact on QoL) (see EMA/CHMP/27994/2008 “Methodological consideration for using progression-free survival (PFS) or disease-free survival (DFS) in confirmatory trials”).

- More mature PFS data and more mature OS data, and information on time to second progression (PFS2) were recommended.

- Time from randomization to second progression / PFS2 would be of some importance as supportive endpoints.

- In Europe, the testing procedures employed for identification of germline BRCA mutations are considered acceptable and are embedded in current clinical practice. It was advised, that for an indication that would include tumour BRCA mutated patients, it would be essential to develop a tumour based testing infrastructure that would ensure such testing could be utilised to support the identification of appropriate patients. This could be delivered through a laboratory based testing infrastructure and/or through the delivery of a CE marked tumour test. The Applicant considered that this was feasible and is exploring options to make a tumour test available.

GCP

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

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

Table 15: Tabular overview of clinical studies

Study Phase	**Phase I: Tolerability & preliminary efficacy**		**Phase II**					
Study ID	**00002**	**00024**	**00019**	**00041**	**00012**	**00020**	**00042**	**00009**
Level of evidence	Supportive	Supportive	**Pivotal**	**Key Supportive**	**Key Supportive**	Supportive	Supportive	Supportive
Study population	Patients with malignant advanced solid tumours	Patients with malignant advanced solid tumours	Patients with PSR high-grade serous ovarian cancer who were in partial or complete response to platinum-based chemotherapy	Patients with PSR ovarian cancer	Patients with partially platinum sensitive or platinum resistant *gBRCA* mutated ovarian cancer	Patients with *gBRCA* mutated or high-grade serous/ undifferentiated ovarian cancer	Patients with advanced *gBRCA* mutated solid tumours	Patients with advanced *gBRCA* mutated ovarian cancers
Study design	First in human SAD MAD	Comparative bioavailability of capsule *vs* tablet formulation	Randomised Double blind Placebo controlled Multicentre	Randomised Open-label Multicentre	Randomised Open-label Active control Multicentre	Open-label Non-comparative Multicentre	Open-label Non-comparative Multicentre	Open-label Non-comparative Multicentre
Dosage regimen	10, 20, 40, 80 mg od 60, 100 mg bid 100, 200, 400, 600 mg bid	PK phase: 50, 100 mg od Capsule Continued supply phase: 400 mg bid capsule	400 mg bid, maintenance monotherapy	200 mg bid (combination with C/P) 400 mg bid (maintenance monotherapy)	200 or 400 mg bid	400 mg bid	400 mg bid	100 or 400 mg bid
Duration of treatment			28 -day cycle until objective disease progression, withdrawal or meeting discontinuation criteria	Combination: at least 4 21-day cycle Maintenance: until objective disease progression or discontinuation	Until disease progression or withdrawal from treatment for another reason	28 -day cycle until objective disease progression, withdrawal or meeting discontinuation criteria	28 -day cycle until objective disease progression, withdrawal or meeting discontinuation criteria	28-day cycle; continued treatment if patient was deriving benefit from and tolerating treatment

Study ID	00002	00024	00019	00041	00012	00020	00042	00009
Efficacy endpoint(s)	Response rate	Tumour shrinkage	Prim. PFS Sec. OS	Prim. PFS Sec. OS	Prim PFS	Response rate	Response rate	Response rate
Number of subjects randomized/treated	58[§]	77*	265/264	162/156	97/96	91/90 (65 with ovarian cancer)	317/298	58/57
Number of BRCA mutated ovarian cancers	49*	53*	136	41	97	17	193	58
Study Status	Completed	Ongoing (tablet only)	Ongoing; primary PFS analysis and interim OS analysis completed	Ongoing; primary PFS analysis and interim OS analysis completed	Completed	Completed	Completed	Completed

[§] number of patients in efficacy expansion
* Capsule dosed patients only
bid: twice daily; od: once daily; . SAD: single ascending dose (study); MAD: multiple ascending dose (study); PSR: Platinum-sensitive relapsed

2.4.2. Pharmacokinetics

In addition to non-clinical pharmacokinetics studies (see Table 6), the clinical pharmacology package for the capsule formulation included single- and multiple-dose pharmacokinetic (PK) data, data on absorption, distribution, metabolism and excretion (ADME) and a PK/pharmacodynamic (PD) report (using PARP inhibition as a PD endpoint). It also included a population PK/PD analysis in 293 ovarian cancer patients across 6 clinical studies to describe the influence of covariates including patient age, weight and race on the pharmacokinetics of olaparib and to explore the relationship of pharmacokinetics to the assessments of efficacy and safety.

Table 16: Overview of clinical studies contributing to PK investigation of olaparib

Study No	Study description	Dose(s)	Number randomised/treated and type of subject
D0810C00001 KU36-64 Study 01	Phase I, rising single dose and multiple dose safety and tolerability in Japanese patients	100, 200 and 400 mg single dose; 100, 200 and 400 mg twice daily	3/3; 3/3 and 7/6 Japanese patients with malignant solid tumours
D0810C00002 KU36-92 Study 02	Phase I, rising single and multiple dose safety and tolerability followed by biological evaluation of olaparib	10, 20, 40, 60, 80, 100, 200, 400 and 600 mg single dose; 10, 20, 40 and 80 mg once daily; 60, 100, 200, 400 and 600 mg twice daily; 200 mg twice daily	3/3, 3/3. 5/5, 4/4, 3/3, 9/9, 6/6, 8/8, 5/5 in dose escalation phase; 52/52 in efficacy expansion phase Patients with malignant solid tumours in dose escalation phase; patients with germline *BRCA* mutations in efficacy expansion phase
D0810C00007 KU36-13 Study 07	Phase I pharmacodynamic concentration - response study	10, 30, 100, 200 and 400 mg twice daily	12/12, 12/12, 12/12, 12/12, 12/12 Intermediate/high-risk breast cancer patients scheduled for elective surgery
D0810C00008 KU36-44 Study 08	Ph II efficacy and safety study in g*BRCA* mutated breast cancer	100 and 400 mg twice daily	27/27, 27/27 Patients with advanced breast cancer with a germline *BRCA* mutation
D0810C00009 KU36-58 Study 09	Ph II efficacy and safety study in g*BRCA* mutated ovarian cancer	100 and 400 mg twice daily	24/24, 34/33 Patients with advanced ovarian cancer with a germline *BRCA* mutation
D0810C00010 KU36-37 Study 10	Phase I, absorption, distribution, metabolism and excretion study	100 mg single dose of [^{14}C]-olaparib.	7/6 Patients with malignant solid tumours
D0810C00012 Study 12	Phase II efficacy and safety of olaparib vs PLD in g*BRCA* ovarian cancer	Olaparib: 200 and 400 mg twice daily Doxorubicin: 50 mg/m^2	32/32, 32/32 and 33/32 Patients with advanced ovarian cancer with a germline *BRCA* mutation

D0810C00024 Study 24	Phase I study to determine relative bioavailability of tablet formulation, tablet MTD and appropriate Phase III tablet dose*	Rel. bio. Phase: Single 50, 100 or 400 mg capsule vs single 25, 50 or 250 mg tablet. Tablet dose escalation phase: 250 to 450 mg bd. Efficacy expansions: 400 mg bd capsule, 200, 300 and 400 mg bd tablet	Cancer patients with advanced solid tumours. 134 patients in total received treatment. Of these, the number receiving capsule is as detailed below: Rel. bio Phase = 18 patients Efficacy expansions: Group 1 = 11 patients Group 2 = 9 patients Goup 6 = 18 patients

Table 17: Overview of population-PK analyses contributing to the investigation of olaparib

Studies from which the analysis is derived	Analysis description	Number of subjects	Doses
Study 02 and 07	Population PK and PD analysis of Studies 02 and 07	115 patients for PK; 94 patients for PD	10, 20, 40 and 80 mg once daily; 10, 30, 60, 100, 200, 400 and 600 mg twice daily
Studies 01, 02, 08, 09, 12 and 24	A pooled population analysis of the pharmacokinetic, efficacy and adverse event data obtained following dosing of the olaparib capsule formulation to patients dosed in studies 01, 02, 08, 09, 12 and 24	293 patients	10, 20, 40 and 80 mg once daily; 60, 100, 200, 400 and 600 mg twice daily

In the pharmacokinetics studies, standard non-compartmental analysis (NCA) was performed. Standard pharmacokinetic parameters (C_{max}, AUC, AUC_{0-t}, AUC_{0-24}, λz, CL/F, V_{area}/F, $t_{1/2}$, t_{max}, amount and percentage of dose excreted in urine and CL_R) were determined by non-compartmental data analysis.

In the population pharmacokinetic (PK) analysis and exposure-response relationship modelling in patients performed, NONlinear Mixed Effects Modelling program (NONMEM) software was used.

Various analytical methods were developed and validated in different matrices: Plasma, urine and tumour tissues.

Absorption

Non-compartmental analysis of the plasma concentration data obtained following administration of a single oral dose of olaparib to patients in Study 02 (10 to 600 mg) and Study 24 (50, 100 and 400 mg), showed that absorption of drug was rapid with maximum plasma concentrations typically achieved between 1 and 3 hours after dosing (range: 0.5 to 8 hours).

Exposure to olaparib showed high interindividual variability, increased approximately proportionally with dose up to a dose of 100 mg but less than dose-proportionally thereafter. Similar data were obtained following single and multiple dosing to Western patients in Study 24 (single doses of 50, 100 and 400 mg; multiple dosing at 400 mg bd) and to Japanese patients (100, 200 and 400 mg) in Study 01.

In vitro study KMX006 showed that olaparib is a substrate to MDR1 transporter (also known as P-gp). In Caco-2 cells, bi-directional transport of olaparib was explored at concentrations of 10, 260 and 700 µM. At low concentrations (10 µM) olaparib was shown to have a propensity for efflux by P-glycoprotein (Pgp; MDR1) but at concentrations in excess of 260 µM the efflux was saturated (efflux ratio <2). Since the solubility of olaparib in human intestinal fluid is 0.16 mg/ml (368 µM), MDR1-mediated efflux would be expected to be saturated following dosing with olaparib at the 400 mg dose (dose:volume ratio = 1.6 mg/ml) and is therefore unlikely to impact on absorption of the drug.

In clinical study 10 (Mass-balance study) conducted in 6 female patients dosed with 100 mg, the total related drug material excreted in the urine was approximately 44%. This showed that at 100 mg dose at least a 44% fraction of the drug is absorbed. However, it could be anticipated that the drug fraction absorbed at the 400 mg claimed dose would be much lower as absorption appeared to be limited by dissolution of the drug.

The absolute bioavailability of olaparib has not been determined.

Distribution

Based on data from Study KPJ019, the *in vitro* protein binding of olaparib was shown to be moderate and showed evidence of concentration dependence (91.1, 91.2, 90.9 and 81.9% at concentrations of 0.01, 0.1, 1 and 10 µg/ml). It was not determined whether the binding is to human serum albumin, to α1-acid glycoprotein or to both and the *ex vivo* protein binding of olaparib (i.e. binding in samples from patients treated with olaparib) was not determined. The pooled population PK analysis of the data from Studies 02, 08, 09, 12 and 24 gave no indication that baseline albumin level was a significant covariate for either olaparib clearance or olaparib initial volume of distribution in man suggesting that changes in protein binding of olaparib are unlikely to explain the observed variability in exposure or result in changes in exposure.

Non-compartmental analysis of the single dose pharmacokinetic data following doses of 10, 20, 40 and 80 mg in Study 02 and doses of 50 and 100 mg in Study 24, indicated distribution out of the central compartment with a mean apparent volume of distribution (Varea/F) of 54.4 L . Following dosing of a 400 mg dose in Study 24 however, the mean apparent volume of distribution (Varea/F) was 167 L, although this was highly influenced by the value from one patient. Excluding that patient, the mean apparent volume of distribution following the 400 mg dose was 88.0 L (Study 24), suggesting that the bioavailability of olaparib may be decreasing as administered dose is increased beyond 100 mg.

From the revised population PK analysis of the pooled Study 1, 2, 8, 9, 12 and 24 data, the mean estimate for the central volume of distribution (V2) was 3.75 L and the mean peripheral volume (V3) was 60.3 L, indicating a volume of distribution at steady state for the whole population of approximately 64 L. Estimates of the inter-patient variability indicated coefficients of variation of greater than 90%. Volume of distribution was found to increase with increasing dose with the volume of distribution following the 400 mg dose estimated to be ~177 L.

Determination of concentrations of olaparib in tumour biopsies collected from intermediate and high risk breast cancer patients scheduled for elective surgery (Study 07) showed that measurable concentrations (>40 ng/g) were present in all but one of the samples collected from patients dosed at 30, 100, 200 and 400 mg bd confirming that tumour exposure to drug had been achieved. In the patients dosed at 400 mg bd, tumour concentrations ranged from 63.4 to 1830 ng/g (146 to 4217 nM (assuming the density of the tissue = 1.0 to convert the concentration from ng/g to ng/ml) with all of the patients dosed achieving tumour concentrations above 100 nM (i.e. at concentration shown to result in maximal inhibition of PARP-1 in *in vitro* experiments conducted in SW620 cell cultures).

Elimination

Identification of elimination pathways in human was primarily supported by the mass-balance study conducted in 6 female patients (Study 10). *In vitro* studies were also performed in order to identify the metabolism routes. From these investigations, it appeared that olaparib is slowly eliminated mainly by metabolism but also by renal route. The excretion of unchanged drug in urine was approximately 15 % of the total dose administered.

At doses up to 100 mg, mean apparent plasma clearance was 5.12 ± 2.23 SD L/h and the mean terminal half-life (t½) was 7.05 hours. At a dose of 400 mg however, mean apparent clearance was 8.64 ± 7.11 SD L/h and mean terminal half-life was 11.9 hours.

Metabolism

Data regarding metabolism routes of olaparib were collected from *in vitro* and clinical studies (mainly mass-balance study Study 10).

- In-vitro investigations

Information regarding metabolism pathways could be obtained mainly from studies KMX039 and KMX009 conducted respectively in human hepatocytes and human liver microsomes. In these studies numerous metabolites (11 different compounds) have been formed and identified. Although low metabolic turnover was observed the principal metabolites formed corresponded to those previously seen in incubations with human liver microsomes and CYP3A4 supersomes (KMX009). The formation of the principal metabolites was mediated by CYP enzymes. Olaparib is mainly metabolised by CYP3A4/5.

- Mass-balance study (Study 10)

Study 10 was a phase I, open, non-randomised, single-centre mass balance study where each patient received a single oral 100 mg dose of [^{14}C]-olaparib (120 µCi; 4.44 MBq), composed of one 50 mg [^{14}C]-olaparib capsule and one 50 mg non-radiolabelled olaparib capsule. Once excreta levels fell below the level of detection for radioactivity, patients who were free from intolerable toxicity and, in the investigator's opinion were eligible to continue treatment, received twice-daily (bd) dosing with 100 mg (2 x 50 mg capsules) non-radiolabelled oral olaparib capsules.

After administration of a single, oral 100 mg [^{14}C]-olaparib dose, absorption of olaparib was rapid with maximum plasma concentrations achieved at 1.5 to 2 hours after dosing. Thereafter plasma concentrations fell rapidly and had fallen below the limit of sensitivity of the assay by 16 to 24 hours after dosing in all but one patient where concentrations were still measurable at 168 hours after dosing. The geometric mean Cmax and AUC for olaparib were respectively 3.56 µg/ml and 19.9 µg.h/ml. Plasma radioactivity concentrations were generally higher than those of unchanged drug and declined in parallel. Olaparib represented, on average, 60% of the circulating radioactivity. The plasma: blood ratio for radioactivity suggested a small degree of association of drug related material with red blood cells. Over the 7 day collection period, a total of 85.8% of the dosed material was recovered in the excreta with approximately 44% recovered in the urine and 42% in the faeces.

Metabolite profiling (KMX032) by HPLC-RAD and HPLC-MSn of 0-12 hour pooled plasma showed that unchanged olaparib was the main component present accounting for an average of 70% of the chromatogram radioactivity (range = 56.2 to 83.9%). Three metabolites were detected by HPLC-RAD, M12, M15 and M18, each accounting on average for approximately 10% of the chromatogram radioactivity (9.3, 10.3 and 13.7% respectively). A further 20 components were detectable only by HPLC-MSn. The three major metabolites were identified as a ring-opened hydroxy-cyclopropyl moiety (M12), a mono-oxygenated metabolite (M15) and a dehydrogenated piperazine (M18), the latter being derived during MS analysis from M39 (a mono-oxygenated moiety).

The major component present in human urine, accounting for a mean of 15% (range = 10 to 19% of the radiochemical dose, was unchanged olaparib. A total of 37 metabolites were observed in human urine. Eighteen were quantifiable by HPLC-RAD with M15 accounting for approximately 6% of the dose and the remaining components individually representing <2.34%. The remaining metabolites were detectable only by HPLC-MSn.

At least 20 components were observed in the pooled faecal samples with 6 components accounting for >1% of the dose and the remaining metabolites detectable only by HPLC-MSn. The major component for 3 of the 6 patients was unchanged olaparib, accounting for approximately 7, 9 and 14% of the dose; M15 was the major component present in the samples from the other 3 patients (0.9, 8.4 and 1.2% of the dose).

In summary, unchanged olaparib was the major component present in majority of the samples analysed (plasma, urine and faeces). All but 5 of the metabolites detected in human samples, (each representing <1% of the dosed material) were also shown to be present in samples from the rat. All the metabolites detected by HPLC-RAD in human plasma were produced by male rats with the percentage of the radiochromatogram accounted for by each of those peaks being similar for the two species (9.3, 10.3 and 13.7% in man; 12.3, 9.4 and 7.9% in rat for M12, M15 and M18 respectively). The major components present in human excreta were unchanged olaparib and M15 (15 and 6% of the urinary radioactivity respectively; 0.6 to 14% and 5% of the faecal radioactivity respectively). The main site of metabolism of olaparib was the piperazine carboxycyclopropyl moiety although both the fluorophenyl and phathalazinone ring systems were also subject to metabolism, albeit to a lesser extent. The majority of the metabolism could be attributed to oxidation reactions with a number of components subsequently undergoing glucuronide or sulphate conjugation.

Excretion

In the human mass balance study (Study 10), excreta were collected from female cancer patients for 7 days after administration of a single radiolabelled olaparib dose. Over this period the mean total amount of dosed radioactivity recovered was 85.8% ± 7.4 SE with 44.1% excreted in the urine and 41.8% in the faeces. Total recovery of drug-related material from 4 of the patients was good (>90%) but was comparatively low in the remaining two (61% and 65%). In these two patients very little or no faecal material was produced over the 72 to 96 hour period following dosing and faecal excretion of radioactivity appeared to be delayed with little drug related material recovered in the faeces in the first 4 days after dosing and material still being excreted at up to 21 days after dosing. The rate and extent of recovery of material via the urinary route in these two patients however, was similar to that in the other 4 patients suggesting that their slower faecal excretion may be a consequence of slow gastrointestinal tract transit.

Approximately 15% of the dose was excreted as unchanged olaparib in the urine. Renal clearance was slightly higher than the rate of renal filtration implying there may be a small degree of active secretion (or a combination of active secretion followed by reabsorption) involved in the renal elimination of olaparib.

Dose proportionality and time dependencies

<u>Dose proportionality</u>

Information regarding dose proportionality of C_{max} and AUC of the capsules could be obtained from the data of dose escalation studies (Study 01 and Study 02) after single and repeated oral doses of olaparib varying from 10 mg up to 600 mg. Additional data, using sparse sampling and a population analysis based approach, were obtained following multiple dosing of patients in the efficacy expansion cohort of Study 02 (200 mg bd) and from patients in Studies 8, 9, 12 and 24 (100, 200 and/or 400 mg bd).

- Single dose

Exposure increased approximately proportionally with dose between the 50 and 100 mg doses but less than proportionally thereafter. The average terminal half-life at the lower doses was approximately 8 hours (range: 5.19 to 11.3 hours). Following the 400 mg dose however, the plasma concentration time profiles appeared flatter perhaps reflecting prolonged absorption, and the average terminal half-life in this cohort was 11.9 hours (range: 7.15 to 17.8 hours). Mean apparent clearance and mean apparent volume of distribution also appeared to be greater at the 400 mg dose level than at the two lower doses perhaps indicating a reduction in bioavailability at this higher dose.

The data from Study 02 showed that whilst exposure to olaparib (C_{max} and AUC_{0-10}) increased approximately proportionally with dose up to 100 mg it increased less than dose proportionally thereafter. For a 4-fold increase in dose from 100 mg to 400 mg, geometric mean Cmax and AUC_{0-12} increased only 1.8 and 1.7-fold respectively.

- Multiple dose

Following twice daily dosing at 60, 100, 200, 400 and 600 mg, at doses less than 100 mg, average exposure appeared to increase proportionally with dose but less than proportionally as the dose was increased further (mean C_{max} and AUC_{0-12} increased only 2.1 and 2.2–fold for a 4-fold increase in dose (100 to 400 mg bd)).

Time dependencies

Based on its single dose half-life, it would be expected that steady state exposure would be achieved within 3 to 4 days after commencing dosing with olaparib. In study 2, 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.

PK data were collected beyond the end of the first month of dosing of olaparib to patients in the Group 6 patients in Study D0810C00024. PK sampling was performed on Day 1, 29 and 57 of dosing. There was no consistent pattern that suggested exposure to olaparib is changing on continued dosing beyond Day 29 with 7 of the 14 patients for whom a ratio could be calculated showing a <20% change, one showing an approximately 25% decrease in exposure and 6 showing a increase in exposure of approximately 30% or greater, changes which could just be a consequence of intra-occasion variability.

Population PK analysis

Two pooled population clinical pharmacology analyses have been carried out using the data from a number of studies conducted during the development programme.

In the first study (analysis of pooled data from studies 02 and 07), a structural (bi-compartment) PK model was defined and the systemic exposure in patients with sparse data was predicted by the model. The PK-PD relationship was investigated. In this investigation the PARP-1 activity was used as a biomarker of the drug effectiveness.

A linear, two-compartment model with consecutive zero- and first-order absorption and first order elimination from the central compartment was used to describe the plasma concentrations of olaparib. Using this model the population apparent clearance, volume of distribution, duration of the zero-order absorption, absorption rate constant and lag time of olaparib were found to be 7.28 L/h, 34.6 L, 0.655 (~39 min), 0.502 h-1, and 0.182 h (11 min) respectively. The population relative bioavailability in patients in study KU36-13 was found to be 75% lower than in study KU36-92. This difference may be explained by the different formulation batches with different solubility properties used between the two studies. The population used in the pooled analysis was a mixed of different type of cancer patients with different disease status (early and advanced disease) which could also explain this difference of bioavailability between the two studies and patients.

The inter-individual variability on PK parameters was moderate to large from 49% to 61%. The inclusion Inter-occasion variability (IOV) was found to improve the modelling especially for the Vss. This variability on Vss was moderate to large with a CV of 61%. The covariates influencing the PK characteristics of olaparib were the BMI, Age and dose on clearance and dose on F1:

The clearance increases when the BMI decreases. Patients with a low BMI value (18 kg/m^2) taking a 100 mg dose of olaparib, would have a (CL/F) 65 % higher than the typical patient. The clearance decreases proportionally when the age decreases. A patient aged 70 years would have a plasma clearance about 18% lower than the typical patient. The bioavailability decreases when the dose increases. F1 decreases not more than 32%, when the treatment dose increases from 100 to 400 mg.

None of the covariates were shown to have a statistically significant impact on the absorption parameters and on the distribution.

Analysis of the pharmacodynamic data indicated plasma exposure correlated with PBMC PARP-1 inhibition and suggested that maximum inhibition could be achieved with high plasma exposure. However, this relationship could not be extended to dose, since the reducing bioavailability seemed to significantly increase the variability in olaparib plasma exposure observed at higher doses (doses > 100 mg).

In the second study (analysis of data from studies 01, 02, 08, 09, 12 and 24), the above mentioned model was refined and used in order to predict the systemic exposure in patients included in this study. The PK-efficacy and PK-side effect correlations have been investigated based on these predictions. The same model than that described and commented above (pooled data from studies 02 and 07) was used.

Table 18: Final PK parameters estimated with FO, SAEM and MCMC

Minimisation method	Runtime (h)	Clearance (L/h) [1]	Volume of distribution V2+V3 (L) [1]	Relative bio-availability[1]	Effect of dose on F1[1]
FO	~0.1 h	2.26	64	0.960	-0.280
		(1.65; 2.86)	(40; 88)	(0.91; 1.01)	(-0.309; -0.255)
SAEM	~3.6 h	1.71	80	0.960	-0.325
		(1.41; 2.0)	(50; 109)	(0.92; 0.99)	(-0.337; -0.313)
MCMC	~2.7 h	2.73	52.82	0.947	-0.280
		(2.70; 2.79)	(48.31; 57.32)	(0.91; 0.99)	(-0.29; -0.27)

[1] Estimated parameter with 95% CI

CI Confidence interval; FO First-order estimation method; MCMC Full Markov Chain Monte Carlo Bayesian Analysis Method; PK Pharmacokinetic; SAEM Stochastic Approximation Expectation Maximisation Bayesian Analysis Method

Data derived from: Table 45, Population PK report for Studies 1, 2, 8, 9, 12 and 24.

In conclusion the PK of olaparib was described by a two-compartment system with both zero and first order absorption:

• The non-linearity of PK of olaparib was described in F varying with the administered dose. The bioavailability was found to be altered by the dissolution performance of the batch of capsules dosed. For the 400 mg dose the population bioavailability was equal to 0.27 for fast release profile dissolution batches.

• Estimation of PK parameters as CL/F and V/F are similar to those derived with NCA analysis in study 24.

• No clinical impact of covariates on the pharmacokinetics of olaparib.

Using individual estimates of steady state exposure (steady state AUC, Cmax and Cmin), together with baseline characteristics and the administrated dose three markers of response (CA125, tumour response, tumour size change) were investigated. Dose (log-transformed) was the only significant factor for CA125 response and tumour size change, whereas log dose together with study as a categorical factor were important predictors for tumour response in the present pooled analysis. Results of the analysis suggested that 400 mg was more effective than 100 or 200 mg with respect to all these parameter changes. Analysis of CA125 suggested a 56% probability of response for 400 mg compared to 31% for 200 mg, while the predicted proportion of patients with partial or complete response was 35 % for 400 mg and 28 % for 200 mg. A 32% reduction of tumour size is predicted for the 400 mg dose after 200 days of treatment compared to 17% and 3% for the 200 and 100mg doses.

Special populations

Age

The effect of patient age was assessed on the absorption parameters, the apparent clearance and the apparent volume of distribution of olaparib were assessed as part of the covariate analysis performed in the revised population analysis of the pooled data from Studies 01, 02, 08, 09, 12 and 24. Age was not found to be a statistically significant covariate that warranted inclusion in the final PK model. The median values and the spread of the data indicated similarity between the two groups suggesting no impact of age on olaparib pharmacokinetics.

Pharmacokinetic interaction studies

Influence of food (Study D081AC00001)

This was a 2-part, Phase I, multicentre study in patients with advanced solid tumours. Part A was a randomised, open-label, 3-period crossover study to determine the effect of food on the PK profile of olaparib. Each patient received a single 400 mg oral dose of olaparib (given as eight 50 mg capsules) in each of the 3 treatment periods (once in the overnight fasted state, once immediately following a high-fat meal and once immediately following a standard meal), with a washout period of at least 5 and no more than 14 days between doses. Food intake was instructed as follows: Patients fasted for at least 10 hours after which they were given the recommended meal. Patients should have eaten the meal within 30 minutes (in the event the patient was unable to eat the meal in 30 minutes, they were still considered evaluable as long as they had consumed at least 75% of it within 45 minutes). The olaparib was administered 30 minutes after the start of the meal (or a maximum of 45 minutes after the start of the meal, if the meal was not completed), after which patients fasted until 4 hours post dose. Water was allowed as desired except for 1hour before and after olaparib capsule administration.

The results of this study showed that whilst the consumption of both the meals altered the pharmacokinetics of olaparib, the effect was not as marked as had been predicted from *in vitro* and *in silico* modeling. Following the high fat meal, the rate of absorption was slowed (median t_{max} delayed by ~3 hours), C_{max} was unchanged (TR = 1.00; 90% CI: 0.92-1.09) and AUC was increased by ~20% (TR = 1.19; 90% CI: 1.08-1.31). Similarly following the standard meal, the rate of absorption was slowed (median t_{max} delayed by ~2 hours), C_{max} increased slightly (TR = 1.10; 90% CI: 1.02-1.20) and AUC was increased by ~20% (TR = 1.21; 90% CI: 1.10-1.33). Although the average magnitude of effect was not large there was clearly a statistically significant effect of food and examination of the data for individual patients in the study showed that approximately 10% of patients had a 70% or greater increase in AUC in the fed state and approximately 20% had a 50% or greater increase.

Potential for interactions related to hepatic cytochrome P450 (CYP)

- *Olaparib as a victim drug*

SimCYP population pharmacokinetic simulations of the separate effect of co-administration of itraconazole and rifampicin (clinically relevant CYP3A inhibitor and inducer respectively) on olaparib pharmacokinetics in humans, when administered at the recommended human dose, were performed. The itraconazole (200 mg bd x 7 days) simulation indicated olaparib (400 mg bd x 7 days) Cmax and AUC(156-168 hours) would increase by 2.8 and 3.5-fold respectively. The rifampicin simulation (600 mg x 6 days) indicated olaparib (400 mg bd x 6 days) Cmax and AUC(132-144 hours) in the presence of rifampicin would be reduced to 33% and 29% respectively of the values in the absence of rifampicin.

- *Olaparib as a perpetrator: inhibitor and inducer*

CYP inhibition

The direct and time dependant CYP inhibitory potential of olaparib was tested against a panel of enzyme activities in study KMX001. Human hepatic microsomal protein was incubated at 37ºC with selective CYP substrates in the presence of olaparib at a range of concentrations between 0.1 and 100 µM (0.043 to 43.4 µg/ml) in order to assess inhibition of CYP enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4). The effects of furafylline, 8-methoxypsoralen, ThioTEPA, trimethoprim, sulphaphenazole, benzylnirvanol, quinidine, disulfiram and ketoconazole, known potent inhibitors of CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4, respectively, were also examined as model inhibitors. For CYP3A4, both testosterone and midazolam were included as substrates. In addition, in order to evaluate the time dependent inhibition of the selected CYP isozymes, human hepatic microsomal protein was pre-incubated at 37ºC for 15 minutes with olaparib (10 µM) and NADPH, prior to addition of the relevant CYP substrate.

Results showed no direct inhibition of CYP1A2, 2B6, 2A6, 2C8, 2E1, 2D6 by olaparib at the higher studied concentrations whereas at 100µM a decrease about 46%, 22% and 26% in 3A4, CYP2C9 and 2C19 activity was observed, respectively. Because inhibition of enzyme activity did not exceed 50% of the control value, IC50 was not been calculated by the Applicant.

A further study to investigate time-dependant inhibition of CYP3A, which used midazolam as substrate (more sensitive than testosterone in the previous direct and time dependant inhibition assessment; KMX001) generated values of KI = 72.2 µM and Kinact = 0.0675 min-1. Using the approach outlined in the EMA guidance, the effect of a time dependant inhibitor on the exposure of a co-administered agent was R = 1.011.

CYP induction

The objectives of the study KMX002 were to measure the extent of change of specific CYP450 marker enzymes (for CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4) following exposure of human hepatocytes to olaparib.

Fresh human hepatocytes were cultured for 36 hours prior to exposure to olaparib at concentrations of 0.3, 3 and 30 µM. Cells were also incubated with omeprazole and phenobarbital as prototypical inducers of CYP1A2 and CYP2B6 and rifampicin as an inducer of CYP2C9, CYP2C19 and CYP3A4 isoforms, respectively. After exposure to olaparib and inducers for ca.48 hours, selective substrates for CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4-mediated activities were introduced (namely 7-ethoxyresorufin, bupropion, diclofenac, S-mephenytoin and testosterone, respectively) and the effects of olaparib on these activities quantified in comparison with those elicited by the prototype inducers.

There was no evidence of an induction effect on catalytic activities associated with CYP1A2, CYP2C9, CYP2C19 and CYP3A4. Small but notable increases in bupropion hydroxylation in hepatocytes treated with olaparib at 30 µM indicated that the compound was a weak inducer of CYP2B6-mediated enzyme activity *in vitro*. The magnitude of this effect was, however, small in comparison with that elicited by the positive control phenobarbital. Testosterone 6β-hydroxylase activity (CYP3A) showed a concentration related decrease in activity, which may suggest olaparib functioned as a time dependent inhibitor of CYP3A enzymes in this study.

Interaction related to efflux transporters: P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), multidrug resistance protein 2 (MRP2)

- *Olaparib as a substrate of P-glycoprotein, BCRP and MRP2*

Two studies were undertaken to investigate whether olaparib was a substrate of efflux human drug transport proteins P-gp, BCRP and MRP2 (KMX006 and KMX020).

In study KMX006, monolayers of MDCKII cells transfected with human MDR1 or human BCRP were used to study the directional transport of olaparib. In addition, isolated membranes containing high levels of either human MDR1 or human BCRP were used to study direct interaction of olaparib with the transporter associated ATPase activity.

Reference substrates and inhibitors were used to validate the test systems. Olaparib (0.1 to 10 µM) was added to either the apical compartment or the basolateral compartment and both a-b and b-a flux assessed. In addition, the effect of MDR1 inhibitors verapamil (50 µM) and ketoconazole (25 µM) on olaparib flux in this system was investigated. The data showed olaparib b-a flux was greater than a-b; the corrected efflux ratio was 6.0 to 7.5 and independent of concentration. Verapamil had no effect on olaparib b-a efflux while ketoconazole reduced b-a efflux by 40 to 62%. Verapamil, a known substrate of MDR1, was unable to reduce MDR1-mediated transport of olaparib, suggesting that verapamil and olaparib do not bind to the same binding sites on MDR1. The MDCKII-corrected efflux ratio (ER) was between 4.1 – 5.9 for olaparib (compared to an ER of 4.85 for the MDR1 reference substrate vinblastine sulphate). Together, these data indicated olaparib was an MDR1 substrate.

A similar investigation to the above, using MDCKII cells transfected with BCRP and Ko143 (5 µM) as inhibitor was undertaken. The MDCKII-corrected ER was 0.5 - 1.0 for olaparib (compared to an ER of 3.5 for the BCRP reference substrate cimetidine). In this system, olaparib b-a flux was only fractionally greater than a-b flux (corrected efflux ratio 0.6 to 1.0) indicating olaparib was not a BCRP substrate.

In additional experiments in study KMX006, membrane vesicles isolated from Sf9 insect cells transfected with either MDR1 or BCRP were incubated in the presence of olaparib (0.046 to 100 µM) and orthovanadate sensitive ATPase activity was monitored. In the MDR1 containing Sf9 vesicles olaparib increased the ATPase activity confirming olaparib was a substrate. No increase in activity occurred in the BCRP containing vesicles confirming olaparib was not a substrate.

- *Olaparib as a P-gp, BCRP and MRP2 inhibitor*

Three studies (KMX006, KMN040 and KMX020) were undertaken to investigate the potential of olaparib to inhibit the efflux transporters P-gp (MDR-1), BCRP and MRP2.

In study KMX006, MDCKII cells were transfected with MDR1. Vinblastine sulphate (1 µM), a proto-typical substrate, was included on the apical or basolateral side of the membrane and the trans-membrane apical to basolateral (a-b) or basolateral to apical (b-a) flux measured in the absence and presence of olaparib (10 µM). The effect of olaparib was to reduce b-a flux of vinblastine sulphate by 14% and to increase a-b flux by 1.3 fold, which may indicate a weak inhibitory effect.

A similar investigation to the above, using MDCKII cells transfected with BCRP and with cimetidine (10 µM) as a prototypical substrate, was conducted. Olaparib reduced the b-a flux of cimetidine by 59%, which indicated inhibitory potential.

In the same study, membrane vesicles isolated from Spodoptera frugiperda (Sf9) insect cells transfected with either MDR1 or BCRP were incubated in the presence of the reference substrates verapamil (40 µM) or sulfasalazine (10 µM) respectively and ATPase activity was monitored in the absence and presence of olaparib (0.046 to 100 µM). The data indicated olaparib may function as an inhibitor of MDR1 activity but had no effect on BCRP.

In study KMN040, the inhibitory potential of olaparib (0.1 to 100 µM) against MDR1 and BCRP, in MDCKII cells able to express each protein and maintained in Transwell culture, was explored more thoroughly. The experimental design was similar to that used in study KMX006. The prototypical substrates of MDR1 and BCRP were [3H]-digoxin (0.05 µM) and [3H]-2-amino-1-methyl-6-phenylimidazo-[4,5-b]pyridine (1 µM; [3H]-PhIP) respectively. Olaparib had no additional inhibitory effect in MDCK-MDR1 cells compared to control cells; which indicated olaparib had minimal or no MDR1 inhibitory potential. When incubated with MDCKII-BCRP cells, 100 µM olaparib inhibited [3H]-PhIP efflux by 47%; as this was < 50% an IC50 value was not calculated.

In study KMX020, the capacity of olaparib (10 µM) to function as an inhibitor of the multidrug resistance protein 2 (MRP2), when the transporter was expressed in MDCKII cells maintained in the Transwell format, was investigated. Cells were preloaded with the MRP2 substrate calcein (1 µM) prior to exposure to olaparib. In the presence of olaparib, calcein efflux to the apical compartment was inhibited by 24% indicating inhibitory potential. In the second assay, isolated membranes of Sf9 insect cells containing high levels of human MRP2 were used to study direct interaction of KU-0059436 with the transporter associated ATPase activity. KU-0059436 did not enhance the basal vanadate sensitive ATPase activity in Sf9-MRP2 isolated membranes except at the highest concentration tested (100 µM). Incubation with concentrations up to 100 µM KU-0059436 did show an inhibitory effect on the probenecid-stimulated ATPase activity of MRP2, which was most clear at 3.7 µM (in the presence of GSH) and at 10 µM KU-0059436 (in the absence of GSH), but it was not concentration-dependent.

A further study investigated the potential for olaparib (0.3 – 100 µM) to inhibit carboxy-2',7'-hydroxyfluorescein (CDCF; 5 µM) uptake into inside out MRP2 containing membrane vesicles. MK571 (100 µM) was used as a positive control. In this assay, MK571 caused >97.7% inhibition of MRP2 uptake activity while olaparib had no significant inhibitory effect, indicating olaparib does not inhibit MRP2.

Interaction related to uptake transporters OATP1B1, OCT1, NTCP

Three in vitro studies (KMX042, KMN037 and KMN046) were undertaken to investigate the potential for olaparib to inhibit hepatic uptake transporters OATP1B1 (organic anion transporting polypeptide), NTCP (sodium taurocholate co-transporting peptide) and OCT1 (organic cation transporter 1).

In study KMX042, the mechanism of uptake of olaparib into isolated human hepatocytes was assessed by measuring the accumulation of olaparib (0.1 – 100 µM) into hepatocytes. Olaparib (1 µM) was then incubated in the absence and presence of a range of known transporter inhibitors (rifamycin SV, taurochenodeoxycholic acid, cyproheptadine, diclofenac and cyclosporin A) to determine if there was an active component to its hepatic uptake. The effect of olaparib (1.00 to 100 µM) on organic anion transport

polypeptide-1B1 (OATP1B1) uptake of [3H]-estrone-3-sulfate (1 µM), sodium taurocholate transport protein (NTCP) uptake of [3H]-taurocholic acid (0.1 µM) and organic cation transport polypeptide-1 (OCT1) uptake of [3H]-1-methyl-4-phenylpyridium (MPP+; 1 µM) by human hepatocytes was also investigated. Inhibition of [3H]-estrone-3-sulfate and [3H]-taurocholic acid uptake (26 and 23% inhibition respectively) was only observed when olaparib was included at 100 µM so IC50 values could not be calculated. Inhibition of MPP+ uptake was observed across the olaparib concentration range with a maximum 84% inhibition observed. Technical issues with the assay led to uncertainty about the robustness of this result and further work is warranted; however, a tentative olaparib IC50 against OCT1 was calculated as 11.9 µM.

In study KMN037, the effect of olaparib (1.00 to 100 µM) on OATP1B1 uptake of [3H]- estradiol glucuronide (0.02 µM) in human embryonic kidney-293 (HEK-293) cells was investigated. In HEK-vector control cells, no difference in [3H]-EG uptake was observed in the presence of olaparib at concentrations up to 100 µM, indicating no inhibition of uptake by endogenous transporters in this cell line. In HEK-OATP1B1 cells, uptake of the probe substrate decreased over the concentration range studied, from 1.319 pmoles/min/mg in the absence of olaparib to 0.294 ± 0.020 pmoles/min/mg at the highest concentration of 100 µM. Concentration related inhibition of up to 80% was noted indicating olaparib inhibited the uptake of [3H]-EG via human OATP1B1 with an estimated apparent IC50 value of 20.3 µM.

In study KMN046, the effect of olaparib (0.10 to 100 µM) on OATP1B1 uptake was investigated using a clinically relevant probe-substrate pravastatin (0.135 µM) in HEK-293 cells. In the presence of olaparib, uptake of [3H]-pravastatin in HEK-OATP1B1 cells decreased over the concentration range studied, from 0.757 ± 0.078 pmoles/min/mg in the absence of olaparib to 0.362 ± 0.051 pmoles/min/mg at the highest concentration of 100 µM. The data indicates that olaparib inhibited the uptake of [3H]-pravastatin via human OATP1B1 in HEK293 cells, with an estimated apparent IC50 value of 27.1 µM.

The relationship between the calculated therapeutic maximum plasma concentration (11.0 µM), the unbound maximum plasma concentration (1.99 µM) following 400 mg olaparib in the capsule formulation and IC50 for OATP1B1 is presented in table 19. Similarly, the relationship between the calculated unbound maximum liver plasma concentration (Iin free) and IC50, expressed as R, is presented in table below. Using defined criteria (EMA 2013; FDA 2012), the Applicant claims that the relationship between I free or Iin free and IC50 suggest clinical investigation of OATP1B1 and OCT1 interactions may both be valuable.

Table 19: Inhibition of hepatic uptake transporters by olaparib

Study	Transport protein	Test system	Probe substrate	Maximum inhibition (%)	IC_{50} (µM)	I_{total}/IC_{50} [a]	R[a]	I_{free}/IC_{50} [b]
KMX042	OATP1B1	Human hepatocytes	[^{3}H]-estrone-3-sulfate	25.7	NC	NC	NC	NC
KMX042	OCT1	Human hepatocytes	[^{3}H]-1-methyl-4-phenylpyridium	77.7	11.9	0.924*	2.09*	0.167*
KMX042	NTCP	Human hepatocytes	[^{3}H]-taurocholic acid	22.7	NC	NC	NC	NC
KMN037	OATP1B1	HEK-293	[^{3}H]-estradiol glucuronide	79.5	20.3	0.542	1.64	0.098
KMN046	OATP1B1	HEK-293	[^{3}H]-pravastatin	66.5	27.1	0.4.6	1.48	0.073

[a] US FDA criteria, $R = 1 + (I_{inlet\ max} \times fu / IC_{50})$. I_{inlet} max calculated using fraction absorbed = 1, absorption rate (Ka) = 0.1 min-1, liver blood flow (Qh) = 1500 ml/min and fraction unbound = 18%.
b EMA draft guidance. Ifree calculated using fraction unbound = 18.1%.
* Should be interpreted cautiously due to concern about robustness of IC50 data

A further study investigated uptake of olaparib (1 – 100 µM) by human embryonic kidney-293 (HEK293) cells that over expressed one of OATP1B1, OATP1B3 and OCT1. Incubations included prototypical substrates (OATP1B1 and OATP1B3 used 0.15 µM atorvastatin; OCT1 used 5 µM N-methyl-4phenylpyridinium iodide [MPP+]) and were conducted for 2, 5 and 10 minutes. In this study, although the prototypical substrates functioned in the relevant cell line as expected, there was no evidence that olaparib was a substrate for any of OATP1B1, OATP1B3 or OCT1.

The potential for olaparib to act as an inhibitor of human uptake transporters OCT1, OCT2, OAT1, OAT3, OATP1B3 and human efflux transporters MATE1 and MATE2K was investigated in study 13ASTRUKP7S2,. Each drug transport protein, individually expressed in HEK293 cells, was incubated in an established assay format using appropriate prototypical substrates in the absence and presence of a relevant standard inhibitor. Olaparib (0.3-100 µM) was included and substrate uptake rate monitored. In previous studies (KMN037 and KMN046), the potential of olaparib to inhibit OATP1B1 was investigated as submitted previously and the IC50 values are also included in Table 20.

Table 20: Assessment of potential for olaparib to inhibit OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1 and MATE2K

Transporter	Key location	Substrate & concentration	Olaparib concentration (µM)	IC_{50} (µM)
OATP1B1	Liver	[^{3}H]-Estradiol glucuronide (0.02 µM)	1.0-100	20.3
OATP1B1	Liver	[^{3}H]-Pravastatin (0.135 µM)	0.1-100	27.1
OATP1B3	Liver	Atorvastatin (0.15 µM)	0.3-100	No inhibition
OCT1	Liver	N-methyl-4phenylpyridinium iodide (5 µM)	0.3-100	37.9
OCT2	Kidney	N-methyl-4phenylpyridinium iodide (5 µM)	0.3-100	19.9
OAT1	Kidney	Para-aminohippurate (10 µM)	0.3-100	No inhibition
OAT3	Kidney	Furosemide (5 µM)	0.3-100	18.4
MATE1	Kidney	Metformin (50 µM)	0.3-100	5.50
MATE2K	Kidney	(4-(4-(Diethylamino)styryl)-N-methylphenylpyridinium iodide (1 µM)	0.3-100	47.1

Table 21: Interpretation of potential for olaparib to inhibit OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K using EMA criteria

Transporter	IC_{50} (µM)	Key location	25 x $[I]_{in,hepC,max}$ (µM)	50 x $C_{max\ free}$ (µM)	$IC_{50}/25x[I]_{in,hepC,max}$	$IC_{50}/50xC_{max\ free}$
OATP1B1	20.3	Liver	325	NA	0.062	NA
OATP1B1	27.1	Liver	325	NA	0.083	NA
OCT1	37.9	Liver	325	NA	0.117	NA
OCT2	19.9	Kidney	NA	119.5	NA	0.167
OAT3	18.4	Kidney	NA	119.5	NA	0.154
MATE1	5.50	Kidney	NA	119.5	NA	0.046
MATE2K	47.1	Kidney	NA	119.5	NA	0.394

NA Not applicable

In study 13, ASTRUKP7S2, olaparib was shown to inhibit OCT1, OCT2, OAT3, MATE1 and MATE2K (but not OATP1B3 or OAT1), while in KMN037 and KMN046 olaparib was shown to inhibit OATP1B1.

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). Among the 17 members of the PARP family, at least these three proteins were found to be implicated in DNA repair mechanisms (Murai et al, 2012; Beck et al, 2014; Helleday, 2011).

The mechanism of action of olaparib is not fully elucidated. Inhibition of catalytic activity of enzymes results in trapping both PARP-1 and PARP-2 on DNA in complexes with olaparib, which prevents completion of DNA repair. This mechanism is considered as primary for cytotoxic action of PARP inhibitors (Murai et al, 2012; Smith et al, 2014). Other mechanisms related to DNA repair could also be involved (Shah et al, 2013). Moreover, off-target pharmacology of PARP inhibitors is not completely understood (Antolin and Mestres, 2014).

The main mechanism of action of olaparib is thought to be related to 'synthetic lethality': inhibition of DNA repair by PARP inhibitor resulting in selective killing of cancer cells with defects in particular DNA repair pathway. In particular, in the absence of functional BRCA1 or BRCA2 proteins, DNA breaks cannot be repaired using homologous recombination and repair is performed by alternative pathways, which are highly error prone and result in gross genomic instability and subsequent cell death.

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.

Study 02

This open-label, dose-escalating, non-randomised, multi-centre phase I study was designed to establish the PARP inhibitory dose range (PID) and maximum tolerated dose (MTD) of olaparib and to explore the safety, tolerability, PK and PD profiles and anti-tumour activity in the patient population.

There were two distinct phases: a dose escalation phase and a dose expansion phase using the recommended dose established in the escalation phase.

Optional PK and PD assessments were to be performed on patients in all groups. All patients were assessed for safety.

The following doses and treatment regimens were used:

- The starting dose was 10 mg/day. Olaparib was administered once daily as an oral dose of 10, 20, 40, or 80 mg to patients for 14 consecutive days followed by a 7 day rest period.
- Olaparib was administered twice daily as an oral dose of 60 or 100 mg to patients for 14 consecutive days followed by a 7 day rest period.
- Olaparib was administered twice daily as an oral dose of 100, 200, 400 or 600 mg to patients for 28 consecutive days.

The protocol allowed patients to receive up to 2 cycles, although provisions were made for patients to receive more than 2 cycles if the patient was deriving benefit from the treatment (in the investigator's opinion) and was tolerating the treatment without dose limiting toxicities.

This study included patients aged at least 18 years with histologically or cytologically confirmed malignant advanced solid tumour refractory to standard therapy or for which no suitable effective standard therapy exists and who have evaluable or measurable disease (as defined by RECIST).

Overall, 98 patients were enrolled in the study and received study treatment (46 patients entering the dose escalation phase and 52 patients entering the dose expansion phase) and 60 (61.2%) patients had BRCA 1/2 mutations, of which 49 were ovarian cancer patients. The 200 mg bd dose level was selected for the expansion phase and contains the most patients (58).

At the time of data cut-off (17 December 2008), 11 patients with BRCA 1/2 mutations were still receiving treatment and 87 patients had discontinued the study for the following reasons: 71 patients due to

disease progression, 5 patients refused further treatment, 4 patients due to unacceptable toxicity, 3 patients due to intercurrent illness, 3 patients due to the investigator's decision, and for one patient, death was the reason for discontinuation.

Summary of efficacy results

An overall RECIST response rate (complete or partial response) of 14.3% (14 in 98 patients) was observed in this study with responses noted at olaparib dose levels of 200 mg and 400 mg bd.

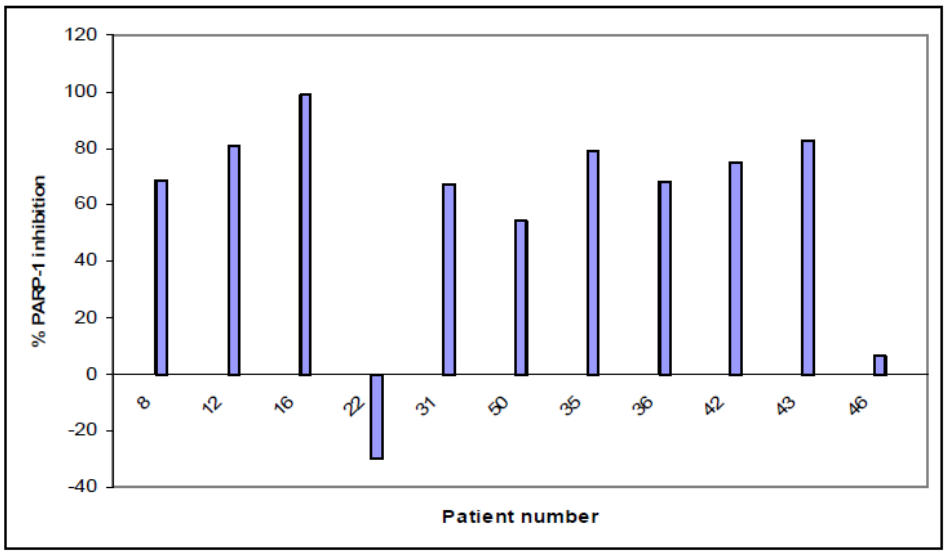
All observed RECIST responses occurred in patients with confirmed genetic BRCA mutations (with 12 out of 49 with ovarian cancer) or a strong familial history of cancer.

Summary of pharmacodynamic results

All samples were analysed using an electrochemiluminescence-based method to determine levels of PARP-1 enzyme protein and levels of PAR (poly adenosine ribose chain) producing activity both in the presence and absence of an excess of exogenously added olaparib.

Tumour biopsy samples were obtained from a total of 11 patients who had received 8 days of dosing with olaparib at doses ranging from 40 mg once daily to 600 mg twice daily.

The calculated % PARP-1 inhibition values are shown in Figure 1.



Note : The following doses of olaparib were taken by the 11 patients: 40 mg od (8), 80 mg od (12), 60 mg bd (16), 100 mg bd (22), 200 mg bd (31, 50), 400 mg bd (35, 36 and 42), 600 mg bd (43, 46).

The following doses of olaparib were taken by the patients shown in the above figure: 40 mg od (Patient 001-01-0008); 80 mg od (Patient 002-01-0012); 60 mg bd (Patient 002-01-0016); 100 mg bd (Patient 001-01-0022); 200 mg bd (Patients 002-01-0031 and 001-01-0050); 400 mg bd (Patients 001-01-0035, 001-01-0036 and 001-01-0042); 600 mg bd (Patients 002-01-0043 and 001-01-0046)

Figure 1: % PARP-1 inhibition in tumour biopsy samples: PD population

The PID range was determined to be at olaparib doses above 40 mg od.

Summary of safety results

Two dose limiting toxicities were encountered at the 600 mg bd dose level (CTCAE grade 4 thrombocytopenia and CTCAE grade 3 somnolence) and therefore 400 mg bd was considered to be the maximum tolerated dose (MTD).

Study 07

This was a Phase I open-label study to identify an effective biological dose to be used for further clinical studies of olaparib by using biomarkers of PARP activity to delineate a PARP inhibitory concentration response curve for the selected doses of olaparib in breast tumour.

Intermediate and high risk breast cancer patients were randomly allocated to 1 of 5 dose cohorts (10 mg bd, 30 mg bd, 100 mg bd, 200 mg bd, and 400 mg bd) and received treatment for 4 or 5 days prior to surgery.

Overall, 60 patients were randomized, 12 in each dose cohort, and all patients completed treatment.

Summary of pharmacodynamic results

The sample collection time information provided for collection of both PBMC and tumour samples was complete for all patients. The % inhibition of PARP-1 in the tumour sample and in the PBMC sample collected at the time of surgery was highly variable. The % inhibition of PARP-1 in tumour samples ranged from 20 to 80%.

Comparison of the PAR producing activity and PARP-1 enzyme levels between tumour samples and samples of normal breast tissue showed that, although there was variability in both datasets, levels of PARP-1 enzyme and PAR producing activity appeared to be higher (on average 3- to 4-fold and 9-fold higher, respectively) than those in normal breast tissue.

Population PK/PD analysis

PARP-1 inhibition in PBMCs

The PARP-1 inhibition and plasma concentration data from the two above studies were pooled and subjected to non-linear mixed effects modelling in order to evaluate the level of PARP-1 inhibition in the PBMC samples and the relationship between the extent of PARP-1 inhibition and plasma concentrations/pharmacokinetic parameters.

The results of the modelling showed that the PARP-1 inhibition data were well described by an inhibitory Emax effect compartment model but that inter-individual variability on the parameters of the fitted model was high (approximately 50%). The estimated IC50 for PARP-1 inhibition was 19 ng/ml (44 nM). The pharmacodynamic effect of olaparib in the PBMC samples was achieved rapidly after dosing (maximal inhibition was seen at 6 hours, the first sample collected post dose) and was found to outlast the presence of olaparib concentrations in the plasma, with a half-life for the recovery of PARP-1 activity following cessation of olaparib dosing, of approximately 36 hours. The extent of inhibition of PARP-1 activity in PBMCs showed large inter-individual variability with % inhibition values within the same dose level ranging from 20% to 80% and a population average of 50 – 60%. The extent of inhibition showed a relationship with plasma exposure to olaparib with maximum inhibition achieved at plasma exposures (steady state AUC) in excess of 1000 ng.h/ml (1 µg.h/ml (2.30 µM.h)).

PBMC PARP-1 inhibition data was also generated from samples collected from patients dosed in Study D0810C00001. Consistent with the Study 02 and 07 data, these data showed that following dosing at 100, 200 and 400 mg, approximately 50 - 60% PARP-1 inhibition had been achieved by 6 hours after the first dose and that the same level of inhibition was maintained on multiple dosing. The extent of PARP-1 inhibition observed was independent of dose.

In tumour biopsies

PARP-1 inhibition was also determined in tumour biopsy samples collected from selected patients in Study 02 and from all patients in Study 07 using the electrochemiluminescence technique. The level of PARP-1 inhibition and relationships between the extent of PARP-1 inhibition and plasma concentrations/pharmacokinetic parameters were again determined using population PKPD analysis of the pooled data. This showed that inhibition of PARP-1 in tumour increased with increasing drug exposure with the mean population extent of inhibition estimated at 70% from the baseline value. As seen previously for the PBMC samples, inhibition reached a maximum at exposures (steady state AUC) values greater than around 1000 ng.h/ml (1 µg.h/ml or 2.30 µM.h).

The plasma concentrations of olaparib achieved in Study 07 were approximately 50% lower than those observed in patients dosed in Study 02 (or indeed in any other olaparib study), and therefore the dose-exposure relationship from Study 02 alone was used to convert the plasma exposure associated with maximal inhibition back into a potential therapeutic dose. This would suggest that a dose of 40 mg and above would be predicted to reliably deliver a steady state AUC of ~1 µg.h/ml and therefore achieve maximal PARP-1 inhibition.

With regard to higher levels of PARP-1 enzyme and PAR producing activity in the tumour than those in normal breast tissue, it was not possible to calculate the extent of PARP-1 inhibition in normal breast tissue; consequently dose and exposure-response curves for olaparib in normal breast tissue could not be defined.

Exposure-response relationships with efficacy endpoints

The population analysis of the pooled data from Studies 02, 08, 09, 12 and 24 included an exploration of relationships between olaparib plasma exposure and the following efficacy endpoints: change in tumour size, CA-125 response, objective tumour response and progression free survival. It should be noted that since this analysis was based only on data from patients where pharmacokinetic sampling had been performed, they are based on a small dataset.

No evidence of a relationship between olaparib pharmacokinetic parameters (steady state Cmax, Cmin or AUC) and efficacy endpoints could be found in the data included in the analysis.

Secondary pharmacology

In the phase II study D0810C00012 (olaparib versus liposomal doxorubicin in patients with advanced BRCA1 or BRCA2 ovarian cancer), one case of QT prolongation was reported. Elevation of QTcF from 429 msec at baseline to 552 msec at day 29 was observed during olaparib treatment in one patient allowed to cross over to olaparib from pegylated doxorubicin. The patient also experienced adverse effects of hypokalaemia and hyponatraemia. The investigator considered the QTcF increase as clinically significant and possibly the result of electrolyte imbalance.

Olaparib as a single dose showed no clinically relevant effect on QTcF based on a total of 60 patients from study D0816C00004 (following 300 mg bd for 5 days) and 59 patients from study D0816C00007 (100 mg).

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Full PK profiling was performed in four studies (Study 01, Study 02, study 10 and study 24). Sparse samples were collected in studies 07, study 08, study 09 and study 12 compiled and analysed with data from the already mentioned studies with full sampling using population-PK approach.

Following single and multiple dosing of olaparib to Caucasian patients at doses between 10 mg and 600 mg (Study 02), absorption was reasonably rapid with Cmax typically achieved at between 1 and 3 hours after dosing (range: 0.5 to 8 hours). Exposure to olaparib showed high inter-individual variability. On multiple dosing there is no marked accumulation, with steady state exposures achieved within ~3 to 4 days (see SmPC section 5.2).

In vitro study showed that olaparib is a substrate of MDR1 transporter. In Caco-2 cells, olaparib was shown to have a propensity for efflux by P-glycoprotein (Pgp; MDR1). It is anticipated that efflux would be saturated at the concentrations actually observed in clinical situations.

The mechanism of absorption has not clearly elucidated. However, there are indications that dissolution is the limiting step for absorption.

The influence of food intake on the bioavailabilty of olaparib capsules was investigated. The data demonstrated that exposure to olaparib is slightly (approximately 20%) enhanced when the capsules were administered within 30-45 min following a standard or high fat food intake. Co-administration with food slowed the rate (tmax delayed by 2 hours) and marginally increased the extent of absorption of olaparib (AUC increased by approximately 20%). Therefore, it is recommended that patients should take olaparib at least one hour after food, and refrain from eating preferably for up to 2 hours afterwards (see SmPC sections 4.2 and 5.2).

There are indications that olaparib is transferred largely to extra-vascular tissue. However, no reliable estimation of the Vd could be made as there were noticeable discrepancies between NCA and population-PK estimation. Measurable levels of olaparib were observed in tumours biopsies in all patients, however it is not clear if the drug levels evolve proportionally to the dose or to the systemic exposure. The results of the additional protein binding study showed that, as anticipated, the free fraction increased with increasing (and more physiological relevant) concentrations, although the increase in free fraction was less than proportional to the change in drug concentration. The *in vitro* protein binding of olaparib at plasma concentrations achieved following dosing at 400 mg twice daily was ~82%. Therefore, it is considered that the variability in plasma protein binding with the concentration could add to the observed high variability in exposure of olaparib.

In vitro, CYP3A4 was shown to be the enzyme primarily responsible for the metabolism of olaparib. As the genetic polymorphism of this iso-enzyme is not known to actually modulate the enzyme capability, no specific investigation was conducted by the applicant with regard to genetic polymorphism.

Following oral dosing of ^{14}C-olaparib to female patients, unchanged olaparib accounted for the majority of the circulating radioactivity in plasma (70%) and was the major component found in both urine and faeces (15% and 6% of the dose respectively). The metabolism of olaparib was extensive. The majority of the metabolism was attributable to oxidation reactions with a number of the components produced undergoing subsequent glucuronide or sulphate conjugation. Up to 20, 37 and 20 metabolites were detected in plasma, urine and faeces respectively, the majority of them representing < 1% of the dosed material. A ring-opened hydroxycyclopropyl moiety, and two mono-oxygenated metabolites (each~10%) were the major circulating components, with one of the mono-oxygenated metabolites also being the major metabolite in the excreta (6% and 5% of the urinary and faecal radioactivity respectively) (see SmPC section 5.2).

The elimination route of olaparib was not sufficiently elucidated. However, there are indications that Olaparib is slowly eliminated mainly by metabolism but also by renal route. The excretion of unchanged drug in urine was approximately 15 % of the total dose administered.

The total clearance by oral route (CL/F) was dependent upon dose and estimated to vary from approximately 4 to 15 L/h with doses varying from 100 to 400 mg. Such differences are likely due to the lower bioavailability at higher doses. The elimination half-life of olaparib was also dependent upon the dose.

Overall, the pharmacokinetics of olaparib at the 400 mg twice daily capsule dose were characterised by an apparent plasma clearance of ~8.6 L/h, an apparent volume of distribution of ~167 L and a terminal half-life of 11.9 hours.

The mass-balance study showed that olaparib is excreted both by renal and faecal route in a balanced way. Following a single dose of ^{14}C-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.

No PK investigations of metabolites have been carried out by the applicant. The pharmacological activity of the 3 main circulating metabolites is unknown. Mass-balance study suggested that olaparib levels decline more rapidly than the total radioactivity, this is may be linked to the formation of metabolite(s) with lower clearance and potential for accumulation. Structural identification of M12, M15 and M18 has not been achieved. Therefore, these metabolites have not been monitored and potential for accumulation after repeated administration could not be excluded. For the same reasons, the pharmacodynamics potencies of these metabolites are still not known.

The plasma binding of the metabolites of olaparib is also unknown until now. As also the pharmacological activity of the metabolites is unknown, the protein binding could be of interest for the three major metabolites in plasma (M12, M15 and M39, each accounting for ~10% of dose in plasma). The applicant will provide more information based on the plasma samples collected during the Renal Impairment study and will explore metabolite profiling and identification as a secondary objective in the ongoing Study D0816C00006 as detailed in the RMP.

Dose proportionality and time dependencies

Olaparib pharmacokinetics appeared to be almost proportional to the dose in the range of 10 up to 100 mg. For higher doses, systemic exposure evolved markedly less than proportionally to the dose, suggesting dissolution-step limiting absorption. After repeated dose, very limited potential for accumulation was observed. Based on the available data, time dependency in olaparib pharmacokinetics is not anticipated.

Population PK analysis

Inter-subject variability appeared to be high, but no reliable estimation of it could be made from the available data. Conventional studies have been performed in a very limited number of patients and the reliability of the estimation of inter-subject variability from the population-PK analyses is questionable. Within-subject variability (%CV) could not be estimated from the available data.

Special population

No investigations have been performed in renal impaired patients and liver impaired patients. In addition, no reliable information could be derived from the population-PK analysis. Considering that renal route is not predominant in the elimination of olaparib (see mass-balance study), olaparib can be administered in patients with mild renal impairment (creatinine clearance > 50 ml/min) but is not recommended in patients with moderate (creatinine clearance < 50 ml/min) and severe impairment (creatinine clearance < 30 ml/min) since there were limited clinical data. Considering the lack of data in patients with hepatic impairment (serum bilirubin > 1.5 time upper limit of normal), olaparib is also not recommended in this population. In line with the risk management plan, the company will provide the results of the two ongoing studies in patients with liver impairment (study D0816C00005) and renal impairment (study D0816C00006).

No conclusions regarding the influence of ethnicity on olaparib pharmacokinetics could be made from the available data. On one hand comparison of NCA data obtained in Caucasian patients (study 02) and Japanese (study 01) showed a significant lower exposure in the latter group of patients. It is not clear if such difference is linked to ethnicity or to fluctuation in the performances of the capsules between batches. On the other hand, only few data from non-Caucasian patients have been included in the analysed dataset.

Overall, there are insufficient data to evaluate the potential effect of race on olaparib pharmacokinetics as clinical experience is predominantly in Caucasians (94% of patients included in the population analysis were Caucasian) (see SmPC section 4.2). Based on the limited data available the CHMP could not conclude that there is a marked ethnic difference in the PK of olaparib between Japanese and Caucasian patients.

The applicant will analyse the data collected in olaparib clinical studies in non-Caucasian patients in order to further elucidate the influence of ethnicity (see Risk Management Plan).

The claimed indication implies the use of olaparib in female patients only. Few data are available in male patients. Therefore, no conclusions could be made regarding the influence of gender on olaparib pharmacokinetics.

There are no data in obese (BMI > 30 kg/m^2) or underweight (BMI < 18 kg/m^2) patients. No specific recommendation of use in underweighted and obese patients can be made on the basis of the available data. The population analysis of the available data has found no evidence that patient weight affects olaparib plasma concentrations.

There were limited data in patients aged 75 and over. The population analysis of the available data has found no relationship between olaparib plasma concentrations and patient age. Based on the available data no adjustment in starting dose is deemed to be necessary in elderly patients.

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

Interactions

No formal drug interaction studies have been submitted.

In vitro, olaparib produced little/no inhibition of CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 or 2E1 and is not expected to be a clinically significant time dependent inhibitor of any of the P450 enzymes. *In vitro* data also showed that olaparib is not a substrate for OATP1B1, OATP1B3, OCT1, BCRP or MRP2 substrate and not an inhibitor of OATP1B3, OAT1 or MRP2.

In relation to study KMX001, since substrates were incubated at their Km ([S]*=Km), one can stipulate that Ki= IC50/2. At the hepatic level, the calculated Ki value for CYP3A4 was likely >50µM (IC50 is >100µM) but this was lesser than the cut-off value of 50× Cmax,ss, unbound for olaparib i.e. 99,5 µM. Therefore, a clinically relevant drug-drug interaction due to olaparib CYP inhibition at the systemic level cannot be ruled out.

In the enterocyte, where CYP3A4 is in abundance, olaparib concentrations were higher and calculated Ki values for competitive inhibition was lower than the cut-off value of 0.1×dose/250 ml i.e. 368,24 µM for olaparib. Therefore, a clinically relevant drug-drug interaction due to olaparib CYP inhibition at the intestinal level could not be ruled out. Moreover, the time-dependent inhibition by olaparib was studied but only one concentration of olaparib was tested and not the most relevant, i.e. 10µM. This did not allow an estimation of the time-dependent inhibitory effect of olaparib notably on CYP3A at the intestinal level since olaparib concentrations were expected to be higher than 100µM. Therefore, the Applicant is recommended to conduct another *in vitro* study to investigate CYP3A4 inhibition by olaparib using concentrations up to 370 µM (the cut off for intestinal inhibition) (study ADME-AZS-Wave3-140725).

The applicant provided evidence of the time-dependent inhibition of CYP3A by olaparib with a KI = 72.2µM and Kinact = 0.0675 min-1. However, considering this feature and using the basic model for prediction of *in vitro-in vivo* interaction, according to the EMA Guideline on the Investigation of drug interactions, the clinical relevance of such an effect is unlikely since the AUC ratio with inhibitor to without was < 1.25.

The applicant provided the results of an *in vitro* study measuring the extent of change of specific CYP450 marker enzymes (for CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4) following exposure of human hepatocytes to olaparib (study KMX002). At the highest olaparib concentration (30 µM), minor induction of CYP2B6 activity was observed (<40% positive control) and smaller effects on CYPs 2C9 and 2C19 activities were noted. Nevertheless, the study setup was not considered acceptable notably due to two major limitations. Although the cell model and control substrates/inducers (excepted for CYP2B6) were adequate, the three tested concentrations (0.3 µM, 3µM and 30µM) of olaparib did not cover the worst case concentrations expected in the hepatocytes for the studied cytochromes (i.e. 50-fold the mean unbound Cmax plasma concentration obtained as steady-state or 99.5 µM), and in the intestinal tract for CYP3A (i.e. 0.1×dose/250 ml or 368.24 µM). Furthermore, olaparib induction potential was assessed by the fold-induction with olaparib relative the corresponding control, also known as the measure of activity whereas the measure of the mRNA change is considered more predictive of the inducing potential of a new drug entity than the enzymatic activity measure, notably because this is not affected by inhibition. Due to these limitations, the study was not considered sufficiently reliable to draw a conclusion on the inducing profile of olaparib towards the studied CYPs. Therefore, it remained unclear whether or not olaparib may be a CYP1A2, 2B6, 2C9 and 19 and 3A inducer at clinically relevant concentrations. The Applicant is recommended to conduct further *in vitro* investigations to clarify this issue. Olaparib's potential to induce CYPs should be tested at relevant concentrations up to 100µM, except for CYP3A4 which should be studied up to 370µM, using preferably mRNA levels for the detection (study 1404083).

In addition, clinical studies to evaluate the impact of known CYP3A4 inhibitors and inducers have not yet been conducted and it is therefore recommended, as reflected in the SmPC, that known strong inhibitors (e.g., itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or inducers (e.g., phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) of these isozymes should be avoided with olaparib (sections 4.4 and 4.5 of the SmPC). Interactions with CYP3A4 inducers/inhibitors is a safety concern included in the risk management as missing information and the applicant should provide results of CYP3A4 interaction and CYP3A4 induction studies using the tablet formulation (studies D0816C00007, D0816C00008).

The effect of olaparib as UGTs inhibitor has not been studied. The EMA DDI guideline recommends to study inhibition of UGTs known to be involved in drug interactions, including UGT1A1 and UGT2B7, if one of the major elimination pathways of the investigational drug is direct glucuronidation. However, some currently marketed drugs (e.g. atazanavir, erotinib, indinavir) are potent UGT inhibitors whereas they do not undergo a major glucuronidation, and considering the major involvement of UGT in paracetamol and morphine metabolism (two drugs often prescribed in oncology field), the Applicant is recommended to investigate the effect of olaparib as a UGT inhibitor (study 8305966).

According to the data from in study KMX006, olaparib is a P-gp substrate *in vitro* (corrected efflux ratio or CER > 2). Furthermore, data displayed in the study KMX0040 showed that olaparib as a P-gp inhibitor can be discarded at the systemic level whereas at the intestinal level, where olaparib concentrations were higher than 100 µM, the effect is still unknown. Therefore the Applicant is recommended to investigate olaparib's potential to inhibit intestinal P-gp at concentrations up to 370 µM (study ADME-AZS-Wave3-140714).

Clinical studies to evaluate the impact of known P gp inhibitors and inducers have not been conducted.Therefore, in the event that a patient already receiving olaparib requires treatment with a CYP3A inhibitor or P gp inhibitor, careful monitoring of olaparib associated adverse events and management of those events via the dose reduction strategy is recommended.

The Applicant provided further data as regards the inhibitory effect of olaparib towards MRP2. Results showed that olaparib is not expected to inhibit this transporter at clinically relevant concentrations.

The ability of olaparib to be an OATP1B1 substrate was studied in KMX042 study. The Applicant claimed that data suggest a possible involvement of this transporter in the hepatic uptake of olaparib but this effect was assessed qualitatively and not quantitatively (no kinetic parameters has been determined). No conclusion can be drawn due to the variability of the test system.

In vitro olaparib inhibited OATP1B1 uptake of pravastatin with an IC50 = 27 µM. Given that the calculated cut-off value of 25× $C_{u,inlet}$ of olaparib is approximately 300µM, the risk for clinically relevant drug-drug interactions due to OATP1B1 inhibition cannot be discarded. In study 13ASTRUKP7S2, there was no evidence that olaparib was a substrate for any of OATP1B1, OATP1B3 or OCT1, although the prototypical substrates functioned in the relevant cell line as expected. In addition, although data from studies KMN037 and KMN046 showed olaparib is an inhibitor of OATP1B1, new data from study 13ASTRUKP7S2 showed it not to be an inhibitor of OATP1B3. Thus additional interactions with statins through that mechanism would not be expected. For safety reason, a drug-drug interaction study with a statin was not encouraged.

Overall, based on the available PK data, it was considered appropriate to warn on a risk of interaction with drugs known to be substrate of CYP3A, CYP1A2, CYP2B6, CYP2C9, CYP2C19, P-gp, BRCP, OATP1B1, OCT1 and OCT2 in section 4.5 of the SmPC.

The potential for olaparib to induce CYP3A, CYP1A2, CYP2B6, CYP2C9, CYP2C19 and P gp is unknown and it cannot be excluded that olaparib upon co administration may reduce the exposure to substrates of these metabolic enzymes and transport protein. The efficacy of hormonal contraceptives may be reduced if co administered with olaparib (see SmPC sections 4.4, 4.5 and 4.6).

Olaparib may inhibit CYP3A4 *in vitro* and it cannot be excluded that olaparib may increase the exposures to substrates of this enzyme *in vivo*. Therefore, caution should be exercised when substrates of CYP3A4 are combined with olaparib, in particular those with a narrow therapeutic margin (e.g. simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine).

In vitro olaparib may be an inhibitor of P-gp and is an inhibitor of BRCP, OATP1B1, OCT1 and OCT2. It cannot be excluded that olaparib may increase the exposure to substrates of P-gp (e.g. statins, digoxin, dabigatran, colchicine), BRCP (e.g. methotrexate, rosuvastatin and sulfasalazine), OATP1B1 (e.g. bosentan, glibenclamide, repaglinide, statins, and valsartan), OCT1 (e.g. metformin) and OCT2 (e.g. serum creatinine). In particular, caution should be exercised if olaparib is administered in combination with any statin (see SmPC sections 4.5).

Pharmacodynamics

The pharmacodynamics of olaparib, based on an assessment of its ability to inhibit Poly (ADP-Ribose) polymerase-1 in vivo in peripheral blood mononuclear cells and in tumour biopsies, have been characterised in patients with advanced solid tumours (study 02) and patients with intermediate to high risk breast cancer scheduled for elective surgery (study 07).

Overall, evidence of inhibition of PARP-1 activity has been seen in PBMC and tumour samples from patients dosed with olaparib at all dose levels studied (10 mg to 600 mg) but the data showed wide inter-individual and intra-individual variability in the extent of inhibition achieved.

An assessment of γH2AX foci appears to be more reliable biomarker, but PD data were provided in few ovarian cancer tissue samples and surrogate tissues (hair follicles).

The link between the clinical efficacy of olaparib and PD biomarker could not be established since PD samples were either collected from a study in which efficacy was not an endpoint or where BRCA mutation status was not known.

In a pooled population based analysis of PK/PD data, investigations were undertaken to provide a PK/PD (descriptive and statistical) evaluation of the relationship of the pharmacokinetics (predicted plasma concentration) of olaparib to the inhibition of PARP-1 (PD effect) in both PBMC and tumour samples, and to correlate the plasma concentration time profile to tumour concentrations of olaparib. The PK/PD relationship established for PARP-1 inhibition did not appear to be predictive of clinical outcome. A relationship between PK parameters and efficacy or tolerability endpoints has not been defined.

Overall, available pharmacodynamic data indicated that the observed clinical efficacy is not only due to the inhibition of PAR-forming activity, but involves some other mechanisms either related to DNA repair or not (*Pettitt et al, 2013; Benson et al, 2006; Schiewer et al, 2012, Do et Chen, 2013, Curtin et Szabo, 2013*). It is not known to what degree the off-target effects might contribute to anti-tumour effects. The Applicant provided a discussion based on available pre-clinical and clinical data as well as on literature data concerning potential anti-tumoral (or pro-tumoral) effects of olaparib related to known functions of PARP-1 and PARP-2 (other than those related to DNA damage repair). In particular, potential anti-tumoral olaparib activity in relation to its PARP interference in cell death signalling, transcriptional regulation, cell proliferation, immune regulation, estrogen receptor signalling and angiogenesis could not be excluded. For instance, anti-angiogenic activity is suggested by pre-clinical and clinical data (*Tentori et al, 2007; Dean et al, 2012; Liu et al, 2014).*

For the time being, PARP inhibition is probably the main contributor to the efficacy of olaparib. Other mechanisms are not excluded and could play a role, but this is difficult to establish based on the currently available evidence.

The long-term effects of PARP-inhibition related to DNA damage induction in normal cells (either fully BRCA-competent or harbouring haploinsufficiency) were discussed by the Applicant. Risks related to chronic DNA damage following olaparib exposure, whether in individuals harbouring gBRCA mutation or not, are not completely elucidated. It cannot be excluded that in conditions of hypoxia some cells may develop reduced homologous recombination repair functionality what would make haplo-insufficient cells potentially more sensitive to the action of olaparib. In such cells exposure to olaparib could lead to an induction of genomic instability and potential tumor transformation. Although rare, cases of MDS/AML and of other new primary malignancies were reported in patients treated with olaparib. Altered mRNA profiles were observed in primary 'normal' (haplo-insufficient) breast and ovarian cells in patients with germline BRCA1 or BRCA2 mutations, indicating that phenotypic differences do occur in these cells (*Bellacosa et al, 2010*). BRCA1 mutant breast cells showed enhanced colony formation potential ex vivo as well as impaired lineage commitment in differentiation assays (*Burga et al, 2009; Proia et al, 2011*).

BRCA1 and BRCA2 haploinsufficiency alone can compromise genome stability by triggering spontaneous recombination events that are likely to account for the increased risk of cancer promoting mutations *(Cousineau et al, 2007; Kote-Jarai et al, 2006).* Mutation of a single allele of BRCA1 was shown to lead to genomic instability in human breast cancer epithelial cells *(Konishi et al, 2011).* It was proposed that BRCA1 haploinsufficiency, causing genomic instability, may be contributive to breast cancer initiation *(Natrajan R et al, 2012).*

The Applicant was asked to discuss which investigational methods could allow to address the potentially enhanced risk of secondary malignancies in BRCA-haploinsufficient and in BRCA-proficient cells following exposure to olaparib. The provided non-clinical models did not allow concluding on the absence of potential olaparib contribution to tumorigenesis in BRCA-haploinsufficient background in the context of long-term exposure. The consequences of long-term exposure of normal cells to olaparib were not sufficiently documented. However, it is acknowledged that experiments with ex vivo exposure of human cells to olaparib would be of value, but not relieve the concerns about secondary malignancies in BRCA-haploinsufficient patients and this issue can only be properly addressed by rigorous monitoring post-marketing in patients receiving olaparib. This is considered as missing information which is appropriately addressed in the RMP.

Regarding the secondary pharmacology, at this moment it is not thought that olaparib has a significant effect on QTc.

2.4.5. Conclusions on clinical pharmacology

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 relevant recommendations included in the SmPC. Besides, further studies are planned and ongoing to further evaluate the effect of a potent inhibitor or inducer on olaparib pharmacokinetics (see RMP).

The use of olaparib in special populations and long term toxicity of olaparib are also adequately addressed in the RMP.

2.5. Clinical efficacy

2.5.1. Dose response studies

Study 09

This was an international, multi-centre, proof-of-concept, single-arm, Phase II study. Two sequential patient cohorts received continuous oral olaparib in 28-day cycles initially at 400 mg bd and subsequently at 100 mg bd.

The patient population participating in this study comprised 58 women with advanced BRCA1- or BRCA2-associated ovarian cancer (includes patients who are found to have loss-of-function mutations in the BRCA-1 or BRCA-2 genes as determined by the BRACAnalysis assay).

One patient was not allocated to treatment and was excluded from all analysis sets.

Of the remaining 57 patients (respectively 24 and 33 in the 100 and 400 mg bd group):

- 24 successfully completed the full study schedule up to and including cycle 6,

- 5 patients (respectively 2 and 3 in the 100 and 400 mg bd group) were ongoing at the data cut-off for the CSR (17 March 2009),

- 33 patients (respectively 17 and 16) discontinued olaparib before completing the full study schedule mostly due to disease progression (respectively 16 and 10 patients).

Following implementation of protocol amendment 3, 6 patients in the 100 mg bd group dose escalated to 400 mg bd.

In the ITT analysis set the confirmed RECIST ORR (Objective tumour response i.e. Complete Response and Partial Response) overall was 33.3% at 400 mg bd and 12.5% at 100 mg bd (14 out of 57 i.e. 24.6% in total).

With regard to secondary efficacy variables:

- Overall clinical benefit rate (CR + PR + SD = stable disease for ≥8 weeks ± 1 week visit window) was greater in the 400 mg bd group than in the 100 mg bd group (69.7% vs 41.7%);

- The median duration of response was 290 days (range 126 to 506 days) for the 400 mg bd group and 269 days (range 169 to 288 days) for the 100 mg bd group. One out of 3 responses in the 100 mg bd group and 3 out of 11 responses in the 400 mg bd group were ongoing at data cut-off;

- The median best percentage change from baseline in the 400 mg bd group was a 29.0% reduction in tumour size compared to a 0% reduction in the 100 mg bd group;

- Median (95% CI) PFS was 177.0 (85-323) days in the 400 mg bd group and 58.0 (56-110) days in the 100 mg bd group.

Data on platinum sensitivity status at study entry directly were not collected as part of Study 09. The date of completion of the last platinum containing chemotherapy and the start date of the next treatment were collected and used to retrospectively assign a platinum sensitivity status, presuming that the start of next treatment indicated progressive disease. Using the indirect criteria as described above to assign a platinum sensitivity status, the majority of patients entering the study were platinum resistant with 7/33 (21%) patients treated with olaparib 400 mg bd considered to be platinum sensitive (PD >6 months after completion of last platinum); and 26/33 (79%) patients platinum resistant (PD ≤6 months of completion of last platinum). Of the 7 patients considered to be platinum sensitive, 1 (14%) was a responder; of the 26 patients considered to be platinum resistant, 10 (38%) were responders (complete response or a partial response by RECIST criteria) during treatment with olaparib 400 mg bd.

Study 12

This was a Phase II, open-label, randomised, comparative, multicentre study to compare the safety and efficacy of 2 different doses of olaparib with intravenous liposomal doxorubicin in the treatment of patients with advanced breast cancer gene BRCA1- or BRCA2-associated ovarian cancer who have failed previous platinum-based chemotherapy. Patients were randomised (1:1:1) to receive either olaparib 200 mg twice daily (bd) orally, olaparib 400 mg bd orally, or liposomal doxorubicin 50 mg/m^2 intravenously (iv).

Half of patients were platinum resistant in this study.

Patients were treated until they had radiologically-confirmed progressive disease (PD) or were withdrawn from treatment for another reason. Once patients on olaparib or liposomal doxorubicin had been withdrawn from treatment, other treatment options were at the discretion of the investigator.

Once patients on liposomal doxorubicin had centrally confirmed objective radiological progression, they were given the opportunity to begin treatment with olaparib (400 mg bd dose level) if eligible to do so.

Of the 97 patients randomised into the study, all olaparib patients (32 in each group) and 32 liposomal doxorubicin patients received study treatment.

At data cut-off for PFS analysis (15 September 2009), 10 (31.3%), 12 (37.5%), and 7 (21.9%) patients in the olaparib 200 mg bd group, olaparib 400 mg bd group, and the liposomal doxorubicin group, respectively, were still receiving their initial study treatment.

At the time of the PFS analysis, a total of 14 patients had crossed over from the liposomal doxorubicin group to the olaparib 400 mg bd group.

At time of final analysis of OS (30 April 2010), a total of 27 (84.4%), 26 (81.3%), 29 (90.6%) patients in the olaparib 200 mg bd group, olaparib 400 mg bd group, and the liposomal doxorubicin group, respectively, discontinued treatment prematurely.

The statistical analysis of investigator-assessed PFS showed no statistically-significant difference between olaparib monotherapy and liposomal doxorubicin (HR 0.88, 80% CI 0.62 to 1.28, p=0.6604). Olaparib 400 mg was numerically superior to olaparib 200 mg bd versus liposomal doxorubicin [olaparib 400 mg bd: HR 0.86, 80% CI 0.56 to 1.30, olaparib 200 mg bd: HR 0.91, 80% CI 0.60 to 1.39]), but neither was statistically significantly different to liposomal doxorubicin.

In addition, the CIs were too wide to draw conclusions regarding the subgroup analyses of PFS.

With regard to secondary efficacy variables (Objective response rate, disease control rate, duration of response, tumour size, CA-125 levels, overall survival, and quality of life) there was no statistically significant difference between either olaparib group and the liposomal doxorubicin group for any of the parameters. Treatment with olaparib 400 mg bd was generally numerically superior to treatment with olaparib 200 mg bd but there was no marked difference in efficacy.

2.5.2. Main studies

Pivotal study

Study D0810C00019

Study D0810C00019 was a phase II randomised, double blind, multicentre study to assess the efficacy of olaparib in the treatment of patients with platinum sensitive relapsed (PSR) high grade serous ovarian cancer following treatment with two or more platinum containing regimens.

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

- Female patients aged ≥18 years ;
- Histologically diagnosed serous ovarian cancer or recurrent serous ovarian, including primary peritoneal and fallopian tube cancer (including patients with macroscopic peritoneal metastases outside the pelvis or distant metastases). Formalin fixed, paraffin embedded tumour sample from the primary or recurrent cancer had to be available for central testing;
- Patients had to have completed at least 2 previous courses of platinum-containing therapy (e.g., carboplatin or cisplatin) not necessarily sequential:
    - For the penultimate platinum-based chemotherapy course prior to enrolment on the study, a patient had to have been defined as platinum-sensitive after this treatment (defined as 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. The response could be confirmed as per RECIST (the assessment did not need to be confirmed ≥4 weeks later) and/or a CA-125 GCIG confirmed response (at least a 50% reduction in CA-125 levels from the last pre-treatment sample, confirmed 28 days later).

– Patients had to have been treated on the study within 8 weeks of completion of their final dose of the platinum-containing regimen.

– Chemotherapy course must have consisted of a minimum of 4 treatment cycles.

- Pre-treatment CA-125 value within the upper limit of normal (ULN). If greater than ULN, the second assessment , 7 days after, <15% more than the first;
- Normal organ and bone marrow function measured within 28 days prior to administration of study treatment;

- Eastern Co-operative Oncology Group (ECOG) performance status ≤2 and life expectancy ≥16 weeks;
- Evidence of non-childbearing status: negative urine or serum pregnancy test within 28 days of study treatment for women of childbearing potential, or postmenopausal status. Patients of child bearing potential and their partners, who were sexually active, had to agree to use 2 highly effective forms of contraception throughout their participation in the study and for 3 months after last dose of study drugs

Main Exclusion Criteria

- Patients with 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 PARP inhibitors and chemotherapy, radiotherapy (except for palliative reasons) within 2 weeks from the last dose prior to study entry.
- Patients with second primary cancer, 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 symptomatic uncontrolled brain metastases.

Treatments

Treatments administered

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.

Due to the potential effect of food on absorption, patients were instructed to take their doses of olaparib or matching placebo at least 1 hour after food and to refrain from eating for a further 2 hours. The olaparib capsules were to be swallowed whole and not chewed, crushed, dissolved or divided.

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.

Any toxicity observed during the course of the study was managed by supportive medical care and/or interruption of the dose (maximum of 4 weeks on each occasion) if deemed appropriate by the Investigator. Where toxicity reoccurred following re-challenge with olaparib or matching placebo capsules, and where further dose interruptions were considered inadequate for management of toxicity, then the patient was to be considered for dose reduction or had to permanently discontinue treatment with olaparib or matching placebo.

Any patient enrolled on the study that missed a scheduled dose (>2 hours after the scheduled dose time) the missed dose was not to be taken and the patient was to take their next normal dose at its scheduled time.

Prior and concomitant therapy

Patients could not have received prior olaparib or other PARP inhibitor treatment. Patients could have received prior bevacizumab, except in the regimen immediately prior to randomisation. Retreatment with olaparib was not permitted following progression on olaparib.

Other medications considered necessary for the patient's safety and well-being could be given at the discretion of the investigators.

- No other chemotherapy, hormonal therapy (hormone replacement therapy [HRT] was acceptable) or other novel agent was permitted during the course of the study for any patient (the patient could receive a stable dose of corticosteroids during the study provided these were started at least 4 weeks prior to enrolment).

- Palliative radiotherapy was allowed for pre-existing small areas of painful metastases that could not be managed with local or systemic analgesics provided there was no evidence of disease progression.

- Prophylactic cytokine (Granulocyte Colony-Stimulating Factor) administration was not to be given in the first cycle of the study.

- An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs. Effects with olaparib are unknown and, therefore, they were not to be administered to patients in the study.

- *In vitro* data have shown that the principal enzyme responsible for the formation of the 3 main metabolites of olaparib is CYP3A4 and, consequently, although the contribution of metabolic clearance to total drug clearance in man is currently unknown, to ensure patient safety all patients were to avoid concomitant use of drugs, herbal supplements and/or ingestion of foods known to modulate CYP3A4 enzyme activity and drugs that are known to be CYP3A4 substrates from the time they entered the screening period until 30 days after the last dose of study medication.

- Patients should refrain from drinking grape fruit juice and eating star fruit (averrhoa carambola) while taking the study medication.

Objectives and Outcomes/endpoints

Table 22: Main study objectives and variables

Objective			Variable
Priority	Type	Description	Title and description
Primary	Efficacy	To determine the efficacy (assessed by PFS) of olaparib (capsule formulation) compared to placebo in the overall population	Progression free survival Defined as the time from randomisation to the earlier date of objective assessment of progression (per RECIST 1.0 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	Time to discontinuation of olaparib/placebo treatment (TDT)

		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.	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 Homologous recombination deficient (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.

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 Clinical Study Protocol (CSP).

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

Route (iii) archival tumour samples in patients who consented to genetic analysis were analysed for mutations in *BRCA*1 and *BRCA*2: the sequence variants were classified, by the Applicant. This was retrospectively performed.

<u>BRCA testing methodologies</u>

- Germline BRCA testing

The integrated BRACAnalysis assay was a test for the detection and classification of variants in the BRCA1 and BRCA2 genes using genomic DNA obtained from whole blood. Integrated BRACAnalysis included complete Sanger sequencing of the BRCA1 and BRCA2 genes and an assessment of large rearrangements in the BRCA1 and BRCA2 genes. The tests were independent of each other but data from both was used to give a thorough assessment of BRCA1 and BRCA2 mutation status. Sequence analysis consisted of sequencing of all translated exons and immediately adjacent intronic regions of the BRCA1 and BRCA2 genes (a total of over 17,600 base pairs analysed). This test was also designed to detect duplications and deletions involving the promoter region and coding exons of BRCA1 and BRCA2. The amplified products were sequenced in forward and reverse directions and the resulting sequencing data was analysed with the developed proprietary DNA sequence analysis software. Any potential variants, called by the software, were then routed for review and verification. All potential clinically significant variants were independently confirmed by repeated PCR amplification of the indicated gene region(s) and re-sequencing. Large rearrangement analysis consists of a comprehensive rearrangement test of both BRCA1 and BRCA2 by quantitative PCR analysis (BRACAnalysis Rearrangement Test or BART).

This analysis was used to determine copy number abnormalities indicative of deletion or duplication mutations across the BRCA1 and BRCA2 genes. A software analysis was used to normalise the copy number of individual amplicons in the BRCA1 gene against BRCA2, plus three control genes. Any sample with a potential large rearrangement mutation was reviewed and verified. Patient samples positive for deletions or duplications were confirmed by a repeat multiplex quantitative PCR analysis.

- Tumour BRCA testing

An informative genomic profiling platform, based on next generation sequencing, was used to identify a patient's individual molecular alterations. A targeted assessment of key cancer related genes, utilizing next generation sequencing with routine cancer specimens was performed. The test simultaneously sequenced all coding exons of 282 cancer-related genes to an average depth of at least 250-fold coverage (250 sequencing reads covering each nucleotide position in the exons). This assay could detect genomic alterations including base substitutions, small base insertions and deletions, larger copy number alterations (exon amplification or deletions) and rearrangements (recurrent translocations in 20 genes as well as large scale rearrangements in all 282 genes) using routine formalin fixed paraffin embedded (FFPE) tissue samples. This assay included the BRCA1 and BRCA2 genes. The tumour BRCA data generated by patient E-code reported the sequencing coverage for the BRCA1 and BRCA2 genes, the specific nucleotide variants, as well as copy number changes and gene rearrangements

The Applicant 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 case report form (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, 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 indicated a genetic variant of unknown significance, or
- patients who have undergone complete 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 *BRCA* test reported and did not have *BRCA* result recorded from tumour analysis or a *BRCA* result recorded in the CRF.

BRCA variant classification

Several BRCA variant classification systems are available.

Biological Classification	Classification used in the study (BRACAnalysis assay)	BIC Classification	BReast CAncer IARC database	ACMG
Disrupts normal gene function	Deleterious Suspected Deleterious	Clinically important = Yes	Definitely Pathogenic Likely pathogenic	Class 1 Class 2
Uncertain Does not disrupt normal gene function	Variants of unknown significance Variant, favour polymorphism Benign polymorphism	Clinically Important = Unknown Clinically Important = No	Uncertain Likely not pathogenic or of clinical significance Not pathogenic or of no clinical significance	Class 3 Class 4 Class 5

* BIC = Breast Cancer Information Core; ACMG = American College of Medical Genetics; IARC = International Agency For Research On Cancer

In the study, BRCA1 and BRCA2 variants were classified into one of the five categories below.

Variant classification	Description
Deleterious mutation	All mutations (nonsense, insertions, deletions) that prematurely terminate the protein product before the last documented deleterious mutation of the gene. In addition, some specific mis-sense mutations and non-coding intervening sequence mutations are recognized as deleterious on the basis of compelling scientific data derived from linkage analysis of high risk families, functional assays, biochemical evidence and/or demonstration of abnormal mRNA transcript processing.
Genetic variant, suspected deleterious	Includes genetic variants for which available evidence indicates a strong likelihood, but not definitive proof, that the mutation is deleterious.
Genetic variant of uncertain significance (VUS)	Includes mis-sense variants and variants that occur in analyzed intronic regions whose clinical significance has not yet been determined, as well as terminating variants that truncate the gene distal to the last known deleterious mutation.
Genetic variant, favour polymorphism	Includes genetic variants for which available evidence indicates that the variant is highly unlikely to contribute substantially to cancer risk.
No mutation detected (NMD)	Includes genetic variants in the protein coding region that neither alter the amino acid sequence nor are predicted to significantly affect exon splicing and base pair alterations in the non-coding portions of the gene that have been demonstrated to have no deleterious effect on the length of stability of the mRNA transcript. These also include genetic variants for which published data demonstrate absence of clinical significance.

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.

The HRD status of patients could not be established because the Applicant did not have a diagnostic test to identify patients with HRD tumours. The analysis of efficacy in the HRD sub-population formed an exploratory objective of the study. This will be addressed when a suitable identification process has been defined.

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 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 Data cut off (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.

Interim analyses

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, the Applicant 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).

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. 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:

a. >6 to ≤12 months.

b. >12 months.

2. Objective response to the last platinum-containing regimen prior to enrolment on the study

a. CR (defined as normal radiological findings and CA-125 within the normal range):

b. PR (defined as a RECIST PR and/or GCIG CA-125 response)

3. The ethnic descent of the patient:

a. Jewish

b. 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

Definition of Analysis Sets

Efficacy data from this study was summarised and analysed on an intent-to-treat (ITT) basis using randomised treatment. The primary analysis population was based on the FAS.

Two main analysis sets were used in the statistical analyses:

Full analysis set (FAS): Included all randomised patients and compared the treatment groups on the basis of randomised treatment, regardless of the treatment actually received or protocol deviations.

Safety analysis set: A subset of the FAS that included all patients who received at least 1 dose of study medication (olaparib or placebo). Treatment group comparisons were based on the initial dose of study treatment actually received.

Statistical Methodology

Analysis of variables

Progression Free Survival (PFS)

There was 1 comparison of interest for PFS, namely olaparib (capsule formulation) compared with olaparib matching placebo in the overall population.

PFS was analysed using a Cox proportional hazards model. All efficacy analyses were adjusted according to the true levels of the covariates (Ethnic descent, platinum sensitivity, response to final platinum therapy), regardless of the levels declared at randomization in the IVRS.

The primary analysis of PFS did not censor patients who started subsequent therapy prior to progression.

As prespecified in the SAP, a global interaction test was to be performed to test the overall strength of evidence for consistency over all the subgroups defined by the stratification factors plus BRCA status. If the global interaction test was found to be statistically significant ($p<0.1$) an attempt to determine the cause and type of interaction would be made.

Several sensitivity analyses of PFS were performed. An evaluation-time bias analysis using generalised log-rank tests for interval-censored failure time data was carried out to assess possible time-assessment bias. Attrition bias was assessed by repeating the primary PFS analysis except that the actual PFS event times were used rather than the censored times of patients who progressed or died in the absence of progression immediately following 2, or more, non-evaluable tumour assessments. A supportive analysis of PFS using the stratified log rank test was performed (stratified by ethnic descent, platinum sensitivity and response to final platinum therapy). An exploratory analysis using the full analysis set (FAS) that included BRCA status in the Cox model was also carried out.

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.

Sub-group analyses of PFS were performed using a Cox proportional hazards model with factors for treatment, ethnic descent, platinum sensitivity, and response to final platinum therapy. If there were too few results available for a meaningful analysis of a particular subgroup (it was not considered appropriate to present analyses where there were less than 20 events in a subgroup), the relationship between that subgroup and PFS was not formally analysed but descriptive summaries were provided.

The following sub-groups were explored:

- *BRCA* mutated / *BRCA* wild type or variant of unknown significance / *BRCA* status missing (see definitions above);
- age <50 years; age ≥50 to <65 years; age ≥65 years;
- race=White;
- non-Jewish descent;
- CR at baseline / PR at baseline (Note, response to previous platinum covariate was defined using presence of disease at baseline via RECIST data; presence = PR, absence = CR);
- Time to progression (TTP) penultimate platinum 6 to 12 months / >12 months.

In the original CSR the sub-group analysis by *BRCA* status was based on g*BRCA* status recorded on the CRF at entry to the study, whilst the current analysis additionally considers both germline and tumour *BRCA* status at entry and hence the sample size for the current analyses by *BRCA* status was larger than in the original CSR.

Overall Survival (OS)

The analysis of OS was to use the same methodology and model as described for the primary analysis of PFS and was prospectively defined to be performed only if at the time of the PFS analysis there were sufficient events (20 or more) to make it meaningful. A Kaplan Meier plot of OS was presented by treatment group.

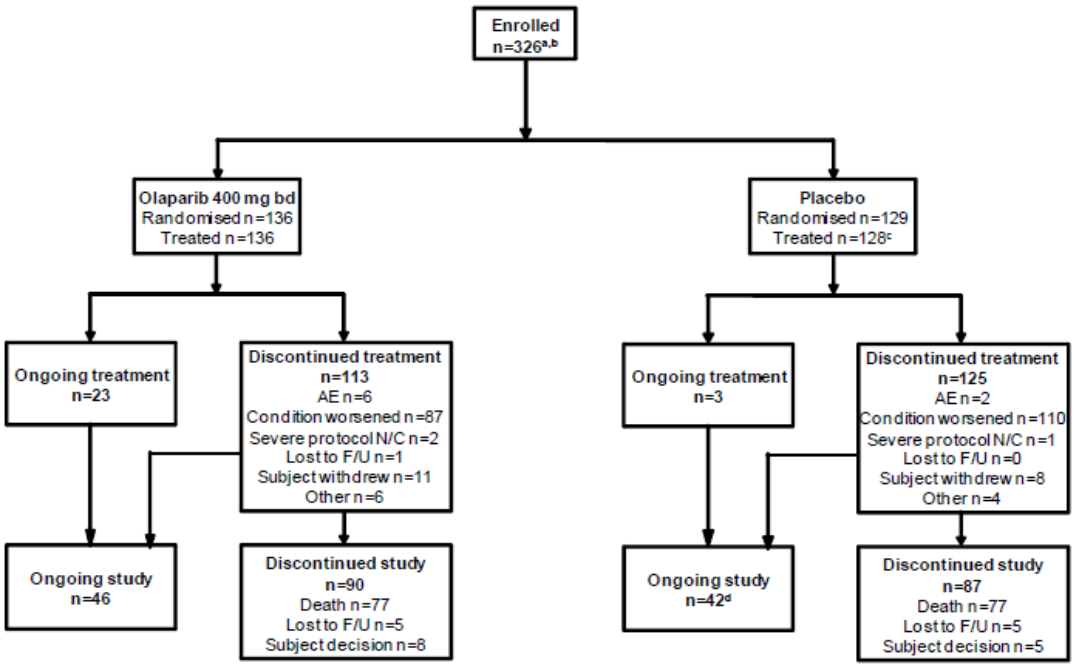
Three additional exploratory analyses of intermediate clinical endpoints were conducted at the time of the 58% interim OS analysis, to evaluate whether PFS benefits are maintained with longer follow up, and to assess time to second progression:

- time to discontinuation of olaparib/placebo treatment (TDT), defined as the time from randomisation to discontinuation of olaparib/placebo treatment or death;
- time to first subsequent therapy or death (TFST), defined as the time from randomisation to the start date of the first cancer therapy received following the discontinuation of olaparib/placebo or death;
- time to second subsequent therapy or death (TSST), defined as the time from randomisation to the start of a patient's second cancer therapy subsequent to the discontinuation of olaparib/placebo or death.

No adjustments were made for multiplicity introduced by analysing multiple endpoints (excluding OS), or analyses within the *BRCA* subgroups. The multiplicity adjustment for OS was amended when there were insufficient OS events at the time of the PFS analysis and an interim at 100 deaths (~40% maturity) added. In October 2012, the protocol was further amended and the OS analysis at 60% maturity was classed as a subsequent interim analysis with a final analysis planned to occur at approximately 85% maturity. This amendment detailed the change to the multiplicity adjustment in order to continue controlling the overall alpha at 2.5% (1-sided); the significance level at the 40% interim analysis was as specified in November 2011 (p-value <0.0005 1-sided), the significance level at the 60% analysis would be p<0.015 (1-sided) and at each subsequent analysis half the remaining alpha will be spent, unless it is the final analysis where all the remaining alpha will be spent (see also protocol amendments below).

Results

Participant flow



a Informed consent received.
b 61 patients were enrolled but not randomised as they were screen failures.

c One patient was randomised to the placebo group but voluntarily withdrew her consent (and completely withdrew from the study) without receiving treatment.
d One patient withdrew from the study prior to data base lock, 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.

Recruitment

The first patient was enrolled on 28 August 2008 and the last patient was enrolled on 9 February 2010.

The Clinical Study Report presented the 58% interim overall survival data cut-off: 26 November 2012 and the primary progression free survival analysis (data cut-off: 30 June 2010).

Conduct of the study

The main protocol amendments to the CSP are described below:

Amendment 01 (27 November 2008)

- Primary objective expanded to include patients with HRD tumours
- Inclusion criterion 4 amended to reflect that response to the last platinum-containing chemotherapy had to be maintained at study entry. Additionally, following feedback from study investigators, the window between last dose of platinum-containing regimen and starting study treatment was extended from 6 weeks to 8 weeks from the last chemotherapy treatment. The last chemotherapy regimen was to have consisted of at least 4 treatment cycles to exclude patients who could have had a poor prognosis.
- Clarification that patients could continue to receive study treatment following objective disease progression if the investigator felt the patient was benefiting from treatment, and the patient did not meet any other discontinuation criteria.
- Clarification that dose delays/modifications were not mandated for cases of leucopenia and/or anaemia.

Amendment 02 (14 May 2009)

- An interim analysis of PFS was included in the study to provide an early indication of efficacy and the text was revised to account for the statistical implications of this (including the determination of sample size). The text was revised to discuss the IDMC that will perform the interim analysis.

Amendment 03 (17 May 2010)

- As of February 2010, it was decided that the interim analysis of PFS was no longer required.
- Analysis of PFS in the HRD population was removed as a co-primary objective because an assay to identify HRD patients was not available at the time of primary analysis. The analysis may be performed when an assay becomes available, hence has been changed to become an exploratory objective, and will be reported separately from the CSR.

Amendment 04 (2 November 2010 i.e. after the primary PFS database lock and when the results of the primary analysis were known.)

- The duration of the study was amended based on the current best estimate of the OS event rate and the number of OS events required for the final analysis. As there were insufficient events for a meaningful analysis of OS at the time of the PFS analysis then the significance level for the single, later analysis of OS will be set at 2.5% (1-sided). The final analysis of OS is scheduled to take place when there are a similar number of OS events as PFS events in the primary analysis, to enable the data to be assessed with a similar level of precision. For example, with 137 events there will be 80% power to demonstrate superior OS at the 1-sided 2.5% level if the true HR is 0.62 (approximate medians 24 months versus 39 months). Assuming a median survival of 24 months in the control arm and 12 months non-linear recruitment starting 6 months after FSI (to approximately reflect observed recruitment) the final data cut-off for OS is expected to occur around 46 months after First Subject In.

Amendment 05 (1 November 2011)

- Addition of an interim analysis of OS, to be performed when approximately 100 deaths have occurred, with the final analysis of survival at the same maturity as the PFS analysis:
- This interim analysis was scheduled in order to provide sufficient confidence to be able to start a Phase III study. Improving survival is recognised to be an important clinical outcome for maintenance treatment and although the final OS analysis of Study D0810C00019 will provide this confidence, the event rate is slow and the data will not be available for at least 12 months.

Amendment 06 (17 October 2012)

- After the interim analysis of OS is performed when approximately 100 deaths have occurred, a subsequent interim analysis of survival will be performed at approximately the same maturity as the PFS analysis (~60% maturity) (per amendment 05). The final survival analysis will be performed at approximately 85% maturity (~222 deaths). Collection of survival data will not continue beyond 85% maturity.

Protocol deviations

A total of 52.8% patients (57.4% olaparib versus 48.1% placebo) were defined as having “important” deviations in the study that could potentially have influenced the assessment of efficacy with a total of:

- 79 patients (29.8%) were mis-stratified in the interactive voice response system (IVRS) by study sites, with a larger proportion of patients in the olaparib group compared with the placebo group (35.3% olaparib vs 24.0% placebo). The randomisation was stratified by 3 factors and the majority of the discrepancies between data recorded on the IVRS and the CRF were due to Time to Penultimate Platinum disease progression (22 patients were entered into the IVRS as having 6-12 months to penultimate progression but as >12 months on the CRF, the converse for 14 patients) and Response to prior disease (28 patients were recorded on the IVRS as being in complete response but had disease at baseline according to RECIST, the converse for 21 patients);

- 34.0% of patients had “important” deviations other than IVRS mis-stratifications (33.8% olaparib vs 34.1% placebo). Only a minority were considered to have the potential to impact the overall efficacy conclusions.

The other “important” deviations are considered to be unlikely to have affected the efficacy analyses.

Baseline data

Demographic and Baseline characteristics

Table 23: Summary of demographic and patient characteristics at baseline: FAS and BRCA mutated subgroup

	FAS		*BRCAm*	
	Olaparib 400 mg bd (n=136)	**Placebo (n=129)**	**Olaparib 400 mg bd (n=74)**	**Placebo (n=62)**
Age (years)				
Mean (SD)	58.9 (10.95)	58.5 (9.89)	57.6 (10.37)	55.5 (10.53)
Median (range)	58.0 (21-89)	59.0 (33-84)	57.5 (38-89)	55.0 (33-84)
Age group (years), n (%)				
<50	30 (22.1)	20 (15.5)	19 (25.7)	16 (25.8)
≥50 to <65	61 (44.9)	74 (57.4)	38 (51.4)	35 (56.5)
≥65	45 (33.1)	35 (27.1)	17 (23.0)	11 (17.7)
Race, n (%)				
White	130 (95.6)	126 (97.7)	70 (94.6)	61 (98.4)
Black/African American	2 (1.5)	1 (0.8)	2 (2.7)	0
Asian	2 (1.5)	2 (1.6)	1 (1.4)	1 (1.6)
Other	2 (1.5)	0	1 (1.4)	0
Ethnic population, n (%)				
Jewish descent[a]				
No	115 (84.6)	112 (86.8)	60 (81.1)	48 (77.4)
Yes	21 (15.4)	17 (13.2)	14 (18.9)	14 (22.6)
Ashkenazi Jewish	17 (12.5)	12 (9.3)	12 (16.2)	10 (16.1)
Sephardic Jewish	1 (0.7)	1 (0.8)	1 (1.4)	1 (1.6)
Mizrahim Jewish	2 (1.5)	1 (0.8)	1 (1.4)	0
Other	0	3 (2.3)	0	3 (4.8)
Missing	1 (0.7)	0	0	0
ECOG performance status, n (%)				
(0) Normal activity	110 (80.9)	95 (73.6)	62 (83.8)	45 (72.6)
(1) Restricted activity	23 (16.9)	30 (23.3)	11 (14.9)	15 (24.2)
(2) In bed <50% of the time	1 (0.7)	2 (1.6)	0	1 (1.6)
Unknown	2 (1.5)	2 (1.6)	1 (1.4)	1 (1.6)

	FAS		*BRCAm*	
	Olaparib 400 mg bd (n=136)	Placebo (n=129)	Olaparib 400 mg bd (n=74)	Placebo (n=62)
Primary tumour location				
Ovary	119 (87.5)	109 (84.5)	65 (87.8)	54 (87.1)
Fallopian Tube	3 (2.2)	3 (2.3)	1 (1.4)	2 (3.2)
Primary peritoneal	14 (10.3)	16 (12.4)	8 (10.8)	6 (9.7)
Other	0	1 (0.8)[d]	0	0
Tumour grade				
Well Differentiated (G1)	0	0	0	0
Moderately Differentiated (G2)	36 (26.5)	34 (26.4)	17 (23.0)	15 (24.2)
Poorly Differentiated (G3)	97 (71.3)	89 (69.0)	55 (74.3)	46 (74.2)
Undifferentiated (G4)	2 (1.5)	4 (3.1)	1 (1.4)	0
Unassessable (GX)	1 (0.7)	2 (1.6)	1 (1.4)	1 (1.6)
Platinum sensitivity[b]				
>6 to ≤12 months	53 (39.0)	54 (41.9)	28 (37.8)	26 (41.9)
>12 months	83 (61.0)	75 (58.1)	46 (62.2)	36 (58.1)
Objective response[c]				
CR	57 (41.9)	63 (48.8)	36 (48.6)	34 (54.8)
PR	79 (58.1)	66 (51.2)	38 (51.4)	28 (45.2)

a In the FAS, one patient was classified as not of Jewish descent at the previous data cut-off (30 June 2010) and is now classified as being of Jewish (Ashkenazi) descent.
b Platinum sensitivity = time to progression after the completion of platinum therapy. Note: Platinum sensitivity refers to the penultimate platinum not the platinum regimen that was just completed by the patient.
c Objective Response: CR = Patients with no target lesions and no non-target lesions at baseline; PR = Patients with target lesions and/or non-target lesions at baseline. Note: This is the response from the platinum regimen just prior to therapy. Data for 1 patient who did not receive platinum therapy are also included.
d One Patient had location of Other – FIMBRIA
bd Twice daily; *BRCA* Breast cancer susceptibility gene; *BRCAm gBRCA* and/or *tBRCA* mutated; CR Complete response; CSR Clinical study report; ECOG Eastern Cooperative Oncology Group; FAS Full analysis set; *gBRCA* Germline *BRCA*; PR Partial response; SD Standard deviation; *tBRCA* Tumour *BRCA*

Table 24: Summary of patient FIGO stage at diagnosis: FAS

	Number (%) of patients		
	Olaparib 400 mg bd n=136	Placebo n=129	Total n=265
FIGO stage[a]			
Stage IB	0	1 (0.8)	1 (0.4)
Stage IC	3 (2.2)	3 (2.3)	6 (2.3)
Stage II	1 (0.7)	0	1 (0.4)
Stage IIA	2 (1.5)	1 (0.8)	3 (1.1)
Stage IIB	3 (2.2)	1 (0.8)	4 (1.5)
Stage IIC	5 (3.7)	6 (4.7)	11 (4.2)
Stage III	10 (7.4)	7 (5.4)	17 (6.4)
Stage IIIA	4 (2.9)	3 (2.3)	7 (2.6)
Stage IIIB	8 (5.9)	12 (9.3)	20 (7.5)
Stage IIIC	81 (59.6)	76 (58.9)	157 (59.2)
Stage IV	17 (12.5)	17 (13.2)	34 (12.8)
Unknown	2 (1.5)	2 (1.6)	4 (1.5)

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.

Treatment compliance

Estimated compliance was derived from the actual administration days divided by the total planned administration days (i.e. last dose date - first dose date + 1), (excluding dose interruption days).

Table 28: Summary of estimated study treatment compliance: FAS

Estimated compliance (%)	Olaparib 400 mg bd n=136	Placebo n=129	Total n=265
n	136	128	264
Mean (standard deviation)	96.9 (8.93)	99.0 (3.39)	97.9 (6.89)
Median (range)	100.0 (25.0 to 100.0)	100.0 (75.9 to 100.0)	100.0 (25.0 to 100.0)

bd Twice daily; FAS Full analysis set.
Data cut-off: 26 November 2012.

Numbers analysed

At DCO (26 November 2012), 23 (16.9%) and 3 (2.3%) patients in the olaparib and placebo groups, respectively, were still receiving study treatment.

Twenty-three patients withdrew consent prior to DCO (26 Nov 2012), 21 of whom were censored for OS >2 months prior to DCO.

The analysis sets and the number of patients in each analysis set are summarised in the 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. One Patient (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. One Patient (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. One Patient (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 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.
bd Twice daily; CA-125 Cancer antigen-125; FACT-O Functional Analysis of Cancer Therapy - Ovarian; FOSI FACT/NCCN Ovarian Symptom Index; HRQL Health-related quality of life; RECIST Response Evaluation Criteria in Solid Tumours; TOI Trial outcome index.

Patients with a BRCA mutation

Table 30: Correlation between gBRCA and tBRCA mutation status: Full Analysis Set

Germline *BRCA* status	**Tumour *BRCA* status**				
	Mutant	Wild type	Unknown[a]	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%)**
Unknown[a]	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.
**BRCA*m: defined as either tumour or germline mutation (n=136).
***BRCA*wt: or unknown significance dataset: defined as wild type or variant of unknown significance by either germline or tumour (and not *BRCA*m) (total n=118).
Note: Three patients were classified as BRCAwt in their tumours whilst having a mutant classification in their germline. These 3 discrepancies were considered to be false negatives as the changes present in the blood samples were present in the tumour sample but the detection threshold used in the tumour assay was not reached.

Table 31: Summary of patient disposition: patients with BRCA mutation

	Number (%) of patients		
	Olaparib 400 mg bd n=74	Placebo n=62	Total n=136
Patients randomised	74 (100.0)	62 (100.0)	136 (100.0)
Patients who received treatment	74 (100.0)	62 (100.0)	136 (100.0)
Patients ongoing study treatment at data cut-off[a]	15 (20.3)	3 (4.8)	18 (13.2)
Patients who discontinued initial study treatment[a]	59 (79.7)	59 (95.2)	118 (86.8)
Adverse event	5 (6.8)	0	5 (3.7)
Condition under investigation worsened	42 (56.8)	52 (83.9)	94 (69.1)
Severe non-compliance to CSP	0	1 (1.6)	1 (0.7)
Voluntary discontinuation by patient	9 (12.2)	4 (6.5)	13 (9.6)
Other	3 (4.1)	2 (3.2)	5 (3.7)
Patients ongoing study	30 (40.5)	22 (35.5)[b]	52 (38.2)
Patients who terminated study	44 (59.5)	40 (64.5)	84 (61.8)
Death	37 (50.0)	34 (54.8)	71 (52.2)
Patient lost to follow-up	1 (1.4)	4 (6.5)	5 (3.7)
Voluntary discontinuation of patient	6 (8.1)	2 (3.2)	8 (5.9)

a Percentages are calculated from number of patients who received treatment.
b One Patient withdrew from the study prior to data base lock,but at the time of database lock the necessary CRF pages were not available therefore this patient appears incorrectly as ongoing.
bd Twice daily; *BRCA* Breast cancer susceptibility gene; CSP Clinical Study Protocol.
Data cut-off: 26 November 2012.

Outcomes and estimation

Primary variable: Progression free survival in the overall study population

Table 32: 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)

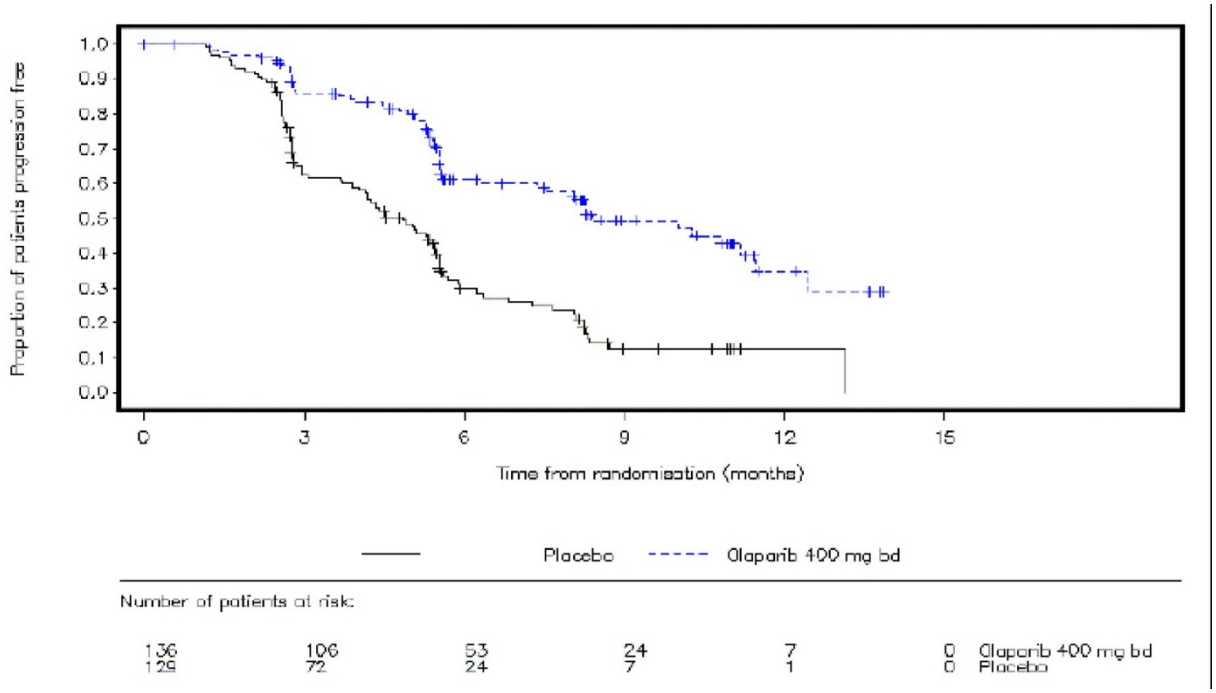
bd Twice daily; FAS Full analysis set; PFS Progression free survival; RECIST Response Evaluation Criteria in Solid Tumours.
Note: This table presents data from the original analysis prior to a re-analysis of the PFS data (30 June 2010 data cut-off).
a Death in the absence of RECIST progression.
Data cut-off: 30 June 2010.

Table 33: 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 2: 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 34: 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

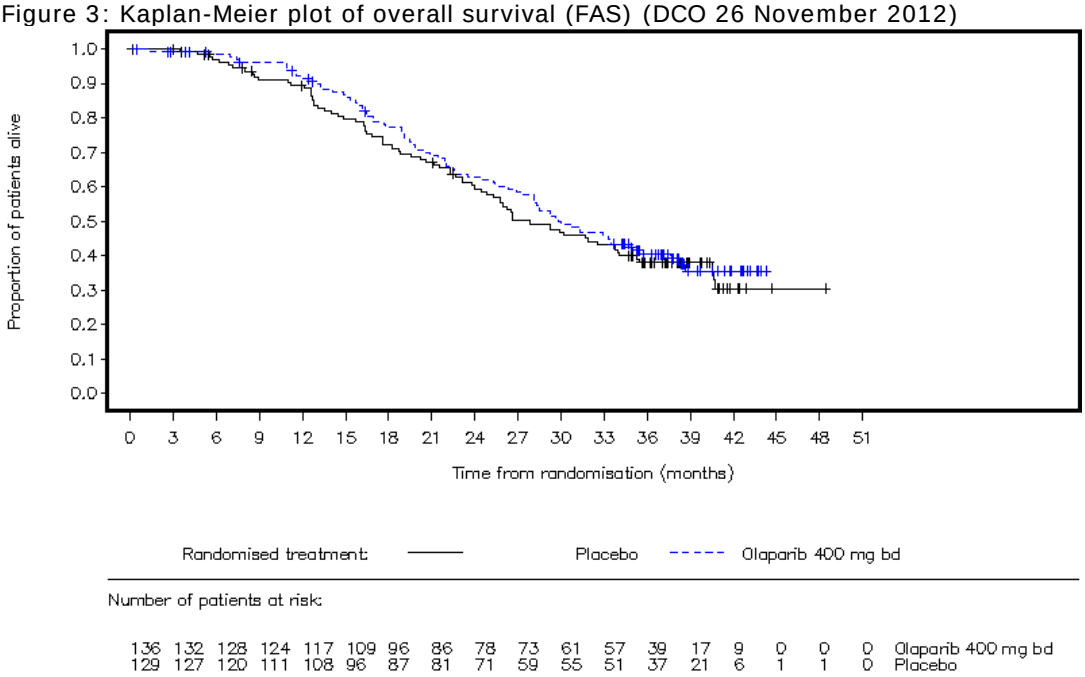
Overall survival in the overall study population

Table 35: Summary of analysis of overall survival: FAS

	Olaparib 400 mg bd n=136	Placebo n=129
n (%) of deaths	77 (56.6%)	77 (59.7%)
Median overall survival, months[a]	29.8	27.8
80% CI for median	28.2, 33.4	25.8, 32.5
95% CI for median	27.2, 35.7	24.4, 34.0
Treatment effect		
Hazard ratio[b]	0.88	
80% CI	0.72, 1.09	
95% CI	0.64, 1.21	
2-sided p-value	0.442	

a Calculated using the Kaplan-Meier technique.
b Analysis was performed using a Cox proportional hazards model with factors for treatment, ethnic descent, platinum sensitivity and response to final platinum therapy.
A hazard ratio <1 favours olaparib.
CI Confidence interval; FAS Full analysis set.
Data cut-off: 26 November 2012.

Figure 3: Kaplan-Meier plot of overall survival (FAS) (DCO 26 November 2012)



bd Twice daily; FAS Full analysis set.

Objective response rate in the overall study population

Table 36: Summary of best objective response: FAS

	Number (%) of patients	
	Olaparib 400 mg bd n=136	**Placebo n=129**
Response		
Total	7 (5.1)	2 (1.6)
Complete response[a]	0	0
Partial response[a]	7 (5.1)	2 (1.6)
Non-response		
Total	129 (94.9)	127 (98.4)
NED[b]	49 (36.0)	42 (32.6)
No disease at baseline	49 (36.0)	42 (32.6)
Stable disease ≥11 weeks	46 (33.8)	25 (19.4)
Stable disease without unconfirmed response	37 (27.2)	25 (19.4)
Unconfirmed partial response[c]	9 (6.6)	0
Progression	24 (17.6)	55 (42.6)
RECIST progression	23 (16.9)	55 (42.6)
Early death[d]	1 (0.7)	0
Not evaluable	10 (7.4)	5 (3.9)
NED <11 weeks	3 (2.2)	2 (1.6)
Stable disease <11 weeks	2 (1.5)	0
No valid baseline assessments	0	1 (0.8)
No evaluable follow-up assessment	5 (3.7)	2 (1.6)

a Response requires confirmation.
b No measurable and no non-measurable disease at baseline and no evidence of new lesions on or after 11 weeks.
c Partial response (PR) or complete response (CR) achieved but either no confirmation assessment performed or a confirmation assessment performed but response not confirmed.
d Death in the absence of an evaluable RECIST assessment.
bd Twice daily; NED No evidence of disease; FAS Full analysis set; RECIST Response Evaluation Criteria in Solid Tumours.
Data cut-off: 30 June 2010.

Others secondary endpoints in the overall study population

Table 37: Summary of results from secondary endpoints

	Olaparib	**Placebo**	
	(N=136)	(N=129)	
Disease control rate at 24 weeks (Number of patients, %)			
Yes	73 (53.7)	33 (25.6)	
No	63 (46.3)	96 (74.4)	
	(N= 57)	(N= 48)	
Total number of confirmed CR or PR (%)	7 (12)	2 (4.2)	
Median time to onset of response	3.1 months	4.1 months	
Median duration of response based on Kaplan-Meier estimate	5.6 months	NC	
Percentage change in tumour size			**Difference / 95%CI / p**
Week 12	(N=56) LS mean= 0.7%	(N=47) LS mean= 21.2%	-20.5 [-44.8, 3.8] p=0.09751
Week 24	(N=56) LS mean= -0.8%	(N=47) LS mean= 26.4%	-27.1 [-51.9, -2.4] p=0.03185
	(N=135)	(N=128)	
Best percentage change from baseline in CA-125 (U/mL)			
Mean (standard deviation)	-5.20 (59.463)	43.87 (181.587)	
Median (range)	-16.67 (-100.00 to 346.15)	0.00 (-99.50 to 1436.84)	
(Number of patients, %)	(N=61)	(N=53)	**Odds ratio / 95%CI / p**
RECIST response	16 (26.2)	2 (3.8)	
Confirmed	7 (11.5)	2 (3.8)	
Unconfirmed	9 (14.8)	0	
CA-1235 response	1 (1.6)	1 (1.9)	
Confirmed RECIST response and/or CA-125 response (in the absence of progression)	8 (13.1)	3 (5.7)	2.47 [0.67, 11.81] p=0.18155
Time to earlier of CA-125 or RECIST progression	(N=136)	(N=129)	**Hazard ratio / 95%CI / p**
Total number of events (%)	66 (48.5)	106 (82.2)	0.35 [0.25, 0.47] <0.00001
Median time to progression	8.3 months	3.7 months	

Health-related quality of life in the overall study population

Table 38: Summary of best response for total FACT-O: Evaluable for total FACT-O set

	Olaparib 400 mg bd n=114	Placebo n=111
Improved[a]	24 (21.1)	21 (18.9)
No change[b]	68 (59.6)	63 (56.8)
Worsened[c]	20 (17.5)	24 (21.6)
Non-evaluable	2 (1.8)	3 (2.7)

a Two visit responses of 'improved' a minimum of 21 days apart without an intervening visit response of 'worsened'. Improved is defined as a change from baseline of greater than or equal to +9.
b Does not qualify for a best response of 'improved'. Two visit responses of 'no-change' or a response of 'no change' and a response of 'improved', a minimum of 21 days apart without an intervening visit response of 'worsened'. No change is defined as a change from baseline of greater than -9 but less than +9.
c Does not qualify for a best response of 'improved'. A visit of 'worsened' without a response of 'improved' or 'no change' within 21 days. Worsened is defined as a change from baseline of less than or equal to -9.
bd Twice daily; FACT-O Functional Analysis of Cancer Therapy – Ovarian.
Data cut-off: 30 June 2010.

There was no statistically significant difference between treatment groups (Odds ratio 1.17, p=0.65).

The main analysis of HRQoL was based on the Trial Outcomes Index (TOI), which is one of the scores derived from the FACT-O, and includes a summary of physical well-being, functional well-being, and ovarian cancer additional concern scores. The compliance rate across all time points was approximately 70% in each treatment group.

Table 39: Summary of best response for TOI: Evaluable for TOI set

	Olaparib 400 mg bd n=115	Placebo n=111
Improved[a]	23 (20.0)	20 (18.0)
No change[b]	72 (62.6)	67 (60.4)
Worsened[c]	16 (13.9)	20 (18.0)
Non-evaluable	4 (3.5)	4 (3.6)

a Two visit responses of 'improved' a minimum of 21 days apart without an intervening visit response of 'worsened'. Improved is defined as a change from baseline of greater than or equal to +7.
b Does not qualify for a best response of 'improved'. Two visit responses of 'no-change' or a response of 'no change' and a response of 'improved', a minimum of 21 days apart without an intervening visit response of 'worsened'. No change is defined as a change from baseline of greater than -7 but less than +7.
c Does not qualify for a best response of 'improved'. A visit of 'worsened' without a response of 'improved' or 'no change' within 21 days. Worsened is defined as a change from baseline of less than or equal to -7.
bd Twice daily; TOI Trial outcome index.
Data cut-off: 30 June 2010.

There was no statistically significant difference in improvement rate between treatment groups (Odds ratio 1.14 (95% CI 0.58, 2.24, p=0.69902).

Exploratory analyses

Results of the exploratory analyses (Overall updated with additional scan data and data corrections) for the proxies for more mature PFS performed at the interim OS DCO (26 November 2012) are presented in the table below.

Table 40: Exploratory analyses: TDT, TFST and TSST: FAS

Analysis	Events:Patients	Median time (months)	HR	80% CI	95% CI	p-value
Time to discontinuation of olaparib/placebo treatment (TDT)	Olaparib: 113:136 (83.1%) Placebo: 125:128 (97.7%)	8.6 4.6	0.39	0.33, 0.47	0.30, 0.51	<0.00001
Time to first subsequent therapy or death (TFST)	Olaparib: 95:136 (69.9%) Placebo: 118:128 (92.2%)	13.4 6.7	0.40	0.33, 0.48	0.30, 0.52	<0.00001
Time from randomisation to start of second subsequent therapy (TSST)	Olaparib: 88:136 (64.7%) Placebo: 108:128 (84.4%)	19.1 14.8	0.53	0.44, 0.64	0.40, 0.71	0.00001

CI Confidence interval; FAS Full analysis set; HR Hazard ratio; PFS Progression free survival.

Of patients randomised to olaparib, 84 (78.5%) received subsequent cancer therapy following disease progression; correspondingly 108 patients randomised to placebo (87.8%) received subsequent therapy. Over one third of eligible patients received 3 subsequent therapies (35.5% of the olaparib group and 43.1% of the placebo group) and approximately 11% of patients received 5 or more subsequent lines of treatment (9.3% of the olaparib group and 12.2% of the placebo group).

The most commonly reported treatments included those containing platinum or doxorubicin or topotecan. Sixteen patients in the placebo arm compared to zero patients in the olaparib arm received a PARP inhibitor as a subsequent therapy in the overall population. Approximately a quarter of placebo treated patients in the BRCA mutated subgroup (14/62; 22.6%) received a subsequent PARP inhibitor.

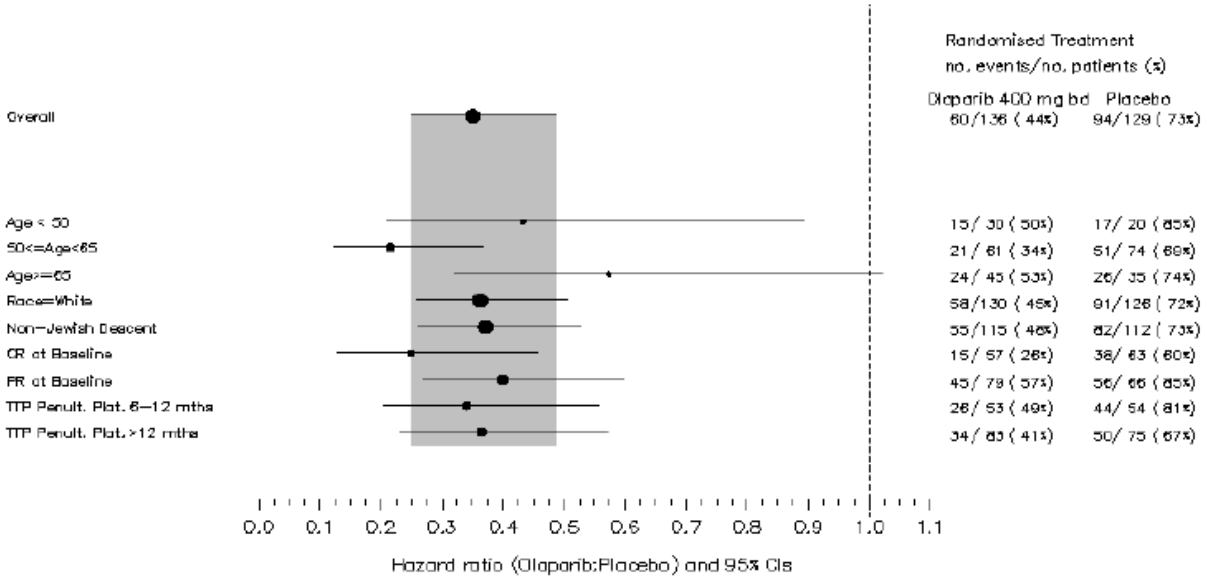
Subgroup analyses

This section presents analyses of data from patients with BRCA-mutated ovarian cancer, and over all the subgroups defined by the stratification factors plus BRCA status.

Subgroup analyses of PFS

Overall study population

Figure 4: Forest plot of analysis of PFS by subgroup: FAS



Note: bd Twice daily; *BRCA* Breast cancer susceptibility gene; CR Complete response; FAS Full analysis set; PFS Progression free survival; PR Partial response; TTP Time to progression.
Data cut-off: 30 June 2010.

BRCA subgroup

Table 41: Summary of primary analysis of PFS: patients with BRCA mutation

	Olaparib 400 mg bd n=74	Placebo n=62
Number of events: total number of patients (%)	26:74 (35%)	46:62 (74%)
Median PFS (months)	11.2	4.3
Increase in median PFS (months)	6.9	
HR (95% CI)	0.18 0.10, 0.31	
P value (2-sided)	p<0.00001	

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; *BRCA* Breast cancer susceptibility gene; CI Confidence interval; FAS Full analysis set; PFS Progression free survival.
Data cut-off: 30 June 2010.

The investigator-assessed PFS benefit in patients with BRCA mutation status was confirmed by blinded independent central radiological review (HR 0.22; 95% CI 0.12-0.40; p<0.00001; median not reached versus 4.8 months).

Table 42: Summary of analysis of progression-free survival by BRCA subgroup: Full Analysis Set

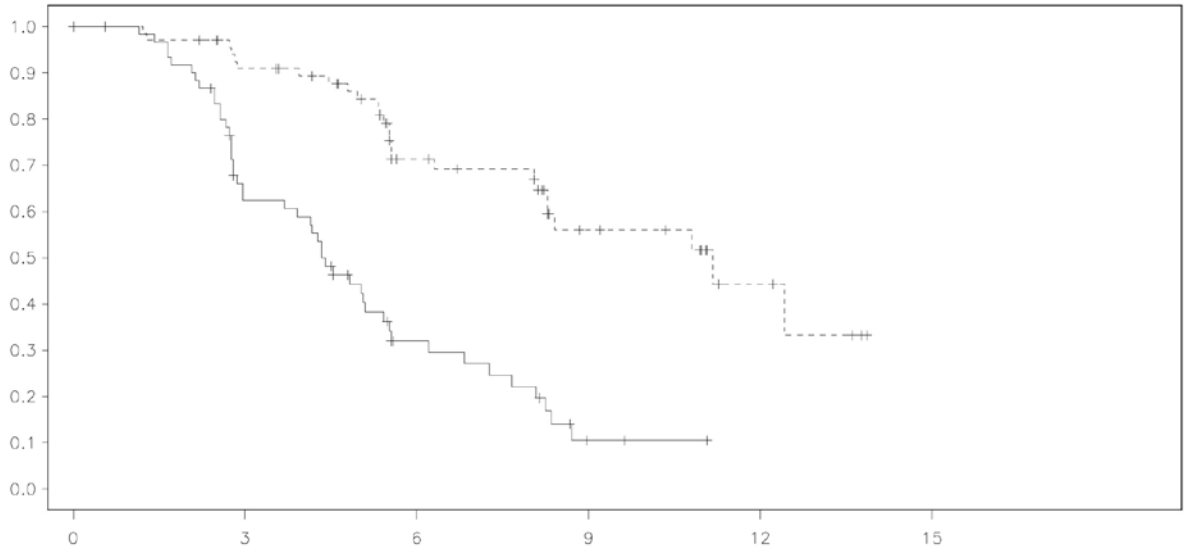
					Treatment effect		
Subgroup	Group	N	Number(%) of events	Hazard ratio[a]	80% CI	95% CI	2-sided p-value
Full analysis set	Olaparib 400 mg bd	136	60 (44.1)	0.35	0.28,0.43	0.25,0.49	<0.00001
	Placebo	129	94 (72.9)				
gBRCA mutant	Olaparib 400 mg bd	53	17 (32.1)	0.17	0.11,0.25	0.09,0.31	<0.00001
	Placebo	43	33 (76.7)				
gBRCA wild type/unknown sig.[b]	Olaparib 400 mg bd	50	24 (48.0)	0.50	0.35,0.69	0.29,0.82	0.00572
	Placebo	64	44 (68.8)				
gBRCA missing	Olaparib 400 mg bd	33	19 (57.6)	0.43	0.27,0.68	0.21,0.87	0.01970
	Placebo	22	17 (77.3)				
gBRCA non missing	Olaparib 400 mg bd	103	41 (39.8)	0.30	0.23,0.39	0.20,0.45	<0.00001
	Placebo	107	77 (72.0)				
BRCA mutant	Olaparib 400 mg bd	74	26 (35.1)	0.18	0.13,0.26	0.10,0.31	<0.00001
	Placebo	62	46 (74.2)				
BRCA wild type/unknown sig.[b]	Olaparib 400 mg bd	57	32 (56.1)	0.54	0.40,0.72	0.34,0.85	0.00745
	Placebo	61	44 (72.1)				
BRCA missing	Olaparib 400 mg bd	5	2 (40.0)	NC			
	Placebo	6	4 (66.7)				
BRCA non missing	Olaparib 400 mg bd	131	58 (44.3)	0.33	0.27,0.42	0.24,0.47	<0.00001
	Placebo	123	90 (73.2)				

[a] Analysis was performed using a Cox proportional hazards model with factors for treatment, ethnic descent, platinum sensitivity and response to final platinum therapy.
[b] BRCA wild type or BRCA mutation of unknown significance.
A hazard ratio of <1 favours olaparib. NC = not calculated.
Analysis incorporates the most accurate data known at the time of analysis.
Data cut-off: 30 June 2010.

The BRCAm subgroup showed a differential benefit to the FAS (a global interaction test including treatment by covariate [including BRCA status] interaction terms was reported as p=0.146). Adding the above RECIST and covariate correction including the additional gBRCA CRF data the fully corrected p-value was 0.09.

A global interaction test of PFS was performed when germline and/or tumour BRCA status was known for 96% of the study population and although not significant (p=0.142), the BRCA status by treatment interaction was found to be a significant quantitative interaction (p=0.025).

Figure 5: Kaplan-Meier plot of progression free survival for the olaparib 400 mg bd and placebo groups: patients with BRCA mutation patients (53% maturity investigator assessment)



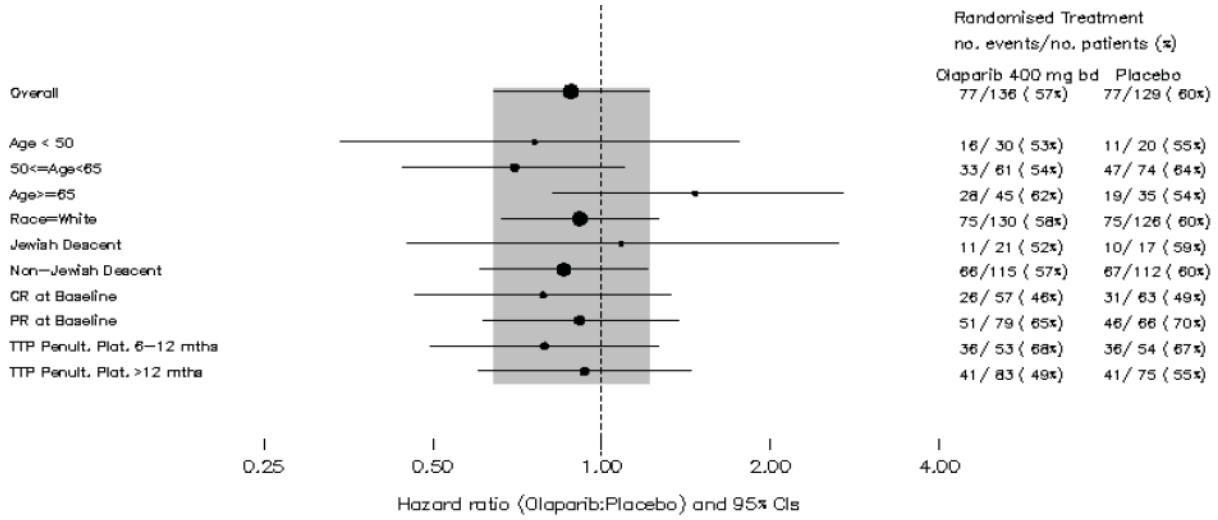
months	0	3	6	9	12	15
n-olaparib	74	59	34	15	5	0
n-placebo	62	35	13	2	0	0

-----olaparib 400 mg bd twice daily, ____placebo, x-axis=time from randomisation in months, y-axis=PFS (progression-free survival), n-olaparib= number of patients at risk-olaparib, n-placebo=number of patients at risk-placebo
bd Twice daily; *BRCA* Breast cancer susceptibility gene.
Data cut-off: 30 June 2010.

Subgroup analyses of OS

Overall study population

Figure 6: Forest plot of analysis of Overall Survival by subgroup: FAS



A hazard ratio <1 implies a lower risk of death on olaparib.
Cox proportional hazards model with factors for treatment, ethnic descent, response to final platinum & TTP on penultimate platinum.
Size of circle is proportional to the number of events.
Grey band represents the 95% confidence interval for the overall (all patients) hazard ratio.

bd Twice daily; CR Complete response; FAS Full analysis set; PFS Progression free survival; PR Partial response; TTP Penult. Plat. Time to death on penultimate platinum therapy.
Data cut-off: 26 November 2012.

BRCA subgroup

The OS analysis was performed at 52% maturity in patients with BRCAm.

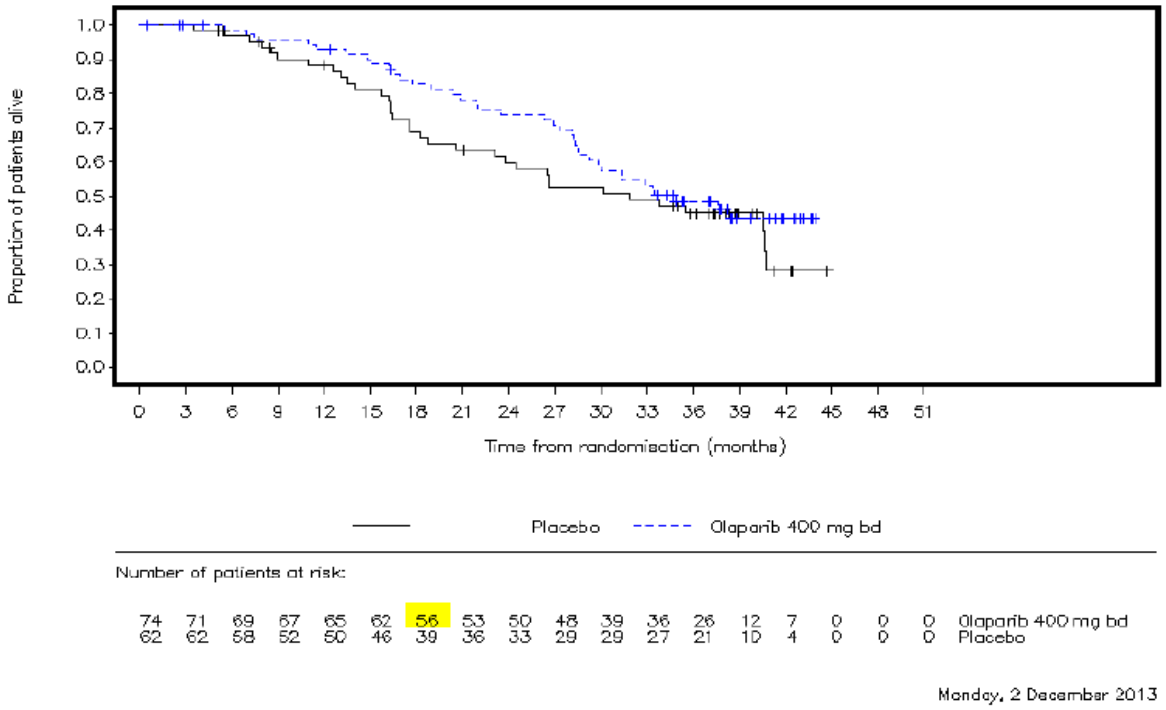
Table 43: Summary of analysis of overall survival: patients with a BRCA Mutation

	Olaparib 400 mg bd n=74	Placebo n=62
Number of events: total number of patients (%)	37:74 (50%)	34:62 (55%)
Median OS (months)	34.9	31.9
HR (95% CI)	0.73 (0.45-1.17)	
P value (2-sided)	p=0.19175	

a Calculated using the Kaplan-Meier technique.
b Analysis was performed using a Cox proportional hazards model with factors for treatment, ethnic descent, platinum sensitivity and response to final platinum therapy.
A hazard ratio <1 favours olaparib.
CI Confidence interval; FAS Full analysis set.
Data cut-off: 26 November 2012

There was no OS advantage in ovarian cancer patients who do not have a BRCA mutation (BRCAwt HR 0.99; 95% CI 0.63, 1.55; p=0.95724; median OS 24.5 months versus 26.2 months).

Figure 7: Kaplan-Meier plot of overall survival: patients with BRCA mutation



bd Twice daily.
Data cut-off: 26 November 2012.

Exploratory analyses in BCRA subgroup

Table 44: Exploratory analyses: TDT, TFST and TSST: patients with a BRCA mutation

Analysis	Events:Patients	Median time (months)	HR	80% CI	95% CI	p-value
Time to discontinuation of olaparib/placebo treatment (TDT)	Olaparib: 59:74 (79.7%) Placebo: 59:62 (95.2%)	11 4.6	0.36	0.28, 0.46	0.24, 0.53	<0.00001
Time to first subsequent therapy or death (TFST)	Olaparib: 46:74 (62.2%) Placebo: 54:62 (87.1%)	15.6 6.2	0.33	0.25, 0.44	0.22, 0.50	<0.00001
Time from randomisation to start of second subsequent therapy (TSST)	Olaparib: 42:74 (56.8%) Placebo: 49:62 (79.0%)	23.8 15.2	0.44	0.33, 0.58	0.29, 0.67	0.00013

CI Confidence interval; FAS Full analysis set; HR Hazard ratio; PFS Progression free survival.
Data cut-off: 26 November 2012.

Table 45: Summary of best response for total FACT-O: Evaluable for total FACT-O set in patients with a BRCA mutation

	Olaparib 400 mg bd n=63	Placebo n=53
Improved[a]	17 (27.0)	11 (20.8)
No change[b]	35 (55.6)	26 (49.1)
Worsened[c]	10 (15.9)	14 (26.4)
Non-evaluable	1 (1.6)	2 (3.8)

a Two visit responses of 'improved' a minimum of 21 days apart without an intervening visit response of 'worsened'. Improved is defined as a change from baseline of greater than or equal to +9.
b Does not qualify for a best response of 'improved'. Two visit responses of 'no-change' or a response of 'no change' and a response of 'improved', a minimum of 21 days apart without an intervening visit response of 'worsened'. No change is defined as a change from baseline of greater than -9 but less than +9.
c Does not qualify for a best response of 'improved'. A visit of 'worsened' without a response of 'improved' or 'no change' within 21 days. Worsened is defined as a change from baseline of less than or equal to -9.
bd Twice daily; FACT-O Functional Analysis of Cancer Therapy – Ovarian.
Data cut-off: 30 June 2010

Table 46: Summary of best response for TOI: Evaluable for TOI set in patients with a BRCA mutation

	Olaparib 400 mg bd n=64	Placebo n=53
Improved[a]	16 (25.0)	10 (18.9)
No change[b]	38 (59.4)	30 (56.6)
Worsened[c]	7 (10.9)	10 (18.9)
Non-evaluable	3 (4.7)	3 (5.7)

a Two visit responses of 'improved' a minimum of 21 days apart without an intervening visit response of 'worsened'. Improved is defined as a change from baseline of greater than or equal to +7.
b Does not qualify for a best response of 'improved'. Two visit responses of 'no-change' or a response of 'no change' and a response of 'improved', a minimum of 21 days apart without an intervening visit response of 'worsened'. No change is defined as a change from baseline of greater than -7 but less than +7.
c Does not qualify for a best response of 'improved'. A visit of 'worsened' without a response of 'improved' or 'no change' within 21 days. Worsened is defined as a change from baseline of less than or equal to -7.
bd Twice daily; TOI Trial outcome index.
Data cut-off: 30 June 2010.

Ancillary analysis

In Study 19, of the 136 patients known from germline and/or tumour testing to have a BRCA mutation, 18 patients were identified with a BRCA mutation in the tumour in the absence of a mutation being identified in the germline (somatic BRCA mutation). For ten patients, complete analysis of the BRCA genome, using the Integrated BRACAnalysis assay, was conducted and the mutation detected in the tumour was known not to be detected in the germline. Based on the mutations identified in the tumour sample from these 10 patients, there was no reason to believe that the Integrated BRACAnalysis test would not have detected them if they were present in the germline sample (9 mutations in the coding sequence and 1 large deletion). For eight patients, germline testing was carried out at local laboratories in accordance with usual clinical practice and the patients were considered not to be BRCA mutated. The details of the local testing procedures used are not known thus it cannot be ruled out if the germline mutation was not detected due to incomplete screening of the BRCA genes by the local laboratory. These 18 patients were included in the BRCA mutated group of 136 patients in total.

The limited data for the somatic tumour BRCA (sBRCA) mutated patients showed that fewer patients on olaparib reported progression events or death events compared with placebo.

Table 47: Summary of progression-free survival and overall survival: sBRCA mutated population in Study 19

	N events/patients (%)
PFS	
Olaparib 400 mg bd	3/8 (38%)
Placebo	6/10 (60%)
OS	
Olaparib 400 mg bd	4/8 (50%)
Placebo	6/10 (60%)

Summary of main study

The following table 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 48: Summary of Efficacy for trial D0810C00019 (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 - 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 58% interim overall survival data cut-off: 26 November 2012		

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		
	Number of subjects	136	129
	Median PFS, months	8.4	4.8
	80% CI for median 95% CI for median	[8.1,11.2] [7.4,11.5]	[4.2, 5.3] [4.0, 5.5]
	Median OS, months	29.8	27.8
	80% CI for median 95% CI for median	[28.2,33.4] [27.2,35.7]	[25.8,32.5] [24.4,34.0]
	Exploratory analyses: TDT TFST TSST (Median time, months)	 8.6 13.4 19.1	 4.6 6.7 14.8
	BRCA mutant subgroup		
	Number of subjects	74	62
	Median PFS, months	11.2	4.3
	Median OS, months	34.9	31.9
	Exploratory analyses: TDT TFST TSST (Median time, months)	 11 15.6 23.8	 4.6 6.2 15.2
Effect estimate per comparison	Overall population		
	Primary endpoint (PFS)	Comparison groups	Olaparib - placebo
		HR	0.35
		80% CI for median 95% CI for median	[0.28,0.43] [0.25,0.49]
		P-value (Cox proportional hazards model)	<0.00001

	Secondary endpoint OS	Comparison groups	Olaparib - placebo
		HR	0.88
		80% CI for median 95% CI for median	[0.72,1.09] [0.64,1.21]
		P-value (Cox proportional hazards model)	0.442
	Exploratory analyses: TDT TFST TSST	Comparison groups	Olaparib - placebo
		HR	0.39 0.40 0.53
		80% CI / 95% CI for median	[0.33, 0.47] / [0.30, 0.51] [0.33, 0.48] / [0.30, 0.52] [0.44, 0.64] / [0.40, 0.71]
		P-value	<0.00001 <0.00001 0.00001
	BRCA mutant subgroup		
	Primary endpoint (PFS)	Comparison groups	Olaparib - placebo
		HR	0.18
		80% CI for median 95% CI for median	[0.13,0.26] [0.10,0.31]
		P-value (Cox proportional hazards model)	<0.00001
	Secondary endpoint OS	Comparison groups	Olaparib - placebo
		HR	0.73
		80% CI for median 95% CI for median	[0.53,0.99] [0.45,1.17]
		P-value (Cox proportional hazards model)	0. 19175
	Exploratory analyses: TDT TFST TSST	Comparison groups	Olaparib - placebo
		HR	0.36 0.33 0.44
		80% CI / 95% CI for median	[0.28, 0.46] / [0.24, 0.53] [0.25, 0.44] / [0.22, 0.50] [0.33, 0.58] / [0.29, 0.67]
		P-value	<0.00001 <0.00001 0.00013
Notes	For PFS in BRCA wt/VUS, olaparib versus placebo: HR 0.54 (95% CI 0.34, 0,85; p=0.00745)		

Clinical studies in special populations

The number of elderly patients involved across the clinical trial programme (studies submitted with the MAA) are provided below.

eCTD	Age 65-74 number[a]/total number[b] (all ages)	Age 75-84 number[a]/total number[b] (all ages)	Age 85+ number[a]/total number[b] (all ages)
Efficacy and Safety Studies			
D0810C00004	29/189	0/189	0/189
D0810C00005 (KU36-29)[c]	22/66	3/66	0/66
D0810C00006 (KU36-93)	1/19	2/19	0/19
D0810C00009	15/57	0/57	0/57
D0810C00012	9/96	4/96	0/96
D0810C00019	63/264	16/264	1/264
D0810C00020	18/90	4/90	0/90
D0810C00021	6/54	0/54	0/54
D0810C00039	42/123	7/123	0/123
D0810C00041	39/156	5/156	0/156
D0810C00042	40/298	9/298	0/298
D0810L00001	7/44	0/44	0/44
D9010C00008	4/33	4/33	0/33
Total number of patients in Module 5.3.5 studies	**295/1489**	**54/1489**	**1/1489**
Human PK Studies			
D0810C00001 (KU36-64)	3/12	0/12	0/12
D0810C00002 (KU36-92)	19/98	2/98	0/98
D0810C00008 (KU36-44)	4/54	0/54	0/54
D0810C00010 (KU36-37)	1/6	0/6	0/6
Human PD Studies			
D0810C00007 (KU36-13)	10/60	2/60	0/60
Biopharmaceutical Studies			
D0810C00024	13/134	6/134	0/134

a Number of patients within each age category that were randomised and received study treatment
b Total number of patients in the study that were randomised and received study treatment
c For D0810C00005, the treatment date was missing for 7 patients. As a result, the ages of these 7 patients were based on their date of consent for the study.
eCTD Electronic Common Technical Document; MAA Marketing Authorisation Application; PD Pharmacodynamic; PK Pharmacokinetic

Supportive studies

Study D0810C00041

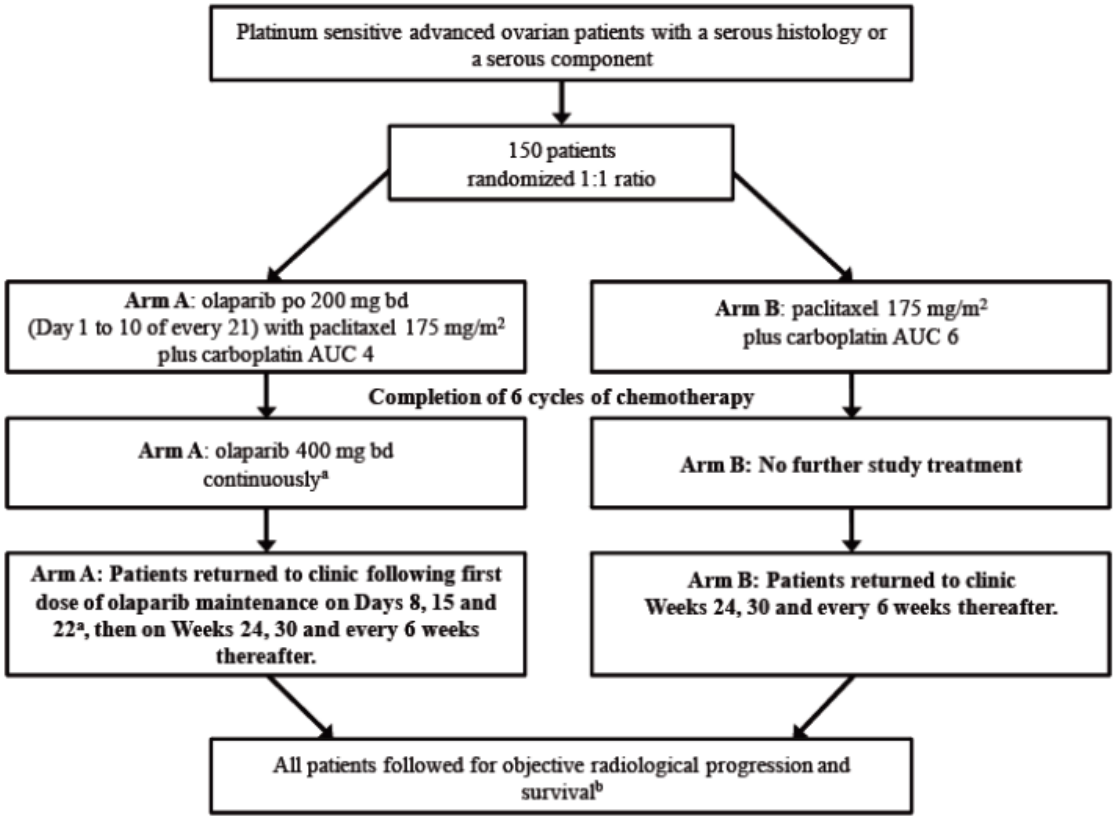
This was a Phase II, Open-Label, Randomised, Comparative, Multicentre Study to Compare the Efficacy and Tolerability of Olaparib in Combination with Paclitaxel and Carboplatin Versus Paclitaxel and Carboplatin Alone in Patients with Platinum Sensitive Advanced Serous Ovarian Cancer

Design

This was a Phase II open-label, randomised, comparative, multicentre study in patients with advanced platinum-sensitive (disease progression >6 months after completion of their last platinum regimen) serous ovarian cancer who had received no more than 3 previous platinum-containing regimens. Patients were randomised in a 1:1 ratio to 1 of 2 treatment groups, each of which comprised 2 phases. - Group A ("O/C4/P"; n=81): combination phase – olaparib (200 mg bd on days 1-10 of a 21-day cycle) in combination with paclitaxel and carboplatin (AUC4) for 6 cycles; maintenance phase – olaparib monotherapy (400 mg bd).

- Group B ("C6/P"; n=81): combination phase – paclitaxel and carboplatin (AUC6) for 6 cycles; post completion (maintenance phase) – no treatment was administered.

Figure 8: Overview of study 41 design



a Upon completion of Cycle 6 (ie, 21 days after last dose of chemotherapy), patients randomised to the O/C4/P arm (Arm A) were to continue to receive olaparib at the maintenance dose of 400 mg bd continuously. Patients who prematurely discontinued the combination of O/C4/P were permitted to participate in the olaparib maintenance phase as long as they had completed at least 4 cycles of study treatment in the combination phase and had not received any other anti-cancer therapy between completion of the combination phase and commencing olaparib maintenance. Patients randomised to O/C4/P who had not completed at least 4 cycles of chemotherapy were to receive no further study treatment, and other treatment options were at the discretion of the investigator.
b Following confirmed objective disease progression as per RECIST criteria, patients continued to be contacted to assess survival status until final analysis of OS and to collect subsequent cancer therapy details including best response (unless patient withdrew consent).
AUC Area under the plasma concentration-time curve; bd Twice daily; CSR clinical study report; O/C4/P Olaparib in combination with carboplatin AUC4 and paclitaxel; OS Overall survival; po Per os; RECIST Response Evaluation Criteria in Solid Tumours

Objectives

The primary objective was to compare the efficacy of olaparib in combination with paclitaxel and carboplatin versus paclitaxel and carboplatin alone, as assessed by PFS (blinded independent central review).

Key secondary objectives included OS, percentage change in tumour size, ORR, CA-125 and/or RECIST response, CA-125 response rate, safety and tolerability.

Retrospective exploratory analyses (including TSST) were conducted in the overall population and by *BRCA* mutation status. An analysis of efficacy by *BRCA* mutation status was pre-specified in the SAP that was finalised prior to unblinding of the data for primary analysis.

Inclusion/Exclusion criteria

Key inclusion criteria included:

• Aged ≥18 years of age (patients in Japan were to be ≥20 years old).

• Histologically or cytologically diagnosed ovarian cancer with a serous histology or serous component, including primary peritoneal and fallopian tube cancer.

Patients who had received no more than 3 previous platinum-containing regimens and were progression free, in the opinion of the investigator, for a minimum of 6 months following completion of their last platinum-containing regimen, prior to randomisation in the study.

• At least 1 lesion, not previously irradiated, that could be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which had to have short axis ≥15 mm) with CT or MRI and which was suitable for accurate repeated measurements.

• ECOG PS ≤2

Key exclusion criteria included:

• Any previous treatment with PARP inhibitors 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.

Statistical Methods

The primary outcome variable, PFS, was based on the blinded independent central review of RECIST v1.1 data. Stratified log-rank test with strata defined for the number of prior platinum-containing treatment line (1 or >1) and time to disease progression or death following previous platinum-containing therapy (>6 to ≤12 months versus >12 months) were used for PFS and OS.

Analyses by BRCA mutation status

Table 49: Study 41: Summary of gBRCA and tBRCA mutation status

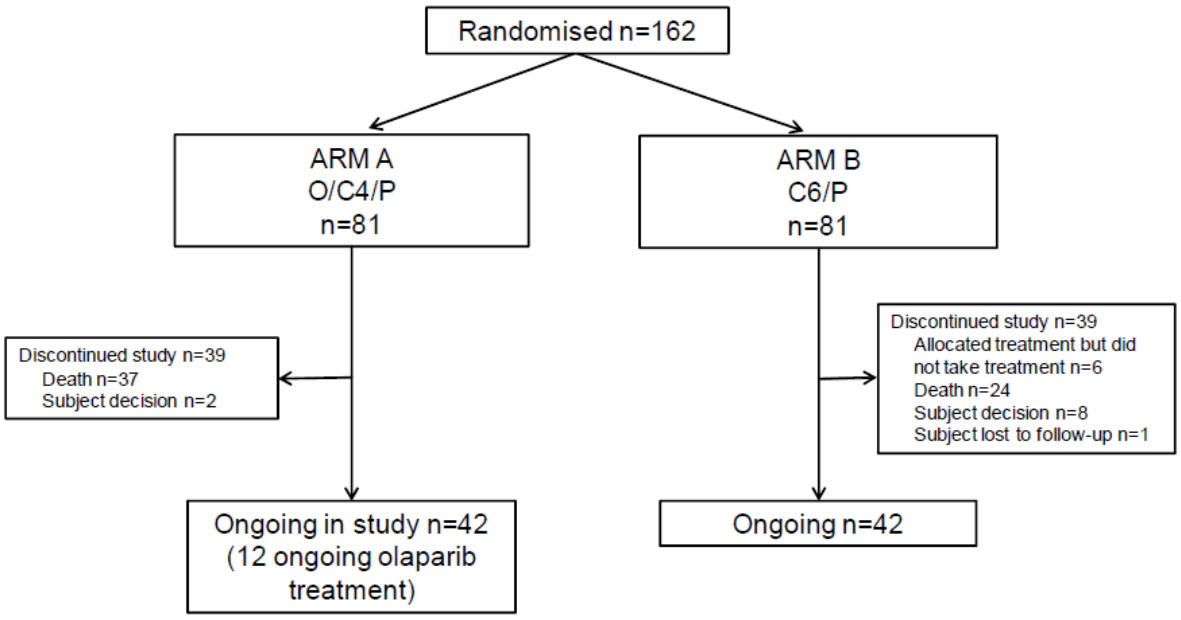
		Tumour *BRCA* (n)				
		Mutant	Wild type	Unknown/VUS	Missing[a]	Total
Germline *BRCA* (n)	Mutant	9*	2*	1*	11*	**23**
	Wild type	1*	5**	0**	5**	**11**
	Unknown/VUS	1*	0**	0**	0**	**1**
	Missing[a]	16*	49**	7**	55	**127**
	Total	**27**	**56**	**8**	**71**	**162**

a Missing = *BRCA* mutation status not determined (no data or incomplete data and no deleterious, suspected deleterious or variant of unknown significance observed).
**BRCAm* dataset: defined as either tumour or germline mutation (total n=41).
***BRCAwt* or unknown (VUS) significance dataset: defined as wild type or variant of unknown significance by either germline or tumour (and not *BRCAm*) (total n=66).
BRCA Breast cancer susceptibility gene; *BRCAm gBRCA* and/or *tBRCA* mutated; *BRCAwt*/VUS *gBRCA* and/or *tBRCA* wild type/VUS; CSR Clinical study report; *gBRCA* Germline *BRCA*; *tBRCA* Tumour *BRCA*;
VUS Variants of unknown significance

Patient disposition

Patients were enrolled at 43 sites in 12 countries (Australia, Belgium, Canada, Czech Republic, Germany, Italy, Japan, the Netherlands, Panama, Spain, UK, USA). A total of 162 patients were randomised in this study, with 81 patients randomised to each group.

Figure 9: Summary of patient disposition: All patients



Data cut-off: 26 November 2012.

Patient demographics and baseline characteristics

The majority of patients were White (85.8%) with a mean age of 58.5 years (range 27 to 79 years).

Table 50: Summary of patient characteristics at baseline: FAS

	Number (%) of patients		
	O/C4/P N=81	C6/P N=81	Total N=162
Number of prior platinum containing treatment lines			
1	58 (71.6)	53 (65.4)	111 (68.5)
>1	23 (28.4)	28 (34.6)	51 (31.5)
Time to disease progression on completion of the previous platinum therapy			
>6 to ≤12 months	39 (48.1)	40 (49.4)	79 (48.8)
>12 months	42 (51.9)	41 (50.6)	83 (51.2)
ECOG performance status			
(0) Normal activity	58 (71.6)	63 (77.8)	121 (74.7)
(1) Restricted activity	21 (25.9)	15 (18.5)	36 (22.2)
(2) In bed <50% of the time	2 (2.5)	1 (1.2)	3 (1.9)
Missing	0	2 (2.5)	2 (1.2)
Primary tumour location			
Peritoneum	3 (3.7)	1 (1.2)	4 (2.5)
Ovary	69 (85.2)	72 (88.9)	141 (87.0)
Fallopian Tube	4 (4.9)	2 (2.5)	6 (3.7)
Primary peritoneal	4 (4.9)	3 (3.7)	7 (4.3)
Other	1 (1.2)	2 (2.5)	3 (1.9)
Missing	0	1 (1.2)	1 (0.6)

AUC Area under the plasma concentration-time curve; BRCA Breast cancer susceptibility gene; C6/P Carboplatin AUC6/paclitaxel; CSR Clinical study report; ECOG Eastern Cooperative Oncology Group; FAS Full analysis set; O/C4/P Olaparib in combination with carboplatin AUC4 and paclitaxel

There was an imbalance in the number of prior platinum treatment lines, which was accounted for in the statistical analysis by the pre-specified covariates.

Table 51: Summary of BRCA mutation status: FAS

***BRCA* mutation status**	**Number (%) of patients**	
	O/C4/P n=81	**C6/P n=81**
*BRCA*m	20 (24.7)	21 (25.9)
*BRCA*wt	30 (37.0)	29 (35.8)
BRCA mutation of unknown significance	4 (4.9)	3 (3.7)
BRCA missing	27 (33.3)	28 (34.6)

BRCA Breast cancer susceptibility gene; *BRCA*m Breast cancer susceptibility gene mutated; *BRCA*wt Breast cancer susceptibility gene wild type; FAS full analysis set.
Data cut-off: 26 November 2012.

Efficacy results

Table 52: Summary of key efficacy outcome variables: study 41

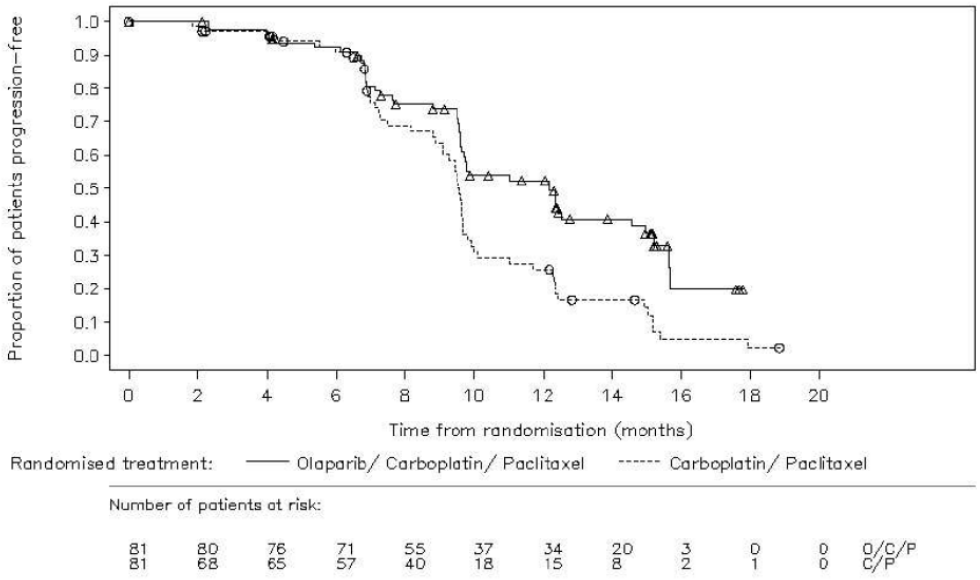
	Full Analysis Set		*BRCA* mutated		*BRCA* wild type / VUS		*BRCA* status missing	
	O / C4 / P	C6 / P	O / C4 / P	C6 / P	O / C4 / P	C6 / P	O / C4 / P	C6 / P
PFS – DCO 10 Oct 2011 – Full Analysis Set								
Number of events: total number of patients (%)	47:81 (58%)	55:81 (68%)	7:20 (35%)	16:21 (76%)	24:34 (71%)	24:32 (75%)	16:27 (59%)	15:28 (54%)
Median PFS (months)	12.2	9.6	Not reached	9.7	NR	NR	NR	NR
HR (95% CI)	0.51 (0.34-0.77)		0.21 (0.08-0.55)		0.77 (0.41-1.44)		0.64 (0.27-1.52)	
P value (2-sided)	p=0.0012		p=0.0015		p=0.4129		p=0.3095	
Time to first subsequent therapy or death (TFST) – DCO 26 Nov 2012 – Full Analysis Set								
Number of events: total number of patients (%)	59:81 (73%)	57:81 (70%)	9:20 (45%)	16:21 (76%)	28:34 (82%)	23:32 (72%)	22:27 (82%)	18:28 (64%)
Median time (months)	14.8	11.3	Not reached	11.3	NR	NR	NR	NR
HR (95% CI)	0.63 (0.44-0.92)		0.13 (0.04-0.33)		0.85 (0.49-1.50)		0.83 (0.42-1.65)	
P value (2-sided)	p=0.0160		p<0.0001		p=0.5725		p=0.5909	
Time to second subsequent therapy or death (TSST) – DCO 26 Nov 2012 – Full Analysis Set								
Number of events: total number of patients (%)	50:81 (62%)	44:81 (54%)	8:20 (40%)	13:21 (62%)	22:34 (65%)	16:32 (50%)	20:27 (74%)	15:28 (54%)
Median time (months)	21.3	25.1	Not reached	18.1	NR	NR	NR	NR
HR (95% CI)	0.94 (0.62-1.41)		0.35 (0.13-0.88)		1.28 (0.66-2.52)		1.52 (0.75-3.16)	
P value (2-sided)	p=0.7571		p=0.0258		p=0.4641		p=0.2502	
OS (interim – 38% maturity) – DCO 26 Nov 2012 – Full Analysis Set								
Number of events: total number of patients (%)	37:81 (46%)	24:81 (30%)	—	—	—	—	—	—
Median OS (months)	Not reached	Not reached	—	—	—	—	—	—
HR (95% CI)	1.38 (0.83-2.29)		—		—		—	
P value (2-sided)	p=0.2113		—		—		—	

OS (final – 62% maturity [FAS]) – DCO 31 January 2014								
Number of events: total number of patients (%)	54:81 (67%)	47:81 (58%)	10:20 (50%)	10:21 (48%)	22:34 (65%)	19: 32 (59 %)	22:27 (81%)	18:28 (64%)
Median OS (months)	33.8	37.6	Not reached	39.2	33.7	36. 7	28.8	27.1
HR (95% CI)	1.17 (0.79-1.73)		1.28 (0.39-4.18)		1.23 (0.65-2.33)		1.17 (0.57-2.37)	
P value (2-sided)	p=0.4379		p=0.6861		p=0.5285		p=0.6699	

AUC Area under the plasma concentration-time curve; *BRCA* Breast cancer susceptibility gene; C6/P Carboplatin AUC6/paclitaxel; CI Confidence interval; CSR Clinical study report; DCO Data cut-off; FAS Full analysis set; HR Hazard ratio; O/C4/P Olaparib in combination with carboplatin AUC4 and paclitaxel; OS Overall survival; PFS Progression-free survival; VUS Variants of unknown significance
Data derived from: Tables 11.2.1.3 and 11.2.1.4, Study 41 CSR; Tables 11.0.2.7 and 11.0.2.7.1, Study 41 CSR Erratum; and Tables 11.0.2.1.9 and 11.0.2.7.0, Study 41 CSR Addendum 2

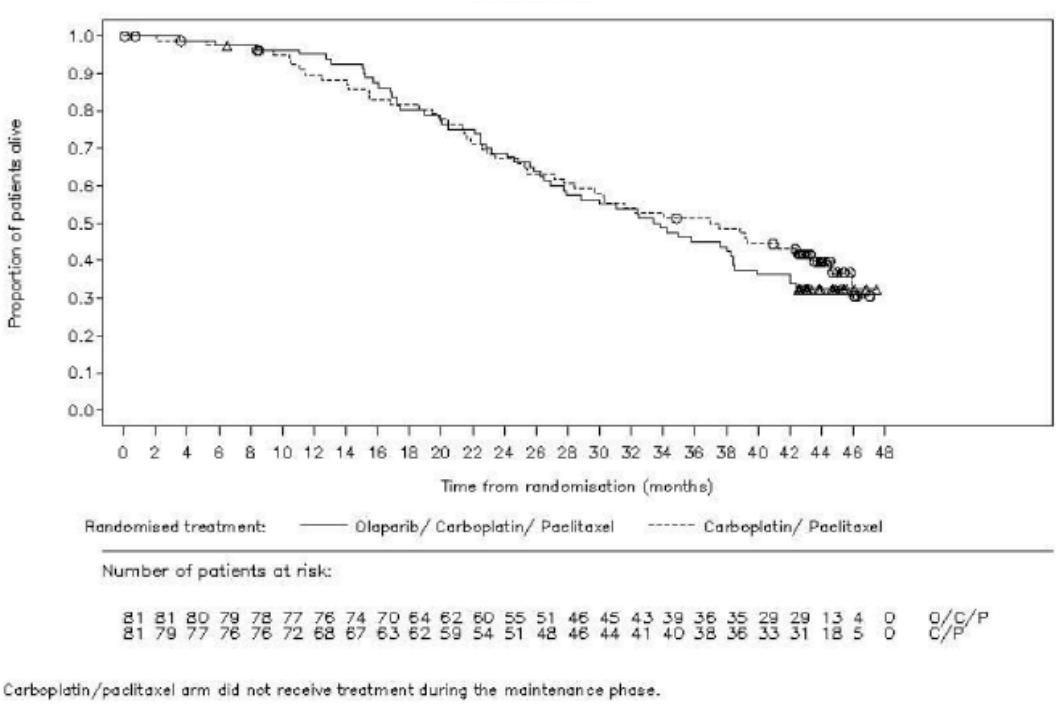
PFS

Figure 10: Kaplan-Meier plot of time to PFS in overall population (DCO 10 October 2011)



Overall survival analysis

Figure 11: Study 41: Kaplan-Meier plot of OS in Full Analysis Set (DCO 31 January 2014)



Carboplatin/paclitaxel arm did not receive treatment during the maintenance phase.

C/P Carboplatin/paclitaxel; CSR Clinical study report; DCO Data cut-off;
O/C/P Olaparib/carboplatin/paclitaxel; OS Overall survival
Data derived from: Figure 11.0.2.4, Study 41 CSR Addendum 2

Survival rates

Table 53: Study 41: Survival rates in the FAS and by BRCA mutation status (DCO 31 January 2014)

	Full Analysis Set		*BRCA* mutated		*BRCA* wild type/VUS		*BRCA* status missing	
	O/C4/P	C6/P	O/C4/P	C6/P	O/C4/P	C6/P	O/C4/P	C6/P
Survival rates	N=81	N=81	N=20	N=21	N=34	N=32	N=27	N=28
6 months (%)	97.5	97.5	100	100	100	100	92.6	92.4
1 year (%)	95.0	89.6	100	94.4	100	93.8	84.9	80.9
2 year (%)	68.8	67.2	85.0	77.8	64.7	75.0	61.7	50.1
3 year (%)	45.0	51.4	60.0	66.7	44.1	50.0	34.7	42.4

AUC Area under the plasma concentration-time curve; *BRCA* Breast cancer susceptibility gene; C6/P Carboplatin AUC6/paclitaxel; CSR Clinical study report; DCO Data cut-off; FAS Full analysis set; O/C4/P Olaparib in combination with carboplatin AUC4 and paclitaxel; VUS Variants of unknown significance
Data derived from: Table 11.0.2.7.0, Study 41 CSR Addendum 2

Potential differences in patients with BRCA1 and BRCA2 mutations

Table 54: Study 41: Assessment of endpoints by BRCA1m and BRCA2m status

	BRCA1m		*BRCA2m*	
Endpoint	Olaparib	Control	Olaparib	Control

Table 54: Study 41: Assessment of endpoints by BRCA1m and BRCA2m status

	BRCA1m		*BRCA2m*	
PFS	4 (33%)	12 (75%)	3 (38%)	4 (80%)
TSST	8 (67%)	12 (80%)	3 (38%)	4 (80%)
OS	7 (58%)	9 (56%)	3 (38%)	1 (20%)

Study D0810C00020

This was a Phase II, Open Label, Non-Randomised Study of AZD2281 in the Treatment of Patients with Known BRCA or Recurrent High Grade Serous/Undifferentiated Tubo-Ovarian Carcinoma and in Known BRCA or Triple Negative Breast Cancer to Determine Response Rate and Correlative Markers of Response

Patients were enrolled into 4 study cohorts:

1) triple negative breast cancer with unknown *gBRCA* mutation status;

2) known *gBRCA* mutated breast cancer;

3) high-grade serous/undifferentiated tubo-ovarian carcinoma with unknown *gBRCA* mutation status;

4) known *gBRCA* mutated ovarian cancer.

All patients received olaparib 400 mg bd until disease progression or until the investigator believed it was in the best interest of the patient to stop treatment. Patients with unknown *gBRCA* status at entry had to provide a DNA sample for *gBRCA* mutation analysis. Data are summarised primarily by confirmed mutation status and tumour type determined from the study data, not the groups defined for study entry.

The primary objective was to determine ORR as evaluated according to RECIST guidelines.

The key secondary objectives included identification of markers of olaparib efficacy through analysis of tumour material; investigation of PFS in patients treated with olaparib; assessment of the safety and tolerability profile of olaparib.

The total study population comprised 91 women (enrolled from 6 centres in Canada), including 65 patients with histologically or cytologically confirmed ovarian cancer (58 serous and 7 non-serous); 13/58 serous and 4/7 non-serous ovarian patients were *gBRCA* mutation carriers. Mean age for the patients with ovarian cancer was 59.4 years (range 39 to 84 years). Patients were heavily pre-treated; 37 patients with ovarian cancer had received 3 or more prior chemotherapy treatments. In total, 64/65 ovarian cancer patients received olaparib, and were included in the safety analysis set. Of the 26 breast cancer patients who received treatment with olaparib, 24 patients were considered to have completed the study.

Ovarian cancer: ORR for all patients with ovarian cancer was 29% (18/63 patients had responses; 95% CI 18.90%, 40.70%). Within this overall group, the ORR in ovarian cancer patients who were *gBRCA* mutation carriers was numerically greater than in those who did not harbour a *gBRCA* mutation (ORR 41% [7/17 patients had responses; 95% CI 21.6%, 64.0%] versus 24% [11/46 patients had responses; 95% CI 13.9%, 37.9%], respectively). Secondary efficacy analyses in patients with ovarian cancer: overall disease control rate (CR + PR + stable disease [SD]) at 16 weeks was 48% (95% CI 37% to 60%); median duration of response was 277 days; median best percentage change from baseline in tumour size was a 14.2% reduction; median PFS as determined by RECIST criteria was

219 days (95% CI 110 to 273 days). In addition, of 54 patients with ovarian cancer who were evaluable for CA-125 response, 13 (24.1%) had a complete response and 4 (7.4%) had a partial response; overall response rate was 31% (95% CI 21% to 45%) and median best change from baseline in CA-125 was a 38.5% reduction. Overall, 23/64 (35.9%) ovarian cancer patients had either a RECIST or a CA-125 response. Median PFS for the ovarian cancer patients overall, determined by either RECIST or CA-125 response, was 108 days (95% CI 55 to 220 days).

Study D0810C00042

This was a Phase II, Open-Label, Non-Randomised, Non-Comparative, Multicentre Study to Assess the Efficacy and Safety of Olaparib Given Orally Twice Daily in Patients With Advanced Cancers Who Have A Confirmed Genetic BRCA1 And/Or BRCA2 Mutation.

This was a single-arm, open-label study. After starting treatment with olaparib 400 mg bd orally, patients attended periodic clinic visits for assessment of safety and efficacy until confirmed objective disease progression occurred according to RECIST v1.1. Following confirmed disease progression, patients discontinued olaparib treatment but could receive any other cancer treatment at the investigator's discretion.

The primary objective was to assess the efficacy of oral olaparib in patients with advanced cancer who had a confirmed germline *BRCA1* and/or *BRCA2* mutation by assessment of tumour response.

Key secondary objectives were to assess the efficacy of oral olaparib in patients with advanced cancers who had a confirmed germline *BRCA1* and/or *BRCA2* mutation, by assessment of objective response rate, progression-free survival, overall survival, duration of response and disease control rate, as well as to determine the safety and tolerability of oral olaparib in patients with advanced cancers who had a confirmed germline *BRCA1* and/or *BRCA2* mutation.

A total of 298 patients (62 breast cancer patients, 193 ovarian cancer patients, 23 pancreatic cancer patients, 8 prostate cancer patients, and 12 patients with another type of cancer) received olaparib at 13 sites in 6 countries (Israel, USA, Australia, Germany, Spain, and Sweden). All 298 patients were included in the safety analysis set. Patients were ≥18 years of age with histologically and/or cytologically confirmed malignant solid tumours that were refractory to standard therapy and for which no suitable, effective/curative therapy existed. Patients had to have a confirmed documented deleterious or suspected deleterious *gBRCA* mutation. The demographic characteristics of this heavily pre-treated advanced disease study population were generally representative of each tumour type, independent of *gBRCA* status. Seventy-three (24.5%) patients had received at least 3 regimens of previous chemotherapy prior to study entry. A total of 151 (50.6%) patients had 4 or more chemotherapy regimens.

A total of 78/298 (26.2%) patients experienced a complete or partial tumour response in this study. Responses were observed in all tumour type categories: 8/62 (12.9%) breast cancer patients, 60/193 (31.1%) ovarian cancer patients, 5/23 (21.7%) pancreatic cancer patients, 4/8 (50%) prostate cancer patients and 1/12 (8.3%) patients with other cancer types.

The overall median duration of response from onset of response was 208 days; 204 days in the breast cancer group, 225 days in the ovarian cancer group, 134 days in the pancreatic cancer group, 326.5 days in the prostate cancer group, and 165 days in the other cancer group. At 16 weeks, disease control was observed in 155 (52%) patients in the study; 23 (37.1%) in the breast cancer group, 112 (58%) in the ovarian cancer group, 11 (47.8%) in the pancreatic cancer group, 5 (62.5%) in the prostate cancer group, and 4 (33.3%) in the other cancer group.

The proportion of patients who were progression free at 6 months was 29% in the breast cancer group, 54.6% in the ovarian cancer group, 36.4% in the pancreatic cancer group, and 62.5% in the prostate cancer group. The proportion of patients who were alive at 12 months was 44.7% in the breast cancer group, 64.4% in the ovarian cancer group, 40.9% in the pancreatic cancer group, and 50% in the prostate cancer group.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

At the time of the study 19, there were no therapeutic agents approved for maintenance treatment of ovarian cancer after a response to platinum-containing regimens and no standard treatment after standard platinum based chemotherapy was clearly defined. In this context, using placebo as comparator to determine the efficacy of olaparib was considered acceptable.

Study 19 enrolled patients with high-grade serous ovarian cancer. Patients with low grade ovarian carcinoma (grade 1) were excluded from the study. High-grade serous ovarian cancers (HGSOC) are known to be enriched for defects in an essential DNA damage repair pathway called homologous recombination (Bowtell 2010). In the absence of any convincing clinical efficacy/safety data in other histological types than 'high grade serous', the indication is restricted to patients with high grade serous ovarian cancer (excluding grade 1 based on the investigators/pathologists' assessment) (see section 4.1 of the SmPC).

The study was performed in serous ovarian cancer patients with partially platinum-sensitive disease (platinum-free interval of 6 to 12 months) and platinum-sensitive disease (platinum-free interval of > 12 months) who had received 2 or more previous platinum-containing regimens. The last chemotherapy course must have consisted of a minimum of 4 treatment cycles, although complete standard platinum based chemotherapy patients is at least 6 cycles. However, across both arms, the majority of patients received 6 or more cycles of platinum immediately prior to randomisation. Therefore, it can be assumed that chemotherapy received immediately prior to randomisation was given according to standard clinical practice in both arms and that there was no under treatment that would have favoured the experimental arm.

Platinum sensitivity was defined as disease progression greater than 6 months after completion of their penultimate platinum regimen (from last dose) prior to enrolling on this study. In the last platinum regimen prior to enrolling on this study, patients had to demonstrate an objective stable maintained response (CR [complete response] or PR [partial response]) and this response had to be maintained to allow entry to the study. The assessment of response (PR or CR) to platinum as described in the proposed indication prior to initiation of olaparib maintenance therapy should be confirmed as per RECIST and/or as per CA-125 criteria as defined by Gynecologic Cancer InterGroup (GCIG) (at least a 50% reduction in CA-125 levels from the last pre-treatment sample, confirmed 28 days later) following completion of two or more previous platinum containing chemotherapy (see SmPC section 5.1).

Patients with stable disease (SD) following platinum-based chemotherapy were not included in the pivotal maintenance Study 19. Additional studies are needed to support efficacy of olaparib for maintenance in patients with stable disease following platinum-based chemotherapy. At this time, this population could not be included in the scope of the indication.

The primary endpoint was PFS although it was highlighted in the protocol assistance that overall survival (OS) is in general preferred as primary endpoint. However, the CHMP agreed that different subsequent therapies are expected to confound OS data making difficult the interpretation of the OS data. A final OS analysis for study 19 will be conducted at 85% maturity of the overall population (75% maturity estimated for the BRCA mutated population) will be provided by the Applicant as an Annex II condition.

Knowledge of BRCA mutation status prior to study entry was not mandated, as it was considered by the Applicant that the population of patients with platinum-sensitive relapsed serous ovarian cancer would already be suitably enriched for HRD tumours. Neither primary nor secondary objectives were planned in the BRCA subgroup. Patients were classified as BRCA mutated by virtue of having BRCA mutated status in either their blood or tumour sample, although both copies of the BRCA gene must be altered/mutated before an individual will develop cancer. At the time of the final PFS analysis and first interim OS analysis (38% maturity), gBRCA mutation status was known for only a small subset of patients (97/265; 36.6%). Final BRCA status was determined, mostly retrospectively, for almost all patients.

Based on the efficacy data obtained from study 19 (see efficacy data below) in patients with BRCA mutation detected in either the germline or the tumour and considering that data from studies 19 and 41 showed that, when mutations are detected in the germline these mutations are also present in the tumour tissue (although there was a false negative rate associated with the detection of single exon indels), it is considered that patients are eligible for olaparib treatment if they have a confirmed deleterious or suspected deleterious BRCA mutation (i.e., a mutation that disrupts normal gene function) in either the germline or the tumour (detected using an appropriately validated test) (see SmPC section 5.1).

Efficacy data and additional analyses

Dose-response studies

Study 09 assessed the efficacy of olaparib when dosed at 100 mg bd and 400 mg bd. Activity was seen at the lower dose and some of these responses were durable, but there was a numerical advantage for the higher dose. Study 12 investigated the efficacy of olaparib 200 mg bd, olaparib 400 mg bd and PLD, showing a slight numerical advantage of olaparib 400 mg bd compared to treatment with olaparib 200 mg without any statistically significant difference between the groups. Pharmacodynamic data did not evidence a relationship between the magnitude of effect and the dose administered. Furthermore, neither study 09 nor study 12 provided statistically significant difference between the different investigated doses. Higher numbers (%) of patients with most common AEs (any grade and at least grade 3) were observed in patients receiving 400 mg bid versus 200 mg bid. However, the efficacy and tolerability of a lower starting dose (i.e. 200 mg bd) has not been studied in the maintenance treatment setting. In addition, the safety profile of the 400 mg bd capsule dose in the maintenance treatment setting is consistent with that observed in the larger monotherapy pool of patients who have received this dose and is considered to be acceptable (see clinical safety). Therefore, the proposed dose of 400 mg bd was considered acceptable.

Pivotal study

The study 19 met its primary objective of statistically significantly improved PFS for olaparib maintenance monotherapy compared with placebo in the overall population (HR 0.35; 95% CI 0.25 0.49; p<0.00001), moreover, pre planned subgroup analysis by BRCA mutation status identified patients with BRCA mutated ovarian cancer (n=136, 51.3%) as the subgroup that derived the greatest clinical benefit from olaparib maintenance monotherapy (see SmPC section 5.1).

The benefit on PFS was partly maintained at second progression. No negative effects on subsequent lines of therapy were observed with favourable TSST in the overall population (HR of 0.53, p<0.0001, medians 14.8 and 19.1 months) used as a surrogate for PFS2.

At the time of interim OS analyses at 58% maturity of the overall population, there was no evidence of a detrimental effect in OS in the olaparib treated patients. The OS survival data were not yet sufficiently mature to allow comparison between two groups. The final OS survival analysis will be done at 85% maturity (after 226 deaths) (see Annex II conditions).

In addition, the observed benefit of olaparib in patients with BRCA mutated ovarian cancer will be further defined in the ongoing SOLO-2 study, a randomised (2:1) phase III study in 264 patients (see Annex II conditions). SOLO-2 will also allow a prospective validation of 'BRCA mutated' biomarker.

No statistically significant differences were observed between olaparib and placebo in patient reported symptoms or HRQoL as measured by improvement and worsening rates in the FACT/NCCN Ovarian Symptom Index (FOSI), Trial Outcome Index (TOI) and Functional Analysis of Cancer Therapy–Ovarian total score (FACT O total) (see SmPC section 5.1). Although quality of life results did not show significant differences between groups, additional data will be provided from the ongoing confirmatory phase III study SOLO-2 (D0816C00002) (see above).

There are no data on retreatment with Lynparza following subsequent relapse (see SmPC section 4.2 and 5.1).

The indication claimed was limited to 'BRCA mutated' tumours (due to germline and somatic BRCA mutations). The choice of this subgroup (51% of patients) was considered a priori acceptable as it was based on a biological rationale.

In BRCA-mutated patients (n=136) there was a statistically significant improvement in PFS, TFST, and TSST. The median PFS improvement was 6.9 months over placebo for olaparib treated patients (HR 0.18; 95% CI 0.10 0.31; p<0.00001; median 11.2 months versus 4.3 months). The investigator assessment of PFS was consistent with a blinded independent central radiological review of PFS. The time from randomisation to start of first subsequent therapy or death (TFST) was 9.4 months longer for olaparib treated patients (HR 0.33; 95% CI 0.22–0.50; p<0.00001; median 15.6 months versus 6.2 months). The time from randomisation to start of second subsequent therapy or death (TSST) was 8.6 months longer for olaparib treated patients (HR 0.44; 95% CI 0.29 0.67; p=0.00013; median 23.8 months versus 15.2 months. There was no statistically significant difference in OS (HR 0.73; 95% CI 0.45 1.17; p=0.19; median 34.9 months versus 31.9 months). Within the BRCA mutated population the disease control rate at 24 weeks was 57% and 24% for patients in the olaparib and placebo groups, respectively (see SmPC section 5.1). Therefore, a clinically relevant benefit was demonstrated for this group of patients.

In the 'BRCA wildtype/VUS" group (non-'BRCA mutated' patients) a progression-free survival hazard ratio of 0.54 (95% confidence interval (CI) 0.34, 0.85; p=0.00745) was observed.

Additional expert consultation

The SAG was consulted on the availability of biomarkers to better define olaparib-sensitive patient population and on whether a trial could confirm hypotheses on efficacy in the groups of BRCA mutated and BRCA wild-type population. In relation to BRCA mutated population (BRCA1 and BRCA2), the SAG condisered that in view of the current state of knowledge that there was no better validated biomarker method available than the detection of BRCA mutation (somatic and germline) by gene sequencing although there are other mechanisms involved in DNA repair. BRCA mutation detected by gene sequencing was considered a valid and predictive marker to identify patients that could benefit from olaparib. However, the SAG was uncertain about the true effect of olaparib in this patient population due to the shortcomings of the pivotal study being a small phase II randomised study with a large percentage of censored observations for PFS analysis, and in view of the absence of improvement in overall survival.

In relation to BRCA wild-type population, there is currently no validated, robust and routinely applicable test available to identify patients who will likely respond or may not respond to olaparib. In order to allow identification of olaparib-sensitive patients in this population, the SAG considered that a prospective randomised trial was necessary and should be based on adequate molecular identification of sensitive tumours. This prospective study should be of sufficient size and investigate other genes that might influence DNA-repair processes, especially homologous recombination repair (HRR). In view of the genetic variability of tumours with somatic mutation, tumours samples should be preferably taken both in primary and relapse tissues. In addition, tumour sensitivity upon platinum treatment was not considered an adequate criterion to select patients who may respond to PARP inhibitors as it may induce reversion of BRCA mutations and clinically tumour sensitivity to platinum-treatment is difficult to assess unambiguously.

Extended sample analysis of study 19 was also not expected to generate convincing data to properly identify patients who will likely respond to olaparib. However, robust exploratory and validation strategies can be put in place using this data set to generate hypotheses that may support future prospective studies, or confirm outcome of other biomarker driven prospective studies.

The SAG discussed the feasibility of a post-approval prospective study. In relation to BRCA mutated patient population, a confirmatory phase III randomised double-blind placebo-controlled multicentre study to assess the efficacy of olaparib as maintenance monotherapy in patients with BRCAm platinum sensitive relapsed (PSR) high grade serous ovarian cancer (HGSOC) (SOLO-2) is ongoing and it is foreseen that enrolment of the last patient will occur in 2015. The outcome of this study is expected to provide further evidence on the safety and efficacy of olaparib in the BRCA mutated patient population and the marketing authorisation of olaparib in this patient population is not expected to hamper the conduct of this trial.

Regarding BRCA wild type population, the SAG considered that the sample size of the study proposed by the Applicant was too small and has serious concerns about the external validity of the study in view of the suspected high biological heterogeneity of tumours in this patient population. A large phase 3 trial in patient with high grade serous might be considered appropriate but marketing authorisation of olaparib for this indication would seriously hamper successful execution of such a study. Retrospective molecular analysis of tumours from patients in this study might allow the identification of specific genes involved in DNA repair to be identified as biomarkers for response to olaparib.

Considering the shortcomings of study 19 and the less convincing PFS results in the wild type population, the inclusion of BRCA wild type patients in the indication could be of concern in view of uncertainty about long term safety and the resulting overall benefit-risk balance.

The SAG also discussed extrapolation of efficacy/safety results from germline to somatic "BRCA mutated" ovarian cancer patients. If proven to be pathological mutations, the SAG expected that olaparib will have similar activity/biological effect in tumours with somatic mutations to the activity in tumours with germline mutations.

However, the SAG was concerned about extrapolation in terms of the magnitude of the effect in view of potential differences in biological composition such as higher level of heterogeneity and degree of genomic instability in tumours with somatic mutations versus tumours with germline mutations. In view of the limited data available, additional evidence in somatic BRCA mutated patients would be of value.

Based on available data and taking into account the SAG view, the CHMP considered the detection of BRCA mutation (somatic and germline) by gene sequencing was a biomarker of significant clinical value for selection of patients given an apparent and clinically significant PFS benefit in the whole ‘BRCA-mutated’ group and current unavailability of biomarkers that could better predict responses in patients.

In the study 19, the BRCA mutation status based on local testing was known at study entry for 37% of patients (36% in the olaparib group and 37% in the placebo group). Further germline or tumor status was studied retrospectively for 60% and 79%, respectively. The composite nature of biomarker 'BRCA mutated' was discussed as it comprised: (1) BRCA testing based on CRF data for germline mutation testing (blood-based tests); (2) BRCA testing of germline mutations by next generation sequencing (NGS) technology; (3) BRCA testing of mutations in tumors by NGS. While PFS HRs were similar irrespective of BRCA tests used in BRCAm group of patients (0.10; 0.15; 0.16, respectively), a slightly lower HR was noticed for local testing. In the context of current changes in technologies in practice for detection of germline BRCA mutations a spectrum of mutations could be different and, consequently, more heterogeneous population than that tested in clinical trials could become eligible for the treatment with olaparib (Norquist et al, 2013). Depending on types of mutations determined, the responses of patients might differ. Currently there is no evidence of such differential activity of olaparib. However, at the time of the Study 19 start, patients that were clinically selected for genetic testing and counselling might represent a higher proportion of the study patient population, than it would be in currently ongoing studies and in clinical practice in the future. The phase IV study in patients with relapsed platinum sensitive ovarian cancer who are in complete or partial response following platinum based chemotherapy and who carry loss of function germline or somatic BRCA mutation(s) will provide further information addressing this uncertainty (see Annex II conditions).

The Applicant is also planning to conduct a randomised Phase III study in patients with somatic BRCA mutated ovarian cancer (study SOLOIST) and is recommended to share the results when available.

Although grouping of patients with germline BRCA mutations and patients harbouring somatic BRCA mutations was acceptable on the basis of biological rationale, it was nevertheless questioned from clinical perspective, since patients with germline BRCA mutations (BRCA1 and BRCA2) constitute clinically distinct groups, with age differences and differences in survival rates. It is currently not clear whether differences in outcomes between BRCA1 and BRCA2 mutated cancers would be observed in patients with somatic BRCA mutations. The Applicant is recommended to further investigate the prognostic and predictive value of tests that would allow quantitative assessment of genomic instability and homologous recombination deficiencies in patients with specific mutations in BRCA1/BRCA2 and other HRR-related genes. The Applicant is also recommended to assess efficacy and safety of olaparib in patients with large genomic rearrangements in BRCA1 and BRCA2 genes.

In addition, for patients with sBRCAm, only few data are currently available even though consistent results were observed. In addition, whether these patients can be considered as truly somatic remain uncertain since 8 of 18 patients were considered as germline BRCA wildtype based on local testing, which might miss detection of germline BRCA mutation depending on testing method. Among 37 patients categorised as long term responders (defined as patients on treatment for >2 years) in Study 19, 3 patients were defined as patients with somatic BRCA mutations and 2 of them were treated with olaparib. Therefore, the CHMP considered that further efficacy data in patients with sBRCA mutation should be provided as Annex II condition.

As to intra-tumor heterogeneity, the available data are still limited and were provided using experimental DNA-based methodology. DNA-based approach used by the Applicant was confined to a single, archival tumour samples per patient and so does not inform about temporal and inter-lesional variation. The Applicant is recommended to investigate tumour heterogeneity and mechanisms of resistance in patients with BRCA-mutated tumours and tumours harbouring mutations in HRR-related genes.

No studies have been conducted in paediatric patients and the efficacy of olaparib in children and adolescents has not been established (see SmPC section 4.2).

2.5.4. Conclusions on the clinical efficacy

The pivotal study 19 provided initial and clinically significant evidence of PFS benefit in patients harbouring BRCA-mutated tumors (germline and/or somatic mutations). The definition of this group was based on several biomarkers defined overall as 'BRCA mutation', some of which were used retrospectively. A prospective validation of a biomarker 'BRCA mutation' will be provided by the SOLO-2 study (D0816C00002). The results of this study will substantiate the assessment of efficacy results reported by the study 19. Further efficacy data will verify the impact of the olaparib on several clinical outcomes relevant to assessment of efficacy in maintenance setting. A more comprehensive analysis of quality of life will allow to substantiate an observed benefit, while further understanding of mechanisms of resistance due to optional collection of samples post-progression performed in SOLO-2 study will allow to address potential uncertainties pertaining to long-term benefit.

The OS data performed at 58% maturity (52% for BRCA mutated group) did not show statistically significant differences between olaparib-treated and placebo-treated patients. To further address efficacy at long term, the final OS analysis will be provided and will occur at 85% of maturity for overall study population (at 75% for BRCA mutated population).

There are limited data in patients with somatic BRCA mutations (see SmPC sections 4.2 and 5.1). However, activity similar to that in patients with germline BRCA mutations is expected based on strong biological rationale. In addition, available clinical data indicate efficacy of olaparib in patients with somatic BRCA mutations. Nevertheless, clinical data need to be further acquired in these patients. Therefore, it is requested to address uncertainties mainly with respect to efficacy of olaparib in this subpopulation of patients within the overall group of patients with 'BRCA-mutated' tumors. An open-label phase IV study will provide further clinical data in patients harbouring tumors with somatic BRCA mutations.

Therefore, the CHMP considers the following measures (PAES) necessary to address issues related to efficacy:

- In order to further define the long term efficacy of olaparib in patients with platinum sensitive relapsed BRCA mutated high grade serous ovarian cancer, the MAH should submit the final Overall Survival (OS) analysis of D0810C00019, a phase II randomised, double blind, multicentre study.
- In order to further confirm the observed efficacy of olaparib in patients with platinum sensitive relapsed BRCA mutated high grade serous ovarian cancer, the MAH should submit the results of study D0816C00002 (SOLO-2), a phase III randomised double-blind placebo-controlled multicentre study.
- In order to further define the efficacy of olaparib in the subpopulation of patients with platinum sensitive relapsed somatic BRCA mutated high grade serous ovarian cancer, the MAH should conduct and submit the results of a phase IV, open label, single arm, non-randomised, multicentre study in patients with relapsed platinum sensitive ovarian cancer who are in complete or partial response following platinum based chemotherapy and who carry loss of function germline or somatic BRCA mutation(s).

The MAH is required to provide the final CSRs (see Annex II) and interim reports in line with the RMP (see section 2.8).

2.6. Clinical safety

Across the entire clinical programme, as of 20 May 2013, an estimated 2034 patients with ovarian, breast, pancreatic, gastric or a variety of other solid tumours have received treatment with olaparib

across the dose range 10 mg once daily (od) to 600 mg bd in Applicant-sponsored, investigator-sponsored, and collaborative group studies. Olaparib has been given as either monotherapy (15 studies, an estimated 1162 patients) or in combination with other chemotherapy/anti-cancer agents (23 studies, an estimated 872 patients). Many of these combination studies are ongoing.

The safety data summarised in the dossier are primarily from 801 olaparib-treated patients from the Applicant-sponsored studies where olaparib was administered as a monotherapy at a dose of 400 mg bd (capsules) (see Table 55).

Patient exposure

The data from patients treated with olaparib in pivotal Study 19 were pooled with the data from patients receiving olaparib 400 mg bd in other monotherapy studies for the treatment of a range of tumour types, including ovarian cancer and BRCA-mutated cancers, providing a larger source of safety information (n=735).

Table 55: Number of patients exposed to olaparib 400 mg bd monotherapy

Study/pooled dataset	Number of patients receiving olaparib 400 mg bd (all tumour types)	Number of patients receiving olaparib 400 mg bd with *BRCA* mutated ovarian cancer
Olaparib 400 mg bd monotherapy pooled data set[a] :	**735**	**397**
Study 19 *(pivotal Ph II PSR ovarian cancer study)*	136	74
Study 1 *(Ph I dose escalation study in Japanese patients)*	6	NA
Study 2 *(Ph I FTIM study)*	8	5[b]
Study 7 *(Ph I concentration-response study)*	12	NA
Study 8 *(Ph II gBRCA breast proof of concept study)*	27	NA
Study 9 *(Ph II gBRCA ovarian proof of concept study)*	33	33
Study 12 *(Ph II gBRCA ovarian monotherapy dose finding)*	55[c]	54[d]
Study 20 *(Ph II relapsed ovarian and breast cancer study)*	90	17
Study 24 *(Ph II formulation comparison study)*	37	21
Study 42 *(Ph II advanced gBRCA mutated tumours study)*	298	193
Study D9010C00008 *(Ph II monotherapy colorectal cancer study)*	33	NA
Study 41 maintenance phase *(Ph II ovarian combination followed by maintenance)*	**66**	**20**
Total	**801**	**417**

Patient numbers are derived from individual CSRs.

a Patients were included in the monotherapy pooled dataset if their first dose on study was olaparib 400 mg bd capsule. In Study 12, patients who crossed over from liposomal doxorubicin to olaparib 400 mg bd were also included. In Study 24, patients were included if their first dose was olaparib 400 mg bd capsule; those who took olaparib 400 mg bd tablet first were excluded, even if they took 400 mg bd capsule at a later date

b In the CSR for Study 2, 6 patients are stated as having BRCAm ovarian cancer; however this includes a patient with a tumour location of 'other female genital' and this patient has not been included in the BRCAm ovarian cancer subgroup of the monotherapy pool.

c N=55 comprises 32 patients who started on olaparib 400 mg bd and 23 patients who crossed over from doxorubicin to olaparib 400 mg bd. There were 2 patients who, after crossing over from doxorubicin, did not actually receive olaparib.

d Study 12 was performed in patients with BRCAm ovarian cancer; however, 1 patient has been excluded from the BRCAm ovarian cancer subgroup of the monotherapy pool as no tumour location was recorded.

Table 56: Number (%) of patients on treatment: 400 mg bd monotherapy pooled dataset, Safety Analysis Set

Treatment duration	All patients (advanced solid tumours) N=735	*BRCAm* ovarian cancer N=397
>0	735 (100)	397 (100)
≥1 month	674 (91.7)	380 (95.7)
≥3 months	499 (67.9)	303 (76.3)
≥6 months	320 (43.5)	207 (52.1)
≥12 months	140 (19.0)	94 (23.7)
≥18 months	72 (9.8)	49 (12.3)
≥24 months	41 (5.6)	25 (6.3)
≥30 months	28 (3.8)	20 (5.0)
≥36 months	19 (2.6)	13 (3.3)
≥42 months	4 (0.5)	3 (0.8)

Note: Rows are cumulative and subjects are included if they have taken treatment up to that day

Table 57: Number (%) of patients on treatment: Study 19, Safety Analysis Set

	All patients		*BRCAm*	
Approximate treatment month (actual days)	Olaparib 400 mg bd N=136	Placebo N=128	Olaparib 400 mg bd N=74	Placebo N=62
Day 1	136 (100)	128 (100)	74 (100)	62 (100)
≥1 month (28 days)	133 (97.8)	128 (100)	72 (97.3)	62 (100)
≥3 months (84 days)	126 (92.6)	108 (84.4)	68 (91.9)	50 (80.6)
≥6 months (168 days)	99 (72.8)	53 (41.4)	57 (77.0)	23 (37.1)
≥9 months (252 days)	75 (55.1)	28 (21.9)	45 (60.8)	14 (22.6)
≥12 months (364 days)	54 (39.7)	14 (10.9)	34 (45.9)	8 (12.9)
≥18 months (532 days)	40 (29.4)	8 (6.3)	26 (35.1)	7 (11.3)
≥24 months (728 days)	32 (23.5)	5 (3.9)	21 (28.4)	5 (8.1)
≥30 months (896 days)	28 (20.6)	3 (2.3)	20 (27.0)	3 (4.8)
≥36 months (1092 days)	19 (14.0)	3 (2.3)	13 (17.6)	3 (4.8)
≥42 months (1260 days)	4 (2.9)	1 (0.8)	3 (4.1)	1 (1.6)

Duration of treatment was collected in days. An approximation of treatment duration in months was made by dividing the timepoints 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.

The maximum follow-up in the olaparib arm was 1344 days (approximately 3 years and 8 months), based on the study Data Cut-Off (DTO) of 26 November 2012. A safety update of Study 19 was conducted with a DCO of 31 January 2014. The maximum follow-up in the olaparib arm as of 31 January 2014 was 1764 days (approximately 4 years and 10 months). With this increased follow up period, the number of patients remaining on treatment in Study 19 decreased from 26 (23 on the olaparib arm and 3 on the placebo arm) to 20 (19 on the olaparib arm and 1 on the placebo arm) of which 6 olaparib treated patients and the 1 placebo patient were gBRCAm. The median total treatment duration in Study 19 has not changed since the study DCO of 26 November 2012.

Table 58: Duration of treatment: Study 19, Safety Analysis set

	All patients Olaparib 400 mg bd	**Placebo**	**BRCAm Olaparib 400 mg bd**	**Placebo**
	N=136	**N=128**	**N=74**	**N=62**
Total treatment duration (days)[a]				
Mean (standard deviation)	444.7 (399.64)	203.1 (210.60)	505.4 (424.79)	231.5 (273.54)
Median (range)	263.5 (3-1349)	141.0 (34-1293)	337.0 (8-1331)	139.5 (34-1293)
Total treatment years	165.59	71.19	102.46	39.32
Actual treatment duration (days)[b]				
Mean (standard deviation)	438.0 (397.75)	201.2 (210.37)	497.0 (423.04)	230.2 (273.51)
Median (range)	258.5 (2-1349)	138.5 (34-1293)	328.5 (2-1331)	138.5 (34-1293)
Total treatment years	163.07	70.52	100.76	39.10
Duration of therapy at starting dose (days)[c]				
Mean (standard deviation)	336.3 (386.67)	190.3 (214.94)	381.7 (420.60)	214.6 (278.73)
Median (range)	170.0 (2-1349)	132.5 (1-1293)	190.0 (5-1331)	130.0 (1-1293)
Total treatment years	125.20	66.70	77.38	36.46

[a] Total treatment duration = (last dose date - first dose date +1).

[b] Actual treatment duration = total treatment duration, excluding dose interruptions.

[c] Duration of therapy at starting dose = actual treatment duration for the dose assigned.

Table 59: Summary of duration of olaparib treatment in maintenance phase of study 41

Treatment duration (days)	Olaparib (Post-O/C4/P) n=66
Olaparib total duration [a]	
Mean (standard deviation)	344.7 (276.4)
Median (range)	246,5 (12-852)
Total treatment days	22751
Olaparib actual duration [b]	
Mean (standard deviation)	335.8 (273.2)
Median (range)	234.0 (12-846)
Total treatment days	22160

[a] Total treatment duration = (last dose date - first dose date + 1). For last cycle of C6/P, duration is based on the infusion date + 21 days.

[b] Total duration of maintenance dosing phase excluding periods where no dose taken.

In study 41, the mean daily dose 659.7 mg and the mean dose adherence was 79.7% at the interim OS analysis data cut-off.

Key demographic and baseline characteristics

The majority of patients in the pooled dataset (508/735) had ovarian cancer (including 'ovarian', 'primary peritoneal', 'peritoneum', and 'fallopian tubes'). Patients with other advanced solid tumours, including breast (n=140), colorectal (n=37), pancreas (n=24) or prostate (n=8) cancers were also treated in these studies. Patients were also being treated for different stages of their disease. With the exception of Study 19 where olaparib was administered in the maintenance setting to responding patients, the treatment setting was as a late line of therapy to patients with relapsed, progressive disease.

Key demographic and baseline characteristics for the 7 studies contributing the majority (96%) of patients to the pooled data set are presented below. The majority of patients had ovarian cancer. Overall, the demographic characteristics of patients (age, race and ECOG PS) were globally similar across studies. For detailed characteristics of Study 19 population, please refer to description of the population in the Efficacy part.

Table 60: Key demographic and baseline characteristics by study: patients randomised to olaparib 400mg

Study	Study 19	Study 41	Study 12[a]	Study 08[a]	Study 09[a]	Study 20[b]	Study 42
N (all patients)	136	66	32	27	33	64	298
N (*BRCA* mutated)	74	20	32	27	33	17	298
Median age, years (range)	58 (21–89)	59 (27–78)	53.5 (35–76)	44 (32–72)	54 (35–74)	58 (39–84)	56 (29–79)
Race (% White)	96	86.4	100	96.3	93.9	90.6	95.0
ECOG PS (%)							
0	80.9	71.6	59.4	44.4	63.6	40.6	54.7
1	16.9	25.9	40.6	48.1	36.4	51.6	38.6
2	0.7	2.5	0	7.4	0	6.3	6.4
Unknown	1.5	0	0	0	0	1.6	0.3
Median number of prior chemotherapy regimens (range)	3 (2–11)	1 (1–5)	3 (1–6)	3 (1–5)	3 (1–10)	3 (1–10)	4 (1–14)

a Data presented for patients randomised to receive olaparib 400 mg bd.
b Data presented for patients with ovarian cancer

Adverse events

Table 61: Number (%) of patients who had at least one AE in any category: 400 mg bd monotherapy pool, Safety Analysis Set

AE category[a]	All patients (advanced solid tumours) N=735	*BRCAm* ovarian cancer N=397
Any AE	718 (97.7)	387 (97.5)
Any AE causally related to study treatment[b]	640 (87.1)	357 (89.9)
Any AE of CTCAE Grade 3 or higher	334 (45.4)	189 (47.6)
Any AE with outcome = death	14 (1.9)	10 (2.5)
Any SAE (including events with outcome = death)	185 (25.2)	110 (27.7)
Any AE leading to discontinuation of study treatment	43 (5.9)	23 (5.8)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
[b] As assessed by the investigator.
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; CTCAE Common Terminology Criteria for Adverse Events.

DCO for MAA: 26 November 2012

Table 62: Number (%) of patients who had at least one AE in any category: Study 19, All Patients, Safety Analysis Set (safety update)

AE category[a]	Olaparib 400 mg bd N=136			Placebo N=128		
	DCO for MAA	DCO for Safety Update	Change (n)	DCO for MAA	DCO for Safety Update	Change (n)
Any AE	132 (97.1)	132 (97.1)	0	119 (93.0)	119 (93.0)	0
Any AE causally related to study treatment[b]	121 (89.0)	122 (89.7)	1	93 (72.7)	93 (72.7)	0
Any AE of CTCAE Grade 3 or higher	55 (40.4)	56 (41.2)	1	28 (21.9)	28 (21.9)	0
Any AE with outcome = death	2 (1.5)	1 (0.7)	-1	0	0	0
Any SAE (including events with outcome = death)	25 (18.4)	25 (18.4)	0	11 (8.6)	11 (8.6)	0
Any AE leading to discontinuation of study treatment	7 (5.1)	6 (4.4)	-1	2 (1.6)	2 (1.6)	0

a Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
b As assessed by the investigator.
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; CSR Clinical study report; DCO Data cut-off; MAA New Drug Application; SAE Serious adverse event.
DCO for MAA: 26 November 2012; DCO for safety update: 31 January 2014

The AE pattern seen in the *BRCAm* subgroup was generally consistent with that seen in all patients (Table 62 and Table 63). An analysis of safety in the population of patients with a confirmed *gBRCA* mutation (n=96) was consistent with the *BRCAm* subgroup and the total population.

Table 63: Number (%) of patients who had at least one AE in any category: Study 19, BRCAm Subgroup, Safety Analysis Set (safety update)

AE category[a]	Olaparib 400 mg bd N=74			Placebo N=62		
	DCO for MAA	DCO for Safety Update	Change (n)	DCO for MAA	DCO for Safety Update	Change (n)
Any AE	72 (97.3)	72 (97.3)	0	58 (93.5)	58 (93.5)	0
Any AE causally related to study treatment[b]	67 (90.5)	67 (90.5)	0	45 (72.6)	45 (72.6)	0
Any AE of CTCAE Grade 3 or higher	28 (37.8)	29 (39.2)	1	11 (17.7)	11 (17.7)	0
Any AE with outcome = death	2 (2.7)	1 (1.4)	-1	0	0	0
Any SAE (including events with outcome = death)	16 (21.6)	16 (21.6)	0	6 (9.7)	6 (9.7)	0
Any AE leading to discontinuation of study treatment	6 (8.1)	5 (6.8)	-1	0	0	0

a Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
b As assessed by the investigator.
Includes AEs with an onset date between the date of first dose and 30 days following the date of last dose of study treatment.
Safety Update 4-month safety update; AE Adverse event; bd Twice daily; *BRCAm gBRCA* and/or *tBRCA* mutated; CTCAE Common Terminology Criteria for Adverse Events; CSR Clinical study report; DCO Data cut-off; *gBRCA* Germline breast cancer susceptibility gene; MAA New Drug Application; SAE Serious adverse event; *tBRCA* Tumour breast cancer susceptibility gene.

An analysis of Study 19 safety by germline BRCA mutation status is presented below.

Table 64: Summary of number (%) of patients who had at least one AE in any category

AE Category	**Olaparib 400 mg bd (n=136)**			**Placebo (n=129)**		
	***gBRCAm* subset (n=53)**	***gBRCAwt* subset (n=48)**	***gBRCA* missing (n=35)**	***gBRCAm* subset (n=43)**	***gBRCAwt* subset (n=62)**	***gBRCA* missing (n=24)**
Any AE	52 (98.1)	48 (100)	32 (91.4)	41 (95.3)	60 (96.8)	18 (75.0)
AE grade 3 or higher	17 (32.1)	22 (45.8)	16 (45.8)	8 (18.6)	15 (24.2)	5 (20.8)
AE with outcome - death	1 (1.9)	0	1 (2.9)	0	0	0
SAE	11 (20.8)	9 (18.8)	5 (14.3)	3 (7)	4 (6.5)	4 (16.7)
AE leading to discontinuation	5 (9.4)	1 (2.1)	1 (2.9)	0	2 (3.2)	0

In Study 41 (maintenance phase), more patients had at least one AE reported in the olaparib arm (97.0%) compared with the no treatment (Post C6/P) arm (78.2%). There were more patients with AEs of CTCAE grade ≥3 reported in the olaparib arm (31.8%) versus the no treatment arm (16.4%). The percentage of patients reported with an SAE was similar in the olaparib and no treatment arms (10.6% and 7.3%, respectively). In olaparib arm, 7 patients (10.6%) had an AE leading to discontinuation of olaparib reported and 1 patient had an AE with outcome=death.

Table 65: Number (%) of patients with the most common AEs (reported in ≥10% in either group): 400 mg bd monotherapy pooled dataset, Safety Analysis Set

Preferred term	All patients (advanced solid tumours) N=735	*BRCAm* ovarian cancer N=397
Any AE	718 (97.7)	387 (97.5)
Nausea	459 (62.4)	263 (66.2)
Fatigue	407 (55.4)	233 (58.7)
Vomiting	266 (36.2)	153 (38.5)
Anaemia	189 (25.7)	110 (27.7)
Diarrhoea	180 (24.5)	113 (28.5)
Abdominal pain	167 (22.7)	103 (25.9)
Decreased appetite	133 (18.1)	69 (17.4)
Headache	132 (18.0)	71 (17.9)
Constipation	119 (16.2)	66 (16.6)
Dyspepsia	118 (16.1)	75 (18.9)
Dysgeusia	105 (14.3)	69 (17.4)
Cough	103 (14.0)	55 (13.9)
Dizziness	96 (13.1)	60 (15.1)
Back pain	94 (12.8)	59 (14.9)
Peripheral oedema	92 (12.5)	49 (12.3)
Dyspnoea	90 (12.2)	46 (11.6)
Abdominal distension	83 (11.3)	52 (13.1)
Arthralgia	77 (10.5)	39 (9.8)
Urinary tract infection	75 (10.2)	52 (13.1)
Upper abdominal pain	69 (9.4)	42 (10.6)
Asthenia	65 (8.8)	47 (11.8)

Number (%) of patients reporting AEs sorted by decreasing frequency of events in the All patients group.
Includes AEs with an onset date between the date of first dose and 30 days following the date of last dose of study treatment.
Of the 735 patients in the pooled dataset, the most common tumour types were ovarian (508), breast (140), colorectal (37), pancreas (24) and prostate (8) cancer.

Table 66: Number (%) of patients with most common AEs (≥10% in either group): Study 19, Safety Analysis Set (safety update)

Preferred Term	Number (%) of patients					
	Olaparib 400 mg bd N=136			Placebo N=128		
	DCO for MAA	DCO for Safety Update	Change (n)	DCO for MAA	DCO for Safety Update	Change (n)
Patients with any AE	**132 (97.1)**	**132 (97.1)**	**0**	**119 (93.0)**	**119 (93.0)**	**0**
Nausea	96 (70.6)	96 (70.6)	0	46 (35.9)	46 (35.9)	0
Fatigue	71 (52.2)	71 (52.2)	0	50 (39.1)	50 (39.1)	0
Vomiting	46 (33.8)	47 (34.6)	1	18 (14.1)	18 (14.1)	0
Diarrhoea	37 (27.2)	37 (27.2)	0	31 (24.2)	31 (24.2)	0
Abdominal pain	34 (25.0)	34 (25.0)	0	34 (26.6)	34 (26.6)	0
Anaemia	29 (21.3)	29 (21.3)	0	7 (5.5)	7 (5.5)	0
Constipation	28 (20.6)	29 (21.3)	1	14 (10.9)	14 (10.9)	0
Decreased appetite	28 (20.6)	28 (20.6)	0	17 (13.3)	17 (13.3)	0
Headache	28 (20.6)	29 (21.3)	1	16 (12.5)	17 (13.3)	1
Upper abdominal pain	24 (17.6)	24 (17.6)	0	10 (7.8)	11 (8.6)	1
Cough	24 (17.6)	24 (17.6)	0	13 (10.2)	13 (10.2)	0
Dyspepsia	24 (17.6)	24 (17.6)	0	11 (8.6)	11 (8.6)	0
Arthralgia	23 (16.9)	24 (17.6)	1	18 (14.1)	18 (14.1)	0
Back pain	22 (16.2)	23 (16.9)	1	14 (10.9)	14 (10.9)	0
Dysgeusia	22 (16.2)	22 (16.2)	0	8 (6.3)	8 (6.3)	0
Nasopharyngitis	20 (14.7)	21 (15.4)	1	14 (10.9)	14 (10.9)	0
Asthenia	19 (14.0)	19 (14.0)	0	12 (9.4)	12 (9.4)	0
Dizziness	18 (13.2)	19 (14.0)	1	9 (7.0)	9 (7.0)	0
Abdominal distension	17 (12.5)	17 (12.5)	0	11 (8.6)	11 (8.6)	0
Dyspnoea	16 (11.8)	17 (12.5)	1	8 (6.3)	8 (6.3)	0
Upper respiratory tract infection	16 (11.8)	17 (12.5)	1	8 (6.3)	8 (6.3)	0
Urinary tract infection[a]	***13 (9.6)***	***15 (11.0)***	***2***	***7 (5.5)***	***7 (5.5)***	***0***
Hot flush	5 (3.7)	4 (2.9)	-1	15 (11.7)	15 (11.7)	0

a New AE: AE did not meet the criteria (≥10%) for the equivalent table in the original MAA.
Number (%) of patients with AEs sorted by decreasing frequency of events reported in the olaparib 400 mg bd group at MAA DCO.
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; CSR Clinical study report; DCO Data cut-off; MAA New Drug Application.
DCO for MAA: 26 November 2012; DCO for safety update: 31 January 2014

Additionally in Study 19, AEs of stomatitis, muscle spasms and peripheral neuropathy, although having an overall incidence of <10%, were also reported at a ≥5% greater frequency in the olaparib versus placebo group.

Table 67: Number (%) of patients with most common AEs (≥10% in either group) and adjusted by patient years' exposure: Study 19, BRCAm (safety update)

Preferred term	Number (%) of patients		Event rate (per 1000 patient years)	
	Olaparib 400 mg bd N=74	Placebo N=62	Olaparib 400 mg bd N=74	Placebo N=62
Patients with any AE	**72 (97.3)**	**58 (93.5)**	**-**	**-**
Nausea	54 (73)	20 (32)	2142	600.7
Fatigue	40 (54)	23 (37)	619.6	675.8
Vomiting	27 (37)	5 (8)	346	111.7
Diarrhoea	22 (30)	12 (19)	253.5	297.2
Abdominal pain	17 (23)	18 (29)	180.9	451.8
Anaemia	19 (26)	3 (5)	220.6	66
Constipation	15 (20)	7 (11)	147.1	165.4
Decreased appetite	14 (19)	6 (10)	149.3	135.1
Headache	14 (19)	11 (18)	154.1	262.4
Upper abdominal pain	14 (19)	5 (8)	131.9	110.3
Cough	11 (15)	7 (11)	107.9	173.7
Dyspepsia	13 (18)	4 (7)	122.5	88.6
Arthralgia	12 (16)	10 (16)	121	249.7
Back pain	15 (20)	9 (15)	146.3	222.3
Dysgeusia	14 (19)	4 (7)	140.8	88.8
Nasopharyngitis	11 (15)	4 (7)	96.1	91.6
Asthenia	12 (16)	8 (13)	117.6	186.7
Dizziness	12 (16)	3 (5)	120.5	66.2
Abdominal distension	9 (12)	6 (10)	84.8	134.2
Dyspnoea	5 (7)	3 (5)	43.7	69.9
Upper respiratory tract infection	12 (16)	6 (10)	113.1	149.1
Hot flush	4 (5)	11 (18)	33.8	279.1

Patient years exposure calculated as: last dose – first dose + 30 days divided by 365.25, for completed patients. DCO – first dose divided by 365.25 for ongoing patients. For each event, patient years of exposure is adjusted to Date of event – first dose divided by 365.25 for each patient with selected event.
Safety Update 4-month safety update;
DCO for safety update: 31 January 2014

*CTCAE Grade 3/4 Adverse events (data cut-off 26 November 2012)*The severity of any AE was graded according to the National Cancer Insititute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 3, where applicable.

Table 68: Number (%) of patients with the most common AEs of CTCAE grade 3 or higher (reported in ≥2% patients in either group): 400 mg bd monotherapy pooled dataset, Safety Analysis Set

System organ class/ Preferred term	All patients N=735	*BRCAm* ovarian cancer N=397
Any CTCAE ≥grade 3 AE	**334 (45.4)**	**189 (47.6)**
Blood and lymphatic system disorders	116 (15.8)	66 (16.6)
Anaemia	84 (11.4)	51 (12.8)
Leukopenia	20 (2.7)	14 (3.5)
Neutropenia	21 (2.9)	13 (3.3)
Thrombocytopenia	16 (2.2)	9 (2.3)
Gastrointestinal disorders	105 (14.3)	64 (16.1)
Abdominal pain	24 (3.3)	16 (4.0)
Intestinal obstruction	15 (2.0)	13 (3.3)
Nausea	20 (2.7)	9 (2.3)
Small intestinal obstruction	13 (1.8)	8 (2.0)
Vomiting	24 (3.3)	16 (4.0)
General disorders and administration site conditions	66 (9.0)	38 (9.6)
Fatigue	52 (7.1)	29 (7.3)
Investigations	42 (5.7)	22 (5.5)
Haemoglobin decreased	17 (2.3)	10 (2.5)
Respiratory, thoracic and mediastinal disorders	31 (4.2)	18 (4.5)
Dyspnoea	16 (2.2)	11 (2.8)

Patients reporting multiple AEs of CTCAE grade 3 or higher are counted once for each system organ class/preferred term. Data sorted alphabetically by system organ class and preferred term.
Includes AEs with an onset date between the date of first dose and 30 days following the date of last dose of study treatment.

Table 69: Number (%) of patients with the most common AEs of CTCAE grade 3 or higher (reported in ≥2% patients in either group [All patients]): Study 19, Safety Analysis Set

System organ class/ Preferred term	All patients		*BRCAm*	
	Olaparib 400 mg bd N=136	Placebo N=128	Olaparib 400 mg bd N=74	Placebo N=62
Any AE of CTCAE ≥grade 3	**55 (40.4)**	**28 (21.9)**	**28 (37.8)**	**11 (17.7)**
Blood and lymphatic disorders	12 (8.8)	3 (2.3)	6 (8.1)	2 (3.2)
Anaemia	7 (5.1)	1 (0.8)	4 (5.4)	1 (1.6)
Leukopenia	3 (2.2)	0	2 (2.7)	0
Neutropenia	5 (3.7)	1 (0.8)	3 (4.1)	1 (1.6)
Gastrointestinal disorders	12 (8.8)	10 (7.8)	4 (5.4)	3 (4.8)
Abdominal pain	3 (2.2)	4 (3.1)	0	2 (3.2)
Diarrhoea	3 (2.2)	3 (2.3)	2 (2.7)	1 (1.6)
Nausea	3 (2.2)	0	1 (1.4)	0
Small intestinal obstruction	2 (1.5)	3 (2.3)	0	1 (1.6)
Vomiting	3 (2.2)	1 (0.8)	2 (2.7)	0
General disorders and administration site conditions	13 (9.6)	4 (3.1)	8 (10.8)	1 (1.6)
Fatigue	10 (7.4)	4 (3.1)	5 (6.8)	1 (1.6)
Musculoskeletal and connective tissue disorders	8 (5.9)	0	5 (6.8)	0
Back pain	3 (2.2)	0	2 (2.7)	0

Patients with multiple AEs of CTCAE grade 3 or higher are counted once for each system organ class/preferred term. Data sorted alphabetically by system organ class and preferred term.
Includes AEs with an onset date between the date of first dose and 30 days following the date of last dose of study treatment

The time to first onset for CTCAE grade ≥3 AEs was assessed for the olaparib arm of Study 19 using a cumulative incidence plot. Most grade 3 and higher events occurred during the first 6 months of treatment, with the total incidence reaching approximately 40% during the study.

In study 41, the majority of AEs were CTCAE grade 1 or 2 in severity. Adverse events of CTCAE grade ≥3 were reported in more patients in the olaparib arm (21 [31.8%]) than in the no treatment arm (9 [16.4%]). The most common CTCAE grade ≥3 events reported in the olaparib arm were haematological and were anaemia (6 [9.1%] patients) and neutropenia (3 [4.5%] patients). There were 2 patients in the olaparib arm who had AEs of grade 3 myelodysplastic syndrome reported. All other grade 3/4 AEs were reported in 1 patient only in either arm.

Adverse events by organ system or syndrome

Nausea and vomiting

In Study 19, the reported incidence was approximately twice as high for olaparib treated patients compared to placebo treated patients. Events were predominantly grade 1 or 2 in severity and infrequently led to permanent discontinuation of treatment (2 patients, 1 in each arm, discontinued treatment due to nausea). Cumulative incidence plots and life table plots of the Study 19 data indicated that nausea is reported very early with the probability of having an adverse event of nausea greatest in the first month of treatment. Vomiting was generally first reported in the first 3 to 6 months of treatment with olaparib with the probability of having an AE of vomiting greatest in the first month of treatment, but for some patients the first onset was during the first 6 months.

Events resolved in the majority of patients, generally whilst continuing treatment with olaparib. In Study 19 nausea was no longer present in 70/96 (72.9%) of the patients with an event reported and vomiting was no longer present in 45/46 (97.8%) of the patients with a reported event at the data cut off.

Dose reduction and interruptions were used in a small number of patients to manage the events of nausea and vomiting in Study 19, with 5.1% patients reporting an AE of nausea that led to a temporary dose interruption (8.1% vomiting) and 3.7% required a dose reduction of olaparib treatment for nausea (2.9% vomiting). Treatment for nausea was received by 50% patients in the olaparib arm and in 17% patients in the placebo arm. Treatment for vomiting was received by 30% olaparib treated patients and 17% of placebo treated patients.

Fatigue (including asthenia)

In Study 19, 61.8% of olaparib-treated patients and 46.1% of placebo-treated patients reported fatigue/asthenia. The events were generally CTCAE grade 1or 2 in severity and did not result in any permanent discontinuation of treatment. Cumulative incidence information from Study 19 showed that fatigue and asthenia were generally reported early; the majority of olaparib patients who reported events of fatigue and asthenia reported the first onset within the first 3 months of treatment. Dose reductions and interruptions were used in a small number of patients to manage the events of fatigue and asthenia in Study 19, with 4.4% patients receiving olaparib reporting an AE of fatigue that led to a temporary dose interruption (1.5% asthenia) and 3.7% required a dose reduction of olaparib treatment for fatigue (2.2% asthenia). Fatigue/asthenia was reported at a similar frequency in the 400 mg bd monotherapy pool (61.5% of all patients) as in Study 19 (61.8%), and was generally grade 1 or 2 in severity. There was only 1 SAE in the monotherapy pool, and no AEs leading to discontinuation.

Anaemia

In Study 19, anaemia (grouped terms) was reported as an AE in a higher percentage of patients in the olaparib arm versus the placebo arm (23.5% vs. 7.0%). The prevalence plot for anaemia indicated that at any given time, approximately 5 to 15% of patients were actually experiencing anaemia as an AE. Cumulative incidence information in Study 19 showed that anaemia events were generally reported early, with the majority of patients reporting events of anaemia having first onset within the first 2 months of treatment.

Anaemia was one of the more common AEs that led to dose interruptions or reductions. Study 19 data showed that AEs of anaemia resolved in the majority of olaparib treated patients (20/32) with the AE still present in 10/32, and outcome was not recorded for 2/32 patients.

Anaemia was reported as an AE in a slightly higher proportion of patients in the monotherapy pooled dataset compared with Study 19, both overall and for CTCAE grade 3 or higher events. SAEs or AEs leading to discontinuation were infrequently reported for anaemia.

A review of all cases of anaemia resulting in blood transfusions was performed. In the pivotal study, 14 (10.3%) patients treated with olaparib, needed one or more transfusions during the treatment while one patient (0.8%) required transfusions in the placebo group.

Diarrhoea

In Study 19, AEs of diarrhoea were reported in a similar percentage of patients in the olaparib and placebo arms. Most of the events were CTCAE grade 1 or 2 in severity, and none of the events led to permanent discontinuation of treatment. One case of diarrhoea in the olaparib arm was reported as being serious. Diarrhoea was reported at a similar frequency in the pooled dataset. Although the reporting rate of diarrhoea was similar in the olaparib and placebo arms in Study 19, it was considered to be associated with olaparib due to findings from other comparative studies in the clinical programme (Study 12 and Study 41). In the maintenance phase of the study 41, twice as many patients in the olaparib arm reported events of diarrhoea compared to the no treatment arm (12 [18.2%] vs 4 [7.3%]). The majority of the events in the olaparib arm were CTCAE grade 1. A dose response relationship was observed in 3 monotherapy studies where olaparib 100 mg bd or 200 mg bd was compared with 400 mg bd.

Dyspepsia

In Study 19, AEs of dyspepsia were reported in a higher percentage of patients in the olaparib arm versus the placebo arm. All of these events were CTCAE grade 1 or 2 in severity. None of the events were reported as being serious and none of the events led to permanent discontinuation of treatment. Dyspepsia was reported at a similar frequency in the pooled dataset. An assessment of the incidence of dyspepsia at other olaparib monotherapy doses showed a dose response relationship in Study 12 and Study 8.

Upper abdominal pain

In Study 19, AEs of upper abdominal pain were reported in a higher percentage of patients in the olaparib arm versus the placebo arm. Most of the events were CTCAE grade 1 or 2 in severity. None of the events were reported as being serious and none of the events led to permanent discontinuation of treatment. Upper abdominal pain was reported at a lower frequency in the pooled dataset than in Study 19.

Stomatitis

Study 19 showed patients on olaparib reporting stomatitis more frequently than those on placebo; 12/136, 8.8% patients vs. 4/128, 3.1% patients, respectively. After exposure adjustment per 1000 patient years, stomatitis events on olaparib remained higher; 75.7 vs. 51.4 per 1000 patient years, respectively. The median time to onset for those patients who had an event reported was later for olaparib-treated patients than those on placebo (75 [range 4 to 581] days vs. 36 [range 2 to 168] days). All patients had received platinum based chemotherapy prior to entering the study. All events were non-serious, CTC grade 1 or 2 and 11/12 events resolved on study treatment. Only 1 patient in the olaparib group required dose modification due to an event of stomatitis, which was also associated with herpes zoster and mild oral candidiasis. The majority of events were temporally associated with infections or vomiting, fatigue or treatment with sulfasalazine, which has stomatitis listed as a common associated event in the SmPC.

Considering data relating to reports of stomatitis from the combined monotherapy pooled dataset of 11 studies (including Study 19, the pivotal phase II PSR ovarian maintenance study) 35/735 patients (4.8%) reported stomatitis at the 400 mg bd dose level. All events were nonserious and the majority were CTC grade 1 or 2. Three patients reported stomatitis with CTC grade 3; all reported other concomitant, potentially confounding AEs eg, vomiting, lung infection, pyrexia and anaemia.

Data from Study 41, the phase II comparative study comparing olaparib in combination with paclitaxel and carboplatin followed by maintenance treatment with olaparib, vs. paclitaxel and carboplatin followed

by no treatment, in patients with platinum sensitive advanced serous ovarian cancer has also been reviewed and showed an increased frequency in patients receiving combination chemotherapy treatment (carboplatin + paclitaxel) with olaparib compared to combination chemotherapy without olaparib (14/81, 17.3% vs. 8/75, 10.8%, respectively) and likewise in the maintenance phase of the study the frequency of stomatitis was greater in the olaparib arm 4/66, 6.1% vs. 0/55, 0% in the non-treated arm.

Decreased appetite/anorexia

In Study 19, AEs of decreased appetite/anorexia were reported in a higher percentage of patients in the olaparib arm versus the placebo arm. All of these events were CTCAE grade 1 or 2 in severity, and there were no SAEs or AEs leading to discontinuation of treatment. Decreased appetite/anorexia was reported at a similar frequency in the pooled dataset.

Headache

In Study 19, headache was reported as an AE in more patients in the olaparib arm than in the placebo arm. Most of these events were CTCAE grade 1 or 2 in severity. Headache was not reported as an SAE and there were no AEs of headache leading to discontinuation. In the 400 mg bd monotherapy pooled dataset, headache was reported at a similar frequency. In the maintenance phase of Study 41, more patients in the olaparib arm reported events of headache compared to the no treatment arm (8 [12.1%] vs 1 [1.8%]). In other monotherapy studies of olaparib there was some evidence of a dose response relationship for headache.

Dizziness

In Study 19, dizziness was reported as an AE in more patients in the olaparib arm than in the placebo arm; all events were CTCAE grade 1 or 2 in severity. Dizziness was not reported as an SAE and there were no AEs of dizziness leading to discontinuation. Dizziness was reported at a similar frequency in the pooled dataset. In the maintenance phase of Study 41, more patients in the olaparib arm reported events of dizziness compared with the no treatment arm (7 [10.6%] vs 2 [3.6%]). Across other studies of olaparib monotherapy, a dose response relationship for dizziness was evident in Study 12.

Dysgeusia

In Study 19, AEs of dysgeusia were reported in a higher percentage of patients in the olaparib arm versus the placebo arm. All of these events were CTCAE grade 1 or 2 in severity. None of the events were reported as being serious and none of the events led to permanent discontinuation of treatment. Dysgeusia was reported at a similar frequency in the pooled dataset.

Dyspnoea

Dyspnoea events (including dyspnoea exertional) were reported more frequently for patients receiving olaparib than those receiving placebo (19/136 [14.0%] patients vs 9/128 [7.0%] patients, respectively). When adjusted for extent of exposure, the event rate for ‘dyspnoea’ per 1000 patient years was olaparib 98.0 vs placebo 104.6 and for ‘dyspnoea exertional’ 17.4 for olaparib vs 12.4 placebo. The number of patients with ‘dyspnoea exertional’ was low (3/136 [2.2%] vs 1/128 [0.8%], respectively) and one of these olaparib patients also had dyspnoea. Median time to onset for patients who had ‘dyspnoea’ was 124 days (range 14 to 879 days) for olaparib vs 102 days (range 5 to 364 days) for placebo and those who had ‘dyspnoea exertional’ was 33 days (range 9 to 625 days) for olaparib vs 169 days for placebo.

All olaparib treated patients with dyspnoea-type events had possible alternative causes for the events, such as underlying current medical history eg, dyspnoea (3), anaemia (3), fatigue (2), pleural effusion (1), asthma (1), mitral valve insufficiency (1), post traumatic stress disorder and panic attacks (1), obesity (1), upper abdominal pain (1) and anxiety (1), or concurrent adverse events including:

bronchopneumonia (1), pyrexia (1), anaemia (1) or fatigue (1). The majority of the events were CTC grade 1 or 2 (17/19) and generally resolved on treatment.

Of the two patients with CTC grade 3 dyspnoea, one patient experienced dyspnoea after 92 days of olaparib treatment; study treatment was stopped due to the event. The patient had been receiving several treatments for concurrent bronchopneumonia (CTC grade 2) from day 29 – 101 and again from day 120 onwards. These treatments included cephalosporin antibiotic (orelox), penicillin (tazobac), prednisolone (decortin) and salbutamol. The investigator considered the dyspnoea to be secondary to the bronchopneumonia.

Another patient experienced dyspnoea after 879 days of olaparib treatment which lasted 18 days; study treatment was temporarily stopped due to the event. The patient had a current medical history of post-traumatic stress disorder, panic attacks and alcoholism. A sample of sputum showed large numbers of haemophilus influenza isolates.

Pneumonitis

As of 20 May 2013, 10 olaparib treated patients have reported pneumonitis out of a total of 2034 patients estimated to have received olaparib, giving a cumulative incidence of 0.5% for pneumonitis. Pneumonitis has also been reported for 1 patient randomised to placebo in Study 19 and 1 patient randomised to placebo plus paclitaxel in Study 39. No new reports of pneumonitis have been received since the 20 May 2013. As of 31 January 2014, a total of 2389 patients are estimated to have received olaparib, giving a cumulative incidence proportion of 0.42%.

The pneumonitis events were reported in patients receiving olaparib for a variety of tumour types (ovarian [n=2], NSCLC [n=2], SCLC [n=1], breast [n=2], and 1 each of pancreatic, thymic and gastric cancer), both when given as monotherapy (400 mg bd or 200 mg bd) and when given in combination with other anti-cancer agents (at 50, 100, 200, or 400 mg bd).

Of the 10 patients treated with olaparib reported to have pneumonitis, five died from evidenced disease progression, all of whom had locally advanced disease at baseline (NSCLC, SCLC, thymic cancer stage IV, breast cancer stage IV and pulmonary metastatic breast cancer). Of the surviving 5 patients with pneumonitis, 1 was considered as non-serious by the reporting investigator.

The presentation and course of the pneumonitis cases did not show a consistent clinical or radiographic pattern (as centrally assessed by independent review of chest CT and radiographs), and were confounded by several pre disposing factors (including disease under investigation, locally advanced pulmonary disease, other pre-existing medical conditions, smoking history and/or prior chemotherapy and radiotherapy).

Hepatobiliary disorders

In study 19, twelve patients reported a total of 17 events from the hepatobiliary disorders SOC or Investigations SOC (relating to abnormal hepatic clinical chemistry); 4 patients (2.9%) reported 4 events overall with olaparib and 8 patients (6.3%) reported 13 events overall with placebo. The 4 events reported by 4 patients on olaparib treatment were CTCAE grade 1 hepatic cyst, an SAE of CTCAE grade 5 cholestatic jaundice, CTCAE grade 2 increased ALT and CTCAE grade 1 increased blood alkaline phosphatase. The fatal event of cholestatic jaundice in an 80-year patient was considered due to disease progression.

In total, 37/735 patients (5.0%) across the pooled monotherapy dataset reported 57 events from the hepatobiliary disorders or investigations SOC relating to hepatic toxicity. The most common events reported were hepatomegaly in 5 patients (0.7%), jaundice + cholestatic jaundice in 4 patients (0.5%) and abnormalities in liver biochemistry.

Renal events

Thirty-eight patients overall reported a total of 50 events relating to renal/urinary disorders from the Renal and Urinary Disorders or Investigations SOCs in Study 19; 24 patients (17.6%) reported 31 events overall with olaparib and 14 patients (10.9%) reported 19 events overall with placebo. Among the 735 patients who received 400 mg bd olaparib in the pooled data set, 78 patients reported 92 events from the Renal/Urinary Disorder SOC and an additional 42 events relating to abnormalities in renal chemistry parameters were reported within the Investigations SOC.

The most common renal symptoms reported were related to urinary urgency, frequency or incontinence, e.g. dysuria, pollakiuria, and urinary incontinence, which are commonly reported symptoms for patients with advanced ovarian cancer.

Mild elevations in creatinine with no apparent sequelae have been observed in the absence of an elevation in urea or blood urea nitrogen (BUN) or a reported abnormality on urinalysis (see laboratory findings).

QT prolongation and cardiac toxicity

In Study 19, 1 patient in the olaparib arm had a CTCAC ≥grade 3 SAE of syncope that was considered related to study treatment by the investigator. Two patients in the placebo arm had AEs of syncope, 1 of which was CTCAC ≥grade 3, but neither of which were considered related to study treatment.

In the 400 mg bd monotherapy pooled dataset, 9 (1.2%) patients reported an ECG-related event (either preferred term of prolonged QT [n=2] or syncope [n=7]). This includes the patient in the olaparib arm of Study 19 with syncope mentioned above. Six of these 9 patients had AEs of CTCAE ≥grade 3, 3 patients had events that were considered causally related to olaparib, and 3 patients had SAEs. Of the 7 reported syncope cases in the pooled dataset, 2 were considered by the investigator to be related to study treatment. There were 2 events of prolonged ECG QT in the pooled dataset

Haemorrhages

In Study 19, 32 patients reported a total of 37 haemorrhagic events (21 patients [15.4%] in the olaparib 400 mg bd group reported 24 events and 11 patients [8.6%] in the placebo group reported 13 events). However, since the overall median actual treatment duration was approximately 9 months and 5 months in the olaparib and placebo groups, respectively, the frequencies were not directly comparable. Most of the events in either treatment group were considered to be non-serious; only 4 (2.9%) patients in the olaparib group reported serious adverse event. A patient in the olaparib group had a fatal AE of CTCAE grade 5 haemorrhagic stroke, preceded by an SAE of thrombocytopenia (CTCAE grade 4). The fatal AE was considered related to study drug by the investigator. The remaining 3 SAEs (melaena, intra-abdominal haemorrhage and post procedural haematoma) were all considered unrelated to olaparib.

A total of 90 patients (12.2%) had 110 events of haemorrhage in the pooled dataset of 735 patients who had received 400 mg bd olaparib (including events in Study 19). The majority of the events were considered to be non-serious; 13 (1.8%) patients reported SAEs. All SAEs were considered unrelated to olaparib except 1 event of haemorrhagic stroke (discussed above). Nine (1.2%) patients reported AEs of CTCAE grade 3 or above, with 10 events in 10 (1.4%) of patients were considered related to any treatment.

A review of the haematology laboratory findings in patients with haemorrhagic events did not highlight any clinically significant shift from baseline or a relationship to thrombocytopenia, except for the patient with haemorrhagic stroke.

Gastrointestinal obstructions

In Study 19, there were relatively few AEs representing the topic of gastrointestinal obstruction. Eight patients reported a total of 10 gastrointestinal obstruction type events: 3 patients (2.2%) in the olaparib group each reported 1 event, and 5 patients (3.9%) in the placebo group reported 7 events. The majority of the patients in both treatment groups had events that were considered to be serious (3 [2.2%] out of a total of 3 patients in the olaparib group and 4 [3.1%] out of a total of 5 patients in the placebo group) and resulted in hospitalisation of the patient. Apart from 1 event of subileus and 1 event of intestinal obstruction in the placebo group (both CTCAE grade 2), all the events were CTCAE grade 3 or 4. Apart from one event of intestinal obstruction on placebo, all the gastrointestinal obstruction events were considered by the investigator to be unrelated to study treatment. A total of 40 patients (5.4%) had 54 events of gastrointestinal obstruction in the pooled dataset of 735 patients who had received 400 mg bd olaparib (including events in Study 19). Many patients had a current or past medical history of gastrointestinal obstructions. The majority of the events was considered to be serious (32 [4.4%]patients) and was CTCAE grade 3 or higher in severity (34 [4.6%] patients). None of the patients had events that were considered by the investigator to be related to olaparib. The majority of the gastrointestinal obstruction events resolved (42/54 events).

Myelodysplastic syndrome/acute myeloid leukaemia (MDS/AML)

There were 21 reports of MDS and/or AML in patients treated with olaparib as of 20 August 2014; 14 cases in olaparib monotherapy trials and 7 cases in olaparib combination studies with carboplatin and paclitaxel (n=4), cediranib (n=1) or irinotecan and cisplatin (n=2). A total of 2866 patients are estimated to have received olaparib (as of 20 August 2014), giving a cumulative incidence of 0.73% for MDS/AML. The cumulative incidence reported from control arms of olaparib randomised studies is 0.4% (2/550 patients).Sixteen of the MDS/AML cases were reported in patients with BRCA1/2 mutations (12 with BRCA1 mutations, 3 with BRCA2 mutations and 1 with unspecified BRCA mutation). Of the remaining 5 patients; 3 were BRCA status unknown and 2 were known to be BRCA wildtype. It is difficult to calculate an incidence for MDS/AML in BRCAm patients across the programme because BRCA mutation status was not collected in every clinical study with olaparib. In patients with BRCAm ovarian cancer enrolled in 5 randomised clinical trials, the incidence of MDS/AML was 1.1% (6 cases/546 olaparib-treated BRCAm patients in Studies 19, 12, 41, D0818C00001 [SOLO1] and D0816C00002 [SOLO2]). The incidence in BRCAm control arm patients is 0.6% (2 cases/353 BRCAm control arm patients in Studies 19, 12, 41, SOLO1 and SOLO2).

Other new primary malignancies

Overall, the number of events of new primary malignant tumours (other than MDS/AML reports discussed above) reported was low, with 23 events (in 21 patients) being reported in an estimated 2866 olaparib-treated patients (0.73%) as of 20 August 2014. No new reports of new primary malignancies were received between 20 August 2014 and the 24 September 2014.

Adverse drug reactions

Reporting AEs in terms of exposure-adjusted event rates indicated that for many of the most common events reported at a higher frequency on olaparib compared to placebo, the rate remained higher for olaparib treated patients when adjusted for exposure: nausea, vomiting, anaemia, upper abdominal pain, dyspepsia and dysgeusia. For a number of events however, namely fatigue, constipation, decreased appetite, headache, cough, back pain, nasopharyngitis, dizziness, upper respiratory tract infection, abdominal distension and dyspnoea, the exposure-adjusted event rates appeared either similar between the arms or higher for placebo-treated patients. An assessment of AEs by treatment period of AE onset indicated treatment differences between the arms remained for fatigue, decreased appetite, headache and dizziness with a higher reporting frequency for olaparib-treated patients over placebo-treated patients during the first 0 to 3 months and/or 3 to 6 months on study when the majority of patients on both treatment arms were on study treatment. Based on the above analysis of adverse events by system organ class, adverse events of nausea, vomiting, fatigue (including asthenia), anaemia, dyspepsia, dysguesia, dizziness, headache, upper abdominal pain and decreased appetite were considered associated with olaparib treatment. Although the reporting rate of diarrhoea was similar in the olaparib and placebo arms in Study 19, it was considered to be associated with olaparib due to findings from other studies in the clinical programme (Study 12 and 41). Based on a detailed review of all the available individual patient information with reports of stomatitis, it was considered that there is reasonable temporal evidence to suggest that olaparib may have a causal association with the development of stomatitis.

Muscle spasms were reported more frequently for olaparib versus placebo (9.6% vs. 3.9%). These were isolated events described as cramps in extremities, sometimes intermittent or occasional, all mild and moderate intensity (CTCAE grade 1 or 2) and did not require olaparib dose modifications. All patients had other potential contributory factors for events of muscle cramps, such as arthralgia, peripheral neuropathy, varicose veins, or use of concomitant medication such as thyroxine and raloxifene.

Peripheral neuropathy was reported more frequently for olaparib versus placebo (8.8% vs. 2.3%). Additional AE preferred terms including peripheral sensory neuropathy and polyneuropathy were reported in small numbers of patients. There were no patients with duplicate reporting of these preferred terms, so across these terms 14 (10.3%) patients in the olaparib group and 10 (7.8%) patients in the placebo group reported an event.

Based on the above, no association with olaparib was concluded for muscle spasms and peripheral neuropathy.

Serious adverse event / deaths / other significant events

Serious adverse event

Table 70: Number (%) of patients reporting SAEs: Study 19, All Patients, Safety Analysis Set (safety update)

System Organ Class/ Preferred Term	Olaparib 400 mg bd N=136			Placebo N=128		
	DCO for MAA	DCO for Safety Update	Change (n)	DCO for MAA	DCO for Safety Update	Change (n)
Any SAE	**25 (18.4)**	**25 (18.4)**	**0**	**11 (8.6)**	**11 (8.6)**	**0**
Blood and lymphatic system disorders	5 (3.7)	6 (4.4)	1	0	0	0
Anaemia	3 (2.2)	3 (2.2)	0	0	0	0
Pancytopenia	1 (0.7) [a]	2 (1.5)	1	0	0	0

System Organ Class/ Preferred Term	Olaparib 400 mg bd N=136			Placebo N=128		
	DCO for MAA	DCO for Safety Update	Change (n)	DCO for MAA	DCO for Safety Update	Change (n)
Thrombocytopenia	1 (0.7) [b]	1 (0.7)	0	0	0	0
Cardiac disorders	1 (0.7)	1 (0.7)	0	0	0	0
Cardiovascular insufficiency	1 (0.7)	1 (0.7)	0	0	0	0
Gastrointestinal disorders	7 (5.1)	8 (5.9)	1	7 (5.5)	7 (5.5)	0
Abdominal pain	0	0	0	1 (0.8)	1 (0.8)	0
Constipation	1 (0.7)	2 (1.5)	1	0	0	0
Diarrhoea	1 (0.7)	1 (0.7)	0	0	0	0
Gastritis	0	0	0	2 (1.6)	2 (1.6)	0
Impaired gastric emptying	0	0	0	1 (0.8)	1 (0.8)	0
Intestinal obstruction	1 (0.7)	1 (0.7)	0	1 (0.8)	1 (0.8)	0
Intra-abdominal haemorrhage	1 (0.7)	1 (0.7)	0	0	0	0
Melaena	1 (0.7)	1 (0.7)	0	0	0	0
Nausea	***0***	***1 (0.7)***	***1***	***0***	***0***	***0***
Small intestinal obstruction	2 (1.5)	2 (1.5)	0	3 (2.3)	3 (2.3)	0
Vomiting	1 (0.7)	1 (0.7)	0	0	0	0
General disorders & administration site conditions	2 (1.5)	2 (1.5)	0	0	0	0
Hernia pain	1 (0.7)	1 (0.7)	0	0	0	0
Pyrexia	1 (0.7)	1 (0.7)	0	0	0	0
Hepatobiliary disorders	1 (0.7)	0	-1	0	0	0
Cholestatic jaundice[c]	1 (0.7)	0	-1	0	0	0
Immune system disorders	1 (0.7)	1 (0.7)	0	0	0	0
Iodine allergy	1 (0.7)	1 (0.7)	0	0	0	0
Infections and infestations	4 (2.9)	4 (2.9)	0	3 (2.3)	3 (2.3)	0
Appendicitis	1 (0.7)	1 (0.7)	0	0	0	0
Endophthalmitis	0	0	0	1 (0.8)	1 (0.8)	0
Infective exacerbation of chronic obstructive airways disease	***0***	***0***	***0***	***0***	***1 (0.8)***	***1***
Influenza	0	0	0	1 (0.8)	1 (0.8)	0
Liver abscess	1 (0.7)	1 (0.7)	0	0	0	0
Pneumonia	1 (0.7)	1 (0.7)	0	1 (0.8)	0	-1
Upper respiratory tract infection	1 (0.7)	1 (0.7)	0	0	0	0
Urinary tract infection	1 (0.7)	1 (0.7)	0	1 (0.8)	1 (0.8)	0
Injury, poisoning and procedural complications	2 (1.5)	2 (1.5)	0	0	0	0
Femur fracture	1 (0.7)	1 (0.7)	0	0	0	0
Hip fracture	***0***	***1 (0.7)***	***1***	***0***	***0***	***0***
Post procedural haematoma	1 (0.7)	1 (0.7)	0	0	0	0
Metabolism and nutrition disorders	0	0	0	1 (0.8)	1 (0.8)	0
Dehydration	0	0	0	1 (0.8)	1 (0.8)	0

System Organ Class/ Preferred Term	Olaparib 400 mg bd N=136			Placebo N=128		
	DCO for MAA	DCO for Safety Update	Change (n)	DCO for MAA	DCO for Safety Update	Change (n)
Musculoskeletal and connective tissue disorders	1 (0.7)	2 (1.5)	1	0	0	0
Back pain	***0***	***1 (0.7)***	***1***	***0***	***0***	***0***
Osteoporosis	1 (0.7)	1 (0.7)	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.7)	2 (1.5)	1	1 (0.8)	1 (0.8)	0
Acute leukaemia	***0***	***1 (0.7)***	***1***	***0***	***0***	***0***
Bladder cancer	0	0	0	1 (0.8)	1 (0.8)	0
Breast cancer in situ	1 (0.7)	0	-1	0	0	0
Intraductal proliferative breast lesion	***0***	***1 (0.7)***	***1***	***0***	***0***	***0***
Nervous system disorders	2 (1.5)	2 (1.5)	0	0	0	0
Haemorrhagic stroke[b]	1 (0.7)	1 (0.7)	0	0	0	0
Syncope	1 (0.7)	1 (0.7)	0	0	0	0
Respiratory, thoracic and mediastinal disorders	4 (2.9)	4 (2.9)	0	0	1 (0.8)	1
Asthma	***0***	***0***	***0***	***0***	***1 (0.8)***	***1***
Cough	1 (0.7)	1 (0.7)	0	0	0	0
Dyspnoea	2 (1.5)	2 (1.5)	0	0	0	0
Pulmonary embolism	1 (0.7)	1 (0.7)[d]	0	0	0	0
Vascular disorders	1 (0.7)	1 (0.7)	0	1 (0.8)	1 (0.8)	0
Deep vein thrombosis	1 (0.7)	1 (0.7)	0	0	0	0
Essential hypertension	0	0	0	1 (0.8)	1 (0.8)	0
Vena cava thrombosis	1 (0.7)	1 (0.7)	0	0	0	0

a Patient who later developed MDS (fatal AE)
b Patient who had a fatal AE of haemorrhagic stroke
c Patient had cholestatic jaundice reported at previous DCO: further follow up led to the re-classification of this event to progressive disease therefore the SAE of cholestatic jaundice is no longer reported.
d Patient experienced a second event of pulmonary embolism at the Safety Update DCO but this is not reflected in this table because it is a second occurrence of the same SAE Preferred Term in 1 patient.
Patients reporting multiple SAEs are counted once for each System Organ Class/Preferred Term. Data sorted alphabetically by System Organ Class and Preferred Term.
Includes adverse events with an onset date between the date of first dose and 30 days following the date of last dose of study treatment.
New SAEs which had not been reported at the MAA DCO are indicated by bold italic text.
AE Adverse event; CSR Clinical study report; DCO Data cut-off; MDS Myelodysplastic syndrome; MAA New Drug Application; SAE Serious adverse event.
DCO for MAA: 26 November 2012; DCO for safety update: 31 January 2014

The SAE profile was similar in the *BRCAm* subgroup of patients and the *gBRCA* subgroup.

Table 71: Number (%) of patients reporting SAEs: Study 19, All Patients, Safety Analysis Set (safety update)

System Organ Class/ Preferred term	Olaparib 400 mg bd N=74			Placebo N=62		
	DCO for MAA	DCO for Safety Update	Change (n)	DCO for MAA	DCO for Safety Update	Change (n)
Any SAE	**16 (21.6)**	**16 (21.6)**	**0**	**6 (9.7)**	**6 (9.7)**	**0**

System Organ Class/ Preferred term	Olaparib 400 mg bd N=74			Placebo N=62		
	DCO for MAA	DCO for Safety Update	Change (n)	DCO for MAA	DCO for Safety Update	Change (n)
Blood and lymphatic system disorders	1 (1.4)	2 (2.7)	1	0	0	0
Pancytopenia	***0***	***1 (1.4)***	***1***	***0***	***0***	***0***
Thrombocytopenia	1 (1.4) [a]	1 (1.4)	0	0	0	0
Cardiac disorders	1 (1.4)	1 (1.4)	0	0	0	0
Cardiovascular insufficiency	1 (1.4)	1 (1.4)	0	0	0	0
Gastrointestinal disorders	4 (5.4)	5 (6.8)	1	4 (6.5)	4 (6.5)	0
Abdominal pain	0	0	0	1 (1.6)	1 (1.6)	0
Constipation	***0***	***1 (1.4)***	***1***	***0***	***0***	***0***
Diarrhoea	1 (1.4)	1 (1.4)	0	0	0	0
Gastritis	0	0	0	1 (1.6)	1 (1.6)	0
Impaired gastric emptying	0	0	0	1 (1.6)	1 (1.6)	0
Intestinal obstruction	1 (1.4)	1 (1.4)	0	1 (1.6)	1 (1.6)	0
Intra-abdominal haemorrhage	1 (1.4)	1 (1.4)	0	0	0	0
Melaena	1 (1.4)	1 (1.4)	0	0	0	0
Nausea	***0***	***1 (1.4)***	***1***	***0***	***0***	***0***
Small intestinal obstruction	0	0	0	1 (1.6)	1 (1.6)	0
Vomiting	1 (1.4)	1 (1.4)	0	0	0	0
General disorders & administration site conditions	2 (2.7)	2 (2.7)	0	0	0	0
Hernia pain	1 (1.4)	1 (1.4)	0	0	0	0
Pyrexia	1 (1.4)	1 (1.4)	0	0	0	0
Hepatobiliary disorders	1 (1.4)	0	-1	0	0	0
Cholestatic jaundice[b]	1 (1.4)	0	-1	0	0	0
Infections and infestations	4 (5.4)	4 (5.4)	0	2 (3.2)	2 (3.2)	0
Appendicitis	1 (1.4)	1 (1.4)	0	0	0	0
Infective exacerbation of chronic obstructive airways disease	***0***	***0***	***0***	***0***	***1 (1.6)***	***1***
Influenza	0	0	0	1 (1.6)	1 (1.6)	0
Liver abscess	1 (1.4)	1 (1.4)	0	0	0	0
Pneumonia	1 (1.4)	1 (1.4)	0	1 (1.6)	0	-1
Upper respiratory tract infection	1 (1.4)	1 (1.4)	0	0	0	0
Urinary tract infection	1 (1.4)	1 (1.4)	0	1 (1.6)	1 (1.6)	0
Injury, poisoning and procedural complications	2 (2.7)	2 (2.7)	0	0	0	0
Femur fracture	1 (1.4)	1 (1.4)	0	0	0	0
Hip fracture	***0***	***1 (1.4)***	***1***	***0***	***0***	***0***
Post procedural haematoma	1 (1.4)	1 (1.4)	0	0	0	0
Metabolism and nutrition disorders	0	0	0	1 (1.6)	1 (1.6)	0
Dehydration	0	0	0	1 (1.6)	1 (1.6)	0

System Organ Class/ Preferred term	Olaparib 400 mg bd N=74			Placebo N=62		
	DCO for MAA	DCO for Safety Update	Change (n)	DCO for MAA	DCO for Safety Update	Change (n)
Musculoskeletal and connective tissue disorders	1 (1.4)	2 (2.7)	1	0	0	0
Back pain	***0***	***1 (1.4)***	***1***	***0***	***0***	***0***
Osteoporosis	1 (1.4)	1 (1.4)	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.4)	2 (2.7)	1	0	0	0
Acute leukaemia	***0***	***1 (1.4)***	***1***	***0***	***0***	***0***
Breast cancer in situ	1 (1.4)	0	-1	0	0	0
Intraductal proliferative breast lesion	***0***	***1 (1.4)***	***1***	***0***	***0***	***0***
Nervous system disorders	2 (2.7)	2 (2.7)	0	0	0	0
Haemorrhagic stroke	1 (1.4)	1 (1.4)	0	0	0	0
Syncope	1 (1.4)	1 (1.4)	0	0	0	0
Respiratory, thoracic and mediastinal disorders	3 (4.1)	3 (4.1)	0	0	1 (1.6)	1
Asthma	***0***	***0***	***0***	***0***	***1 (1.6)***	***1***
Cough	1 (1.4)	1 (1.4)	0	0	0	0
Dyspnoea	1 (1.4)	1 (1.4)	0	0	0	0
Pulmonary embolism	1 (1.4)	1 (1.4)	0	0	0	0
Vascular disorders	1 (1.4)	1 (1.4)	0	1 (1.6)	1 (1.6)	0
Deep vein thrombosis	1 (1.4)	1 (1.4)	0	0	0	0
Essential hypertension	0	0	0	1 (1.6)	1 (1.6)	0
Vena cava thrombosis	1 (1.4)	1 (1.4)	0	0	0	0

a Patient (*gBRCAm*) who had a fatal AE of haemorrhagic stroke
b Patient ad cholestatic jaundice reported at previous DCO: further follow up led to the re-classification of this event to progressive disease therefore the SAE of cholestatic jaundice is no longer reported.
Patients reporting multiple SAEs are counted once for each System Organ Class/Preferred Term. Data sorted alphabetically by System Organ Class and Preferred Term.
Includes adverse events with an onset date between the date of first dose and 30 days following the date of last dose of study treatment.
New SAEs which had not been reported at the MAA DCO are indicated by bold italic text.
AE Adverse event; *BRCAm gBRCA* and/or *tBRCA* mutated; CSR Clinical study report; DCO Data cut-off; *gBRCA* Germline breast cancer susceptibility gene; MAA New Drug Application; SAE Serious adverse event; *tBRCA* Tumour breast cancer susceptibility gene.
DCO for MAA: 26 November 2012; DCO for safety update: 31 January 2014

Consistent with Study 19, the most common SOCs reported for SAEs reported by patients in the 400 mg bd monotherapy pool were blood and lymphatic disorders (most commonly reported preferred term anaemia, 2.9% patients) and gastrointestinal disorders (intestinal obstruction, small intestinal obstruction, vomiting, abdominal pain; 1.8 to 1.9% patients). The proportion of patients in the 400 mg bd monotherapy pool reporting SAEs was higher than in Study 19 (25.2% vs 18.4% in the overall population; 27.7% vs 21.6% in the *BRCAm* subgroup), this could reflect the more advanced stage of disease of patients included in the pool (data cut-off 26 November 2012).

In the supportive study 41, serious AEs were reported in 10.6% of patients treated with olaparib compared to 7.3% in the placebo group. Notably, 3 MDS were observed in the olaparib arm, one resolved and 2 unresolved; one fatal case of DIC (disseminated intravascular coagulation) in patient also having MDS was considered as related to study drug.

Deaths

Sixteen patients in the pooled dataset had either a fatal AE only reported, or had death related to disease and a fatal AE reported. In 2 of the 16 patients, no fatal AE commenced until post follow up. There were nine deaths reported in the pooled dataset where the reason was 'other'. These include 6 patients from Study 19. In addition, 1 patient in Study 9 (primary cause of death of acute myeloid leukaemia), 1 patient in Study 12 (primary and secondary causes of death recorded as unknown, but appears to be due to disease progression) and 1 patient from Study 24 (due to disease progression, but recorded as 'other').

Nine of the 16 patients with fatal AEs were from Study 42. Whilst all patients in Study 42 were late line patients (mean number of prior chemotherapy regimens was 4.0), the nine patients in Study 42 reporting fatal AEs had a higher burden of prior chemotherapy (mean 5.6, range 3-10). In 4 of the patients co-morbidities present at study entry contributed to the fatal events.

In the pivotal study, one patient in the olaparib arm was reported to have died due to an AE only; this patient suffered a haemorrhagic stroke, which was considered related to study treatment. Two further deaths were reported in the olaparib arm, where the reason for death was recorded as related to the disease under study and a fatal AE (cholestatic jaundice and myelodysplastic syndrome).

Table 72: Number (%) of patients who died: Study 19, All Patients, Safety Analysis Set (safety update)

Category	Olaparib 400 mg bd N=136			Placebo N=128		
	DCO for MAA	DCO for Safety Update	Change (n)	DCO for MAA	DCO for Safety Update	Change (n)
Total number of deaths	77 (56.6)	86 (63.2)	9	77 (60.2)	93 (72.7)	16
Death related to disease under investigation only	68 (50.0)	77 (56.6)	9	71 (55.5)	87 (68.0)	16
AE with outcome = death only	1 (0.7)	1 (0.7)	0	0	0	0
Death related to disease and an AE with outcome = death	2 (1.5)	1 (0.7)	-1	0	0	0
Other deaths[a]	6 (4.4)	7 (5.1)	1	6 (4.7)	6 (4.7)	0

a Patients who died and are not captured in the earlier categories
Includes events that occurred during treatment, in the 30 day follow up period, or post follow up
AE Adverse event; CSR Clinical study report; DCO Data cut-off; MAA New Drug Application.
DCO for MAA: 26 November 2012; DCO for safety update: 31 January 2014

Table 73: Number (%) of patients who died: Study 19, BRCAm Subgroup, Safety Analysis Set (safety update)

Category	Olaparib 400 mg bd N=74			Placebo N=62		
	DCO for MAA	DCO for Safety Update	Change (n)	DCO for MAA	DCO for Safety Update	Change (n)
Total number of deaths	37 (50.0)	42 (56.8)	5	34 (54.8)	41 (66.1)	7
Death related to disease under investigation only	31 (41.9)	37 (50.0)	6	30 (48.4)	37 (59.7)	7
AE with outcome = death only	1 (1.4)	1 (1.4)	0	0	0	0
Death related to disease and an AE with outcome = death	1 (1.4)	0	-1	0	0	0

Category	Olaparib 400 mg bd N=74			Placebo N=62		
	DCO for MAA	DCO for Safety Update	Change (n)	DCO for MAA	DCO for Safety Update	Change (n)
Other deaths[a]	4 (5.4)	4 (5.4)	0	4 (6.5)	4 (6.5)	0

a Patients who died and are not captured in the earlier categories
Includes events that occurred during treatment, in the 30 day follow up period, or post follow up
AE Adverse event; *BRCAm gBRCA* and/or *tBRCA* mutated; CSR Clinical study report; DCO Data cut-off; *gBRCA* Germline breast cancer susceptibility gene; MAA New Drug Application; *tBRCA* Tumour breast cancer susceptibility gene.

In study 41, there were 3 'other' deaths in the olaparib arm, all of which occurred post-30-day follow up. These were recorded as sepsis (occurred a long time after safety follow-up and after subsequent rounds of chemotherapy), metastatic ovarian cancer (but not recorded as due to disease under investigation), and cardiac infarction (the patient appeared to have progressive disease due to brain metastases, and had recent/prior abnormal ECG findings, along with a history of hypertension and stroke). There was 1 fatal AE of disseminated intravascular coagulation (AE commenced in the follow-up period after the maintenance phase and the patient died post follow up; this patient also had myelodysplastic syndrome).

Laboratory findings

Haematology

Table 74: Number (%) of patients with maximum overall CTCAE grade during treatment for key haematology parameters: Study 19, Safety Analysis Set (safety update)

	All patients					*BRCAm*				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Haemoglobin										
Olaparib 400 mg bd	24/136 (17.6)	58/136 (42.6)	***44***/136 (***32.4***)	***8***/136 (***5.9***)	2/136 (1.5)	11/74 (14.9)	33/74 (44.6)	***24*** /74 (***32.4***)	***5***/74 (***6.8***)	1/74 (1.4)
Placebo	54/128 (42.2)	61/128 (47.7)	12/128 (9.4)	1/128 (0.8)	0	29/62 (46.8)	25/62 (40.3)	7/62 (11.3)	1/62 (1.6)	0
Neutrophils										
Olaparib 400 mg bd	***74***/136 (***54.4***)	***41***/136 (***30.1***)	14/136 (10.3)	3/136 (2.2)	***4***/136 (***2.9***)	***42***/74 (***56.8***)	***20***/74 (***27.0***)	8/74 (10.8)	2/74 (2.7)	***2***/74 (***2.7***)
Placebo	77/128 (60.2)	34/128 (26.6)	14/128 (10.9)	3/128 (2.3)	0	39/62 (62.9)	17/62 (27.4)	5/62 (8.1)	1/62 (1.6)	0
Lymphocytes										
Olaparib 400 mg bd	***66***/136 (***48.5***)	***32***/136 (***23.5***)	***27***/136 (***19.9***)	10/136 (7.4)	***1/136 (0.7)***	35/74 (47.3)	***15***/74 (***20.3***)	***18***/74 (***24.3***)	6/74 (8.1)	0
Placebo	***87***/128 (***68.0***)	24/128 (18.8)	***13***/128 (***10.2***)	4/128 (3.1)	0	***43***/62 (***69.4***)	13/62 (21.0)	***4***/62 (***6.5***)	2/62 (3.2)	0
Platelets										
Olaparib 400 mg bd	***89***/136 (***65.4***)	***39***/136 (***28.7***)	***4***/136 (***2.9***)	3/136 (2.2)	1/136 (0.7)	***50***/74 (***67.6***)	19/74 (25.7)	***1/74 (1.4)***	3/74 (4.1)	1/74 (1.4)
Placebo	***105***/128 (***82.0***)	***21***/128 (***16.4***)	2/128 (1.6)	0	0	***52***/62 (***83.9***)	***8***/62 (***12.9***)	2/62 (3.2)	0	0

Haemoglobin: grade 1 <LLN – 100 g/L, grade 2 <100 – 80 g/L, grade 3 <80 – 65 g/L, grade 4 <65 g/L. Lymphocytes: grade 1 <LLN – 0.8 x 109/L, grade 2 <0.8 – 0.5 x 109/L, grade 3 <0.5 – 0.2 x 109/L, grade 4 <0.2 x 109/L. Neutrophils: grade 1 <LLN – 1.5 x 109/L, grade 2 <1.5 – 1.0 x 109/L, grade 3 <1.0 – 0.5 x 109/L, grade 4 <0.5 x 109/L Platelets: grade 1 <LLN – 75.0 x 109/L, grade 2 <75.0 – 50.0 x 109/L, grade 3 <50.0 – 25.0 x 109/L, grade 4 <25.0 x 109/L.
bd Twice daily; BRCAm gBRCA and/or tBRCA mutated; CTCAE Common Terminology Criteria for Adverse Events; CSR Clinical study report; gBRCA Germline breast cancer susceptibility gene; LLN Lower limit of normal; tBRCA Tumour breast cancer susceptibility gene.

Clinical chemistry

Table 75: Number (%) of patients with maximum overall CTCAE grade during treatment for key clinical chemistry parameters: Study 19, Safety Analysis Set

	All patients					*BRCAm*				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Olaparib 400 mg bd										
ALT	99/135 (73.3)	31/135 (23.0)	3/135 (2.2)	2/135 (1.5)	0	52/74 (70.3)	19/74 (25.7)	1/74 (1.4)	2/74 (2.7)	0
AST	99/136 (72.8)	33/136 (24.3)	1/136 (0.7)	3/136 (2.2)	0	50/74 (67.6)	21/74 (28.4)	1/74 (1.4)	2/74 (2.7)	0
ALP	98/136 (72.1)	37/136 (27.2)	0	1/136 (0.7)	0	49/74 (66.2)	24/74 (32.4)	0	1/74 (1.4)	0
Bilirubin	123/136 (90.4)	8/136 (5.9)	4/136 (2.9)	1/136 (0.7)	0	67/74 (90.5)	5/74 (6.8)	1/74 (1.4)	1/74 (1.4)	0
Creatinine	77/135 (57.0)	47/135 (34.8)	10/135 (7.4)	0	1/135 (0.7)	43/74 (58.1)	26/74 (35.1)	4/74 (5.4)	0	1/74 (1.4)
Placebo										
ALT	86/126 (68.3)	34/126 (27.0)	3/126 (2.4)	3/126 (2.4)	0	37/60 (61.7)	19/60 (31.7)	2/60 (3.3)	2/60 (3.3)	0
AST	80/125 (64.0)	38/125 (30.2)	7/125 (5.6)	0	0	36/59 (61.0)	19/59 (32.2)	4/59 (6.8)	0	0
ALP	90/126 (71.4)	35/126 (27.8)	1/126 (0.8)	0	0	40/60 (66.7)	20/60 (33.3)	0	0	0
Bilirubin	118/127 (92.9)	8/127 (6.3)	0	1/127 (0.8)	0	57/61 (93.4)	4/61 (6.6)	0	0	0
Creatinine	109/127 (85.8)	16/127 (12.6)	2/127 (1.6)	0	0	51/61 (83.6)	8/61 (13.1)	2/61 (3.3)	0	0

Study 19 CSR, Table 11.3.7.4.b and Table 11.3.7.4.c

The clinical chemistry changes observed during Study 19 remained generally mild to moderate in severity and required no treatment/dose modification. The number of patients with changes to CTCAE grade 3 or 4 values during the study remained low and generally similar in the olaparib and placebo groups. This was true for all patients in Study 19 and for the subset of patients with a BRCA mutation. Laboratory data for patients in the *gBRCA* subgroup were consistent with those for all patients and those with a *BRCAm*.

Hepatic function

The majority of patients in the olaparib (95.6%) and placebo arms (95.3%) had AT values ≤3 x ULN (Safety Update). The number of patients with AT values >3x ULN to ≤5x ULN and >5x ULN to ≤10 x ULN was small, and similar in the olaparib arm (2.2% and 0.7%, respectively) and the placebo arm 2.3% and 2.3%, respectively). Two patients had elevations of AT >10 x ULN to ≤20 ULN in the olaparib arm.

In the 400 mg bd monotherapy pooled dataset, AT values of >3x ULN to ≤ 5x ULN, >5x ULN to ≤ 10 x ULN, >10 x ULN to ≤ 20x ULN, and >20x ULN were infrequently reported (4.2%, 2.2%, 1.0% and 0.4% of patients, respectively, safety update).

Renal function

In Study 19, 90.4% of olaparib treated patients had creatinine CTCAE grade 0 at baseline and 9.6% had CTCAE grade 1 at baseline. A small increase in mean and median values for serum creatinine between baseline and Day 8 was observed for olaparib treated patients (median level 71 µmol/L at baseline; 85 µmol/L on Day 8). The median change from baseline on Day 8 for olaparib treated patients was 19.4% compared with 0% change for placebo treated patients. A total of 41/135 (30.4%) patients in the olaparib arm and 7/127 (5.5%) patients in placebo arm had a change from CTCAE grade 0 at baseline to CTCAE grade 1 for creatinine. Median values then remained consistent over time and returned to baseline values on discontinuation of olaparib.

Data from all patients in the 400 mg bd monotherapy pooled dataset were consistent with that of Study 19. In the 400 mg bd monotherapy pooled dataset, 78.4% of all patients had a change from CTCAE grade 0 at baseline to grade 1 for creatinine.

Two additional patients each reported one additional AE of blood creatinine increased; both events were mild or moderate (not CTCAE grade ≥3) (Safety update, 31 January 2014).

Urinalysis

There were no clinically relevant findings for urinalysis in Study 19.

Safety in special populations

Table 76: Number of patients reporting at least one adverse event by age group (Monotherapy pool, olaparib 400 mg bd)

	Monotherapy pool n= 735			
	Age <65	Age 65-74	Age 75-84	Age 85+
	N=587	N=114	N=33	N=1
MedDRA Terms	n/(%)	n/(%)	n/(%)	n/(%)
Total AEs	572 (97.4)	113 (99.1)	32 (97.0)	1 (100.0)
Serious AEs – Total*	142 (24.2)	32 (28.1)	11 (33.3)	0
- Fatal	11 (1.9)	1 (0.9)	1 (3.0)	0
- Hospitalisation/prolong existing Hospitalisation	126 (21.5)	28 (24.6)	10 (30.3)	0
- Life-threatening	30 (5.1)	4 (3.5)	3 (9.1)	0
- Other (Disability incapacity)	12 (2.0)	2 (1.8)	0	0
- Other (medically significant)	64 (10.9)	12 (10.5)	3 (9.1)	0
AE leading to treatment discontinuation	34 (5.8)	7 (6.1)	1 (3.0)	1 (100.0)

* 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

Table 77: Number of patients with, and reports of adverse events within the SOCs/SMQs of most relevance to elderly patients, by age (Monotherapy pool, olaparib 400 mg bd)

MedDRA Terms	Monotherapy pool n= 735			
	Age <65	Age 65-74	Age 75-84	Age 85+
	N=587	N=114	N=33	N=1
	n/(%)	n/(%)	n/(%)	n/(%)
Total Number of patients with AEs	572 (97.4)	113 (99.1)	32 (97.0)	1 (100.0)
Total number of AEs reported	6251	1122	408	21
Psychiatric disorders (SOC)				
Pts n (%)	111 (18.9)	26 (22.8)	7 (21.2)	0
Events n	147	32	9	0
Nervous system disorders (SOC)				
Pts n (%)	286 (48.7)	46 (40.4)	14 (42.4)	0
Events n	531	73	19	0
Accidents and injuries (SMQ)				
Pts n (%)	35 (6.0)	13 (11.4)	4 (12.1)	1 (100.0)
Events n	37	18	4	1
Cardiac disorders (SOC)				
Pts n (%)	38 (6.5)	11 (9.6)	1 (3.0)	0
Events n	51	12	1	0
Vascular disorders (SOC)				
Pts n (%)	89 (15.2)	21 (18.4)	5 (15.2)	0
Events n	99	23	6	0
Cerebrovascular disorders (SMQ)				
Pts n (%)	9 (1.5)	1 (0.9)	0	0
Events n	4	0	0	0
Infections and infestations (SOC)				
Pts n (%)	241 (41.1)	50 (43.9)	13 (39.4)	1 (100.0)
Events n	455	81	23	5
Quality of life decreased (PT)				
Pts and events	0	0	0	0

Patients with renal impairment

Clinical studies conducted to date have entry criteria to exclude patients with serum creatinine >1.5x institutional ULN. Using the Cockcroft-Gault formula this would be expected to exclude patients with a creatinine clearance level of >50 mL/min. Patients meeting the criteria for mild renal impairment have therefore been eligible to participate in clinical studies for which data are available. As creatinine clearance estimates were not required at study entry, a small number of patients falling into the moderate category (after estimation by the Cockcroft-Gault formula) have also received olaparib.

The impact of renal impairment at baseline on the type/frequency of AEs reported with olaparib has been assessed using safety data from the 400 mg bd monotherapy pooled dataset (n=735). Categorisation for renal impairment classification based on glomerular filtration rate (GFR) is defined in the CHMP Note for Guidance 2004. For this assessment of the 735 patients included in the clinical studies of olaparib 400 mg bd, estimates for GFR using creatinine clearance estimation have been calculated indirectly using the Cockcroft-Gault equation, a recognised formula which uses serum creatinine in combination with age, sex and weight to estimate creatinine clearance in mL/min. Normal renal function was defined as creatinine clearance >80 mL/min, mild renal impairment as creatinine clearance 50-80 mL/min, moderate renal impairment as creatinine clearance 30-<50 mL/min and severe renal impairment as creatinine clearance <30 mL/min.

Overall 448 patients were classified as having normal renal function, 237 mild renal impairment, 45 moderate renal impairment and 1 patient severe renal impairment at baseline. Data from 4 patients could not be categorised according to baseline renal impairment because the required data for the calculation was not collected.

The greatest differences in CTCAE ≥grade 3 reporting rates across the groups was observed in the investigations SOC (moderate=11.1%, mild=5.9%, normal=5.1%) and the general disorders and administrative site conditions SOC (moderate=13.3%, mild=11.8%, normal=7.1%). The most commonly reported AEs leading to dose modifications were anaemia, nausea, vomiting and fatigue.

Safety related to drug-drug interactions and other interactions

Drug-drug interactions – transporter proteins

Based on *in vitro data*, there is a potential for olaparib to reduce statin clearance, a drug-drug interaction that may be clinically relevant. No formal olaparib-statin interaction study has been conducted. Therefore, safety data from the olaparib 400 mg bd pooled dataset has been used to investigate any potential for olaparib to increase the frequency of statin-associated toxicities. In the group of 89 patients in the monotherapy pooled dataset who were taking a statin, the frequency of common AEs known to be associated with statins (e.g. nausea, diarrhoea, abdominal pain, back pain, myalgia and increased blood transaminases) were similar to those expected, based on published data (for atorvastatin, fluvastatin, rosuvastatin and simvastatin). Nausea was reported in 53 (59.6%) patients, diarrhoea in 27 (30.3%), abdominal pain in 19 (21.3%), back pain in 13 (14.6%), myalgia in 7 (7.9%), and blood transaminase increased in no patients. There was no evidence to suggest that olaparib potentiated statin-associated toxicities.

Based on *in vitro data*, there is a potential for olaparib to reduce the clearance of OCT transporter substrates (e.g. metformin), a drug-drug interaction that may be clinically relevant. No formal olaparib-metformin interaction study was conducted. Therefore, safety data from the olaparib 400 mg bd pooled dataset has been used to investigate any potential for olaparib to increase the frequency of metformin-associated toxicities. Although patient numbers are relatively small, in the group of 45 patients in the monotherapy pooled dataset who were taking metformin, the frequencies of common AEs known to be associated with metformin were similar to that expected, based on published data. Nausea was reported in 24 (53.3%) patients, vomiting in 18 (40.0%), diarrhoea in 17 (37.8%), decreased appetite in 11 (24.4%), abdominal pain in 9 (20.0%) and taste disturbance (dysphagia) in 1 (2.2%). There did not appear to be a potentiation of common AEs associated with metformin use when given concurrently with olaparib.

Discontinuation due to adverse events

Discontinuations due to adverse events in Study 19 (data cut off: 31 January 2014)

The proportion of patients who permanently discontinued study drug due to AEs was low. Across all patients, 6 (4.4%) patients receiving olaparib and 2 (1.6%) patients receiving placebo had an AE leading to discontinuation reported. No single event leading to discontinuation was reported in >1 patient in either treatment group.

In the olaparib arm, 6 patients had 8 separate events reported, 5 of which resolved with permanent treatment discontinuation, 1 resulted in death (haemorrhagic stroke) and 2 were still present (myalgia and pancytopenia).

The proportion of patients in the gBRCA subgroup with AEs leading to discontinuation was 5/53 (9.4%) in the olaparib group and none in the placebo group.

Study 41 maintenance phase

Few (7 [10.6%]) patients had AEs leading to discontinuation of olaparib monotherapy reported in the maintenance phase. These AEs were anaemia, ascites, dysphagia and haemoptysis (each in 1 patient only), and 3 cases of myelodysplastic syndrome (one of which was recently re-diagnosed as abnormal erythropoiesis). Five reported events resolved with olaparib discontinuation, and 2 remained unresolved (2 cases of myelodysplastic syndrome). Of note, in the combination phase, 15 patients (18.5%) and 12 patients (16.0%) had AEs leading to discontinuation in the O/C4/P and C6/P arms, respectively. More patients in the O/C4/P arm (8.6%) had haematological toxicity leading to discontinuation than in the C6/P arm (0%).

Adverse events leading to dose interruptions/reductions in Study 19 (data cut off: 31 January 2014)

There was no overall increase in the number of patients who had a dose interruption due to an AE, although there were small increases in the incidence of some individual AEs that led to dose interruptions. There was a small increase in the number of patients who reported an AE leading to dose reduction (6 on the olaparib arm [3 gBRCAm] and 3 on the placebo arm [1 gBRCAm]) which was accompanied by small increases in the incidence of some individual AEs that led to dose reductions.

Adverse events leading to dose interruptions were reported for a numerically higher percentage of patients in the olaparib arm of Study 19 (47 [34.6%]) than in the placebo arm (12 [9.4%]). The most common AEs leading to dose interruption in the olaparib arm were vomiting (8.1% of patients), nausea (6.6%), fatigue (4.4%), abdominal pain (3.7%) and diarrhoea (3.7%). Compared with all patients, AEs leading to dose interruptions were reported in a similar proportion of patients in the BRCAm subgroup (36.5% olaparib vs. 9.7% placebo) and in a slightly lower proportion of patients in the gBRCA subgroup (32.1% olaparib vs. 7.0% placebo).

Adverse events leading to dose reductions were also more commonly reported in the olaparib arm of Study 19 (34 [25.0%] patients) than in the placebo arm (6 [4.7%] patients). The most common AEs leading to dose reductions in the olaparib arm were similar to those leading to dose interruptions: vomiting (2.9%), nausea (3.7%), fatigue (4.4%) and anaemia (3.7%). Compared with all patients, AEs leading to dose reductions were reported in a similar proportion of patients in the BRCAm subgroup (25.7% olaparib vs. 3.2% placebo) and in a slightly lower proportion of patients in the gBRCA subgroup (18.9% olaparib vs. 4.7% placebo).

Post marketing experience

Not applicable.

Adverse drug reactions

Table 78: Summary of adverse reactions

	Adverse Reactions	
MedDRA System Organ Class	**Frequency of All CTCAE grades**	**Frequency of CTCAE grade 3 and above**
Metabolism and nutrition disorders	Decreased appetite **160/735 [21.8%]**	Decreased appetite **4/735 [0.5%]**
Nervous system disorders	Headache **132/735 [18.0%]** Dizziness **96/735 [13.1%]** Dysgeusia, **105/735 [14.3%]**	Dizziness **3/735 [0.4%]**, Headache **2/735 [0.3%]**
Gastrointestinal disorders	Nausea **459/735 [62.4%]** **V**omiting **266/735 [36.2%]** Diarrhoea **180/735 [24.5%]** Dyspepsia **118/735 [16.1%]** Upper abdominal pain **69/735 [9.4%]**, Stomatitis **35/735 [4.8%]**	Nausea **20/735 [2.7%]**, Vomiting **24/735 [3.3%]**, Diarrhoea **13/735 [1.8%]** Upper abdominal pain **2/735 [0.3%]** Stomatitis **3/735 [0.4%]**
General disorders and administration site conditions	Fatigue (including asthenia) **452/735 [61.5%]**	Fatigue (including asthenia) **56/735 [7.6%]**
Investigations	Anaemia **314/728 [43.1%]** (decrease in haemoglobin)[a, b], Neutropaenia **97/713 [13.6%]** (decrease in absolute neutrophil count) [a, b], Lymphopaenia **243/551 [44.1%]** (decrease in lymphocytes) [a, b], Increase in blood creatinine **707/727 [97.2%]** [a, d], Mean corpuscular volume elevation **284/647 [43.9%]** [a, c] Thrombocytopaenia **43/728 [5.9%]** (decrease in platelets) [a, b]	Anaemia **87/728 [12.0%]** (decrease in haemoglobin)[a, b], Lymphopaenia **90/551 [16.3%]** (decrease in lymphocytes) [a, b] Neutropaenia **35/713 [4.9%]** (decrease in absolute neutrophil count) [a, b] Thrombocytopaenia **21/728 [2.9%]** (decrease in platelets) [a, b] Increase in blood creatinine **5/727 [0.7%]** [a, d]

[a] Represents the incidence of laboratory findings, not of reported adverse events.

[b] Decreases were CTCAE grade 2 or greater for haemoglobin, absolute neutrophils, platelets and lymphocytes.

[c] Elevation in mean corpuscular volume from baseline to above the ULN (upper limit of normal). Levels appeared to return to normal after treatment discontinuation and did not appear to have any clinical consequences.

[d] Data from a double blind placebo controlled study showed a median increase (in percentage change from baseline) up to 23% remaining consistent over time and returning to baseline after treatment discontinuation, with no apparent clinical sequelae. 90% of patients were CTCAE grade 0 at baseline, and 10% were CTCAE grade 1 at baseline.

2.6.1. Discussion on clinical safety

Patient exposure

Overall, the clinical development programme of olaparib included 2034 subjects with ovarian and other solid tumours who received at least one dose of olaparib, regardless of the dosage and treatment duration. The clinical safety analysis was based on monotherapy and combination, phase 1 and 2 studies. No phase 3 study in the requested indication was submitted.

Pooled safety data from the pivotal study 19 and an additional 10 studies in a total of 735 patients with advanced solid tumours were provided in support of the use of olaparib 400 mg bd monotherapy. Although the pooling of safety data from studies with different indications and different trial design is questionable, a comparison was also provided in patients affected by the BRCAm ovarian cancer receiving olaparib (n=397).

In addition, safety data were also presented for the pivotal study 19 and supportive study 41 (121 patients who entered the maintenance phase of the study 41). Data from study 41 were presented independently considering the potential for carryover of ongoing toxicities from the previous combination phase that may have influenced the overall pool dataset. Data from Study 19 are considered to be the primary source of information contributing to the olaparib safety profile.

In study 19, a greater proportion of patients in the olaparib group continued to receive treatment over time than in the placebo group, this becoming apparent after approximately 6 months. Long-term exposure to olaparib maintenance therapy was initially demonstrated in this study: 54 (39.7%), 32 (23.5%) and 19 (14.0%) of all patients in the olaparib group remained on treatment at 1 year, 2 years and 3 years, respectively. Overall, around half of patients have been treated for 6 months and more (320/735, 43.5% in the pooled dataset and 207/397, 52.1% in the BRCAm ovarian cancer subgroup). Smaller percentages of patients had treatment duration of ≥12 months (respectively 19% and 23.7%). Considering the claimed maintenance setting, the safety dataset contributing to long-term exposure to olaparib appears limited. Further safety data will be provided from ongoing studies (see RMP).

In studies 19 and 41, the mean daily doses for olaparib as maintenance treatment were below 700 mg. The mean dose adherence was lower in the olaparib group (84.4%) compared with the placebo group (96.6%).Dose reduction to 200 mg twice daily (equivalent to a total daily dose of 400 mg) and, if a further final dose reduction is required, to 100 mg twice daily (equivalent to a total daily dose of 200 mg) or treatment interruption to manage adverse events were foreseen by study protocols and are adequately reflected in section 4.2 of the SmPC (dose adjustments).

Adverse events

According to the primary pharmacology of this class of drugs and as confirmed from non-clinical studies with olaparib, the expected toxicities include myelosuppression (anaemia, neutropenia, thrombocytopenia), gastrointestinal effects (nausea, vomiting) and fatigue. Effects on embryo foetal survival and clastogenicity were also reported.

In Study 19, the most common System Organ Classes (SOC) for reported AEs were gastrointestinal disorders, general disorders and administration site conditions, nervous system disorders, and infections and infestations. The most common AEs that were reported at a 5% greater frequency in the olaparib 400 mg bd group compared with the placebo group were nausea, fatigue, vomiting and anaemia. Overall, the profile and incidence of common AEs for the BRCAm subset of patients was similar to that observed in the overall patient population.

In Study 19, a significantly higher percentage of all patients in the olaparib group reported AEs of CTCAE grade ≥3 (40.4%) compared with the placebo group (21.9%). The most common AEs of CTCAE grade ≥3 reported on olaparib treatment were fatigue and anaemia. This was also the case for the subgroup of patients with a BRCAm. Most grade 3 and higher events were reported during the first 6 months of treatment. When compared with data for all patients in the 400 mg bd monotherapy pooled dataset, there was a similar percentage of patients with grade 3/4 AEs, with fatigue and anaemia being the most common grade 3/4 AEs. Grade 3/4 anaemia was reported more frequently in the pooled dataset (11.4%) and in study 41 (9.1%) than in Study 19 (5.1%).

In all patients in Study 19, there was a numerically higher percentage of patients in the olaparib group with a dose interruption (36%) or dose reduction (41.9%) reported compared with the placebo group (respectively 16.4% and 21.9%). Dose interruptions were mainly due to an AE.

The analysis of adverse events by organ system or syndrome showed that gastrointestinal events, haematological toxicity and CNS disorders are very common and as such these adverse drug reactions have been reflected in section 4.8 of the SmPC.

Overall, gastrointestinal toxicities were frequently reported with olaparib therapy and were generally low grade (CTCAE grade 1 or 2) and intermittent and could be managed by dose interruption, dose reduction and/or concomitant medicinal products (e.g. antiemetic therapy). Antiemetic prophylaxis is not required (see SmPC section 4.4 and 4.8).

All events of gastrointestinal obstructions were considered not to be related to olaparib by the study investigator. Available safety data did not show any evidence that olaparib may increase the risk of intestinal obstruction in patients with advanced ovarian cancer.

Considering that asthenia, fatigue, and dizziness have been reported during treatment with olaparib, those patients who experience these symptoms should observe caution when driving or using machines (see section 4.7).

Events from the hepatobiliary disorders SOC or Investigations SOC (abnormalities in liver biochemistry) were reported more frequently in the pooled monotherapy than in olaparib arm in study 19. Two cases of Hy's law were also reported but considered as not related to studied drug. However, the role of olaparib in worsening of the hepatic injury cannot be excluded. A formal study to evaluate the impact of hepatic impairment on olaparib pharmacokinetics and the safety and tolerability profile is ongoing and results will be provided in accordance with RMP.

Mild elevations in creatinine with no apparent sequelae have been observed with olaparib treatment. The clinical significance of these mild creatinine elevations in creatinine is unknown (see SmPC section 4.8 and RMP) but inhibition of organic cation-transporter-2 (OCT2) by olaparib is considered a plausible mechanistic explanation. Further investigations are needed in patients with renal impairment as reflected in the RMP.

In relation to QT prolongation, the clinical data available to date suggest no effect of olaparib on QT interval. One case of QT prolongation was reported when olaparib was combined with itraconazole. It is recommended that known strong inhibitors (e.g., itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) of CYP3A4/5 isozymes should be avoided with olaparib (see SmPC section 4.4).

Haematological toxicity was reported in patients treated with olaparib, including clinical diagnoses and/or laboratory findings of generally mild or moderate (CTCAE grade 1 or 2) anaemia, neutropenia, thrombocytopenia and lymphopenia. Although, anaemia and other haematological toxicities were generally low grade (CTCAE grade 1 or 2), there were reports of CTCAE grade 3 and higher events (see SmPC section 4.8).

Therefore, patients should not start treatment with Lynparza until they have recovered from haematological toxicity caused by previous anticancer therapy (haemoglobin, platelet, and neutrophil levels should be within normal range or CTCAE grade 1). Baseline testing, followed by monthly monitoring, of complete blood counts is recommended for the first 12 months of treatment and periodically after this time to monitor for clinically significant changes in any parameter during treatment.

If a patient develops severe haematological toxicity or blood transfusion dependence, treatment with olaparib should be interrupted and appropriate haematological testing should be initiated. If the blood parameters remain clinically abnormal after 4 weeks of olaparib dose interruption, bone marrow analysis and/or blood cytogenetic analysis are recommended (see SmPC section 4.4).

Pneumonitis was reported in a small number of patients receiving olaparib, and some reports were fatal. The reports of pneumonitis had no consistent clinical pattern and were confounded by a number of pre-disposing factors (cancer and/or metastases in lungs, underlying pulmonary disease, smoking history, and/or previous chemotherapy and radiotherapy). Therefore, if patients present with new or worsening respiratory symptoms such as dyspnoea, cough and fever, or a radiological abnormality occurs, olaparib treatment should be interrupted and prompt investigation initiated. If pneumonitis is confirmed, olaparib treatment should be discontinued and the patient treated appropriately (see SmPC section 4.4 and RMP).

The accumulation of DNA damage following inhibition of PARP might contribute in certain circumstances to the development of MDS/AML. The therapeutic window of olaparib might to be narrower in patients with germline BRCA mutation at long term since these patients have higher predisposition to cancer in general and harbor normal cells with BRCA haploinsufficiency. Myelodysplastic syndrome/Acute Myeloid Leukaemia (MDS/AML) were reported in a small number of patients who received olaparib alone or in combination with other anti-cancer drugs. The majority of cases have been fatal. The duration of therapy with olaparib in patients who developed MDS/AML varied from < 6 months to > 2 years. The cases were typical of secondary MDS/cancer therapy-related AML. All patients had potential contributing factors for the development of MDS/AML; the majority of cases were in g*BRCA* mutation carriers and some of the patients had a history of previous cancer or of bone marrow dysplasia. All had received previous platinum-containing chemotherapy regimens and many had also received other DNA damaging agents and radiotherapy. (see SmPC section 4.4).

Given that patients with gBRCAm are more likely to participate in PARP inhibitor trials, no firm conclusion can be drawn whether incidence is higher in these patients. In addition, it is acknowledged that all patients had received previous chemotherapy with DNA damaging agents including platinum, with many patients having extensive previous chemotherapy with multiple treatment regimens over multiple years including carboplatin, taxanes, anthracyclines, other alkylating and deoxyribonucleic acid (DNA) damaging agents and radiotherapy. However, the median number of prior chemotherapy regimens was 3 for most of the studies in the pooled dataset, indicating that patients were overall not heavily pretreated. The risk of developing AML (and secondary MDS) was associated with the cumulative dose and duration of treatment. The duration of therapy with olaparib in patients with MDS/AML reported was >2 years in 5 out of 16 patients. Since the maximal total treatment duration in study 19 was 1349 days (<4 years), the limitation of the treatment duration with olaparib should be considered. Overall, it is not possible to exclude the contribution of previous treatment to the development or acceleration of MDS/AML. However, considering the previous points, the risk of presenting MDS/AML when receiving olaparib cannot be ruled out. Therefore, myelodysplastic syndrome/acute myeloid leukaemia is considered as an important potential risk as reflected in the RMP. Given the seriousness of the risk and the fact that PARP inhibitors are a new class of agents with limited knowledge of their safety profile, the PRAC and CHMP considered that this risk should be monitored through a registry (see RMP). The applicant will submit within three months of approval the protocol synopsis for the registry as reflected in the RMP.

In addition, if MDS and/or AML are confirmed while on treatment with olaparib, it is recommended that the patient is treated appropriately. If additional anticancer therapy is recommended, olaparib should be discontinued and not given in combination with other anticancer therapy (see SmPC section 4.4).

In relation to other new primary malignancies, the number of events of new primary malignant tumours (including non-melanoma skin cancers) reported was overall low across the development programme for olaparib, with 23 events (in 21 patients) being reported in an estimated 2866 olaparib-treated patients (0.73%) up to 20 August 2014. There was also 1 report of bladder cancer in a patient from the placebo arm of the double blind Study 19 (1/128 [0.78%]). Primary malignancies are considered a potential risk (see RMP) which will be kept under close surveillance. The planned placebo-controlled Phase III studies will be important in providing additional information on this issue. In addition, annual progress reports addressing incidence of MDS/AML and new primary malignancies will be provided together with the PSUR.

In the pivotal study, significantly higher rate of serious AE has been reported in all patients treated with olaparib 400 mg bd compared to placebo: 18.4% vs 8.6% as well as in the BRCAm group treated with olaparib: 21.6% vs 9.7% patients under placebo. Both in study 19 and in the pooled dataset, the most common SOCs for SAEs were gastrointestinal disorders and blood and lymphatic system disorders. The proportion of patients in the 400 mg bd monotherapy pool reporting SAEs was higher than in Study 19 (25.2% vs 18.4%), especially regarding gastrointestinal disorders (9.7% vs 5.1%). Of note, SAEs were more frequent in old people and possibly in the indicated BRCAm population.

A total of 324/735 (44.1%) of all patients in the 400 mg bd monotherapy pooled dataset were reported to have died whilst on treatment, in the 30-day follow up period or post follow up. The majority of deaths were reported as due to the disease under investigation (40.7%). Nine of the 16 patients with fatal AEs were from Study 42. Four patients of the 16 patients with fatal AEs had AEs causally related to olaparib, according to the investigator. Two of them were myelodysplatic syndrome (see discussion on MDS above).

In terms of laboratory findings, five haematology laboratory findings were considered ADRs and are therefore listed in section 4.8 of the SmPC for olaparib: haemoglobin levels, neutrophil and lymphocyte counts, platelets and mean corpuscular volume (MCV). Regarding clinical chemistry, increase in blood creatinine was considered an ADR and added to section 4.8 of the SmPC (see also discussion above).

Overall, in study 19 and in the pooled dataset, the proportion of patients who permanently discontinued olaparib due to AEs was low. The most common SOCs reported for AEs leading to discontinuation were blood and lymphatic disorders and gastrointestinal disorders. In study 19, more patients receiving olaparib with AEs leading to discontinuation were reported: 7 (5.1%) vs 2 (1.6%) patients receiving placebo. In the BRCAm group, the difference was even more significant: 8.1% of patients discontinued in the olaparib arm compared to 0% in the placebo arm. Nevertheless, all reasons of discontinuation were sporadic. Two events were fatal (stroke, jaundice) and two were considered still not resolved (thrombocytopenia and myalgia).

No data were provided in relation to overdose. There is no specific treatment in the event of olaparib overdose, and symptoms of overdose were not established. Therefore, in the event of an overdose, physicians should follow general supportive measures and should treat symptomatically (see SmPC section 4.9).

Clinical studies with olaparib have not reported any medication errors. The recommended dose of Olaparib is 400 mg bid, since olaparib capsules contain 50 mg each, the patient should intake 8 capsules of the medicinal product twice a day. This elevated number of capsules is likely to generate medication errors resulting in the assumption of an inappropriate dose. Therefore, the potential for patient medication errors is considered an important potential risk as adequately addressed in the RMP.

The use of olaparib as monotherapy treatment has been studied in a number of different tumour types. The safety profile of olaparib observed in these studies has been generally consistent with the known safety profile of olaparib 400 mg bd for BRCA-mutated ovarian cancer maintenance treatment. Therefore, the adverse events experienced with off-label monotherapy use in cancers other than the proposed indication (including ovarian cancer with unconfirmed BRCA mutation), would be expected to be generally consistent with the prescribing information. Off–label use will be assessed during routine pharmacovigilance (see RMP).

Overall, no additional safety issues appeared to emerge in the subgroup of the gBRCAm patients. Nevertheless, the relatively small size of this subgroup of patients does not allow drawing firm conclusions. More data are needed to confirm that the safety profile in ‘gBRCA mutated’ patients is consistent with that of patients without this hereditary alteration. The MAH will provide annual progress report addressing the safety issues in patients with gBRCA mutations as part of the PSUR and in line with the RMP. The safety data is expected to be analysed as relative to the disease, to the drug, to the inherited genetic status (gBRCAm, gBRCAwt), to the mutated genes (BRCA1, BRCA2), to the age of the patients, to their ethnologic characteristics and to previous cancer therapies. Although the calculated exposure adjusted events, as well as the low numbers and the existence of other potent causal factor did not support a causal effect of olaparib in dyspnoea, haemorrhagic stroke, myelodysplastic syndrome and pneumonitis, these adverse events will continue to be closely monitored.

Hypersensitivity to the active substance or to any of the excipients is a contraindication (see SmPC sections 4.3 and 6.1).

Special populations

No studies have been conducted in paediatric patients and the safety of olaparib in children and adolescents has not been established (see SmPC section 4.2).

During clinical studies with olaparib, no pregnancy was observed (pregnancy was an exclusion criterion). Based on the mechanism of action of olaparib and taking into account reproductive toxicity including serious teratogenic effects and effects on embryofoetal survival reported in the rat at maternal systemic exposures lower than those in humans at therapeutic doses, olaparib should not be used during pregnancy and in women of childbearing potential not using reliable contraception during therapy and for 1 month after receiving the last dose of olaparib. Furthermore, effective methods of contraception are

recommended for women of childbearing potential. Women of childbearing potential should not become pregnant while on olaparib and not be pregnant at the beginning of treatment. A pregnancy test should be performed on all pre-menopausal women prior to treatment (see SmPC section 4.6).

In addition, a potential interaction of olaparib with hormonal contraceptives which may reduce the efficacy of hormonal contraceptives if co-administered with olaparib cannot be excluded because inhibition of CYP3A has been observed in vitro and no study in Human has been conducted. Therefore, an additional non-hormonal contraceptive method and regular pregnancy tests should be considered during treatment (see SmPC sections 4.5 and 4.6).

The period of 1 month after discontinuation of therapy for the duration of contraception use in females was based on a mean terminal elimination half-life of 18.4 hours (range 6.95 to 34.9 hours) and was considered adequate given the fact that olaparib showed no mutagenic potential in animal studies.

There were no clinical data on fertility. In animal studies, no effect on conception was observed but there are adverse effects on embryofoetal survival.

In addition, no data related to milk excretion of olaparib are available. As a precautionary measure, given the pharmacologic property of the product, olaparib is contraindicated during breast feeding and for 1 month after receiving the last dose (see SmPC sections 4.3 and 4.6).

The review of the safety profile across three age groups (<65 years, 65-74 years and 75-84 years) showed an increase of the frequency of SAEs in the seriousness categories of hospitalisation/prolongation of hospitalisation, and life threatening events and an increase in number of patients experiencing events within the accidents and injuries SMQ with age (mainly due to an increase in reports of fracture). No apparent age associated difference in the number of patients reporting events within the SMQs of Cerebrovascular disorders and in the System Organ Classes of Nervous disorders, Cardiac disorders, Vascular disorders, Infections and Infestations which are potentially more serious in the elderly was shown. The type and frequency of events known to be associated with olaparib were similar across the different age groups and the number of patients discontinuing treatment with olaparib due to AEs was not age dependent. However, the information available in elderly (age ≥ 75 years) is limited (see SmPC section 4.2).

There is also limited clinical data available in non-Caucasian patients. However, no dose adjustment is required on the basis of ethnicity (see SmPC section 4.2). Further data will be collected in the course of olaparib clinical studies in ethnically diverse groups of patients in order to elucidate the influence of ethnicity on olaparib PKs/efficacy/safety profile as reflected in the RMP.

No specific studies in patients with hepatic or renal impairment using olaparib were submitted and data are expected to be provided post-approval as reflected in the RMP. Based on available data, it is considered that olaparib can be administered in patients with mild renal impairment (creatinine clearance > 50 ml/min). However, olaparib is not recommended for use in patients with moderate renal impairment (creatinine clearance < 50 ml/min) or severe renal impairment (creatinine clearance < 30 ml/min) considering the limited data and that safety and efficacy have not been established. Olaparib may only be used in patients with moderate or severe renal impairment if the benefit outweighs the potential risk, and the patient should be carefully monitored for renal function and adverse events (see SmPC section 4.2).

Olaparib is also not recommended for use in patients with hepatic impairment (serum bilirubin greater than 1.5 times upper limit of normal), as safety and efficacy have not been established (see SmPC section 4.2).

Of the inclusion criteria for the pivotal Study 19, Eastern Co-operative Oncology Group (ECOG) performance status ≤2 was selected. Thus, there are very limited clinical data available in patients with performance status 2 to 4 (see SmPC section 4.2 and 5.2). In the real clinical practice it is frequent that patients with recurrent ovarian cancer, who have completed at least 2 previous courses of platinum-containing therapy present a ECOG performance status > 2, therefore patients with ECOG performance status > 2 are considered a missing information (see RMP).*Interactions*

No formal interactions studies were conducted with olaparib while there is a potential to reduce statin clearance and the clearance of OCT transporter substrates (metformin). However, in the subgroup of 45 patients treated with olaparib and metformin concomitantly, safety profile seemed similar to the total safety population.

Co-administration with potent inhibitors or inducers of CYP3A4 is expected to alter the pharmacokinetics and safety/tolerability profile of olaparib. Clinical studies to evaluate the impact of known CYP3A4 inhibitors and inducers have not yet been conducted and it is therefore recommended in the SmPC that known potent inhibitors/inducers of this isoenzyme are not co-administered with olaparib.

Interactions with CYP3A4 inducers/inhibitors and interactions with substrates of transporters proteins are covered in the RMP under missing information and further data are expected post-authorisation (see RMP).

Non-clinical data showed that olaparib may alter the efficacy of vitamin K antagonists. Clinical data available are not sufficiently reliable and robust to conclude to a risk. Therefore, co-administrations of vitamin K antagonists with olaparib and the occurrence of events related to disturbances in the INR values should be closely monitored and discussed in the first PSUR.

A review of the available clinical data (400 mg monotherapy pool), identified no patients who received concomitant treatment with immunosuppressant drugs or vaccines. Since no clinical data on such risk is available and since it cannot be excluded that an interaction could occur, as other chemotherapy agents, caution should be taken if these drugs are co administered with olaparib and patients should be closely monitored (see SmPC section 4.5).

Clinical studies of olaparib in combination with other anticancer medicinal products, including DNA damaging agents, indicate a potentiation and prolongation of myelosuppressive toxicity. Thus, the recommended olaparib monotherapy dose is not suitable for combination with other anticancer medicinal products (see SmPC section 4.5).

2.6.2. Conclusions on the clinical safety

Overall, olaparib monotherapy has been associated with adverse drug reactions generally of mild or moderate severity (CTCAE 1 or 2) and generally not requiring treatment discontinuation. The most frequently observed adverse reactions across clinical trials in patients receiving olaparib monotherapy (≥ 10%) were nausea, vomiting, diarrhoea, dyspepsia, fatigue, headache, dysgeusia, decreased appetite, dizziness, anaemia, neutropaenia, lymphopaenia, mean corpuscular volume elevation, and increase in creatinine.

Adverse reactions such as nausea, vomiting, diarrhoea, and anaemia are manageable through treatment interruption, dose reduction and/or concomitant medicinal products (see SmPC sections 4.2 and 4.8).

Considering the intended indication in maintenance treatment setting, safety data remains limited and longer-term follow-up is required to provide more information about long-term toxicity of olaparib (see RMP). In addition, it is expected that the placebo-controlled phase 3 study (SOLO-2) and the phase IV study in patients with BRCA mutated population, to be completed as a Annex II condition to better

characterise the efficacy of olaparib will also provide further information on the safety profile of olaparib in maintenance setting. Safety data from the study in somatic BRCA mutated patients will contribute to the safety data pool and provide further information on potential differences between safety profiles in gBRCAm and BRCA wild-type patients (with sBRCAm).

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

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

PRAC Advice

The PRAC considered that the risk management system version 4 could be acceptable with revisions as described in the attached PRAC endorsed PRAC Rapporteur assessment report.

The CHMP endorsed this advice with changes to the categories of on-going and planned additional pharmacovigilance studies.

The applicant implemented the changes in the RMP as requested by PRAC and CHMP.

The CHMP endorsed the Risk Management Plan version 5 with the following content:

Safety concerns

Table 79: Summary of safety concerns

Important identified risks	• Anaemia • Thrombocytopenia • Neutropenia • Raised creatinine levels • Nausea including vomiting
Important potential risks	• MDS/AML • New primary malignancies • Pneumonitis • Potential for off-label use • Potential for patient medication errors • Effects on embryofoetal survival and development

Important missing information	• Interaction with CYP3A4 inducers/inhibitors • Interaction with substrates of transporters proteins • Exposure in patients with renal and hepatic impairment • Exposure in elderly • Exposure in ethnically diverse groups • Long-term exposure to/potential toxicity to olaparib • Use in patients with ECOG performance status >2

Pharmacovigilance plan

Table 80: 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)**

D0816C00002 A Phase III randomised, double-blind, placebo-controlled, multicentre study (Phase III clinical study Category 1)	**Primary objective:** To determine the efficacy by PFS (using blinded independent central review (BICR) according to modified RECIST of olaparib maintenance monotherapy compared to placebo in *BRCA*-mutated relapsed ovarian cancer patients who are in complete or partial response following platinum based chemotherapy. **Secondary objective:** - To determine the efficacy of olaparib maintenance monotherapy compared to placebo by assessment of OS, time to earliest progression by RECIST or Cancer Antigen-125 (CA-125), or death, and PFS2 - To compare the effects of olaparib maintenance monotherapy compared to placebo on the rate of deterioration of HRQoL as assessed by the trial outcome index (TOI) of the Functional Assessment of Cancer Therapy – Ovarian (FACT-O) - 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) - To determine the exposure to olaparib in patients receiving olaparib maintenance monotherapy **Safety objective:** To assess the safety and tolerability of olaparib maintenance monotherapy	Anaemia Thrombocytopenia Neutropenia Raised creatinine levels Nausea including vomiting MDS/AML New primary malignancies Pneumonitis Exposure in elderly Exposure in ethnically diverse groups Long-term exposure to/potential toxicity to olaparib	Ongoing	Primary CSR: 1Q2016 Final CSR: 4Q2018
D0810C00019 A Phase II randomised, placebo controlled double blind, study to assess the efficacy of olaparib	**Primary objective:** To determine the efficacy (assessed by PFS) of olaparib (capsule formulation) compared to placebo in the overall population. **Secondary objective:**	Anaemia Thrombocytopenia Neutropenia	Ongoing	Final CSR: 2Q2017

compared with placebo in the treatment of patients with platinum sensitive serous ovarian cancer following treatment with 2 or more platinum containing regimens. (Phase II clinical study Category 1)	- To determine the efficacy of olaparib (capsule formulation) 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 (capsule formulation) compared to placebo. - To determine the effects of olaparib (capsule formulation) compared to placebo on disease related symptoms. - To determine the quality of life of patients treated with olaparib (capsule formulation) compared to placebo.	Raised creatinine levels Nausea including vomiting MDS/AML New primary malignancies Pneumonitis Long-term exposure to/potential toxicity to olaparib		
D0816C0000X[a] A phase IV, open label, single arm, non randomised, multicentre study to assess the efficacy and safety of olaparib maintenance monotherapy in patients with relapsed platinum sensitive ovarian cancer who are in complete or partial response following platinum based chemotherapy and who carry loss of function germline or somatic *BRCA* mutation(s) (Phase IV clinical study Category 1)	Protocol synopsis is under discussion with EMA/CHMP **Primary objective:** To assess the efficacy by investigator assessed progression free survival (PFS) according to modified Response Evaluation Criteria In Solid Tumours (RECIST) 1.1 of olaparib maintenance monotherapy in patients with *sBRCAm* or *gBRCAm* ovarian cancer who are in complete or partial response following platinum based chemotherapy. **Secondary objectives:** - To assess the efficacy of olaparib maintenance monotherapy by assessment of overall survival (OS), time to earliest progression by RECIST or Cancer Antigen-125 (CA-125) or death, and time to investigator assessed second progression (PFS2), or death, in patients with *gBRCAm* or *sBRCAm* ovarian cancer. - To assess the efficacy of olaparib maintenance monotherapy by assessment of time to first subsequent therapy or death (TFST), time to second subsequent therapy or death (TSST) and time from to study treatment	Anaemia Thrombocytopenia Neutropenia Raised creatinine levels Nausea including vomiting MDS/AML New primary malignancies Pneumonitis Exposure in elderly Exposure in ethnically diverse groups Long-term exposure to/potential toxicity to olaparib	Planned	Primary CSR: 1Q2018 Final CSR: 3Q2018

	discontinuation or death (TDT) in patients with *gBRCAm or sBRCAm* ovarian cancer. - To assess the safety and tolerability of olaparib maintenance monotherapy in patients with platinum sensitive relapsed *gBRCAm* or *sBRCAm* ovarian cancer.			
D0816C00008 A Non-randomised, Open-label, Sequential, Multicentre, Two-part, Phase I Study to Assess the Effect of Rifampicin, a CYP Inducer, on the Pharmacokinetics of Olaparib Following Oral Dosing of a Tablet Formulation in Patients with Advanced Solid Tumours (Phase I clinical study, category 3)	**Primary objective:** To investigate the effect of rifampicin on the PK of olaparib following oral dosing of the tablet formulation in patients with advanced solid tumours Secondary objectives: - To characterise the PK of olaparib following oral dosing of the tablet formulation in the presence and absence of rifampicin - To demonstrate exposure to rifampicin - To demonstrate induction of CYP - To investigate safety and tolerability of single and multiple oral doses of olaparib tablets in patients with advanced solid tumours	Provide missing information on the risk of any interaction of olaparib with CYP3A4 inducers.	Ongoing	3Q2014*/ 3Q2015
D0816C00005 An Open-label, Non-randomised, Multicentre, Comparative, Phase I Study to Determine the Pharmacokinetics, Safety and Tolerability of Olaparib following a Single Oral 300-mg Tablet Dose to Patients with Advanced Solid Tumours and Normal Hepatic Function or Mild or Moderate Hepatic Impairment (Phase I clinical study, category 3)	**Primary objective:** to investigate the PK of olaparib after a single oral dose of 300 mg to patients with advanced solid tumours and mild or moderate hepatic impairment compared to those with normal hepatic function. Secondary objective: to investigate the safety and tolerability of single and multiple oral doses of olaparib in advanced solid tumour patients with hepatic impairment and in those with normal hepatic function.	Provide missing information on exposure in patients with hepatic impairment.	Ongoing	2Q2015*/ 1Q2016
D0816C00006 An Open-label, Non-randomised, Multicentre, Comparative, Phase I Study of the	**Primary objective**: to investigate the pharmacokinetics of olaparib after a single oral dose of 300 mg to patients with advanced solid tumours and mild or moderate renal	Provide missing information on exposure in patients with renal	Ongoing	2Q2015*/ 1Q2016

Pharmacokinetics, Safety and Tolerability of Olaparib Following a Single Oral 300-mg Tablet Dose to Patients with Advanced Solid Tumours and Normal Renal Function or Renal Impairment (Phase I clinical study, category 3)	impairment compared to those with normal renal function. Secondary objective: to assess the safety and tolerability of single and multiple oral doses of olaparib in advanced solid tumour patients with renal impairment and in those with normal renal function. Plasma and urine samples from this study will be used for the purpose of metabolite profiling and identification.	impairment.		
D0816C00007 A Non-randomised, Open-label, Sequential, Three-part, Phase I Study to Assess the Effect of Itraconazole (a CYP3A4 Inhibitor) on the Pharmacokinetics of Olaparib Following Oral Dosing of a Tablet Formulation, and to Provide Data on the Effect of Olaparib on QT Interval Following Oral Dosing of a Tablet Formulation to Patients with Advanced Solid Tumours. (Phase I clinical study, category 3)	**Primary objective:** to investigate the effect of itraconazole on the pharmacokinetics (PK) of olaparib following oral dosing of the tablet formulation in patients with advanced solid tumours. Secondary objectives: - to characterise the PK of olaparib following oral dosing of the tablet formulation in the presence and absence of itraconazole, to demonstrate exposure to itraconazole and hydroxy-itraconazole - to investigate the effect of olaparib on QTc following single (Part A) and multiple (Part B) oral doses of the tablet formulation, - to investigate further the safety and tolerability of olaparib tablets in patients with advanced solid tumours (Part C).	Provide missing information on the risk of any interaction of olaparib with itraconazole (CYP3A4 inhibitor) To provide missing information on the effect of olaparib on QT prolongation	Ongoing for Part C	3Q2014*/ 2Q2015
D0818C00001 A Phase III randomised, double-blind, placebo-controlled, multicentre study of olaparib maintenance monotherapy in patients with BRCA-mutated advanced (FIGO Stage III-IV) ovarian cancer following first line platinum based chemotherapy. (Phase III clinical study Category 3)	**Primary objective:** To determine the efficacy by PFS using BICR according to modified RECIST of olaparib maintenance monotherapy compared to placebo in *BRCA*-mutated high risk advanced ovarian cancer patients who are in clinical complete response or partial response following first line platinum-based chemotherapy. **Secondary objective:** - To determine the efficacy of olaparib maintenance monotherapy compared to placebo by assessment of OS, time to earliest progression by RECIST or CA-125, or death, and PFS2	Anaemia Thrombocytopenia Neutropenia Raised creatinine levels Nausea including vomiting MDS/AML New primary malignancies	Ongoing	Primary CSR: 4Q2016 Final CSR: 2Q2020

	- To compare the effects of olaparib maintenance monotherapy compared to placebo on the rate of deterioration of HRQoL as assessed by the TOI of the FACT-O - 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 potential future *BRCA* mutation assays **Safety objective:** To assess the safety and tolerability of olaparib maintenance monotherapy	Pneumonitis Exposure in elderly Exposure in ethnically diverse groups Long-term exposure to/potential toxicity to olaparib		
D081CC00006 BIG 6-13, NSABP B-55 A Phase III randomised, double-blind, parallel group, placebo-controlled multicentre study to assess the efficacy and safety of olaparib versus placebo as adjuvant treatment in patients with germline *BRCA1/2* mutations and high risk HER2 negative primary breast cancer who have completed definitive local treatment and neoadjuvant or adjuvant chemotherapy (Phase III clinical study Category 3)	**Primary Objective**: To assess the effect of adjuvant treatment with olaparib on Invasive Disease Free Survival (IDFS) **Safety Objective:** - To assess the safety and tolerability of adjuvant treatment with olaparib **Secondary Objectives:** - To assess the effect of adjuvant treatment with olaparib on overall survival (OS) - To assess the effect of adjuvant treatment with olaparib on Distant Disease Free Survival (DDFS) - To assess the effect of adjuvant treatment with olaparib on the incidence of new invasive breast primary cancer and/or new epithelial ovarian cancer - To assess the effect of olaparib on patient reported outcomes using the FACIT fatigue scale and EORTC QLQ-C30 QoL scale - 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 germline *BRCA* mutation assays (gene sequencing and large rearrangement analysis)	MDS/AML Anaemia Thrombocytopenia Neutropenia Raised creatinine levels Nausea including vomiting New primary malignancies Pneumonitis Exposure in elderly Exposure in ethnically diverse groups Long-term exposure to/potential toxicity to olaparib	Ongoing	Primary CSR: 2Q2020 Final CSR: 2Q2028

D0819C00003 A Phase III, open label, randomised, controlled, multi-centre Study to assess the efficacy and safety of olaparib monotherapy versus physician's choice chemotherapy in the treatment of metastatic breast cancer patients with germline *BRCA1/2* mutations. (Phase III clinical study Category 3)	**Primary Objective:** To determine the efficacy of single agent olaparib vs. physician's choice chemotherapy (capecitabine, vinorelbine or eribulin) by progression-free survival (PFS) using blinded independent central review (BICR) data assessed by Response Evaluation Criteria in Solid Tumours (RECIST 1.1). **Safety Objective:** To assess the safety and tolerability of single agent olaparib vs. physician's choice chemotherapy (capecitabine, vinorelbine or eribulin). Secondary Objectives - To compare the efficacy of single agent olaparib vs. physician's choice chemotherapy (capecitabine, vinorelbine or eribulin) by assessment of overall survival, time to second progression or death (PFS2) and objective response rate (ORR) using BICR data assessed by RECIST 1.1. - To assess the effect of olaparib on the Health-related Quality of Life (HRQoL) as measured by EORTC QLQ-C30 global QoL scale. - 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). - To determine exposure to olaparib in patients receiving olaparib monotherapy.	MDS/AML Anaemia Thrombocytopenia Neutropenia Raised creatinine levels Nausea including vomiting New primary malignancies Pneumonitis Exposure in elderly Exposure in ethnically diverse groups Long-term exposure to/potential toxicity to olaparib	Ongoing	Primary CSR: 3Q2016 Final CSR: 1Q2018
Study number: TBC A study to collect and/or retrieve prospective data from sizeable patient cohorts with ovarian cancer, representing Real World Evidence from relevant	A study to collect and/or retrieve prospective data from sizeable patient cohorts representing Real World Evidence from relevant countries, to further characterise the safety concern of MDS/AML in ovarian cancer patients. A study synopsis will be submitted	MDS/AML	Planned	3Q2020

countries.	within 3 months of marketing approval.	
(Category 3)		

**Category 1 are imposed activities considered key to the benefit risk of the product. Category 2 are specific obligations. Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)*

Risk minimisation measures

Table 81: Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Anaemia:	Appropriate wording within the SmPC. Caution advised in Section 4.4 '*Special warnings and precautions for use'* on haematological levels required prior to treatment and on the management of severe haematological toxicity during treatment. Section 4.4 and 4.8 *'Undesirable effects'* Haematology testing timeframes for monitoring. Section 4.8 *'Undesirable effects'* lists Anaemia (decrease in haemoglobin) [very common] and Mean Corpuscular volume elevation [very common]. Section 4.2 '*Posology and method of administration'* and Section 4.8-Statement on management of AEs.	None
Neutropenia:	Appropriate wording within the SmPC. Caution advised in Section 4.4 '*Special warnings and precautions for use'* on haematological levels required prior to treatment and on the management of severe haematological toxicity during treatment. Section 4.4 and 4.8 *'Undesirable effects'* Haematology testing timeframes for monitoring. Section 4.8 *'Undesirable effects'* lists neutropenia (decrease in absolute neutrophil count) [very common]. Section 4.2 '*Posology and method of administration' and Section 4.8*-Statement on management of AEs.	None
Thrombocytopenia	Appropriate wording within the SmPC. Caution advised in Section 4.4 '*Special warnings and precautions for use'* on haematological levels required prior to treatment and on the management of severe haematological toxicity during treatment. Section 4.4 and 4.8 *'Undesirable effects'* Haematology testing timeframes for monitoring. Section 4.8 *'Undesirable effects'* lists thrombocytopenia (decrease in platelets) [common]. Section 4.2 '*Posology and method of administration' and Section 4.8* -Statement on management of AEs.	None
Raised creatinine levels	Appropriate wording in SmPC. SmPC Section 4.8 *'Undesirable effects'* lists 'increase in blood creatinine' [very common].	None

	SmPC Section 4.2'*Posology and method of administration*' Statement that patients with normal or mild renal impairment can be treated. Olaparib not recommended for use in patients with moderate or severe renal impairment.	
Nausea including vomiting	Appropriate wording in SmPC. SmPC Section 4.8 'Undesirable effects' lists the following terms: Nausea (very common), vomiting (very common). Statement on management of AEs. Statement that antiemetic prophylaxis is not required.	None 1.
Important potential risks		
MDS/AML	Appropriate wording within the SmPC. Caution advised in Section 4.4 '*Special warnings and precautions for use'* on haematological levels required prior to treatment and on the management of severe haematological toxicity during treatment. Statement on haematology testing timeframes for monitoring. Recommendation statement when to perform bone marrow analysis and/or blood cytogenetic analysis and appropriate course of action if MDS/AML is confirmed.	None
New primary malignancies	None	None
Pneumonitis	Detailed wording in SmPC. Advice provided in Section 4.4 '*Special warnings and precautions for use'* for identification and management of pneumonitis.	None
Potential for off-label use	Appropriate wording in SmPC. Section 4.1 '*Therapeutic indications'*, Section 4.2 *'Posology and method of administration'* and Section 5.1 '*Pharmacodynamic Properties-Detection of BRCA mutation'* provides clear guidance on the disease indication for treatment and BRCA mutation testing.	None
Potential for patient medication errors	Appropriate wording in SmPC. Olaparib is intended for use at the dose specified within the SmPC Section 4.2 '*Posology and method of administration*' and Package Leaflet. SmPC and Package Leaflet provide information and guidance to patients and prescribers on the importance	None

	of adhering to the dose and duration of treatment recommendations.	
Effects on embryofoetal survival and development	Appropriate wording in SmPC. Clear guidance on the appropriate use of olaparib in women of childbearing potential. Breast feeding during treatment and 1 month after the last dose of olaparib is a contraindication (Section 4.3) Caution advised in Section 4.4 *'Special warnings and precautions for use'* and Section 4.6 *'Fertility, pregnancy and lactation'* Statement that olaparib could cause foetal harm when administered to a pregnant women and that olaparib should not be used during pregnancy and in women of childbearing potential not using reliable contraception during therapy and for 1 month after receiving the last dose of olaparib. . Statement on effective contraceptive use for women of childbearing potential. Additional precautionary measure in Section 4.6 'Fertility, pregnancy and lactation' and Section 4.5 *'Interaction with other medicinal products and other forms of interaction'* Statement that due to the potential interaction of olaparib with hormonal contraception additional non-hormonal contraceptive method and regular pregnancy test should be considered during treatment.	None
Missing information		
Drug-drug Interactions with CYP3A4 inducers/inhibitors	Appropriate wording in SmPC. Section 4.4 '*Special warnings and precautions for use'* Statement that co-administration of olaparib with strong CYP3A inducers or inhibitors should be avoided. Section 4.5 '*Interactions with other medicinal products and other forms of interaction'* describes in detail these drug-drug interactions.	None
Drug-drug Interactions with substrates of transporter proteins	Appropriate wording in SmPC. Section 4.5 '*Interactions with other medicinal products and other forms of interaction'* describes in detail that olaparib may be an inhibitor of P-gp and is an inhibitor of BRCP, OATP1B1, OCT1 and OCT2. Statement that olaparib may increase exposure to substrates of P-gp, BRCP, OATP1B1, OCT1 and OCT2. Caution should be exercised if olaparib is administered in combination with any statin.	None

Exposure in patients with renal and hepatic impairment	Appropriate wording in SmPC. SmPC Section 4.2 *Posology and method of administration*'. States that the effect of hepatic impairment on exposure to olaparib has not been studied. Olaparib not recommended for use in patients with hepatic impairment (serum bilirubin >1.5 times upper limit of normal), as safety and efficacy have not been established. SmPC Section 4.2'*Posology and method of administration*' States that patients with normal or mild renal impairment can be treated with olaparib. Olaparib is not recommended for use in patients with moderate or severe renal impairment. Olaparib may only be used in patients with moderate or severe renal impairment if the benefit outweighs the potential risk, and the patient should be carefully monitored for renal function and adverse events.	None
Exposure in the elderly (>65 years)	Appropriate wording in SmPC. Section 4.2 *'Posology and method of administration'* states "No adjustment in starting dose is required for elderly patients. There is limited clinical data in patients aged 75 or over."	None
Exposure in ethnically diverse groups	Appropriate wording in SmPC. SmPC Section 4.2 '*Posology and method of administration'* states: "There are limited clinical data available in non-Caucasian patients. However, no dose adjustment is required on the basis of ethnicity."	None
Long-term exposure to/potential toxicity to olaparib	None	None
Use in Patients with ECOG performance status >2	Appropriate wording in SmPC. SmPC Section 4.2 *Posology and method of administration* states: "Patients with performance status 2 to 4 There are very limited clinical data available in patients with performance status 2 to 4."	None

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant 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

Benefits

Beneficial effects

The study 19 met its primary objective of statistically significantly improved PFS in patients with PSR high-grade serous ovarian cancer treated with olaparib 400 mg bd as maintenance monotherapy compared with placebo. The PFS gain of 3.6 months (medians of 4.8 and 8.4 months) was observed in the overall population with PFS HR 0.35. No negative effects on OS or subsequent lines of therapy were reported.

In patients with BRCA-mutated tumors, a 6.9 months prolongation of median PFS (from 4.3 to 11.2 months) was reported with HR 0.18. The benefit on PFS was partly maintained at second progression: no negative effects on subsequent lines of therapy were observed with favourable TSST (HR 0.44) used as a surrogate for PFS2.

There was no statistically significant difference in OS between olaparib-treated patients and placebo-treated patients (HR 0.73; 95% CI 0.45 1.17; p=0.19; median 34.9 months versus 31.9 months, respectively).

Uncertainty in the knowledge about the beneficial effects

In the pivotal study 19, an interim analysis of OS was performed at 58% maturity. Mature overall survival data at 85% will be provided and allow for a definitive comparison between treatment groups (see Annex II conditions). In addition, the ongoing phase III SOLO-2 trial will further define the efficacy of olaparib in patients with 'BRCA mutated' ovarian cancer.

SOLO-2 will also allow a prospective validation of 'BRCA mutated' biomarker and provide a more comprehensive view on the impact on QoL and further understanding of mechanisms of olaparib resistance.

Available data in patients with somatic BRCA mutations are considered limited. However, there is a biological rationale suggesting similar activity in patients with somatic BRCA mutations as in patients with germline origin of BRCA mutations in their tumors. In addition, the open label study D0816C0000X will provide further efficacy data of olaparib in patients harbouring tumors with somatic BRCA mutations (see Annex II conditions).

Risks

Unfavourable effects

The most frequently observed adverse reactions across clinical trials in patients receiving olaparib monotherapy were nausea, vomiting, diarrhoea, dyspepsia, fatigue, headache, dysgeusia, decreased appetite, dizziness, anaemia, neutropaenia, lymphopaenia, mean corpuscular volume elevation, and increase in creatinine.

High grade adverse events reported in clinical trials included: blood and lymphatic disorders (grade 3 and 4), gastrointestinal disorders (grade 3 and 4) and fatigue (grade 3 and 4).

Adverse events and serious adverse events were significantly more frequent in the olaparib group versus the placebo arm in both overall population and BRCAm sub-group. The incidence of AEs for the BRCAm subset of patients was similar to that observed in the overall patient population.

Based on the available data, the following important safety concerns have been identified for olaparib (see RMP): anaemia, thrombocytopenia, neutropenia, raised creatinine levels, nausea including vomiting. In addition important potential safety concerns include the risk of MDS/AML, new primary malignancies, pneumonitis, potential for off-label use, potential for patient medication errors and effects on embryofoetal survival and development.

Overall, olaparib has been associated with adverse drug reactions generally of mild or moderate severity (CTCAE 1 or 2) and generally not requiring treatment discontinuation.

Uncertainty in the knowledge about the unfavourable effects

The safety data available are considered limited in terms of number of patients and long-term follow-up and therefore does not allow to comprehensively determine long-term toxicities. Long-term exposure to/potential toxicity to olaparib is addressed in the risk management plan. In particular, the causality of olaparib in occurrence of rare cases of MDS/AML could not be firmly established in the context of previous courses of chemotherapy. MDS/AML will be closely monitored as reflected in the RMP.

In addition, the ongoing SOLO-2 study, although performed with the tablet formulation, will provide further long term toxicity data in the BRCAm population. Further safety data will also be available from several post-authorisation studies (see Risk Management Plan), with the aim to compare two clinically distinct groups of patients, patients with germline BRCA mutations and BRCA wildtype patients harbouring somatic BRCA mutations.

With regard to special populations, exposure in elderly, exposure in ethnically diverse groups and exposure in patients with renal or hepatic impairment is limited and further data are expected in these populations (see RMP). The risk of interactions with CYP3A4 inducers/inhibitors and with substrates of transporters is also adequately addressed in the RMP.

Benefit-risk balance

Importance of favourable and unfavourable effects

There is a medical need for the treatment of relapsed high grade serous ovarian cancers. The pivotal study 19 was positive with PFS HR of 0.35 and gain of 3.6 months (medians of 4.8 and 8.4 months). No negative effects on subsequent lines of therapy, HRQoL or OS were observed. Patients defined as ‘BRCA mutated had a statistically significant and clinically meaningful improvement in PFS of 6.9 months compared with placebo. Although more frequent, other adverse events, like gastrointestinal and haematological toxicity were generally of low grade and could be manageable with specific therapy.

Benefit-risk balance

The benefit-risk balance of olaparib 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, is considered positive.

Discussion on the benefit-risk balance

The recommended indication of olaparib is maintenance treatment and PFS benefit is considered clinically relevant in this setting. The indication is limited to patient population with BRCA-mutated tumours (51% of patients in the pivotal study). This population was defined based on analysis of mutations in BRCA1 and BRCA2 genes in blood and tumour samples of patients. This analysis allowed determining the origin of tumour mutations in the majority of patients: either due to mutation in germline (present also in tumor cells) or acquired mutation within tumor (somatic mutation). Given a claimed mechanism of action and well established role of BRCA1 and BRCA2 proteins in homologous recombination repair and considering that a statistical significance was reached in the overall population, the rationale of performing subgroup analysis in this subgroup was considered acceptable.

For patients with BRCA-mutated tumors, median PFS was 11.2 months in the olaparib group compared with 4.3 months in the placebo group, demonstrating that a 6.9-month delay in disease progression could be achieved. Consequently, the subsequent chemotherapeutic regimen could be delayed. Although olaparib treatment was used for one maintenance cycle between two courses of chemotherapy, a benefit was expanded beyond since TSST was also prolonged. No treatment with olaparib was used at subsequent relapses. The observed benefit is considered clinically significant since the course of disease may be modified. Adverse drug reactions reported with olaparib were generally of mild or moderate severity and manageable. Long-term safety data will be provided post-authorisation in line with the risk management plan (see RMP).

The OS data performed at 58% maturity (52% for BRCA mutated group) did not show statistically significant differences between olaparib-treated and placebo-treated patients. Mature OS data from study 19 is required to further address efficacy in the long term (please refer to conclusion on clinical efficacy and Annex II conditions).

The results of study SOLO-2 are required to further confirm the efficacy of olaparib. Further efficacy data from SOLO-2 will verify the impact of the olaparib on several clinical outcomes relevant to assessment of efficacy in maintenance setting (please refer to conclusion on clinical efficacy and Annex II conditions). As of 19th September 2014, the number of patients randomised into SOLO-2 was 204 out of the planned 264 patients (77% complete) and based on the numbers of patients known to be in screening, it is anticipated that recruitment will complete in November 2014. Considering the current status of the SOLO-2, the marketing authorisation of olaparib in this patient population is not expected to hamper the conduct of this trial. Longer-term safety will also be followed-up in this study (see conclusion on clinical safety).

Considering the limited number of observations in patients with somatic BRCA mutations it was discussed how efficacy demonstrated in patients with germline BRCA mutations could be extrapolated to patients with somatic mutations. Based on strong biological rationale and considering the SAG view, similar activity is expected in patients with somatic BRCA mutations to that in patients with germline BRCA mutations. The reported prevalence of somatic BRCA mutations varies but they may represent a substantial proportion of alterations leading to HR deficiencies. Uncertainties relative to efficacy in this group of patients may be related to tumor heterogeneity and involvement of other mechanisms leading to HR deficiency. Although limited, available clinical data indicate efficacy of olaparib in patients with somatic BRCA mutations. An open-label phase IV study is required to address the remaining uncertainty in this

subpopulation of patients (please refer to conclusion on clinical efficacy). Safety data from this study will also contribute to the safety data pool and provide further information on potential differences between safety profiles in gBRCAm and BRCA wild-type patients (with sBRCAm) (see conclusion on clinical safety).

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Lynparza (olaparib) is not similar to Yondelis (trabectedin) within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

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 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, is favourable and therefore recommends the granting of the marketing authorisation 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 marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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 agreeed 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Obligation to complete post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
PAES: In order to further define the long term efficacy of olaparib in patients with platinum sensitive relapsed BRCA mutated high grade serous ovarian cancer, the MAH should submit the final Overall Survival (OS) analysis of study D0810C00019, a phase II randomised, double blind, multicentre study. The clinical study report should be submitted by:	June 2017
PAES: In order to further confirm the efficacy of olaparib in patients with platinum sensitive relapsed BRCA mutated high grade serous ovarian cancer, the MAH should submit the results of study D0816C00002, a phase III randomised double-blind placebo-controlled multicentre study. The clinical study report should be submitted by:	December 2018
PAES: In order to further define the efficacy of olaparib in patients with platinum sensitive relapsed somatic BRCA mutated high grade serous ovarian cancer, the MAH should conduct and submit the results of a phase IV, open label, single arm, non-randomised, multicentre study in patients with relapsed platinum sensitive ovarian cancer who are in complete or partial response following platinum based chemotherapy and who carry loss of function germline or somatic BRCA mutation(s). The clinical study report should be submitted by:	September 2018

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

These conditions fully reflect the advice received from the PRAC.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that olaparib is qualified as a new active substance.