Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Olaparib

Proprietary Product Name: Lynparza

Sponsor: AstraZeneca Pty Ltd

February 2018

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website < https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
~	Approximately
AE	Adverse event
ALT	Alanine transaminase
AML	Acute myeloid leukaemia
AST	Aspartate transaminase
AUC	Area under plasma concentration-time curve
$AUC_{0-\infty}$	Area under plasma concentration-time curve from time zero to infinity
AZD2281	The generic name olaparib is generally used when referring to the drug substance known by the laboratory code AZD2281 or KU-0059436
BCRP	Breast cancer resistance protein
BCS	Biopharmaceutics Classification System
BD	Twice daily
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
CA 125	Cancer antigen (CA)-125 (tumour biomarker)
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
C_{max}	Maximum plasma concentration
C_{min}	Minimum serum concentration
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CSR	Clinical study report

Abbreviation	Meaning
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DCO	Data cut-off
DCR	Disease control rate
DoR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EU	European Union
FACT-O	Functional Assessment of Cancer Therapy – Ovarian
FAS	Full analysis set (the overall study population, unselected for BRCA mutation status, equivalent to intent to treat [ITT] population)
FDA	Food and Drug Administration
gBRCAm	Germline BRCA mutated
gBRCAwt /VUS	Germline BRCA wildtype/variant of unknown significance
GC	Gas chromatography
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GI	Gastro intestinal
GLP	Good laboratory practice
hERG	Human ether-a-go-go-related gene
HPLC	High performance liquid chromatography
HR	Hazard ratio
HRD	Homologous recombination deficient/deficiency
HRQoL	Health-related quality of life
IC_{50}	Half maximal inhibitory concentration

Abbreviation	Meaning
IC_{90}	90% maximal inhibitory concentration
ICH	International Conference on Harmonisation
ITT	Intention to treat
IV	Intravenous
KF	Karl Fischer titration
Ki	Dissociation constant
LMG	Lauroyl macrogol-32 glycerides
MCV	Mean corpuscular volume
MDR	Multi-drug resistance protein
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MMS	methane methylsulfate
MRP2	Multi-drug resistance protein 2
MTD	Maximum tolerated dose
NC	Not calculated
NIR	Near infrared spectroscopy
NLT	Not less than
OATP	Organic anion-transporting polypeptide
OCT	Organic cation-transporter
ORR	Objective response rate
OS	Overall survival
P-gp	P-glycoprotein
PARP	Polyadenosine 5'diphosphoribose polymerase
PBMC	Peripheral blood mononuclear cells
PD	Pharmacodynamic(s)
PFS	Progression-free survival

Abbreviation	Meaning
Ph. Eur	European Pharmacopeia
PK	Pharmacokinetic(s)
PLD	Pegylated liposomal doxorubicin
PO	per oral
PPF	Pre submission planning form (TGA)
PR	Partial response
PSR	Platinum sensitive relapsed
QT	ECG interval measured from the beginning of the QRS complex to the end of the T wave
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
SOC	System Organ Class
tBRCAm	Tumour BRCA mutated
TDT	Time to discontinuation of treatment (defined as time from randomisation to discontinuation of study treatment or death)
TFST	Time to first subsequent therapy (defined as time from randomisation to start of first subsequent therapy or death (that is, following discontinuation of randomised study treatment) t_{max} Time to reach maximum concentration
t_{max}	Time at which the C_{max} of the drug is achieved
TOI	Trial Outcomes Index
TSST	Time to second subsequent therapy (defined as time from randomisation to the start of second subsequent therapy or death)
ULN	Upper limit of normal
USA	United States of America
VUS	Variants of unknown significance
wt	Wildtype

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	23 December 2015
Date of entry onto ARTG:	7 January 2016
ARTG number:	234008
Active ingredient:	Olaparib
Product name:	Lynparza
Sponsor's name and address:	AstraZeneca Pty Ltd PO Box 131 North Ryde NSW 1670
Dose form:	Capsule
Strength:	50 mg
Container:	Bottle
Pack size:	4 x 112 capsules
Approved therapeutic use:	*Olaparib is indicated as monotherapy for the maintenance treatment of patients with platinum sensitive relapsed BRCA-mutated (germline or somatic) high grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) after platinum based chemotherapy. Prior treatment must have included at least 2 courses of platinum based regimens.*
Route of administration:	Oral
Dosage:	Treatment with Lynparza should be initiated and supervised by a physician experienced in the use of anticancer medicinal products. The recommended dose of Lynparza is 400 mg (eight 50 mg capsules) taken twice daily, equivalent to a total daily dose of 800 mg. Please see the Product Information (PI) for further details.

Product background

This AusPAR describes the application by AstraZeneca Pty Ltd (the sponsor) to register Lynparza olaparib 50 mg capsule for the following indication

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

Olaparib is a potent inhibitor of polyadenosine 5'diphosphoribose polymerase (PARP) which exploits deficiencies in DNA repair mechanisms (for example, breast cancer susceptibility gene (BRCA) mutation), to preferentially kill cancer cells. Mutations in the BRCA genes are prevalent in high-grade serous ovarian cancer.

Ovarian cancer patients with a BRCA1 or BRCA2 mutation represent a selected patient group whose tumours have a defective homologous recombination DNA repair pathway (HRD) that can be targeted by the PARP inhibitor olaparib. Olaparib increases the amount of DNA damage in a cell by inhibiting PARP repair enzymes. Tumour cells with non-functioning BRCA proteins cannot effectively repair the DNA damage resulting from PARP inhibition by olaparib, whilst non-tumour cells in patients with BRCA mutated cancers produce normal, functional BRCA proteins and can repair DNA damage effectively and efficiently. This targeting of olaparib in BRCA mutated tumour cells over normal cells leads to a therapeutic window and favourable benefit-risk for olaparib.

Orphan drug designation

Application PM-2013-03913-1: Orphan drug designation as monotherapy for the maintenance treatment of adult patients with platinum sensitive relapse BRCA mutated ovarian, fallopian tube or primary peritoneal cancer who are in response to platinum based chemotherapy.

The current TGA submission is synonymous with the orphan drug indication.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 7 January 2016.

At the time the TGA considered this application; a similar application had been approved in (country, date) or was under consideration in (country date) as outlined in Table 1.

Table 1: International regulatory status

Country	Submission /approval date	Indication
European Union	3 September 2013/ 16 December 2014	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.

Country	Submission /approval date	Indication
Switzerland	16 October 2014/Not yet approved	
United States	3 February 2014/ 19 December 2014	Lynparza is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated as monotherapy in patients with deleterious or suspected deleterious germline BRCA mutated (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy.
Israel	29 September 2014/Not yet approved	

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at < https://www.tga.gov.au/product-information-pi>.

II. Registration time line

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2014-04684-1-4

Description	Date
Submission dossier accepted and first round evaluation commenced	31 March 2015
First round evaluation completed	24 September 2015
Sponsor provides responses on questions raised in first round evaluation	18 November 2015
Second round evaluation completed	21 November 2015
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	15 December 2015
Sponsor's pre-Advisory Committee response	21 December 2015
Advisory Committee meeting	Submission did not go to ACM
Registration decision (Outcome)	23 December 2015
Completion of administrative activities and	7 January 2016

Description	Date
registration on ARTG	
Number of working days from submission dossier acceptance to registration decision*	149

*Statutory timeframe for standard applications is 255 working days

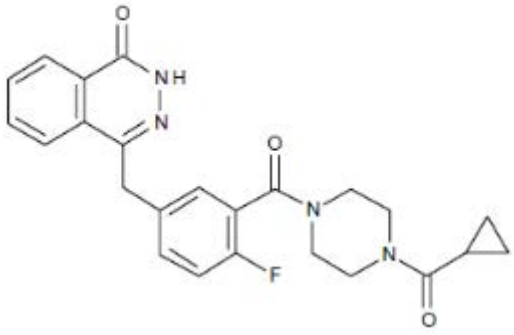
III. Quality findings

Introduction

AstraZeneca Pty Ltd applied to register olaparib 50 mg hard capsules under the trade name Lynparza in high density polyethylene (HDPE) bottles with child resistance closure, to be stored below 30°C with an 18 month shelf life.

The chemical structure of olaparib is shown in Figure 1, below.

Figure 1: Structure of olaparib



Olaparib is a potent inhibitor of polyadenosine 5'diphosphoribose polymerase (PARP) which exploits deficiencies in DNA repair mechanisms (that is BRCA mutation), to preferentially kill cancer cells. Mutations in the BRCA genes are prevalent in high-grade serous ovarian cancer.

The recommended dosing in adults is 400 mg (8 x 50 mg capsules) taken twice daily (bd), giving a total daily dose of 800 mg. The capsules should be taken on an empty stomach and food should be avoided for two hours after dosing.

It is recommended that treatment be continued until progression of the underlying disease. There are no data to support retreatment with olaparib as maintenance following subsequent relapse.

The PI includes a warning not to open the capsules as the active pharmaceutical ingredient (API) is genotoxic.

A food effect study (Study D081AC00001) was conducted in patients with advanced solid tumours.

Drug substance (active ingredient)

Olaparib API is a white to pale yellow crystalline powder. Olaparib exhibits polymorphism and aqueous solubility is low (~ 0.1 mg/mL: a 400 mg dose would require ~ 3000 to 4000 mL to completely dissolve in vitro). Solubility is low independent of pH: olaparib

remains un-ionised across the physiological pH range, so does not form salts. Olaparib is slightly soluble in ethanol (5.5 mg/mL at 37°C). The partition coefficient of olaparib is 1.49. The API is not hygroscopic. The API is a Biopharmaceutics Classification System (BCS) class IV compound (low solubility and moderate permeability).

The drug substance olaparib (International Non-proprietary Name (INN) and United States Adopted Name (USAN)) has the chemical name 4-[(3-{[4-(cyclopropylcarbonyl)piperazin-1-yl]carbonyl}-4-fluorophenyl)methyl]phthalazin-1(2*H*)-one, the Chemical Abstracts Service Registry Number (CAS RN) is 763113-22-0.

Olaparib is achiral. The structure is not closely related to registered kinase inhibitors, or to veliparib (an experimental PARP inhibitor).

The API is made by a synthetic process. The API is purified by recrystallisation and micronised. Structural characterisation was provided using appropriate methods.

The drug substance specification includes tests and limits for 3 identified related substances. The limit for each unspecified impurity is consistent with the International Conference on Harmonisation (ICH) identification threshold. The active substance specifications include tests for appearance (white to pale yellow powder), identification, near infrared spectroscopy (NIR), a limit for other polymorphic forms (NIR), sulfated ash European Pharmacopeia, (Ph.Eur.), particle size distribution, assay high performance liquid chromatography (HPLC), related substances (HPLC), water content, Karl Fischer titration (KF) and residual solvents, gas chromatography (GC).

Impurities were described, classified as process-related impurities and possible degradation products, and qualified. Residual solvents limits in the API meet International Conference on Harmonisation (ICH) requirements.

Drug product

Lynparza olaparib capsules are white and are marked with 'OLAPARIB 50 mg' and the AstraZeneca logo printed in black ink. The capsules are size 0 (approximately 22 mm in length and 7 mm in diameter).

The capsules consist of 50 mg olaparib drug substance suspended in the semi solid lipidic excipient lauroyl macrogol-32 glycerides, within a hypromellose capsule shell which also contains gellan gum, titanium dioxide and potassium acetate. The capsule shell is made of hypromellose (not gelatin).

The formulation is unusual: the fill consists of olaparib drug substance suspended in the semi solid excipient lauroyl macrogol-32 glycerides, which is a mixture of components, both partially hydrolysed oil (the glyceride fraction) and esterified macrogols. Lauroyl macrogol-32 glycerides; forms a microemulsion in water. The dose of lauroyl macrogol-32 glycerides is critical in giving reasonable olaparib bioavailability. Lauroyl macrogol-32 glycerides is included in a very small number of tablet formulations on the ARTG, but at dramatically lower doses. Qualification of this level of the excipient is based on submitted Lynparza data.

The capsule manufacturing process involves suspension in molten excipient, filling/encapsulation and packaging. High pharmacokinetic variability for olaparib might be in part due to product variability in some earlier batches (which showed slower *in vitro* dissolution).

The capsules are packed in HDPE bottles with child resistant closures, each with 112 capsules, in a carton of 4 bottles (total 448 capsules).

The finished product specifications include tests for appearance, identification (HPLC, UV), a limit for other polymorphic forms (NIR), assay (HPLC), impurities (HPLC), uniformity of

dosage units (EP), dissolution (HPLC/UV detection) and microbial quality (EP). Assay limits comply with Therapeutic Goods Order (TGO) 78 at release and expiry.

Capsule dissolution is tested using a paddle apparatus to an appropriate specification.

One degradant increases on storage because of reaction of the olaparib with the formulation; the proposed limit for this was not toxicologically qualified. The product was approved based on clinical experience.

Stability data supported a shelf life of 24 months, store below 30°C; store in original container.

Biopharmaceutics

The same formulation proposed for registration was used in clinical studies.

Following oral administration of olaparib capsule formulation, absorption is rapid with peak plasma concentrations typically achieved between 1 to 3 hours after dosing. On multiple dosing there is no marked accumulation, with steady state exposures achieved within ~3 to 4 days.

Co-administration with food slowed the rate (t_{max} delayed by 2 hours) and increased the extent of absorption of olaparib (Area under plasma concentration time curve (AUC) increased by approximately 20%). Consequently, patients should take Lynparza at least one hour after food, and should refrain from eating for 2 hours afterwards.

The pharmacokinetics of olaparib at the 400 mg twice daily capsule dose are characterised by an apparent plasma clearance of ~ 8.6 L/hour, an apparent volume of distribution of ~ 167 L and a terminal half-life of 11.9 hours. Olaparib is approximately 82% protein bound *in vitro* at plasma concentrations equivalent to those achieved following dosing at 400 mg twice daily.

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 is extensive with the main site of metabolism being the piperazine carboxycyclopropyl ring structure and, to a lesser extent the fluorophenyl and the phathalazinone ring systems. 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 hydroxy-cyclopropyl 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).

No absolute bioavailability study of olaparib has been conducted in man.

Except for changes to the printing on the capsule shells, no changes to the product or manufacturing process have been made between the pivotal clinical study capsule formulation and that proposed for registration, so bioequivalence studies were not required.

No studies have been conducted in man to determine the relative bioavailability of any of capsule variants during formulation development.

A pre-clinical study was undertaken in dogs (Study 0641KD) to investigate the impact of drug loading on exposure from the capsule formulation. This study included an intravenous (IV) arm to investigate absolute bioavailability. As the drug loading increased a decrease in exposure was observed. Reduction in bioavailability with increasing drug

loading was attributed to decreased *in-situ* solubility in luminal fluids resulting from decreased availability of LMG to solubilise olaparib.

A food effect study (Study D081AC00001) was conducted in patients with advanced solid tumours using the proposed capsules. Pharmacokinetic studies including food effects included are discussed in the clinical evaluation report. The key biopharmaceutic findings are summarised below.

Food effect Study D081AC00001

The study used 50 mg capsules, dosed at 400 mg (8 x 50 mg tablets) comparing bioavailability when dosed fasting, with a standard mean and with a high fat meal in patients. The capsule formulation was identical to the proposed capsule formulation for registration.

Pharmacokinetic profiles are broadly conventional but quite variable between subjects. The study showed that food increased mean exposure to olaparib by approximately 20% when administered following either a standard meal or high fat meal compared to the fasted state. The 90% confidence interval for Area under plasma concentration-time curve from time zero to infinity ($AUC_{0-\infty}$) was 1.10 to 1.33 (high fat fed/fasted), somewhat outside standard bioequivalence ranges.

Maximum plasma concentration (C_{max}) increased by 10% following a standard meal, which was attributed to the delay int$_{max}$;[1] from 1.8 hours to four hours with food. Curiously, while with a high fat meal t_{max} was also 4 hours, there was no obvious food effect on C_{max} (90% confidence interval for C_{max} 0.92 to 1.09 high fat fed/fasted).

The study design, conduct and analysis were considered to be satisfactory from a quality perspective.

Another study, Study D0816C00004 evaluated the effect of food on a tablet formulation, increasing exposures 8%, but is not relevant to capsule registration.

The PI recommends:

> *Lynparza should be taken on an empty stomach (at least 1 hour after a meal). Once Lynparza is taken, refrain from eating for 2 hours.*

The PI recommendations match food instructions used throughout the clinical trial program.

Pharmaceutical subcommittee

The application was considered at the 165th meeting of the Pharmaceutical Subcommittee (PSC) of Advisory Committee for Prescription Medicines (ACPM) held Tuesday 24 November 2015. The meeting considered population pharmacokinetic, quality and biopharmaceutic aspects.

The PSC recommendation follows:

The PSC considered the application submitted by AstraZeneca Pty Ltd to register Lynparza capsule containing 50 mg of a new chemical entity, olaparib.

The PSC advised that it supported the pharmacometrician's conclusions.

The PSC provided the following advice:

- batch variability is no longer an issue.

[1] t_{max}: Time at which the maximum serum concentration (C_{max}) of the drug is achieved

- there was no useful information about covariates.
- the 400 mg dose of olaparib was more effective.
- there were no significant exposure adverse event (AE) relationships.

The PSC also advised that the PI should be amended to reflect the recommendations of the PSC.

Quality summary and conclusions

Registration was recommended with respect to chemistry and quality perspective.

IV. Nonclinical findings

Introduction

The sponsor has applied to register a new chemical entity, olaparib (Lynparza), a poly(ADP-ribose) polymerase (PARP) inhibitor. Lynparza is proposed to be used for the maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated high grade serous ovarian cancer (including fallopian tube or primary peritoneal) who are in response (complete response or partial response) to platinum based chemotherapy. The proposed dosing regimen involves oral administration of eight 50 mg capsules (400 mg) taken twice daily, equivalent to a total daily dose of 800 mg.

The submitted nonclinical dossier was in accordance with the relevant ICH guideline for the nonclinical assessment of anticancer pharmaceuticals.[2] The overall quality of the dossier was reasonable with all pivotal safety studies conducted under good laboratory practice (GLP) conditions. The major limitation of the submitted toxicity studies is that exposures were extremely low, generally subclinical. Therefore, the full toxicity profile of olaparib is unlikely to have been revealed in the submitted dossier.

Pharmacology

Primary pharmacology

Rationale and mechanism of action

BRCA1 and BRCA2 proteins are important for the repair of double strand DNA breaks by the error free homologous recombination repair pathway. Mutations in BRCA1 or BRCA2 can lead to errors in DNA repair, predisposing an individual to breast or ovarian cancer. Poly(ADP-ribose) polymerase-1 (PARP-1) is involved in signalling of DNA damage through its ability to recognise and rapidly bind DNA single strand breaks. PARP-1 is also involved in other cellular functions including gene amplification and transcriptional regulation, cell division and differentiation as well as apoptosis and chromosome stability. PARP-2 also has the ability to bind DNA and compensate for PARP-1 activity in DNA single strand break repair. Inhibition of PARP-1 or PARP-2 by olaparib is intended to lead to the persistence of single strand breaks in DNA, generating a protein-DNA adduct. During replication, the single strand breaks bound by trapped PARP results in fork collapse and DNA double strand break formation. In normal cells, these double strand breaks are repaired by homologous recombination. In cells lacking BRCA1 or BRCA2 (for example, BRCA mutated

[2] ICH S9: Nonclinical Evaluation for Anticancer Pharmaceuticals

ovarian tumour cells), there is no effective homologous recombination repair mechanism and the severity of DNA damage leads to cell death.

In vitro

In vitro, olaparib inhibited heterologously expressed PARP-1, PARP-2 and PARP-3 enzyme activity with nanomolar potency (IC_{50} 1 to 5 nM;[3] well below the clinical free minimum serum concentration (C_{min}) of 220 nM).[4] In SW620 cell extracts (a human colorectal adenocarcinoma cell line (wild type BRCA cell line)), olaparib inhibited PARP activity in a concentration dependent manner with an IC_{50} and IC_{90} of 5.4 nM and 60 nM, respectively.

Olaparib (≤ 300 nM) had no effect on the viability of SW620 cells. However, olaparib potentiated the growth inhibitory activity of the alkylating agent, methane methylsulfate (MMS) with a potentiation factor of 3.2 with 300 nM olaparib (the IC_{50} for MMS decreased from 4.35 μg/mL with no added olaparib to 1.34 μg/mL in the presence of 300 nM olaparib). In the presence of MMS, olaparib treatment resulted in PARP1 and PARP2 binding to the chromatin in a number of cells. This was reversible following removal of olaparib. The binding of inhibited PARP-1/2 to chromatin is considered to be important for the cell killing activity associated with olaparib treatment.

Olaparib inhibited the growth of a variety of cell lines (breast, ovarian, pancreatic, non-small cell lung and colorectal cancer, and head and neck small carcinoma). Cell lines with BRCA1/2 mutations or low expression of recombination repair genes/proteins (that is non-BRCA) were more sensitive (IC_{50} < 1 μM) to the growth inhibitory activity of olaparib. There was a significant correlation in the sensitivity to olaparib, cisplatin and carboplatin.

In vivo

The anti-tumour efficacy of olaparib was demonstrated in mouse xenograft/allograft models (human ductal adenocarcinoma and mouse mammary tumour; both were BRCA deficient). Treatment with 50 and 100 mg/kg/day olaparib once daily resulted in decreased tumour volume (8.6% and 1.4%, respectively, of the starting volume by Day 30). Continuous daily dosing was more efficacious than intermittent dosing (1 to 2 weeks on/1 week off), suggesting sustained inhibition of PARP is important for efficacy. Relapse occurred after cessation of treatment and with prolonged treatment. Olaparib treatment after relapse was less efficacious than that observed with initial treatment. These effects were associated with olaparib resistance (see below). The combination of olaparib with platinum drugs increased animal survival and delayed tumour relapse.

The anti-tumour activity of olaparib was significantly less efficacious in cells with a functional BRCA.

The combination of olaparib and platinum therapies delayed tumour relapse and increased mouse survival.

A pharmacokinetic/pharmacodynamic model indicated that the clinical unbound steady state trough concentrations in patients who received 200 and 400 mg twice daily (BD) olaparib exceeded the estimated IC_{90} values from nonclinical studies.

Resistance

Resistance to olaparib treatment was observed in both in vitro and in vivo studies and was associated with an increased expression of P-glycoprotein or breast cancer resistance protein (BCRP). Resistance developed rather quickly in treated mice. If resistance involves up-regulation of transporters such as P-glycoprotein and BCRP, this is unlikely to confer cross resistance to platinum based therapies. A number of published papers indicated another mechanism for olaparib resistance was an intragenic deletion in BRCA2, restoring

[3] $IC_{50;}$ Half maximal inhibitory concentration; $IC_{90:}$ 90% maximal inhibitory concentration
[4] Based on a free fraction of 9%.

wild-type function. This mechanism would also confer resistance to platinum based therapies.[5,6]

Overall, the pharmacology studies support the use of olaparib to treat tumours with a mutated BRCA background.

Secondary pharmacodynamics and safety pharmacology

Olaparib had activity against PARP-1, PARP-2 and PARP-3 at clinically relevant concentrations. Inhibitory activity on PARP-1 and PARP-2 are likely responsible for the desired pharmacological effect. PARP-3 also has a role in DNA repair with some interactions with PARP-1.[7] There are at least 18 members of the PARP superfamily.[8] Aside from PARP-1, -2 and -3, olaparib has only been tested for inhibitory activity against one of these enzymes, tankyrase-1, which has 52% sequence similarity to PARP-1.[8] The inhibitory activity of olaparib on tankyrase-1 was 300 times lower than its activity on PARP-1 (IC_{50} 1.5 μM). Some inhibitory activity on tankyrase-1 and other PARP family members may occur in patients. The effects of this are unknown.

Olaparib had no significant inhibitory activity on >220 receptors, enzymes or ion channels at 10 μM (5 times the free clinical C_{max});[9] and no inhibitory activity against 7 voltage gated cardiac ion channels at 31.6 μM (16 times the free clinical C_{max}). Aside from possible effects on other PARP family members, no off-target effects are expected with the proposed clinical use of olaparib.

Specialised safety pharmacology studies assessed effects on the cardiovascular, central nervous system (CNS) and respiratory systems. All studies were GLP compliant. CNS function in rats (at ≤ 250 mg/kg orally (per os (PO)) and respiratory function in dogs (at ≤ 5 mg/kg PO) were unaffected by treatment. Estimated C_{max} values were 29 μg/mL in rats (from Study 2229/040-DMPK) and 2.13 μg/mL in dogs (from Study D2281 KMD008), 6 and 0.5 times the clinical C_{max}. While a concentration dependent inhibition of human ether-a-go-go-related gene (hERG) K^+ channel tail current was seen with olaparib, the IC_{50} value (226 μM) is approximately 114 times higher than the clinical free plasma C_{max}, and therefore olaparib is not predicted to prolong the QT interval in patients.[10] Consistent with this, no abnormalities were seen in electrocardiograms from dogs treated with ≤ 50 mg/kg PO (in the general toxicity Study 2229/039), though exposures were low; exposure ratio based on C_{max} (ERC_{max}), 0.9. Overall, no adverse effects on CNS, respiratory or cardiovascular function are predicted during clinical use.

Pharmacokinetics

Absorption by the oral route in mice, rats, dogs and humans was rapid (T_{max} 0.3 to 3 hours) and bioavailability in animals was variable (11 to 79%), depending on formulation. The apparent bioavailability of a 400 mg dose was estimated to be 26% in human subjects. Olaparib was a substrate of P-glycoprotein and there was evidence that efflux from this transporter affected apparent permeability in Caco-2 cells. Saturation of P-glycoprotein appeared to occur at concentrations ≥ 260 μM. Intestinal concentrations of olaparib from a

[5] Edwards S L et al., 2008 Resistance to therapy caused by intragenic deletion in BRCA2. *Nature* 2008; 451: 1111–1115
[6] Sakai W et al., 2008 Secondary mutations as a mechanism of cisplatin resistance in BRCA2-mutated cancers. *Nature* 2008; 451: 1116–1120
[7] Bai, P 2015 Biology of poly(ADP-Ribose) polymerases: the factotums of cell maintenance. *Mol. Cell* 2015; 58: 947–958
[8] Amé J –C et al., 2004 The PARP superfamily. (2004) *BioEssays* 2004; 26: 882–893.
[9] Assuming a free fraction of 18%.
[10] QT interval a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle

400 mg dose are estimated to be 3683 μM (based on an intestinal volume of 250 mL), and efflux by P-glycoprotein is anticipated to be saturated at the proposed clinical dose. Following IV administration, elimination half-lives were short in mice, male rats and dogs (t½ 0.7 to 1.7 hours compared with an apparent elimination half-life of 17.3 hours in human subjects). Elimination half-lives were longer in female rats (t½ 8.9 hours), leading to higher exposures in female rats compared with their male counterparts (AUC values were 5 times higher in females). Apparent elimination half-lives in male rats and dogs were longer following oral dosing (2.4 to 4.6 hours). There were no sex differences in any pharmacokinetic parameters in mice or dogs. There was no evidence of accumulation in rats or dogs. In mice, exposures on day 14 were lower (2 to 7 times lower based on AUC) than those seen on day 1, suggesting a possible induction of metabolism in this species. Olaparib exposure was approximately dose-proportional in mice and dogs and greater than dose proportional in rats.

The extent of protein binding in all species was moderate in mice, rats and dogs (% free fraction 27 to 48%) and higher in human plasma (% free fraction 9 to 30%). No concentration-dependence was observed in mouse and rat plasma, but protein binding appeared to be concentration dependent in dog and human plasma (over the range 10 to 40 μg/mL but not at 0.01 to 1.0 μg/mL), associated with saturable binding to alpha-1 acid glycoprotein. The extent of binding to human serum albumin was independent of concentration. The free fraction in human plasma at clinically relevant plasma levels is ≤ 18%. The volume of distribution was similar to or less than total body water in mice, dogs and humans. Following oral administration of ^{14}C-olaparib to mice and rats dogs, radioactivity was widely distributed, but tissue levels were generally similar to plasma/blood levels (except for tissues involved in absorption/excretion). There was minimal penetration of the blood brain barrier (levels in the CNS were undetectable). There appeared to be some retention of drug-related material to pigmented tissues (skin and eyes), based on a slow elimination from these tissues.

Metabolism of olaparib involved removal of the carbonylcyclopropyl group, cyclopropyl ring opening and hydroxylation, monooxygenation of the fluorophenyl group, dihydroxylation of the piperazine group, monooxygenation of the fluorophenyl-carbonyl piperazine moiety and deoxygenation (fluorophenyl and carbonylcyclopropyl piperazine groups). Other metabolites were formed by other hydroxylation or oxidation reactions, ring opening of the piperazine group followed by de-ethylation, sulfation or glucuronidation conjugation reactions. Unchanged olaparib was by far the dominant circulating species in humans and laboratory animals. There were three notable circulating metabolites (M12, M15 and M18; a ring open hydroxycyclopropyl and two mono-oxygenated metabolites) and several trace metabolites in humans. M12, M15 and M18 were also seen in the plasma of male but not female rats. The metabolite profile in female rats (plasma, urine and faeces) indicated less metabolism of olaparib than that seen in male rats (consistent with the longer half-lives and higher AUC values seen in females compared with males). In vitro studies indicated a major role for cytochrome P450 (CYP); CYP3A4/5;[11] with a very minor role of CYP1A1 in the formation of metabolites.

Excretion of olaparib and/or its metabolites was predominantly via the faeces in rats and dogs, while drug-related material was excreted significantly in both the urine and faeces in human subjects. Biliary excretion was demonstrated in rats, though more significant biliary excretion was seen in males than females, which probably accounts for the more significant faecal excretion of radioactivity seen in males.

Overall, the pharmacokinetic profile of olaparib was qualitatively similar in rats, dogs and humans, thus supporting the choice of animal species for toxicity studies.

[11] CYP cytochrome P450

Pharmacokinetic drug interactions[12]

As olaparib is a substrate for CYP3A and P-glycoprotein, inducers/inhibitors of these may affect the systemic exposure to olaparib. Olaparib exposures (C_{max} and AUC) were increased (by 1.42-fold and 2.7-fold, respectively) in human subjects when the drug was co-administered with a CYP inhibitor and co-administration with a CYP inducer decreased olaparib exposures (C_{max} and AUC by 71% and 87%, respectively) (draft PI document). Olaparib was not a substrate for BCRP, MRP2, OATP1B1, OATP1B3 or OCT1.[13]

Olaparib was neither a reversible nor a time-dependent inhibitor of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 or 2E1. Olaparib was both a reversible and a time dependent inhibitor of CYP3A4/5 activity (with midazolam as a substrate). Based on an IC_{50} of 119 μM for reversible inhibition, systemic exposures are unlikely to inhibit hepatic CYP3A activity, but given the much higher concentrations in the gastrointestinal tract (3683 μM from a 400 mg dose), inhibition of intestinal CYP3A activity is possible. Hence, olaparib has the potential to alter the exposure of co-administered drugs that are substrates of intestinal CYP3A4. Olaparib was a time-dependent inhibitor of CYP3A activity. This has unknown clinical relevance.

Some induction of CYP1A2 (mRNA and activity), 2B6 (mRNA and activity) and 3A4 (mRNA only, but by 65 fold) was observed in in vitro studies with human hepatocytes. Given the concentrations at which induction was observed (≥ 4.9 μM compared with a clinical free C_{max} of 0.97 μM), induction of these CYP450 enzymes is unlikely to occur during clinical use. The sponsor states that the possibility of induction at clinical exposures cannot be completely dismissed and has proposed text to be included in the PI document. As clinical exposures were reasonably variable combined with the extent of induction of CYP3A4 mRNA, it may be prudent to retain the information in the final PI document.

No clinically relevant inhibitory activity was seen on OATP1B3, OAT1, OCT1 or MRP2. Olaparib had inhibitory activity on P-glycoprotein and BCRP. This activity is unlikely to be relevant for hepatic efflux, but is potentially relevant for intestinally-expressed transporters. Inhibitory activity was also observed on OATP1B1, OAT3, OCT2, MATE1 and MATE2K (IC_{50} values ranging 5.5 to 47.1 μM). An in vivo interaction with these transporters cannot be dismissed.

In summary, inducers/inhibitors of CYP3A or P-glycoprotein may alter olaparib exposures. Olaparib may alter the exposures of co-administered drugs that are substrates of CYP3A (in the intestine), P-glycoprotein (in the intestine), BCRP (in the intestine), OATP1B1, OAT3, OCT2, multi-antimicrobial extrusion proteins (MATE) MATE1 and MATE2K.

[12] The following assumptions were made:

- molecular weight 434.46, dose 400 mg, C_{max} 10 μM (total), free fraction 18%, intestinal volume 0.25 L, absorption rate constant 0.008 min^{-1} [0.2 h^{-1} from population PK study], bioavailability 26%, kdeg for CYP3A 0.0005 min^{-1}
- for intestinal CYP (CYP3A) and intestinal transporters (P-glycoprotein and BCRP): if the IC_{50} is ≤ 0.1 fold the intestinal concentration, an in vivo interaction is possible
- for systemic CYP, renal uptake and efflux transporters, and hepatic efflux transporters (OAT1, OAT3, OCT2, MRP2, BCRP, P-glycoprotein, MATE1 and MATE2K): if the IC_{50} is ≤ 50 fold the unbound clinical C_{max}, an in vivo interaction is possible
- for hepatic uptake transporters (OCT1, OATP1B1 and OATP1B3): if the IC50 is ≤ 25 fold the unbound hepatic inlet concentration, an in vivo interaction is possible.

[13] MRP2: Multi-drug resistance protein 2; OATP: Organic anion-transporting polypeptide or OCT: Organic cation-transporter

Toxicology

Acute toxicity

The single-dose toxicity of olaparib was assessed in mice and rats using the oral and IV routes. All studies were GLP compliant, used a 14 day observation period and were adequately conducted. The maximum non-lethal oral dose was 300 mg/kg in mice (the highest dose tested) and 240 mg/kg in rats (1.7 and 2.7 times, respectively, the clinical dose of 800 mg/day based on body surface area);[14] indicating a high order of toxicity by the oral route. The maximum non-lethal IV dose was 70 mg/kg in both species. At higher IV doses, deaths occurred immediately post dose. The cause of death was unknown. No clinical signs of toxicity were seen in mice given oral doses of ≤ 300 mg/kg olaparib. Clinical signs in rats following oral dosing included palpebral closure, decreased activity, hypothermia and tremors at ≥ 240 mg/kg and salivation, piloerection, lachrymation, hunched posture and diarrhoea at 300 mg/kg. Similar clinical signs were seen in both species following non-lethal IV doses. All clinical signs were reversible. No target organs for toxicity were identified.

Repeat dose toxicity

Repeat dose toxicity studies by the oral route were conducted in mice (2 weeks), rats (up to 6 months) and dogs (up to 6 months). All studies were GLP compliant. There was limited reporting in the mouse study, thus the discussion below will focus primarily on findings in rats and dogs, two species that were considered appropriate models based on pharmacokinetic parameters. Short term (7 days) studies were conducted in rats and dogs. The full set of parameters were not assessed in these studies, but as exposures in the longer term studies were subclinical and higher exposures were achieved in these short term studies, the findings in these studies are included in the discussion below. The duration of the pivotal studies (6 months), group sizes and the use of both sexes were consistent with ICH guidelines.[15]

The clinical route (PO) was used in all studies. However, animals were dosed only once daily (compared with the proposed clinical dosing regimen of twice daily) and exposures achieved in the 4 and 26 week studies were subclinical. Doses were selected based on toxicity findings in preliminary 7 day repeat dose toxicity studies. There were no premature deaths and bodyweight gain was only impaired at the highest doses in the rat studies. Higher doses may have been achievable in these longer term studies. Due to the low exposures achieved, the full toxicity profile of olaparib is unlikely to be seen in these submitted studies and the majority of the findings described below should be assumed to be potentially clinically relevant.

[14] Assuming a 50 kg individual and mg/kg to mg/m^2 conversion factors of 3, 6 and 33 for mice, rats and humans.

[15] ICH M3(R2): Note for guidance on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals; Guideline on repeated dose toxicity (CPMP/SWP/1042/99 Rev 1); TGA Amendment: Note for Guidance on duration of chronic toxicity testing in animals (rodent and non-rodent toxicity testing); ICH S9: Nonclinical evaluation for anticancer pharmaceuticals

Table3: Relative exposure in repeat dose toxicity studies

Species	Study duration	Dose (mg/kg/day PO)	AUC0–24 hours (µg·h/mL)		Exposure ratio#	
			M	F	M	F
Rat (Wistar Han)	7 days [2229/040]	15	3.68	6.26	0.05	0.08
		100	58.3	123	0.7	1.5
		200	99.4	173	1.2	2.1
	4 weeks [Study 2229/037]	5	0.24	1.64	0.003	0.02
		15	1.06	6.27	0.01	0.08
		40	5.75	15.6	0.07	0.2
	26 weeks [Study TII0012]	1	–	0.37	–	0.005
		5	0.23	3.15	0.003	0.04
		15	1.64	6.75	0.02	0.08
		40	4.23	–	0.05	–
Dog (Beagle)	4 weeks [Study 2229/038]	2.5	4.17		0.05	
		5	6.04		0.07	
		15	16.5		0.2	
	26 weeks [Study TII0011]	1	1.69		0.02	
		3	3.72		0.05	
		10	14.8		0.2	
Human (patients)	steady state	[400 mg bid]	80.8		–	

= animal: human plasma AUC_{0-24h} M = male F = female

Major toxicities

The main target organs for toxicity in both species were the haematopoietic system (including the bone marrow, spleen and thymus), liver and kidney. Other findings were seen in the gastro intestinal (GI) tract, urinary bladder, prostate and thyroid of dogs. All of the findings were reversible or showed a trend to reversion.

The most prominent organ for toxicity was the bone marrow with atrophy and myelotoxicity evident in rats (including animals in the micronucleus test) and dogs. *In vitro*, olaparib inhibited the proliferation of bone marrow cells. Extensive examination of blood cell progenitors in treated rats revealed an increase in total myelopoietic cells and a delay in erythroid cell differentiation, resulting in an increase in the myeloid: erythroid ratio. As a consequence, there was a decrease in circulating red blood cells and reticulocytes, platelets and white blood cells (such as neutrophils, lymphocytes and

monocytes). Secondary to this were alterations in haematopoiesis in the spleen and thymic atrophy/involution. This is an anticipated pharmacological effect of olaparib, as PARP-1 is involved in differentiation processes in the bone marrow and PARP-2 has a role in erythroid differentiation.[7,16]

Extravascular haemolytic anaemia was shown to occur in PARP-2 knockout mice.[16] As well as bone marrow effects, lower red blood cell parameters in olaparib-treated animals may also be attributable to haemolytic anaemia. Changes in the liver (brown pigment and pigmented macrophages) as well as agonal congestion/haemorrhage in multiple organs (liver, kidney, GI tract, and bladder) may be secondary to haemolytic anaemia as a result of PARP-2 inhibition.

Other histopathological changes (papillary mineralisation and pyelitis in the kidney, interstitial inflammatory cell infiltrates and lymphoid aggregates in the prostate, cyst in the parathyroid, cystitis in the bladder, lymphocytic gastritis in the stomach and dilated glands/crypt microabscesses in the caecum) did not always show a relationship with dose, were not consistently seen across studies or across sexes. These findings have an uncertain relationship with olaparib treatment.

Genotoxicity

The potential genotoxicity of olaparib was investigated in the standard battery of tests (bacterial mutagenesis and in vitro clastogenicity assays and a rodent micronucleus test), conducted in accordance with ICH guidelines.[17] All assays were appropriately validated and conducted under GLP conditions. Appropriate bacterial strains were used in the Ames test and concentrations used in the in vitro assays were appropriate. The highest dose in the rat micronucleus study (400 mg/kg PO) is estimated to result in an exposure twice that of the clinical AUC. Negative results were returned in the bacterial mutagenicity test. Olaparib was clastogenic in Chinese hamster ovary (CHO) cells (both with and without metabolic activation) and micronuclei were induced in the rat micronucleus test, indicating olaparib was clastogenic. Given the role of PARP in maintaining genomic stability and repairing DNA strand breakage, these positive findings may be expected based on the pharmacological activity of olaparib. Indeed, micronuclei have been reported in the erythrocytes of mice deficient in PARP-2.[7]

Carcinogenicity

No carcinogenicity studies were conducted, which is considered acceptable, given the intended patient group (ICH S9). Olaparib is clastogenic and secondary malignancies are possible.

Reproductive toxicity

The only reproductive toxicity studies submitted examined effects on fertility (male and female) and embryofetal development toxicity in rats. The lack of a postnatal development study is considered acceptable, given the indication;[18] and the assessment of embryofetal development toxicity in a single animal species is considered acceptable, given the demonstration of embryofetal lethality and teratogenicity in the rat study. Adequate animal numbers were used and the study designs were satisfactory. The major limitation of the submitted studies is that all exposures were subclinical.

[16] Farrés et al., 2015 PARP-2 sustains erythropoiesis in mice by limiting replicative stress in erythroid progenitors. *Cell Death Differ* 2015; 22: 1144–1157.
[17] ICH S2(R1): Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use
[18] ICH S9: Nonclinical Evaluation for Anticancer Pharmaceuticals

Table 4: Relative exposure in reproductive toxicity studies

Species	Study	Dose (mg/kg/day PO)	$AUC_{0-24\ hours}$ (µg·h/mL)	Exposure ratio#
Rat (Wistar Han)	Male fertility [Study 1558GR]a	5	0.24	0.003
		15	1.06	0.01
		40	5.75	0.07
	Female fertility [Study 1557GR]	0.5	0.257	0.003
		15	8.25	0.1
	Embryofetal development [Study 1556TR]b	0.5	0.209	0.003
Human (patients)	steady state	[400 mg BD]	80.8	–

= animal: human plasma $AUC_{0-24\ h}$; [a] data from 4 week repeat dose toxicity study, Study 2229/037; [b] data from dose-ranging study, Study 1555RR

No studies have been conducted to assess placental transfer or excretion into milk of olaparib and/or its metabolites. Based on evidence of embryofetal lethality and teratogenicity in rats, which can be attributed to the pharmacological action of olaparib, it can be assumed that olaparib crosses the placenta.

Treated female rats had extended oestrus, but when paired with untreated males, there was no apparent effect on mating and fertility. Given the subclinical exposures in treated females, it is unknown how much weight can be placed on the negative findings.

There was no effect on sperm counts, motility or progressiveness in treated male rats, and no obvious functional effects on mating and fertility when treated males were paired with untreated females. However, exposures were subclinical, and the study is unlikely to have adequately assessed the effect of olaparib on male fertility. In adult mice, PARP-2 is expressed in pachytene spermatocytes and spermatids. Male mice lacking PARP-2 had reduced sperm counts and reduced functional fertility (fewer numbers of offspring per litter). The rare mutant spermatozoa that were present were immobile and displayed a necrotic appearance.[19] As olaparib inhibits PARP-2, these findings may be seen with pharmacological inhibition of PARP-2. Therefore, an effect on male fertility may have been seen at higher, more clinically relevant, olaparib exposures.

When pregnant females were treated with olaparib during gestation, there was an increased incidence of intrauterine deaths. PARP-1 and PARP-2 are essential during embryogenesis and mice lacking both PARP-1 and PARP-2 were not viable, with growth arresting in the embryonic phase of development.[20] Therefore, the intrauterine deaths are likely associated with the pharmacological action of olaparib. Olaparib treatment during the period of organogenesis led to reduced fetal weights and a higher incidence of fetal malformations (anophthalmia, microphthalmia; misaligned, fused, absent sternebrae

[19] Dantzer, F. et al. (2006) Poly(ADP-ribose) polymerase-2 contributes to the fidelity of male meiosis I and spermiogenesis. *Proc. Natl. Acad. Sci. USA* 2006; 103: 14854–14859

20 Ménissier de Murcia, J. et al. (2003) Functional interaction between PARP-1 and PARP-2 in chromosome stability and embryonic development in mouse. *EMBO J*. 2003; 22: 2255–2263.

and/or vertebrae; kinked, dilated ureter) and variations (delayed ossification, increase in ossification sites, extra 14th rib; variations in the abdominal cavity including slightly dilated ureter, left sided umbilical artery and additional liver lobe). Olaparib is clastogenic and the teratogenic findings are not surprising.

Pregnancy classification

The sponsor has proposed Pregnancy Category D.[21] This is considered appropriate given the malformations observed in the embryofetal development studies.

Immunotoxicity

Bone marrow suppression and reduced circulating white blood cells were seen in olaparib-treated animals. There may be some impairment of immune responses in patients.

Phototoxicity

In tissue distribution studies in rats, pigmented tissues (such as skin and eyes) had some retention of olaparib and/or its metabolites, suggesting a possible concern for phototoxic reactions. Olaparib does not significantly absorb light at ≥ 300 nm, suggesting a low concern for photoreactivity. However, PARP-1 appears to play a role in repairing DNA in skin cells. In vitro, PARP-1 was shown to be involved in removing UV induced DNA lesions in human skin fibroblasts.[22] Also, mice lacking PARP-1 were more susceptible to damage due to γ-radiation.[23] Therefore, retention of olaparib in the skin may impair the ability of cells to recover following UV exposure. Indeed, PARP-/- mice were susceptible to the spontaneous development of skin lesions (~ 30% of older mice developed skin lesions characterised by acanthosis, parakeratosis and spongiosis), possibly due to a poorer reparative response to environmental stresses.[24] There was no evidence of skin lesions in the submitted toxicity studies with olaparib. However, the animals were housed in relatively protected enclosures, the duration of the toxicity studies is relatively short for these effects to manifest, and exposures were extremely low. Therefore, an increased occurrence of skin lesions may be seen in patients. Precautionary warnings regarding UV exposure may be warranted.

Excipient

Lynparza contains the excipient lauroyl macrogol-32 glycerides. While lauroyl macrogol-32 glycerides is not a novel excipient, the daily dose of this excipient with Lynparza exceeds the level achieved with other products. No data assessing the toxicity of lauroyl macrogol-32 glycerides were submitted for this evaluation; however, the toxicity of this excipient has been assessed previously by the TGA. The daily intake of lauroyl macrogol-32 glycerides from Lynparza when taken as directed (according to the draft PI document), is considered acceptable from a toxicological perspective.

[21] Pregnancy Category D is classified as Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.
[22] Robu, M. et al. (2013) Role of poly(ADP-ribose) polymerase-1 in the removal of UV-induced DNA lesions by nucleotide excision repair. *Proc. Natl. Acad. Sci. USA* 2013; 110: 1658–1663.
[23] Ménissier de Murcia, J. et al. (1997) Requirement of poly(ADP-ribose) polymerase in recovery from DNA damage in mice and in cells. *Proc. Natl. Acad. Sci. USA*1997; 94: 7303–7307
[24] Wang, Z.-Q. et al. (1995) Mice lacking ADPRT and poly(ADP-ribosyl)ation develop normally but are susceptible to skin disease. *Genes Develop*. 1995; 9: 509–520.

Impurities

One impurity in the drug substance and one degradant in the drug product specifications have been specified at levels above the qualification thresholds in the relevant ICH guidelines. The proposed limit for the impurity (but not the degradant) has been adequately qualified in the submitted toxicity studies. Control of the degradant to ICH qualification thresholds may be warranted.

Paediatric use

Olaparib is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

Comments on the safety specification of the risk management plan

Results and conclusions drawn from the nonclinical program for olaparib detailed in the sponsor's draft Risk Management Plan (RMP) are in general concordance with those of the nonclinical evaluator.

Nonclinical summary and conclusions

Summary

- The overall quality of the dossier was reasonable with all pivotal safety studies conducted under GLP conditions. The major limitation of the submitted toxicity studies is that exposures were extremely low, generally subclinical. Therefore, the full toxicity profile of olaparib is unlikely to have been revealed in the submitted dossier.
- Olaparib belongs to a novel pharmacological class (PARP inhibitor). In vitro, olaparib inhibited PARP-1, PARP-2 and PARP-3 enzyme activity with nanomolar potency. Olaparib inhibited the growth of a variety of cell lines with BRCA1/2 mutations or low expression of recombination repair genes/proteins. The anti-tumour efficacy of olaparib was demonstrated in mouse xenograft/allograft BRCA-deficient models. The combination of olaparib with platinum drugs increased animal survival and delayed tumour relapse.
- Resistance to olaparib treatment was observed in both in vitro and in vivo studies and was associated with an increased expression of P-glycoprotein or BCRP. This is unlikely to confer cross resistance to platinum based therapies
- Some inhibitory activity on tankyrase-1 and other PARP family members may occur in patients. The effects of this are unknown. Based on a comprehensive screen against several receptors, ion channels and transporters, no other off-target effects are expected with the proposed clinical use of olaparib.
- CNS function in rats and respiratory function in dogs were unaffected by treatment. No electrocardiogram (ECG) abnormalities were seen in the latter species. Olaparib had no effect on hERG K+ tail current at high concentrations suggesting a low potential for QT prolongation.
- Absorption by the oral route in mice, rats, dogs and humans was rapid and bioavailability in animals was variable, depending on formulation. Exposures were higher in female rats compared with their male counterparts. No sex differences were seen in other animal species. The extent of protein binding in all species was moderate in mice, rats and dogs and higher in human plasma. A concentration-dependence was only seen in dog and human plasma. Unchanged olaparib was by far the dominant circulating species in humans and laboratory animals. There were no significant

human-specific metabolites. *In vitro* studies indicated a major role for CYP3A4/5 with a very minor role of CYP1A1 in the formation of metabolites. Excretion of olaparib and/or its metabolites was predominantly via the faeces in rats and dogs, while drug-related material was excreted significantly in both the urine and faeces in human subjects. Biliary excretion was demonstrated in rats.

- Inducers/inhibitors of CYP3A or P-glycoprotein may alter olaparib exposures. Olaparib may alter the exposures of co-administered drugs that are substrates of CYP3A (in the intestine), P-glycoprotein (in the intestine), BCRP (in the intestine), OATP1B1, OAT3, OCT2, MATE1 and MATE2K.
- Single dose toxicity studies in mice and rats indicated a high order of acute toxicity.
- Repeat dose toxicity studies were conducted in rats and dogs (up to 26 weeks) using the oral route. The clinical dosing regimen (twice daily) was not employed in any of the studies (once daily dosing was used in all studies) and exposures to olaparib were subclinical in the pivotal studies. The main target for toxicity in both species was the haematopoietic system (including the bone marrow (myelosuppression and effects on erythroid differentiation), spleen and thymus (secondary to reductions in circulating blood cells)). All effects were reversible or showed a trend to reversion.
- Olaparib was not mutagenic in an Ames test but was clastogenic in vitro (in CHO cells) and in vivo (rat micronucleus test). No carcinogenicity studies were conducted, which is considered acceptable.
- Reproductive toxicity studies with olaparib examined effects on fertility (male and female) and embryofetal development toxicity in rats. Functional fertility was unaffected in treated male and female rats, despite extended oestrus observed in treated females. Exposures were subclinical; therefore little weight can be placed on the negative findings. Olaparib was embryofetal lethal, embryofetotoxic and teratogenic in rats at subclinical exposures.
- In tissue distribution studies, there was some retention of olaparib in pigmented skin. Mice lacking PARP were susceptible to the spontaneous development of skin lesions, possibly due to a poorer reparative response to environmental stresses.
- The daily intake of lauroyl macrogol-32 glycerides from Lynparza when taken as directed is considered acceptable from a toxicological perspective.
- The proposed shelf-life limit for a degradant in the drug product has not been adequately qualified.

Conclusions and recommendation

- The pharmacology studies support the use of olaparib to treat tumours with a mutated BRCA background.
- The combined animal safety studies revealed the following findings of potential clinical relevance:
  - resistance development as a result of over-expression of transporters such as P-glycoprotein and BCRP
  - myelosuppression and haematological toxicity (including anaemia and lymphopaenia)
  - diminished immune reactions and opportunistic infections as a result of effects on blood cells
  - the development of additional malignancies as a result of the genotoxic properties of the compound

- embryofetal toxicity and lethality
- spontaneous skin lesions as a result of a diminished DNA repair system.

There are no objections on nonclinical grounds to the proposed registration of Lynparza.

The nonclinical evaluator also made comments related to the draft PI but these are beyond the scope of the AusPAR.

V. Clinical findings

A summary of the clinical findings is presented in this section.

Introduction

Olaparib is a new chemical entity. It is a potent PARP inhibitor (PARP-1, -2 and -3).

The proposed indication is:

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

Dosage and administration

The dose and administration as set out in the proposed PI is:

> The recommended dose of Lynparza is 400 mg (eight 50 mg capsules) taken twice daily, equivalent to a total daily dose of 800 mg. Lynparza should be taken on an empty stomach (at least 1 hour after a meal). Once Lynparza is taken, refrain from eating for 2 hours.
>
> It is recommended that treatment be continued until progression of the underlying disease.
>
> Special populations:
>
> Children or adolescents: Lynparza is not indicated for use in paediatric patients.
>
> Elderly (> 65 years): No adjustment in starting dose is required for elderly patients.
>
> Renal impairment: Lynparza can be administered in patients with mild renal impairment (creatinine clearance > 50 mL/min). Lynparza 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).
>
> Hepatic impairment: Lynparza is not recommended for use in patients with hepatic impairment (serum bilirubin greater than 1.5 times upper limit of normal (ULN)).
>
> Women of childbearing potential: Women of childbearing potential must use effective contraception during therapy and for 1 month after receiving the last dose of Lynparza. Since it cannot be excluded that olaparib may reduce exposure to substrates of CYP3A through enzyme induction, the efficacy of hormonal contraceptives may be reduced if co-administered with Lynparza.

Clinical rationale

Despite the availability of drugs for the treatment of ovarian, fallopian tube and primary peritoneal cancer, there remains a significant medical need for new therapies. At diagnosis, most patients have advanced disease. Despite > 80% of patients initially responding to platinum based chemotherapy, the majority of these patients ultimately relapse and require further therapy. For patients who develop relapsed disease there is no curative therapy and further treatment is aimed at disease control and maintaining quality of life. Ovarian cancer is a disease of relapse and remission with progressively shorter disease-free and chemotherapy-free periods with successive treatments and all patients will eventually develop chemotherapy refractory disease.

For patients with platinum sensitive disease (as defined by relapse free period > 6 months after the penultimate platinum based chemotherapy) further chemotherapy typically utilises platinum based regimes. Platinum based chemotherapy is associated with significant toxicity and cumulative toxicities usually restrict clinicians to 6 cycles of chemotherapy. There is a strong rationale for considering a maintenance therapy to prolong progression free survival, delay the need for subsequent chemotherapy, maintain quality of life and potentially prolong survival.

Ovarian cancer patients with a BRCA1 or BRCA2 mutation represent a selected patient group whose tumours have a defective homologous recombination DNA repair pathway (HRD) that can be targeted by the PARP inhibitor olaparib. Olaparib increases the amount of DNA damage in a cell by inhibiting PARP repair enzymes. Tumour cells with non-functioning BRCA proteins cannot effectively repair the DNA damage resulting from PARP inhibition by olaparib, whilst non-tumour cells in patients with BRCA mutated cancers produce normal, functional BRCA proteins and can repair DNA damage effectively and efficiently. This targeting of olaparib in BRCA mutated tumour cells over normal cells leads to a therapeutic window and favourable benefit-risk for olaparib.

Consistent with the biological rationale, the greatest clinical benefit has consistently been observed in the subgroups of patients with a gBRCA or BRCA mutated tumour. In patients receiving olaparib monotherapy after achieving a response to platinum based chemotherapy for relapsed ovarian cancer, there is an improvement in progression free survival without a detriment to quality of life. Olaparib has an acceptable toxicity profile permitting prolonged administration as a maintenance therapy as monotherapy.

There is a clear rationale for the development of olaparib in patients with ovarian, fallopian tube and primary peritoneal cancer with either a BRCA 1 or BRCA 2 germline or somatic mutation. This represents an advance in targeting a specific population of ovarian cancers based on an underlying molecular defect in the homologous recombination DNA repair pathway.

Formulation

Unit doses of 10 and 50 mg capsules were used in initial Phase I studies, with only 50 mg capsules being progressed thereafter. Hypromellose capsule shells have been used in all clinical studies.

During Phase I a decision was made to transfer the manufacturing process to the proposed commercial manufacturing site and scale, thereby eliminating the need for late stage bridging studies.

Phase I, and Phase II clinical manufacture at the proposed commercial site: Since establishment of the final manufacturing process at the proposed commercial manufacturing site and scale, more than 30 batches of olaparib capsules have been manufactured.

Proposed commercial product: With the exception of minor cosmetic 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 D0810C00019 and the to be marketed product.

The main difficulty with the olaparib 50 mg capsules is the need for patients to take 16 capsules per day.

Guidance

The Core (Global) and European Union (EU) RMPs have been included in this application at the request of the TGA.

The sponsor provided justification for the lack of absolute bioavailability data with the following:

- Since optimisation of the capsule formulation has already been conducted (based on studies in the dog) and there are no plans to make further changes to it, the benefits of generating absolute bioavailability data (or relative bioavailability data compared to an oral solution/suspension formulation) at this stage of the development of olaparib would be of limited scientific value.
- The solubility of olaparib in aqueous media is approximately0.1 mg/mL and is independent of pH; in human intestinal fluid the solubility is 0.16 mg/mL. Caco permeability experiments have shown it to have moderate permeability and that it has a propensity for P-glycoprotein (P-gp) mediated efflux at low concentrations (10 μM) which becomes saturated at concentrations > 260 μM. Based upon these data, olaparib is a BCS class 4 compound. In vitro experiments have shown olaparib to be a CYP3A substrate. Metabolic clearance has been shown to be a major route of clearance and therefore the bioavailability of the compound could be limited by first pass metabolism. However, at high concentrations, it has also been shown to be an inhibitor of both CYP3A and P-gp. These findings, coupled with the inhibitory effect of the LMG excipient present in the capsule formulation on CYP3A reduce the likelihood of poor bioavailability through P-gp mediated effect or through first pass metabolism at the level of the GI tract.
- The aqueous solubility of olaparib (0.1 mg/mL independent of pH) makes the development of an IV formulation using standard excipients suitable for use in man, technically challenging.
- Since there has never been any intention to market an intravenous formulation of olaparib, the pre-clinical toxicity testing conducted by that route has been limited in nature.
- Administration of the IV formulation in an absolute bioavailability study would involve administration of olaparib via an, as yet, untested route. Consequently, in the event that a formulation suitable for IV dosing to man could be delivered, prior to conducting a clinical absolute bioavailability study, GLP toxicology work following IV dosing followed by dose escalation/safety and tolerability testing in man would be required.
- Olaparib, because of its pharmacological properties, is not suitable for dosing to healthy volunteers and consequently any study would have to be conducted in a late stage cancer patient population in whom all standard treatment options have been exhausted as it would not be ethical to withhold proven treatments from cancer patients for whom other treatment options are available.
- Late stage cancer patients would be unlikely to receive a therapeutic benefit from dosing in a conventional absolute/relative bioavailability study due to the single dose nature of the study and the washout periods required between dose administrations.

The ethics of subjecting late stage cancer patients to an interrupted non therapeutic dosing schedule, the required intensive sampling and visit schedule and restrictions on concomitant medications makes recruitment of suitable patients and obtaining ethics committee approval to conduct an absolute/relative bioavailability study so late in the olaparib development programme a significant challenge.

- Although it may be possible to overcome some of these issues through the use of a micro-dosing approach, preliminary discussions with Contract Research Organisations (CROs) able to deliver such studies have indicated that they have little/no experience or ability to conduct such studies in a cancer patient setting. Recruitment of patients into such a study would require the protocol to offer continued access to olaparib beyond completion of the 'pharmacokinetic (PK) phase', which in turn would require patient support and adverse event monitoring that these CROs are not used to providing. Thus delivery of such a study, if ethical approval was achieved, would require the involvement of multiple organisations and would be logistically challenging.

The sponsor provides the assurance that the submission is consistent with the lodged pre-submission planning form in both scope and scale with the following exceptions:

- The clinical module contains 2 documents not in the pre submission planning form (PPF) submitted comprehensive TOC:
  - Final Pooled QT report D0816C00004 and -07
  - C-QT Pharmacometric Report

    These are not reports of additional studies. They are analyses of studies listed.

    The submission will include US Prescribing Information. This was not indicated in the PPF as Lynparza was not approved in the USA at the time PPF was lodged.

The justification for submitting an absolute/relative bioavailability study for the olaparib capsule formulation is satisfactory.

Contents of the clinical dossier

The clinical dosser documented a full clinical development program of pharmacology, efficacy and safety studies.

The submission contained the following clinical information:

- 10 clinical pharmacology studies, including 10 that provided pharmacokinetic data (Studies D0810AC00001, D0816C00004, D0816C00007, D0816C00008, D0810C00001, D0810C0002, D0810C00007, D0810C00008, D0810C00010, D0810C00024) and 5 that provided pharmacodynamic data (Studies D0810C00001, D0810C0002, D0810C00007 D0816C00004 and D0816C00007)
- 1 population pharmacokinetic analysis
- 3 dose finding studies (Studies D0810C00001, D0810C0002 and D0810C00024) (also referred to as Study 01, 02 and 24 respectively)
- 1 pivotal efficacy/safety study (Study D00810C00019)(also referred to as Study 19)
- 5 other efficacy/safety studies (Studies D0810C00009, D0810C00012, D0810C00020, D0810C00041, D0810C000042)(also referred to as Study 09, 12, 20, 41 and 42 respectively)
- 1 Summary of Clinical Efficacy Outputs
- 1 Summary of Clinical Safety Outputs

- 1 cQT pharmacometric report
- 5 dose finding studies of olaparib in combination with chemotherapy (Studies D0810C00004, D0810C00005, D0810C00006, D0810C00021, D0810L00001)
- 1 Phase II efficacy study of olaparib in combination with chemotherapy (Study D0810C00039)
- 1 Phase II efficacy study of olaparib in colorectal cancer (Study D9010C00008)
- Literature references

The submission also contained; Clinical Overview, Summary of Clinical Pharmacology, Summary of Clinical Efficacy, Summary of Clinical Safety and literature references.

Paediatric data

The submission did not include paediatric data. The sponsor stated that olaparib is not indicated for use in paediatric patients.

There is no clinical value in the sponsor providing data for a paediatric population for the following reasons: epithelial ovarian cancer is not a malignancy of the paediatric population; malignancies associated with BRCA mutations do not occur in paediatric populations.

Good clinical practice

All clinical studies were performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

The protocol, consent from, study subject information sheets were submitted by each investigator and a duly constituted International Review Board for review and approval before study initiation. All patients had provided written informed consent after adequate explanation of the aims, methods, objectives and potential hazards of the study before undertaking any study related procedures.

Pharmacokinetics

Studies providing pharmacokinetic data

Summaries of the pharmacokinetic studies were provided. Table 5 shows the studies relating to each pharmacokinetic topic.

Table 5: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	Primary aim of study
PK in target population	Bioequivalence† - Multi-dose	D0810C00024	PK Parameters
	Food effect	D081AC00001	PK Parameters
		D0816C00004	PK Parameters
PK in special	Target population §	D081AC00001	PK Parameters

PK topic	Subtopic	Study ID	Primary aim of study
populations	Single dose	D0810C00001	Safety
		D0810C00002	Safety
		D0816C00004	PK Parameters
		D0810C00010	PK Parameters
	Multi-dose	D0810C00001	Safety
		D0810C00002	Safety
		D0816C00004	PK Parameters
		D0810C00007	PK Parameters
		D0810C00008	PK Parameters
		D0810C00024	PK Parameters
PK interactions	Itraconazole	D0816C00007	PK Parameters
	Rifampicin	D0816C00008	PK Parameters
	Target population	D081AC00001	PK Parameters
		D0810C00001	Safety
		D0810C00002	Safety
		D0810C00007	PK Parameters

Table 6 lists the pharmacokinetic results that were excluded from consideration due to study deficiencies.

Table 6: Excluded pharmacokinetic studies

Population	Study	Reason
Breast cancer population	D0810C00008	Results not available

Evaluator's conclusions on pharmacokinetics

The pharmacokinetics of olaparib as monotherapy has been extensively studied. This has included both in vitro and in vivo studies. Data has been provided from multiple animal models (mouse, rat, dog and human).

Olaparib is not suitable for testing in a healthy population. All clinical studies in human were conducted in a population with advanced solid organ malignancy representative of the target population. Additionally this has been enriched with data from patients with a BRCA mutation. The overall analysis of olaparib monotherapy is based on individual studies and a population pharmacokinetic evaluation using pooled data from 5 studies.

It is noted that the pharmacokinetic data is overwhelmingly from females and Caucasian patients. There is a lack of ethnic diversity and the pharmacokinetics in these populations potentially may differ from Caucasians. There is also limited clinical data on patients over the age of 75; this is documented in the PI.

Data is currently not available on the pharmacokinetics of olaparib in patients with moderate severe hepatic or renal impairment. Appropriately the proposed PI recommends that olaparib be not administered in patients with hepatic impairment (bilirubin > 1.5 ULN) or moderate renal impairment (creatinine clearance < 50 mL/min).

Clinical drug interaction studies have been performed based on in vitro data and accordingly it is recommended that known potent inhibitors or inducers of CYP3A4/5 should not be co-administered with olaparib.

The PK data in the proposed PI should provide clarification that the PK data is primarily derived from a Caucasian population.

Pharmacodynamics

Studies providing pharmacodynamic data

Summaries of the pharmacodynamic (PD) studies were provided. Table 7 shows the studies relating to each pharmacodynamic topic and the location of each study summary.

Table 7: Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID	Primary aim of the study
Primary Pharmacology	Effect on PARP inhibition	D0810C00001	Safety
		D0810C00002	Safety
		D0810C00024	PK parameters
		D0810C00007	PK parameters
Secondary Pharmacology	Effect on QT	D0816C00004	PK parameters
		D0816C00007	PK Parameters

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

Table 8 lists pharmacodynamic results that were excluded from consideration due to study deficiencies.

Table 8: Excluded pharmacodynamic studies

Population	Study	Reason
Breast cancer	D0810C00008	PD data collection was discontinued and not analysed

Evaluator's conclusions on pharmacodynamics

The pharmacodynamics of olaparib has been adequately studied. This has included both *in vitro* and *in vivo* studies. Data has been provided for cell lines and animal models (mice).

All clinical studies in humans were conducted in a population with advanced solid malignancy representative of the target population. Pooled PD data was derived from 2 clinical studies.

The results of the pharmacodynamic studies demonstrate inhibition of PARP in both peripheral blood mononuclear cells (PBMCs) and tumour tissue and provided data on concentration and pharmacokinetic effects. The data on inhibition of PARP-1 activity in PMBC and tumour samples shows wide inter-individual and intra-individual variability.

The data presented supports olaparib as a maintenance therapy.

Dosage selection for the pivotal studies

The dose of olaparib 400 mg BD (capsule formulation) was selected based on the PD, PK, and safety and tolerability from three Phase I and II trials conducted in patients with advanced solid tumours:

- Study D0810C00002 (non-randomised Phase I study in patients with advanced solid tumours) showed that the maximum tolerated dose of olaparib was 400 mg BD administered on a continuous basis.
- Two 'Proof of Concept' studies (Study D0810C00008 in breast cancer patients with gBRCA mutations and Study D0810C00009 in ovarian cancer patients with gBRCA mutations) showed a greater response rate at the 400 mg BD dose than at the 100 mg BD dose.
- Study D081AC00001 had also assessed the effect of food on the PK of olaparib. Oral dosing at least 1 hour after food with the patient should then refraining from eating for a further 2 hours was consistent with the PK data from this study.

Efficacy

Studies providing efficacy data

- Pivotal efficacy study
  - Study D0810C00019; a Phase II randomised, double blind, and multicentre study to assess the efficacy of AZD2281 (olaparib) in the treatment of patients with platinum sensitive serous ovarian cancer following treatment with two or more platinum containing regimens.
- Other efficacy studies

  There are 6 other efficacy studies submitted relevant to this application. These are restricted to those studies where olaparib has been used as monotherapy in an ovarian cancer population.
  - Study D0810C00009: This is a Phase II, open label, comparative, multicentre study to assess the efficacy and safety of olaparib at 2 dose levels in patients with BRCA1 or BRCA2 associated ovarian cancer. Two sequential patient cohorts received continuous oral olaparib in 28 day cycles initially at 400 mg BD and subsequently at 100 mg BD. This study enrolled 58 patients. The primary endpoint was OR. Secondary endpoints included clinical benefit rate (complete response (CR) + partial response (PR) + SD), progression-free survival (PFS), pharmacodynamics on peripheral blood mononuclear cells, safety and tolerability and olaparib drug exposure.

- Study D0810C00012: a Phase II, open label, randomised, comparative, multicentre study to compare the efficacy and safety of 2 different doses of olaparib versus liposomal doxorubicin in patients with 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 BD orally, olaparib 400 mg BD orally, or liposomal doxorubicin 50 mg/m^2 IV. This study enrolled 97 patients, 32 patients in each olaparib group and 33 patients in the liposomal doxorubicin group. Demographics and disease characteristics were well balanced between the groups. The primary end point was investigator-assessed progression free survival (PFS) for olaparib versus pegylated liposomal doxorubicin (PLD). Secondary end points included odds ratio (OR) (RECIST);[25] duration of treatment response; tumour size; overall survival (OS); safety and tolerability; and HR QoL.
- Study: D0810C00020: a Phase II, open label, non-randomised correlative study of olaparib as a single agent, given 400 mg BD to patients with recurrent triple negative breast or ovarian cancer. This study enrolled both patients with a BRCA1 or BRCA2 mutation and non-carriers. Sixty-five patients were enrolled with ovarian cancer with 15 of these with a BRCA mutation. The primary endpoint was OR. Secondary end points included identification of markers of olaparib efficacy through analysis of tumour material, PFS, safety and tolerability.
- Study D0810C00041: a Phase II, open label, randomised, comparative, multi-centre study to compare the efficacy of olaparib in combination with carboplatin and paclitaxel and then as monotherapy versus carboplatin and paclitaxel in recurrent platinum sensitive ovarian cancer. Included were patients with BRCA mutation and non-carriers. Patients were randomised (1:1) to receive olaparib 200 mg BD days 1 to 10, in combination with paclitaxel 175 mg/m^2 IV Day 1 and carboplatin AUC 4 IV Day 1 of a 21 day cycle for at least 4 cycles then olaparib monotherapy 400 mg BD continuous dosing or paclitaxel 175 mg/m^2 IV day 1 and carboplatin AUC 6 IV Day 1 of a 21 day cycle for 6 cycles with no maintenance treatment. In total, 173 patients were enrolled with 162 patients randomised equally. Of the 81 patients in the combination arm, 66 entered the maintenance phase. The primary endpoint is PFS. Secondary endpoints include OS, safety and PK assessment.
- Study D810C000042: a Phase II, open label, non-randomised, non-comparative, multicentre study to assess the efficacy and safety of olaparib in patients with advanced cancers who had a confirmed BRCA1 and/or BRCA2 mutation. Patients received olaparib 400 mg BD and continued until disease progression. In total 317 patients were recruited, 298 received treatment, 193 with ovarian cancer. The primary endpoint is RR. Secondary endpoints include: objective response rate (ORR), PRS, OS, duration of response (DoR), disease control rate (DCR).
- Study D0810C00002: an open label, dose escalating, non-randomised, multi-centre Phase I study of olaparib administered orally to patients with advanced solid tumours. This study included an expanded cohort of BRCA enriched patients, primarily with ovarian cancer. Patients received doses from 10 mg daily Days 1 to 14 on a 21 day cycle escalated to 600 mg BD. The expansion cohort received 200 mg BD. In total 99 patients were recruited, 53 had ovarian cancer, 49 of which had a mutation in BRCA1 or BRCA2. The primary endpoint was maximum tolerated dose (MTD.) The primary efficacy variables were overall best response (RECIST and RECIST/GCIG), DoR, duration of stable disease and time to disease progression.

- Analyses performed across trials (pooled analyses and meta-analyses):

[25] RECIST: Response Evaluation Criteria in Solid Tumours

It was not considered appropriate by the sponsor to formally pool the efficacy data from these studies with the data from the pivotal study due to differences in study design: olaparib also administered in combination with chemotherapy prior to maintenance (Study D0810C00041); active comparator, non-maintenance design, and a different patient population investigated (Study D0810C00012); and non-maintenance, non-randomised design and different patient populations investigated (Studies D0810C000009, D08109C00020, and D0810C00042).

Evaluator's conclusions on efficacy

The sponsor has provided evidence for the efficacy of olaparib as maintenance therapy in platinum sensitive ovarian cancer after a response to platinum based therapy in patients with a BRCA mutated cancer. It is noted that the pivotal trial is a Phase II randomised study with a matched placebo control. It is appropriate to use PFS as the primary endpoint for this trial. This study was able to demonstrate a PFS benefit and this study was not powered to demonstrate an OS benefit. Survival analysis will be confounded by subsequent therapy and it is reported that 22.6% of patients in the placebo arm with a BRCA mutation were documented to have received subsequent therapy with a PARP inhibitor.

The standard of care for these patients is observation with chemotherapy on progression. Prolonging PFS without compromising QoL is a clinically important endpoint for patients. Due to the increasingly large proportion of patients failing to complete QoL assessments in the pivotal study, overall, it cannot be categorically concluded that no worsening of QoL occurred. Exploratory analysis has also reported a significant delay to first or second subsequent treatment supporting a durable benefit of treatment.

The pivotal study is supported with activity demonstrated in 5 Phase II trials in patients with ovarian cancer. There is consistency in the results from these studies. As anticipated, the greatest benefit is seen in patients who have a mutation in BRCA1 or BRCA2 or HRD. They have provided evidence to support the dose of 400 mg (capsules) BD. It should be noted that the patient population is mainly Caucasian in these studies.

This submission relies on the results of a pivotal Phase II study and supportive studies with Phase III studies ongoing. While results of a Phase III study will provide more robust results and is considered the gold standard, the sponsor has provided justification for the indication of olaparib as maintenance therapy of adult patients with platinum sensitive relapsed BRCA mutated high grade serous ovarian cancer (including fallopian tube or primary peritoneal) who are in response (complete or partial response) to platinum based therapy.

Safety

Studies providing safety data

The dose response and non-pivotal efficacy studies provided safety data, as follows:

- Study D0180C00041 provided data on olaparib as a maintenance therapy, following combination with chemotherapy.
- Studies D0180C00001, D0180C00002, D0180C00007, D018AC00001, D0180C00008, D0180C00009, D0180C00012, D0180C00020, D0180C00024, D0180C000042 and DO910C0008 provided data on olaparib as monotherapy. These trials included patients with an advanced malignancy with 398 of these patients with ovarian cancer.

In each of these studies data was collected at baseline, regular intervals while the patient remained on treatment up until 30 days after receiving the last dose.

AEs, vital signs, haematology, clinical chemistry and electrocardiographs (ECG) were recorded in the clinical pharmacology studies and all studies were conducted in patients with an advanced malignancy.

There were no unexpected changes noted in vital signs or physical examination safety parameters in the olaparib or placebo groups, and no individual abnormalities raised any safety concerns. Diastolic and systolic blood pressure did not change appreciably during the study, with mean and median values over time remaining consistent and similar for the olaparib and placebo groups (Study D0810C00019).

The results of the individual studies were provided.

Patient exposure

The clinical programme for olaparib is broader than the indication being sought in this application. Across the entire clinical programme, as of 20 September 2014, an estimated 3,020 patients with ovarian, breast, pancreatic, gastric and 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 AstraZeneca sponsored, investigator sponsored and collaborative group studies. Olaparib has been given as either monotherapy (28 studies, an estimated 1,810 patients) or in combination with other chemotherapy/anti-cancer agents (30 studies, an estimated 1210 patients).

The safety data presented in the summary of clinical safety is derived primarily from 832 olaparib treated patients from AstraZeneca sponsored studies where olaparib was administered as a monotherapy at a dose of 400 mg BD (capsules) in line with the approval being sought.

The safety data includes the pivotal trial Study D0810C00019, a second maintenance trial Study D0810C00041 and a further 11 monotherapy trials.

Safety issues with the potential for major regulatory impact

Myelodysplastic syndrome / acute myeloid leukaemia

This is a potentially concerning toxicity however there will always be some risk with these agents. The intended use for olaparib is for patients with advanced cancer and where clinically significant benefit is seen, a low risk of this toxicity is acceptable.

In Study D0180C00019 there was a higher rate of anaemia in the olaparib arm (23.5% versus 7.0%). Anaemia did not result in discontinuation in any patient. The majority of patients who developed anaemia had their first onset within the first 2 months. The cumulative incidence plateaus after around 8 months. Anaemia generally resolves while remaining on treatment and resulted in dose reduction in 3.3% of patients on olaparib. Anaemia required transfusion in 27.8% of patients in the olaparib arm.

The incidences of common terminology criteria for adverse events (CTCAE) Grade 3 or 4 toxicities for olaparib are: 7.5% anaemia (0.8% placebo); 5.1% neutropaenia (2.3% placebo); 8.1% lymphopaenia (3.1% placebo) and 2.9% thrombocytopaenia (0% placebo). See Table 9.

In the patients who received olaparib there was a trend for a slight reduction in median haemoglobin and with the median values remaining below the lower limit of normal (LLN) during the treatment period. Median neutrophil levels and platelet levels remained stable and above the LLN in the patients who received olaparib. There was a trend for a slight decrease in median lymphocyte counts over time compared to baseline in patients receiving olaparib.

Mean corpuscular volume (MCV) values for the olaparib treated patients increased to above the ULN. The increase became apparent after 3 months of treatment. The clinical significance of this is unknown. Levels appeared to return to normal at the follow-up and post follow-up visits and did not appear to have any clinical consequences.

Table 9: Summary of maximum overall CTCAE Grade during treatment for key haematology parameters; Safety analysis set

Haematology parameter[a]	n/N (%) of patients				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Olaparib 400 mg bd (n=136)					
Haemoglobin	24/136 (17.6)	58/136 (42.6)	45/136 (33.1)	7/136 (5.1)	2/136 (1.5)
Lymphocytes	66/136 (48.5)	32/136 (23.5)	28/136 (20.6)	10/136 (7.4)	0
Neutrophils	73/136 (53.7)	42/136 (30.9)	15/136 (11.0)	3/136 (2.2)	3/136 (2.2)
Platelets	89/136 (65.4)	39/136 (28.7)	4/136 (2.9)	3/136 (2.2)	1/136 (0.7)
Placebo (n=128)					
Haemoglobin	53/128 (41.4)	62/128 (48.4)	12/128 (9.4)	1/128 (0.8)	0
Lymphocytes	87/128 (68.0)	24/128 (18.8)	13/128 (10.2)	4/128 (3.1)	0
Neutrophils	75/128 (58.6)	34/128 (26.6)	16/128 (12.5)	3/128 (2.3)	0
Platelets	105/128 (82.0)	21/128 (16.4)	2/128 (1.6)	0	0

[a] Haematology: Grade 3 (<80 – 65 g/L) and Grade 4 (<65 g/L); Lymphocytes: Grade 3 (<0.5 – 0.2 x 10^9 g/L) and Grade 4 (<0.2 x 10^9 g/L); Neutrophils: Grade 3 <1.0 – 0.5 x 10^9/L, Grade 4 <0.5 x 10^9/L; Platelets: Grade 3 <50.0 – 25.0 x 10^9/L, Grade 4 <25.0 x 10^9/L.

Safety in special populations

Age

There appeared to be no major difference in the safety profile of patients treated with olaparib aged < 65 years versus ≥ 65 years.

The safety profile was similar in patients in both age groups, with the exception of:

- AEs of CTCAE Grade ≥ 3, which were more frequent in patients, aged ≥ 65 years (51.3%) than those aged < 65 years (43.3%).
- AEs leading to dose modification were more frequently in patients aged ≥ 65 years (51.9%) than those aged < 65 years (36.9%).

Ethnicity

The number of non-White patients is small representing only 3% in the pivotal study and 6.7% patients in the monotherapy pooled data set. Based on very limited data the tolerability profile was consistent with that observed in all patients. No definite conclusions on equivalence of safety can be made.

Hepatic impairment

Clinical studies conducted to date have had entry criteria to exclude patients with total bilirubin > 1.5 x institutional ULN and aspartate transaminase (AST)/ alanine transaminase (ALT) > 2.5 x institutional ULN (unless liver metastases were present, in which case it was > 5 x ULN). A hepatic impairment study using the tablet formulation of olaparib is ongoing.

Olaparib should not be dosed to patients with serum bilirubin > 1.5 x ULN.

Renal impairment

Clinical studies conducted to date had entry criteria to exclude patients with serum creatinine > 1.5 x institutional ULN. A renal impairment study using the tablet formulation of olaparib is ongoing.

In the pooled analysis for patients receiving monotherapy, estimates for glomerular filtration rate (GFR) using creatinine clearance estimation have been calculated indirectly using the Cockcroft-Gault equation found 465 patients had normal renal function, 249 had mild renal impairment, 47 had moderate renal impairment and 1 patient had severe renal impairment at baseline. For patients with moderate renal impairment there was a higher rate of any CTCAE Grade 3 or higher, dose interruptions and dose modifications.

Olaparib should not be dosed to patients with moderately or severely impaired renal function (creatinine clearance < 50 mL/min).

Safety in pregnancy and lactation

Nonclinical data indicate that olaparib can have adverse effects on embryofoetal survival and development. There is no clinical data for this patient group as pregnancy has been an exclusion criterion for all clinical trials. There is no data on excretion of olaparib in breast milk.

Olaparib should not be used in women who are pregnant or lactating.

Safety related to drug-drug interactions and other interactions

Co-administration of olaparib with drugs that are potent inhibitors or inducers of CYP3A4 would alter the PK of olaparib and may impact on its safety/tolerability profile.

All clinical trials conducted to date have excluded co-administration of known potent inhibitors of CYP3A and advised against co-administration of known potent inducers of CYPs. Although the data in Studies D0816C00007 and D0816C0008 were generated using the tablet rather than the capsule formulation, they have indicated the presence of a marked interaction with known examples of such medications (itraconazole and rifampicin).

The product information appropriately recommends that co-administration of olaparib with strong CYP3A inhibitors or inducers should be avoided.

Olaparib has been shown, in vitro, to be a substrate for multi-drug resistance protein (MDR) MDR1. It is possible that olaparib may cause clinically relevant drug interactions with substrates of MDR1.

Olaparib has been shown to be an inhibitor of OATP1B1, OCT 1, OCT2, OAT3, MATE1 and MATE2K. The clinical relevance of these findings is currently unknown.

OATP1B1 is a transporter protein important in the disposition of some statins. There is a potential for olaparib to reduce statin clearance through this mechanism, thereby resulting in possible potentiation of side effects commonly seen with statins to a degree that may be clinically relevant. No formal olaparib statin interaction study has been conducted. In the group of 92 patients in the monotherapy pooled dataset who were taking a statin, the frequencies of common AEs known to be associated with statins (for example, 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).

There is a potential for olaparib to reduce the clearance of OCT transporter substrates (such as metformin) thereby resulting in possible potentiation of side effects commonly seen with metformin to a degree that may be clinically relevant. No formal olaparib-metformin interaction study has been conducted. In the group of 46 patients in the monotherapy pooled dataset who were taking metformin, the frequencies of common AEs

known to be associated with metformin were similar to those expected based on published data.

Co-administration with anti-neoplastic agents, including DNA damaging agents increases myelotoxicity and combination with such agents is currently not recommended.

Evaluator's conclusions on safety

The safety and tolerability of olaparib is supported by the pivotal trial where the comparator was placebo and the pooled results of studies with olaparib. To date, over 3,000 patients have received olaparib in the clinical development programme. In the pivotal trial Study D0810C00019 (Study 19), pooled safety data and Study D0810C00041 (Study 41) maintenance trial, 22.4% of patients remained on treatment greater than 12 months.

The safety of olaparib is supported by the overall low rates of study withdrawals and the mild to moderate severity of most of the AEs. Many of the AE are transient and able to be managed with simple supportive measures. The most common side effects attributable to olaparib include anaemia, nausea, fatigue / asthenia, diarrhoea, anorexia, dyspepsia, upper abdominal pain, stomatitis, headache, dysgusia and dizziness. Rare but imported AEs included: myelodysplastic syndrome (MDS) / acute myeloid leukaemia (AML), second malignancy and pneumonitis. Deaths reported were overwhelmingly related to the disease under investigation, death secondary to an adverse event was reported but infrequent.

There are no major safety issues relating to renal function. It is noted that there is a minor rise in serum creatinine soon after the initiation of olaparib with return to normal on discontinuation. This was not of clinical significance. There is no major safety issue relating to hepatic damage. There is no data on the safety of olaparib in patients with moderate-severe renal or hepatic dysfunction and this should not be used under these circumstances until such data demonstrates safety.

Safety in the > 65 age population has been assessed, however there is minimal data in the > 75 age population; the lack of data in the older age group is acknowledged in the PI. Olaparib is untested and not indicated for the paediatric population.

The safety assessment program has been adequate with extensive pre-clinical assessment and well conducted Phase I trials. It is noted that no study was terminated early due to safety concerns.

First round benefit-risk assessment

First round assessment of benefits

The benefits of olaparib in the proposed usage are:

- Olaparib as monotherapy for the maintenance treatment of adult patients with platinum sensitive relapsed BRCA-mutated high grade serous ovarian, fallopian tube or peritoneal cancer after response to platinum based chemotherapy significantly improves PFS (hazard ratio (HR): 0.18; 95% confidence interval (CI): 0.11, 0.31; $p < 0.0001$). The median PFS was 11.2 months versus 4.3 months for placebo.
- There is a significant improvement in time to first or second subsequent therapy on death HR 0.35 (95% CI: 0.23 to 0.52, $p < 0.00001$) and HR 0.43 (95% CI: 0.25 to 0.71, $p = 0.001$), respectively.

First round assessment of risks

The risks of olaparib in the proposed usage are:

- Due to an increasingly large proportion of patients failing to complete quality of life assessments, olaparib has not been categorically demonstrated to maintain, or improve, quality of life.
- Potential for side effects, most of which are mild-moderate and manageable with simple supportive measures.
- Potential for rare significant adverse events such as MDS/AML, second malignancy and pneumonitis.
- Risk of drug interaction and care should be taken to avoid co-administration with drugs that induce or inhibit CYP3A4/5.
- Safety is not established in patients with moderate-severe renal failure or hepatic impairment.

First round assessment of benefit-risk balance

The benefit-risk balance of olaparib, given the proposed usage, is favourable.

Patients with relapse ovarian, fallopian tube or primary peritoneal cancers have an incurable disease and will receive over the course of their disease multiple courses of chemotherapy. Olaparib has demonstrated significant activity with a 6.9 month improvement in PFS in BRCA mutated high grade serous ovarian, fallopian tube and primary peritoneal cancer while maintaining quality of life. This translated into a delay in the initiation of subsequent chemotherapy.

First round recommendation regarding authorisation

Based on the clinical data submitted it is recommended that the application for olaparib be approved.

Clinical questions

1. Clinical trials provided in this submission include both the capsule (proposed formulation for marketing) and tablet formulation. Study D0810C0024 assessed bioavailability and concluded that the tablet and capsule formulation should not be regarded as bioequivalent. The sponsor should provide a considered summary as to how this may impact on the totality of the efficacy and safety data provided.
2. The sponsor should provide any information it holds on the pharmacological activity of the metabolites of olaparib.

Second round evaluation

A second round clinical evaluation was not required by the Delegate for this submission.

VI. Pharmacovigilance findings

Risk management plan

EU-RMP Version 5 (dated 3 November 2014, data lock point (DLP) 20 May 2014), Core Patient RMP Version 2 (dated 16 December 2014, DLP 1 October 2014) and Australian Specific Annex (ASA) Version 1 (dated 3 February 2015) to Core RMP (Version 2).

Revised Australian Specific Annex Version 1 (dated 5 November 2015).

Summary; Ongoing Safety Concerns

The summary of the ongoing safety concerns as specified by the sponsor in the Core Global RMP is as shown in Table 10.

Table 10: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Anaemia Thrombocytopaenia Neutropaenia Raised creatinine levels Nausea including vomiting
Important potential risks	MDS/AML New primary malignancies Pneumonitis Potential for off label use Potential for patient medicine errors Effects on embryofetal survival and development
Missing information	Interaction with substrates of transporter proteins Exposure in patients with renal and hepatic impairment Exposure in the elderly Exposure in ethnically diverse groups Long-term exposure to potential toxicity to olaparib Use in patients with Eastern Cooperative Oncology Group (ECOG) performance status > 2

RMP reviewer comment at the time of evaluation: Upon comparative review of the EU RMP, the updated data and information in the Core Global RMP was evident; there was an additional notable difference; 'interaction with CYP3A4 inducers/inhibitors' was presented under 'Missing Information' in the Summary of Safety Concerns of the EU RMP. In the Core Global RMP it is identified as an important identified/potential interaction (Core Global RMP p 126) but was not included in the Summary of Safety Concerns or

subsequent discussion. Table 11, from the Core Global RMP, summarised drug-drug interactions with CYP3A4 inducers/inhibitors.

Table 11: Drug-drug interaction with CYP3A4 inducers/inhibitors

Interacting substances	CYP3A4 inducers/inhibitors
Effect of interaction	Potential increase in olaparib exposure and hence toxicity due to interaction with strong inhibitors of cytochrome CYP3A4 and potential decrease in olaparib efficacy due to interaction with strong inducers of cytochrome CYP3A4.
Evidence source	Evidence source has been based on in vitro data and clinical exposure data. A recently completed primary report (Part A and B) from an in vitro drug interaction study (D0186C00007) to determine the magnitude of effect of a co-administered strong CYP3A4 inhibitor on olaparib exposure has confirmed that co administration with itraconazole increased mean C_{max} 1.42 fold (90% CI: 1.33 to 1.52) and increased mean AUC 2.70 fold (90% CI: 2.44 to 2.97) of olaparib. Results from the in vivo drug interaction study with a known strong CYP inducer (rifampicin) on the PK of olaparib following oral dosing of the tablet formulation of olaparib are soon to be completed.
Possible mechanisms	In vitro data have shown that the principle enzyme responsible for the formation of the 3 main metabolites of olaparib is CYP3A4.
Potential health risk	Increase in frequency and/or severity of olaparib toxicity or reduction of efficacy if olaparib is administered with CYP3A4 strong inhibitors or inducers respectively.
Discussion	In vitro data have shown that the principle enzyme responsible for the formation of the 3 main metabolites of olaparib is CYP3A4. Consequently to ensure patient safety olaparib co administration with strong inhibitors of CYP3A4;[a] should be avoided. In addition to avoid potential reductions in exposure due to drug interactions and therefore a potential reduction in efficacy, olaparib co administration with strong CYP3A4 inducers;[b] should be avoided.

Note: a) known strong inhibitors that have most often previously been reported associated with clinically significant drug interactions: itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir (wash out period 1 week);
b) phenytoin, rifampicin, rifapentin, carbamazepine, phenobarbital, nevirapine, and St John's Wort (wash out period for phenobarbital 5 weeks and for any of the others 3 weeks.)

Pharmacovigilance plan

Proposed pharmacovigilance activities

The sponsor proposes routine pharmacovigilance for all safety concerns, and advises that additional information will be collected from Phase III studies relating to anaemia, thrombocytopaenia, neutropaenia, raised creatinine levels, nausea and vomiting, pneumonitis, off-label use, medication errors, embryofoetal survival and development, exposure in elderly, exposure in ethnically diverse groups, and long-term exposure to/potential toxicity of olaparib.

It is noted that the sponsor has provided variable wording of some safety concerns (for example 'use in the elderly' versus 'exposure in the elderly', 'use in patients with liver disease' versus 'exposure in patients with hepatic impairment'). It is recommended that the sponsor use consistent language throughout the RMP documentation in future updates.

A follow-up targeted safety questionnaire (TSQ) is proposed for the safety concerns of MDS/AML, new primary malignancy (including non-melanoma skin cancer) and pneumonitis.

The sponsor has advised the following study will provided information regarding use in patients with liver disease (cirrhosis and fibrosis) and use in patients with mild or moderate kidney disease: 'Routine pharmacovigilance practices, signal identification and review. Phase I study (D0816C00005) 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/normal renal function or mild or moderate renal impairment).

The sponsor advised of studies and other activities completed since the last update of the Pharmacovigilance Plan, including the following investigations:

- Effect of food on the pharmacokinetics of olaparib (Study D081AC00001)
- Itraconazole in combination with olaparib (Study D0816C00007)
- Rifampicin in combination with olaparib (Study D0816C00008)
- Effect of olaparib on QT interval (Studies D0816C00007 and D0816C00004)

The sponsor further identified the following additional pharmacovigilance activities (anticipated milestone/completion dates and number of Australian patients randomised) as shown in Table 12.

Table 12: Additional pharmacovigilance studies

Study	Description	Safety Concern Identified	Milestone/Due Date(s)	Number of Australian Patients Randomised
D0816C00002	Phase III randomised, double-blind, placebo-controlled, multicentre study of olaparib maintenance monotherapy in platinum-sensitive relapsed BRCA-mutates ovarian cancer patients who are in complete or partial response following	Anaemia, thrombocytopaenia, neutropaenia, raised creatinine levels, nausea including vomiting, MDS/AML, new primary malignancies, pneumonitis, exposure in the elderly, exposure	Final report: 4Q2018	17 (enrolment complete)

Study	Description	Safety Concern Identified	Milestone/Due Date(s)	Number of Australian Patients Randomised
	platinum based chemotherapy	in ethnically diverse groups, long-term exposure to/potential toxicity to olaparib.		
D0810C00019	Phase II randomised, double-blind study to assess the efficacy of olaparib compared with placebo in the treatment of patients with platinum sensitive serous ovarian cancer following treatment with 2 or more platinum containing regimens	Anaemia, thrombocytopaenia, neutropaenia, raised creatinine levels, nausea including vomiting, MDS/AML, new primary malignancies, pneumonitis, long-term exposure to/potential toxicity to olaparib.	Final report: 2Q2017	31
D0816C00012	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).	Anaemia, thrombocytopaenia, neutropaenia, raised creatinine levels, nausea including vomiting, MDA/AML, new primary malignancies, pneumonitis, exposure in the elderly, exposure in ethnically diverse groups, long-term exposure to/potential toxicity to olaparib.	Final report: 3Q2018	6
D0816C00010	Phase III open label, randomised, controlled, multicentre study to assess the efficacy and safety of olaparib monotherapy versus physician's choice single agent chemotherapy in the treatment of platinum sensitive relapsed ovarian cancer in patients carrying germline BRCA1/2 mutations.	Anaemia, thrombocytopaenia, neutropaenia, raised creatinine levels, nausea including vomiting, MDA/AML, new primary malignancies, pneumonitis, exposure in the elderly, exposure in ethnically diverse groups, long-term exposure to/potential toxicity to olaparib	Final report: 2Q2020	Nil (in planning phase)
D0816C00005	Open-label, non-randomised, multicentre, comparative Phase I study to the determine the	Provide missing information on exposure in patients with hepatic	Final report: 4Q2016	0

Study	Description	Safety Concern Identified	Milestone/Due Date(s)	Number of Australian Patients Randomised
	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.	impairment.		
D0816C00006	Open-label, non-randomised, multicentre, comparative Phase I study of the 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.	Provide missing information on exposure in patients with renal impairment.	Final report: 4Q2016	0
D0818C00001	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 lie platinum based chemotherapy.	Anaemia, thrombocytopaenia, neutropaenia, raised creatinine levels, nausea including vomiting, MDA/AML, new primary malignancies, pneumonitis, exposure in the elderly, exposure in ethnically diverse groups, long-term exposure to/potential toxicity to olaparib.	Final report: 1Q2022	10 (enrolment estimated to cease in February 2015)
D0816C00009	Randomised, double-blind, placebo-controlled multicentre study of olaparib maintenance monotherapy in patients with platinum sensitive relapsed ovarian cancer who are in complete or partial response following platinum based chemotherapy and whose tumours carry loss of function somatic BRCA mutation(s) and patients with loss of function mutation(s) in tumour	Anaemia, thrombocytopaenia, neutropaenia, raised creatinine levels, nausea including vomiting, MDA/AML, new primary malignancies, pneumonitis, exposure in the elderly, exposure in ethnically diverse groups, long-term exposure to/potential toxicity to olaparib.	Final report: 2Q2020	Nil (in planning phase)

Study	Description	Safety Concern Identified	Milestone/Due Date(s)	Number of Australian Patients Randomised
	homologous recombination repair-associated genes.			
D081CC00006 BIG 6-13, NSABP B-55	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/@ mutations and high risk HER2 negative primary breast cancer who have completed definitive local treatment and neoadjuvant or adjuvant chemotherapy.	Anaemia, thrombocytopaenia, neutropaenia, raised creatinine levels, nausea including vomiting, MDA/AML, new primary malignancies, pneumonitis, exposure in the elderly, exposure in ethnically diverse groups, long-term exposure to/potential toxicity to olaparib.	Final report: 2Q2028	0
D0819C00003	Phase III open label, randomised, controlled multicentre 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.	Anaemia, thrombocytopaenia, neutropaenia, raised creatinine levels, nausea including vomiting, MDA/AML, new primary malignancies, pneumonitis, exposure in the elderly, exposure in ethnically diverse groups, long-term exposure to/potential toxicity to olaparib.	Final report: 4Q2018	0
Study number to be confirmed	Study to collect and/or retrieve prospective data from sizeable patient cohorts representing real world evidence from relevant countries, to further assess the safety concern of MDS/AML in ovarian cancer patients. Study synopsis to be submitted within 3 months of marketing approval.	MDS/AML	Study start: 3Q2015	0

In addition, the sponsor identified additional pharmacovigilance activities to address specific safety concerns:

- Future clinical studies with olaparib will be undertaken using the tablet formulation. The tablet dose selected for Phase III studies (300 mg BD) was considered to be clinically comparable to 400 mg BD olaparib capsules and therefore it was considered

appropriate to evaluate important identified and potential risks further in Phase III studies using the tablet formulation. Further evaluation of important identified and potential risks in clinical studies will be based on clinical data generated with the tablet formulation.

- Four ongoing Phase III studies (Studies D0816C00002, D0818C00001, D081CC00006 and D0819C00003) will provide additional data to help characterise the important potential risks of MDS/AML, new primary malignancies, pneumonitis; and the identified risks of haematological toxicity (anaemia, thrombocytopaenia and neutropaenia), raised creatinine levels and nausea (including vomiting). Two further studies in patients with ovarian cancer are planned to start in 2015 (Studies D0816C00009 and D0816C0010).
- In addition an annual progress report will be provided with an assessment of the emerging safety profile in patient subgroups by gBRCA status based on blinded data from patients with ovarian or breast cancer, participating in these ongoing Phase III studies.

The following is included by the sponsor for post-authorisation efficacy and safety studies as shown in Table 13.

Table 13: Post-authorisation efficacy and safety studies

Study	Safety Objectives	Efficacy Uncertainties Addressed	Status	Date for submission of interim or final reports
D0816C00002 Phase III randomised, double-blind, placebo-controlled, multicentre study	To assess the safety and tolerability of olaparib maintenance monotherapy	Further evidence of efficacy and safety in BRCA mutated patients	Started	Primary CSR: 1Q2016 Final CSR: 4Q2018
D0818C00001 Phase III randomised, double-blind, placebo-controlled, multicentre study	To assess the safety and tolerability of olaparib maintenance monotherapy	Further evidence of efficacy and safety in BRCA mutated patients	Started	Primary CSR: 1Q2017 Final CSR: 2Q2020
D0810C00019 Phase II randomised, double-blind, placebo controlled, multicentre stud	To determine the safety and tolerability of olaparib (capsule formulation) compared to placebo	Further evidence of efficacy and safety in somatic BRCA mutated patients (germline and somatic patients)	Started	Final CSR: 2Q2017
D0816C00012 Phase IV, open label, single arm, non-randomised, multicentre study	To assess the safety and tolerability of olaparib maintenance monotherapy in patients with platinum sensitive relapsed gBRCAm	Further evidence of efficacy and safety in somatic BRCA mutated patients (germline and somatic patients)	Planned	Final CSR 3Q2018

Study	Safety Objectives	Efficacy Uncertainties Addressed	Status	Date for submission of interim or final reports
	or sBRCAm ovarian cancer			
D0816C00010 Phase III, open label, randomised, controlled, multi-centre study	(not specified)	Further evidence of efficacy and safety in BRCA mutated patients	Planned	Primary CSR: 2Q2018 Final CSR: 2Q2020
D0816C00009 Randomised, double blind, placebo controlled, multicentre study	(not specified)	Further evidence of efficacy in patients with loss of function (deleterious or suspected deleterious) somatic BRCA mutation. Assessment of efficacy in patients with a loss of function (deleterious or suspected deleterious) mutation in non-BRCA Homologous Recombination Repair (HRR)-associated genes. All patients will have no evidence of a deleterious germline BRCA mutation	Planned	Primary CSR: 3Q2018 Final CSR: RMP indicates both 2Q2020 and 3Q2020

CSR: Clinical study report; gBRCAm: Germline BRCA mutated

Table 14. Reconciliation of issues outlined in the first round RMP evaluation report (Round 1)

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
It is noted that the Australian Specific Annex (ASA) should provide a table comparing the differences, if any, between advice in the	Please refer to Appendix 1 of the current ASA.	The updated ASA, to include a table comparing the differences between advice in the SmPC;[26] and PI, is noted.

[26] SmPC: Summary of Product Characteristics

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
EU Summary of Product Characteristics and the Australian PI. Updates to the ASA should be in the current format of the TGA guidance and contain such information.		
It is noted that the sponsor has provided variable wording for some safety concerns (for example 'use in the elderly' versus 'exposure in the elderly', 'use in patients with liver disease' versus 'exposure in patients with hepatic impairment'). It is recommended that the sponsor use consistent language throughout the RMP documentation in future updates.	The sponsor notes this comment and will endeavour to use consistent wording in future updates.	The sponsor's response is noted and acceptable from a RMP perspective.
The sponsor has identified potential problems with adherence to the dosing schedule of olaparib. It is recommended that the Consumer Medicines Information be updated to guide patients towards adherence. The proposed CMI currently advises of the following: How much to take: The usual dose is eight capsules taken twice each day (a total of 16 capsules each day). This could be reinforced with text advising that the patient 'should not take less than the prescribed amount' or	Appropriate text has been added to the revised CMI. The revised text (shown in strikethrough for deleted text and bold for added text) is provided below: How much to take: The usual dose is eight capsules taken twice each day (a total of 16 capsules each day). You should not take any more or any less capsules unless your doctor tells you to. How to take it: Swallow the capsules whole with a glass of water. Do not open the capsules.	The sponsor's response is considered satisfactory from a RMP perspective, noting this issue is deferred for final determination by the Delegate.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
words to that effect.		
It is recommended the Australian PI be revised to include the Contraindications identified in the EU SmPC, unless omission can be justified by the sponsor: Hypersensitivity to the active substance or to any excipients Breast-feeding during treatment and 1 month after the last dose.	AstraZeneca confirm that the Australian PI will be revised to include a contraindication for use in patients with hypersensitivity with the following wording: 'hypersensitivity to the active substance or to any excipients'. The hypersensitivity contraindication has been added to the proposed PI; however, it should be noted that this contraindication is not in the Lynparza Core Data Sheet and so is not the company's position. Hypersensitivity has been included within the EU SmPC in accordance with their European guidance regarding SmPCs (European Commission Guideline 20094). AstraZeneca consider that a warning in the Precautions section of the Lynparza PI is sufficient to address concerns regarding breast-feeding during treatment and for 1 month after the last dose of olaparib and a specific contraindication for breast-feeding women is not necessary. A contraindication for breast-feeding was added to the EU SmPC as an imposition of the European Medicines Agency (EMA) during review. This information was added as a precautionary measure, given the pharmacology of olaparib and the lack of data on transmission in breast milk, rather than to any observed effect. Moreover, the risk of patients inadvertently breast feeding and exposing the baby to olaparib in the breast milk is extremely low, as it is very unlikely that the patient in this treatment setting (maintenance treatment of platinum sensitive relapsed (PSR) BRCAm ovarian cancer) would be able to give birth, for the following reasons: The standard treatment for ovarian cancer is surgery, for diagnosis, determination of the extent of the cancer and tumour debulking or cytoreduction, followed by chemotherapy. Debulking surgery usually involves removing not only the ovaries but also the uterus, cervix and fallopian tubes and as much visible disease as possible, thus rendering the patient infertile. Patients eligible to receive olaparib for maintenance treatment according to the proposed indication would have had previous prior therapy with multiple cycles of platinum containing chemotherapy with possible gonadal toxic consequence. In Study 19 (Study D0810C00019) patients had received an average of 3 previous chemotherapy regimens, including 2.6 previous platinum-containing	The sponsor's response is considered satisfactory from a RMP perspective, noting this issue is deferred for final determination by the Delegate.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	chemotherapies, thus demonstrating the impact of potential previous chemotherapy treatment on fertility. Only 3 patients (0.4%) received concomitant treatment with oral contraceptives in the monotherapy pool dataset progestogen/oestrogens. In Study 19, 257 patients (97.0%) overall, had the following surgical procedures hysterectomy 158/265 (59.6%), radical hysterectomy 68/265 (25.7%), salpingo-oophorectomy 28/265 (10.6%), salpingo-oophorectomy bilateral 108/265 (40.8%), salpingo-oophorectomy unilateral 8/265 (3.0%), salpingectomy 3/265 (1.1%), oophorectomy 12/265 (4/5%) and oophorectomy bilateral 9/265 (3.4%), cytoreductive surgery 84/265 (31.7%). Therefore, although a potential risk for the newborn/infants cannot be excluded, the risk is considered manageable by suitable wording in the Precautions Section; a contraindication is not considered necessary.	
The sponsor should update the Core Global RMP Summary of Safety Concerns to include interactions with CYP3A4 inducers/inhibitors as an identified risk, and indicate in the pharmacovigilance plan where planned and ongoing clinical studies are relevant to this safety concern.	The EU Risk Management Plan is being updated to include 'Drug-drug interactions with CYP3A inducers and inhibitors' as an Important Identified Risk, following the completion of the clinical interaction studies D0816C00007 (with a potent CYP3A4 inhibitor: itraconazole) and D0816C00008 (with a potent CYP inducer: rifampicin) and is currently under review with the Pharmacovigilance Risk Assessment Committee (PRAC) and the Committee for Medicinal Products for Human Use (CHMP) at EMA (see the response in Section 5.7). Once EU RMP is endorsed by PRAC and CHMP, the Core RMP revisions will be made. Pharmacovigilance activities for the Important Identified risk of 'Drug-drug interactions with CYP3A4 inducers and inhibitors' will consist of routine pharmacovigilance practices, including signal detection and review, to further characterise the nature and frequency of the risk. There are no planned or ongoing clinical studies specifically to investigate this risk further. Patients receiving potent CYP3A4 inducers and inhibitors have been excluded from recruitment into all olaparib clinical studies. The PI contains a description of interactions between olaparib and CYP3A4 inducers and inhibitors in the 'Precautions Section' and also in the 'Interaction with Other Medicinal Products Section'.	The sponsor's response is considered satisfactory from a RMP perspective. The TGA should be advised when the EU and Core RMPs are finalised, with copies provided.
The sponsor should advise when the EU-	The EU Risk Management Plan is being updated to include 'Drug-drug interactions with CYP3A inducers	The sponsor's response is

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
RMP will be updated to contain the information in the Core Global RMP, and when the updated EU-RMP is anticipated to be provided to the TGA.	and inhibitors' as an Important Identified Risk, following the completion of the clinical interaction studies D0816C00007 (with a potent CYP3A4 inhibitor: itraconazole) and D0816C00008 (with a potent CYP inducer: rifampicin). As a result of the re-categorisation of the risk, the Missing Information topic 'Interaction with substrates of transporter proteins' is being clarified to read 'Drug-drug interactions with inhibitors of P-gp and substrates of CYP enzymes and transporter proteins'. The revised EU RMP has been submitted to the EMA as part of an ongoing Type II variation and is still under review by PRAC and CHMP; once agreement is reached, this version will also be provided to the TGA.	considered satisfactory from a RMP perspective. It is noted that the sponsor has advised that the updated version of the EU RMP will be provided to the TGA upon agreement in the EU jurisdiction.

New and outstanding recommendations from second round evaluation

Outstanding issues relate to Recommendations 6 and 7 of the first round RMP evaluation. These recommendations included the recognition of interactions with CYP3A4 inducers/inhibitors as an identified risk (with associated pharmacovigilance), and a request to the sponsor to advise when the EU-RMP was to be updated and submitted to the TGA.

The sponsor has advised that the EU RMP is currently being updated to include these drug interactions as an important identified risk, with routine pharmacovigilance. The sponsor advised that once the EU RMP is endorsed by PRAC and CHMP, the Core RMP revisions will be made, and versions of the EU and Core RMPs will be provided to the TGA.

Proposed wording for conditions of registration

RMP

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

> Implement RMP (Version 5, dated 3 November 2014, data lock point 20 May 2014) with Australian Specific Annex (Version 1, dated 5 November 2015) and any future updates as a condition of registration.

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Introduction

The breast cancer genes play a role in homologous DNA repair pathways and a germline mutation in either of these genes increases the risk of a range of cancers including breast and ovarian cancer, and also fallopian tube and primary peritoneal carcinoma. Such tumours have thus have lost one pathway for DNA repair and become reliant upon the other key remaining PARP pathway to repair any double stranded DNA breaks. By inhibiting the PARP pathway, tumour cells which have non-functioning homologous DNA repair mechanisms cannot effectively repair the DNA damage, and become reliant upon pathways which are highly error prone and result in gross genomic instability and subsequent cell death. In a study published in 2012, BRCA mutations were detected in 16% of Australian women presenting with serous epithelial ovarian cancer, the most common subtype. While bi-allelic somatic mutations occur, the majority of BRCA deficient tumours are found in women who carry a predisposing BRCA gene mutation. While this group has improved rates of progression-free and overall survival in part due to maintained platinum sensitivity, disease progression is inevitable.[27] These women represent a significant and clearly identifiable cohort of patients, whose tumours have a defective homologous recombination DNA repair pathway (HRD) that can be targeted by the PARP inhibition.

There is a clear rationale for the development of PARP inhibitors in patients with ovarian, fallopian tube and primary peritoneal cancer with either a BRCA1 or BRCA2 germline or somatic mutation. This represents an advance in targeting a specific population of ovarian cancers based on an underlying molecular defect in the homologous recombination DNA repair pathway.

Olaparib is a new chemical entity, reported to be a potent PARP inhibitor (PARP-1, -2 and -3). In addition to the data presented here in ovarian cancer, recent publications have indicated its role and efficacy to be in targeting prostate cancers with homologous DNA repair pathway deficiencies due to deleterious mutations or deletions in BRCA 1/2, CHEK2.[28]

Orphan designation

Olaparib received orphan designation from the TGA on 14 January 2014 as follows: "Olaparib is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated ovarian, fallopian tube or primary peritoneal cancer who are in response to platinum based therapy."

It is noted however, that olaparib's mechanism of action is stated to be related to synthetic lethality induced by blocking one of the remaining intact pathways in the presence of a defect in another DNA repair pathway, and that BRCA mutation is just one such pathway. Future applications would view olaparib as an agent to treat diseases or conditions with homologous DNA repair pathway deficiencies, rather than by anatomical site, histological

[27] Alsop K et al 2012 BRCA Mutation Frequency and Patterns of Treatment Response in BRCA Mutation–Positive Women With Ovarian Cancer: A Report From the Australian Ovarian Cancer Study Group *J Clin Oncol* 2012; 30: 2654-2663. And *J Clin Oncol* 2012; 47: 3777

[28] Mateo J et al, 2015. DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer. *N Engl J Med* 2015; 373: 1697-1708

subtypes or individual gene mutations, which are subsets. This has been validated by the recent publication of efficacy in the treatment of prostate cancer with a range of DNA pathway deficiencies.[28]

Overseas regulatory history

- The EMA granted marketing authorisation on 16 December 2014 for the following indication:

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

  The requirements of registration included the following:

  – 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.

- The Food and Drug Administration (FDA) approved the following on 19 December 2014 under accelerated approval (conditional approval with confirmatory trial evidence required):

  Lynparza is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated as monotherapy in patients with deleterious or suspected deleterious germline BRCA mutated (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy.

  The indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

  The following are requirements either to fulfil the accelerated approval conditions or to post-marketing requirements.

  1. Submit the results of progression free survival (PFS) and overall survival (OS) analyses from Study D0818C00002, SOLO-2, the ongoing randomised double blind, placebo controlled, multicentre trial to assess the efficacy of olaparib maintenance monotherapy relapsed high grade serous ovarian cancer (HGSOC) patients (including patients with primary peritoneal and / or fallopian tube cancer) or high grade endometrioid cancer with BRCA mutations (documented mutation in BRCA1 or BRCA2 that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function)) who have responded following platinum based chemotherapy.

  2. Submit the results of progression free survival (PFS) and overall survival (OS) analyses from Study D0816C00010, a randomised trial establishing the superiority of olaparib over physician's choice single agent chemotherapy in the treatment of platinum sensitive relapsed ovarian cancer in patients carrying deleterious or suspected deleterious germline BRCA1/2 mutations.

3. Provide annual summaries of all cases of acute myelogenous leukemia / myelodysplastic syndrome identified in patients treated with Lynparza (olaparib). These reports should summarise all cases identified up until that reporting date (new cases and those reported in previous years), and should include patients treated with Lynparza on trials and outside of clinical trials (including spontaneous safety reports).
4. Submit the final report for Trial D0816C00006 entitled, 'an open-label, non-randomised, multicentre, comparative, and Phase I study of the pharmacokinetics, safety and tolerability of olaparib following a single oral 300 mg dose to patients with advanced solid tumors and normal renal function or renal impairment.'
5. Submit the final report for Trial D0816C00005 entitled, '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 dose to patients with advanced solid tumours and normal hepatic function or mild or moderate hepatic impairment.'

Quality

The finalised version of the pharmaceutical evaluation report is not yet available, and any action proposed is conditional upon there being no outstanding issues.[29]

Nonclinical

The nonclinical evaluator had no objections on nonclinical grounds to registration of olaparib for the proposed indication. It should be noted that the major limitation of the submitted toxicity studies is that exposures were extremely low, generally subclinical. Therefore, the full toxicity profile of olaparib is unlikely to have been revealed in the submitted dossier.

For details of the nonclinical summary and conclusions please see Section IV above.

Clinical

The clinical evaluator has reviewed the submitted data, which included:

- 10 clinical pharmacology studies, including 10 that provided pharmacokinetic data (Studies D0810AC00001, D0816C00004, D0816C00007, D0816C00008, D0810C00001, D0810C0002, D0810C00007, D0810C00008, D0810C00010, D0810C00024, and 5 that provided pharmacodynamic data (Studies D0810C00001, D0810C0002, D0810C00007 D0816C00004 and D0816C00007)
- 1 population pharmacokinetic analysis
- 3 dose-finding studies (Studies D0810C00001, D0810C0002 and D0810C00024)
- 1 pivotal efficacy/safety study (Study D00810C00019)
- 5 other efficacy/safety studies (Studies D0810C00009, D0810C00012, D0810C00020, D0810C00041, D0810C000042)
- 1 Summary of Clinical Efficacy Outputs
- 1 Summary of Clinical Safety Outputs

[29] At the time of consideration all outstanding issues related to quality aspects were resolved.

- 1 cQT pharmacometric report
- 5 dose-finding studies of olaparib in combination with chemotherapy (Studies D0810C00004, D0810C00005, D0810C00006, D0810C00021, D0810L00001)
- 1 Phase II efficacy study of olaparib in combination with chemotherapy (Study D0810C00039)
- 1 Phase II efficacy study of olaparib in colorectal cancer (Study D9010C00008)
- Literature references

The submitted data was evaluated using TGA adopted EMA Guidelines as follows:

- Guideline on the evaluation of anticancer medicinal products in man
- Points to consider on application with1. Meta-analyses; 2. One pivotal study.
- The Delegate also reviewed the CHMP report available online athttp://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003726/WC500180154.pdf

Paediatric data

The submission did not include paediatric data which is appropriate given ovarian cancer is a disease diagnosed in adulthood.

Pharmacokinetics/pharmacodynamics

The formulation used in the studies submitted was a 50 mg capsule. This requires 16 capsules to be taken daily, and a new tablet formulation is under evaluation in other studies yet to be submitted.

Summary of PK data

The pharmacokinetics (PK) of olaparib have been characterised in patients with advanced solid tumours and in patients with advanced ovarian or breast cancer with a germline BRCA mutation.

Absorption, elimination

Non-compartmental analysis of the plasma concentration data obtained following administration of a single oral dose of olaparib to patients in Study 02 (Study D0810C00002) (10 to 600 mg) and Study 24 (Study D0810C00024) (50, 100 and 400 mg), showed that while for most patients, absorption of drug was rapid, there was marked inter-individual variability (C_{max} 1 to 3 hours after dosing; range: 0.5 to 8 hours). Exposure increased approximately proportionally with dose up to a dose of 100 mg but declined to less than dose-proportionally thereafter (for 4 fold increase in dose from 100 mg to 400 mg, there was a 1.7 fold increase in exposure). On multiple dosing there is no marked accumulation, with steady state exposures achieved within approximately 3 to 4 days. 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 (Study D0810C00001).

The mass-balance study was conducted with a 100 mg dose level in 6 patients, and there was marked inter-individual variability with rapid absorption and clearance to below the limit of sensitivity of the assay by 16 to 24 hours in five patients, while in one individual, concentrations were still detectable some 168 hours later. 44% of the drug appeared in the urine and 42% in the faeces, suggesting that at least 44% was absorbed. 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 principal metabolite, M15 accounted for 6% and 5% of the urinary and faecal excretion, respectively). There was extensive metabolism with up to 37 metabolites detected, each accounting for less than 1% of the circulating drug. Data on the pharmacological activity of the three major circulating metabolites has not been provided.

While in vitro studies showed that olaparib is a substrate of MDR1 transporter, the efflux would be saturated at the concentrations actually observed in clinical situations.

Food intake influences the bioavailability of olaparib capsules with exposure to olaparib slightly (approximately 20%) enhanced when the capsules were administered within 30 to 45 min following a standard or high fat food intake. Co-administration with food slowed the rate (T_{max} 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. This is stated in the PI.

The mechanism of absorption is not clearly defined. Extrapolation of the minimum absorption of 44% observed cannot be assumed for the 400 mg proposed dosing, as evidenced by the lack of dose proportionality beyond 100 mg. This may be in part due to dissolution issues which are described in the Pharmaceutical Chemistry section of the EPAR.

For the future submission of the new tablet formulation used in ongoing studies, the sponsor will have to satisfactorily demonstrate bioequivalence with the formulation presented in this dossier.

There are indications that olaparib is transferred largely to extra-vascular tissue, but it is difficult to state more than this due to the widely varying measurements obtained from the lower dose levels, the higher dose levels and the population PK studies. These included: 54.4 L at 100 mg dose compared with 167 L for a 400 mg dose, this latter value is reduced to 88 L if the single outlier is excluded; from the population PK studies, the Vd was estimated to be 64 L with inter-patient variability exceeding 90%, and values of 177 L for the 400 mg dose.

Measurements following preoperative administration of a range of doses from 30 to 400 mg BD olaparib to breast cancer patients demonstrated tumour levels deemed sufficient to inhibit PARP, but no actual PD data were presented in support of this.

The absence of a clear and predictable relationship makes a rationally devised dosing strategy difficult, especially as the tumour levels of the drug appeared to be achieved at much lower dose levels than those proposed for registration.

At doses up to 100 mg, mean apparent plasma clearance was 5.12 ± 2.23 SD L/hour 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/hour and mean terminal half-life was 11.9 hours.

The use of mean t½without inclusion of the standard deviation implies a lack of precision for this parameter, and with a lack of generalisability. In order to communicate this variability accurately to prescribers, any PK figures should include the range when presented as median values, and the standard deviation if mean values are provided.

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.

Drug interactions

The most important interaction is with CYP3A; *in vitro* data have shown that the metabolism of olaparib is predominantly via CYP3A. Drug interaction studies of the tablet formulation have shown that co-administration of olaparib with itraconazole, (a known potent inhibitor of CYP3A and P-gp) increased olaparib C_{max} and AUC by an average of 1.42 and 2.70 fold and that co-administration with rifampicin (a known potent CYP inducer) reduced olaparib C_{max} and AUC by an average of 71 and 87% respectively. It is therefore recommended that patients receiving olaparib are not treated with known potent inhibitors or inducers of CYP3A4.

Olaparib inhibited MDR1 and clinical interactions through inhibition of biliary or GI tract efflux of MDR1 substrates are possible. Olaparib also inhibited hepatic uptake transporters (OATP1B1 and OCT1) and renal uptake transporters (OCT2, OAT3, MATE1 and MATE2K) in vitro suggesting that drug interactions with substrates of these transporter proteins (for example statins, metformin, creatinine) could be possible. Clinical studies to investigate the magnitude of such an interaction have not been performed. The sponsor is requested to state what trials are underway to investigate this further, when they are likely to be completed (see *Questions for sponsor*, below).

Delegate comments on PI

While information on drug interactions is included in the PI, it is currently reported with a lot of other information which obscures this important prescribing advice. Therefore, the sponsor is requested to:

1. Prioritise the positive interactions (for example CYP3A4, MDR1) and advice regarding these first, including the impact on olaparib metabolism as well as induction of the enzyme.
2. include a list of medicines that should be avoided and include grapefruit, star fruit and Seville oranges in this list, and also include this information in the CMI (this is taken from Study 19 conditions).
3. provide information in the PI about drugs that are affected by MDR1 as this is not common knowledge.

The list stating the absence of interactions with other CYPs can then be stated after this.

Renal and hepatic impairment

The effects of renal or hepatic impairment on exposure to olaparib have not yet been studied. The Delegate notes that submission of the trials evaluating the PK of olaparib in these two conditions are post-marketing requirements mandated by the FDA, and the sponsor is required to submit these same final reports simultaneously to the TGA for evaluation as a Category 1 application (see conditions of registration).

These planned trials appear to be testing a single dose of 300 mg (presumed to be a tablet) given the wide individual variability in PK parameters, it is anticipated that there would need to be large numbers of patients and that clinical parameters may be more informative of the benefit-risk in these populations than any PK measurements or predictions based upon the single dose administered. It is recommended therefore, that if no significant adverse events are reported in these limited studies, that such patients be included in clinical trials where efficacy and safety endpoints are used to gather more meaningful information regarding the use of olaparib in such patients.

Given the failures of the population PK modelling, this would not be considered a suitable method of providing information on special populations and it is noted that the sponsor does not plan to continue with the model presented in this submission (see below).

Population PK analyses

The following is taken from the Population PK report for olaparib. It is presented italics to make the start and end of the excerpt clear:

> '*Summary of Findings: PK/PD Report*
>
> *The purpose of the population PK/PD analysis was to describe the relationship between olaparib exposure and inhibition of PARP-1 activity. Deficiencies in the quality of the data and model development process marred the quality of the PK/PD analyses. Consequently, the results should be interpreted qualitatively. Accordingly, the major finding of the analysis was that PARP-1 inhibition in PBMC increased with increasing olaparib plasma concentration.*
>
> *Implications of findings*
>
> *The PK, exposure-response and PK/PD (PARP-1) analyses conducted were not sufficiently rigorous to be applied quantitatively to inform the clinical pharmacology of olaparib or guide dosing in special populations. Therefore, the analyses had no implications for the Australian PI.*
>
> *No assessment of benefit-risk was possible based on the evaluated analyses.'*

The following is taken from the Pharmaceutical Subcommittee (PSC) minutes following the 24 November 2015 meeting:

The PSC supported the pharmacometrician's conclusions and advised that:

- batch variability is no longer an issue
- there was no useful information about covariates
- the 400 mg dose of olaparib was more effective
- there were no significant exposure AE-relationships.

The PSC noted that the draft PI did not make specific reference to data generated as part of the pharmacometric analyses and that the reporting of PK data is sparse. The PSC advised that the PK section could be expanded to include the study population and the observed variability reported in PK parameters (CL/F, V/F and estimated half-life) from the PopPK studies.

The uncertainties identified in the population PK studies mirror those presented in the overview above regarding the PK and PD data above. The Delegate has requested the sponsor include a statement at the start of the Pharmacokinetics section to reflect the limitations of any PK or PD data in the PI to inform prescribers.

Summary

The PK studies done to date leave significant uncertainties about the absorption, distribution and elimination of olaparib. There is a high degree of inter-individual variability in almost every PK parameter measured, and this has not been adequately explained nor conveyed in the PI (see PI changes). The intra-individual variability was less marked, which suggests an individual variation in the ability to absorb the micro emulsion preparation. Tumour levels of the drug deemed effective for PARP inhibition were reached across a range of doses but it is not clear if that is due to dose level or the systemic exposure. As with many of the PK parameters presented the explanations are inferred rather than established with direct evidence.

The population PK modelling yielded similarly highly variable results, requiring an inter occasion variable to be built in to predict more accurately and consistently. While it was considered established PARP inhibition increased in peripheral mononuclear blood cells

with increasing plasma concentration, a correlation with plasma levels and oral dose has not been established.

The uncertainties due to these highly variable parameters may impair the identification of a dose-dependent signal for efficacy and/or safety. The dissolution issues during early development, and also the large number of capsules currently required (8 capsules twice daily) may be resolved in future dose forms.

The PK and Drug Interaction section of the PI do not currently convey the uncertainties about the PK data, and lack clarity in providing clinically meaningful advice to prescribers about relevant drug interactions, respectively. Strategies such as dose reduction or withholding doses to manage toxicities are not reliably informed by the PK or PD data. Thus characterisation of the safety and efficacy of the drug, and generation of useful prescribing information, is reliant upon, and more informed by, monitoring of patients and the generation of signals in the clinical setting rather than being prospectively informed by PK and PD parameters. PI changes have been recommended to improve this.

It is noted, however, that efficacy (improved PFS) has been demonstrated at the 400 mg BD dose and is generally well tolerated with largely manageable side effects; therefore, these deficiencies do not preclude registration for the proposed usage.

Pharmacodynamics/dose selection

Primary pharmacology

Inhibition of PARP-1 activity was explored as a pharmacodynamic endpoint in both tumour and surrogate tissue (peripheral blood mononuclear cells - PBMCs) collected primarily from the patients dosed in Studies 02 and 07.

Study 02 (Study D0810C00002) was an open-label, dose-escalating, non-randomised, multi-centre Phase I study 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.

Enrolled: 99 patients, 77 female, 21 male; mean age 54.7 (19 to 82). 88.9% White.

60 (61.2%) patients had BRCA 1/2 mutations, 49 were ovarian cancer patients.

Completed: 98 patients.

Analysed: 98 patients for safety analysis set, 71 for efficacy data set.

Regimens were used incorporating a range of doses, either 14 days on, 7 days off or continuously: the lowest being 10 mg/day for 14/21 day cycles up to the highest of 600 mg BD continuously. Two dose limiting toxicities were encountered at the 600 mg BD dose level (CTCAE grade 4 thrombocytopaenia and CTCAE grade 3 somnolence) and therefore 400 mg BD was considered to be the maximum tolerated dose (MTD). The 200 mg BD dose level was selected for the expansion phase in this study and contained the most patients (58).

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. Of key relevance to the proposed treatment population, all observed RECIST responses occurred in patients with confirmed BRCA mutations (including 12 out of 49 with ovarian cancer) or a strong familial history of cancer. At the time of data cut-off (17 December 2008), 11 patients with BRCA 1/2 mutations were still receiving treatment.

Pharmacodynamic results

The % inhibition of PARP-1 activity ranged from 7% to 99% (mean = 68 % ± 25 SD) and showed no apparent relationship with dose. The PID range was determined to be at olaparib doses above 40 mg BD (although lower doses were not tested in this study).

The mean olaparib plasma concentration IC_{50} for inhibition of PARP-1 activity in PBMCs was estimated as 281 ng/mL. The level of PARP-1 inhibition achieved following dosing with olaparib was typically 50 to 60 %. The PBMC PARP-1 inhibition dose response curve appeared to be flat with moderate inter individual variability at the dose levels investigated (10 to 600 mg), the maximum drug effect appeared to have been achieved at olaparib doses ≥ 40 mg. For an approximate 65-fold AUC range, the maximum % PARP-1 inhibition increased only approximately 20 %. The data obtained for γH2AX foci induction in hair follicles was consistent with the PARP-1 inhibition data in PBMC samples and showed a rapid onset of effect after dosing, an effect that was sustained on continuous dosing and no apparent relationship between the magnitude of effect and the dose administered.

PARP-1 inhibition indicated that olaparib was acting as a PARP inhibitor but did not predict clinical response. There was no relationship between olaparib dose and the degree of PARP-1 inhibition, nor was there a correlation between PARP-1 inhibition and the clinical efficacy observed. Thus PARP-1 inhibition is not a predictive biomarker (maximal inhibition at 40 mg/day olaparib) and cannot fully explain the clinical benefit observed at much higher doses (200 mg/day and 400 mg/day). It is noted that this assay only measures PARP-1 inhibitory activity and olaparib is stated to inhibit PARPs 1, 2 and 3; therefore, it is possible that inhibition of these other enzymes is contributing to the efficacy observed. There may also be other mechanisms of action. The impact of metabolites of olaparib on DNA repair and other off-target effects are not known. The sponsor stated in the response that the low levels of the individual metabolites has made retrieval and further characterisation of such metabolites difficult.

Study 07 (Study D0810C00007)

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

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 randomised, 12 in each dose cohort, and all patients completed treatment.

Summary of pharmacodynamic results

The PARP-1 inhibition in the tumour sample and in the PBMC sample collected at the time of surgery was highly variable across samples. The PARP-1 inhibition 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.

Dose selection/dose response studies

The dose of olaparib 400 mg BD (capsule formulation) was selected based on toxicity (MTD 400 mg twice daily) and clinical benefit. There was no clear correlation between

dose, exposure and the degree of inhibition of PARP-1.This underscores that the PK and PD for olaparib are poorly understood, that the mechanism of action remains to be fully elucidated and an off-target mechanism of action cannot be excluded.

It is noted that a 300 mg BD dose (tablet formulation) is being used for clinical trials currently underway, but the sponsor has proposed the capsule formulation for registration.

Efficacy

Pivotal study

Study D0810C00019 was a Phase II randomised, double blind, multicentre study to assess the efficacy of 400 mg olaparib twice daily (capsule formulation) compared with placebo in the treatment of patients with platinum sensitive relapsed (PSR) high grade serous ovarian cancer, primary peritoneal or fallopian tube cancer (including patients with macroscopic peritoneal metastases outside the pelvis or distant metastases) following treatment with two or more platinum containing regimens. Following completion of chemotherapy, 265 patients were randomised to receive maintenance olaparib 400 mg twice daily (136 patients) or placebo (129 patients).

Although initially planned as a second co-primary endpoint, PFS in Homologous repair deficiency (HRD) population was not reported and this became an exploratory endpoint as the sponsor did not have a diagnostic method for determining this population. A retrospective analysis based on HRD determined on archived samples may become available in the future. BRCA status was used retrospectively as the only available test for a population with HRD.

The population with a BRCA mutation is a valid subset of HRD, but was determined retrospectively and therefore the results are not drawn from randomised data. It is also uncertain whether somatic BRCA mutated ovarian cancer would respond to therapies in the same was as gBRCA-mutated given the potential to revert to a wild type phenotype, as well as a greater potential for tumour heterogeneity. It is also likely, given other potential mutations or epigenetic causes of HRD, that there are other groups who might also have benefited.

The inclusion criteria state all patients must have received at least 2 prior platinum containing regimens. Those enrolled has received an average of 3 previous chemotherapy regimens (range 2 to 11) and 2.6 previous platinum-containing chemotherapies (range 2 to -8).

The large number of platinum containing regimens (up to 8) reflects the maintained sensitivity to this agent which is more often observed among women with a germline BRCA mutation. It is unclear whether this would be the case where there is a somatic BRCA mutation, due to tumour heterogeneity. The proposed indication does not specify the number of prior treatments, and consideration of this is given in the benefit risk discussion.

The statistical analysis plan was consistent with a proof of concept study: if the true HR was 0.75 and the overall Type I error rate was 20% (1 sided) that is, there would be approximately 80% power to demonstrate a promising difference in favour of olaparib.

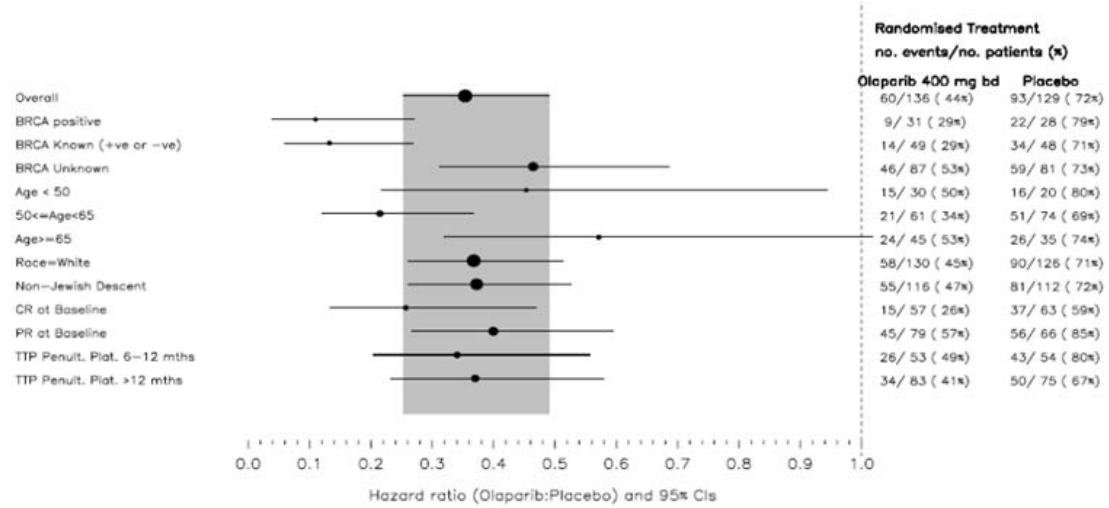
This is not a study designed for regulatory purposes, as it lacks power to demonstrate key endpoints. Furthermore, the lack of randomisation of the data supporting the proposed usage is a further weakness. Thus the totality of the data supporting efficacy and unmet need are requisite considerations for registration.

Primary endpoint

The primary endpoint was progression free survival (PFS) was based on an intention to treat (ITT) analysis. The median PFS was 3.6 months longer in the olaparib arm compared with the placebo group: 8.4 months (95% CI 7.4, 11.5 months) versus 4.8 months (95% CI 4.0, 5.5 months) in the placebo group; HR 0.35 (95% CI: 0.25, 0.49; p < 0.00001), indicating a 65% reduction in risk of disease progression or death in the olaparib group compared with the placebo group over the study period. A blinded, independent, central review of the data also showed results consistent with the investigator assessment (hazard ratio, 0.39; 95% CI 0.27, 0.55; p < 0.001).

The forest plot demonstrates that there was concordance across a range of subgroups, with the exception of those ≥ 65 years of age.

Figure 2: Forest plot of analysis of PFS by subgroup; FAS



Secondary endpoints

Overall survival: At the first analysis of OS there were 154 deaths out of 265 patients (initially planned to be analysed after 222 deaths or 85% of patients), median overall survival was 29.8 months (95% CI: 27.2 to 35.7 months) with olaparib and 27.8 months (95% CI 22.4 to 34.0 months) with placebo. The HR was 0.88 (95% CI: 0.64, 1.21; p = 0.438).

This study was not statistically powered to demonstrate an overall survival benefit at the time of the analysis of the primary endpoint PFS. Furthermore, any difference in OS between treatment arms cannot be ascribed solely to the effect of olaparib given the extensive treatment switching: 78.5% of patients in the olaparib arm and 87.8% in the placebo arm receiving subsequent treatments, with more than one third received more than 3 subsequent therapies. In the BRCA group, 22.6% went on to receive a PARP inhibitor. Crossover to olaparib was not permitted within the study design.

- Objective response rate (RECIST 1.0 criteria): Partial response rates were slightly higher in the olaparib arm: 12.3% versus 4.2%.
- Disease control rate: 52.9% and 24.8% patients had disease control (confirmed CR + confirmed PR + SD + NED) at 24 weeks in the olaparib and placebo groups, respectively.
- Duration of response: There were too few responders to assess this.
- Tumour size: Tumour size was evaluated in less than half the patients in either arm (57 patients in the olaparib group and 48 patients in the placebo group), and at

24 weeks, there was a statistically significantly lower mean percentage tumour growth in the olaparib (n = 56, LS mean = 0.0%) compared with placebo group (n = 47, LS mean = 33.5%) (Difference in LS means = -33.4; 95% CI: -59.4, -7.4; p = 0.01221).

- CA 125 response (GCIG criteria): One patient in each group had a CA 125 response but the numbers with raised CA 125 were small. There was no statistically significant difference between the 2 treatment groups in combined RECIST and CA 125;[30] response (odds ratio 2.47, p = 0.18155).
- Time to progression based on CA 125 (GCIG criteria): Median time to progression was 8.3 months in the olaparib group compared with 3.7 months in the placebo group; a 4.6 month longer median time to progression in the olaparib group. The HR was 0.35 (95% CI: 0.25, 0.47; p < 0.00001), consistent with PFS results (primary endpoint).
- Identification of Homologous Recombination Deficient (HRD) subset of tumours: Olaparib demonstrated a PFS benefit in the maintenance treatment of the 36.2% of patients with BRCA mutated ovarian cancer (HR 0.18; 95% CI 0.11-0.31; p < 0.00001; median 11.2 versus 4.3 months). The efficacy of olaparib in patients with gBRCA mutation was similar to that observed in patients with BRCA mutation (germline and/or tumour mutation).

The number of patients who completed QOL was 226 for trial outcomes index (TOI) and 225 for Functional Assessment of Cancer Therapy – Ovarian (FACT-O), and there was no significant difference between the scores for either for the two treatment arms.

Exploratory endpoints

While the following exploratory endpoints were reported to have a p value < 0.00001, the nature of this endpoint precludes statistical significance being demonstrated or claimed. Thus it is not considered appropriate to include them in the PI. See PI Changes.

Table 15: Exploratory analyses: TDT, TFST and TSST: FAS (taken from p105 CHMP report)

Analysis	Events:Patients	Median time	HR	80% CI	95% CI	p-value
Time to discontinuation of olaparib/placebo treatment (TDT)	Olaparib: 113:136 (83.1%)	8.6	0.39	0.33, 0.47	0.30, 0.51	<0.00001
	Placebo: 125:128 (97.6%)	4.6				
Time to first subsequent therapy or death (TFST)	Olaparib: 95:136 (69.9%)	13.4	0.40	0.33, 0.48	0.30, 0.52	<0.00001
	Placebo: 118:128 (92.1%)	6.7				
Time from randomisation to start of second subsequent therapy (TSST)	Olaparib: 88:136 (64.7%)	19.1	0.53	0.44, 0.64	0.40, 0.71	0.00001
	Placebo: 108:128 (84.4%)	14.8				

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

BRCA subgroup: 74 (54%) patients in the olaparib arm and 62 (48%) in the placebo arm had BRCA mutations either detected as germline or somatic mutations in tumours.

95% confidence intervals for the analyses of median PFS and OS are not provided on these nonrandomised datasets.

[30] CA 125: Cancer antigen (CA)-125 (tumour biomarker)

Determination of BRCA status: BRCA mutation testing was not mandatory for patients to participate in the study, and for some was known prior to enrolment. Where undertaken, BRCA mutation status was determined by BRCA testing (integrated BRCA analysis assay) of blood samples or next generation sequencing of tumour specimens.

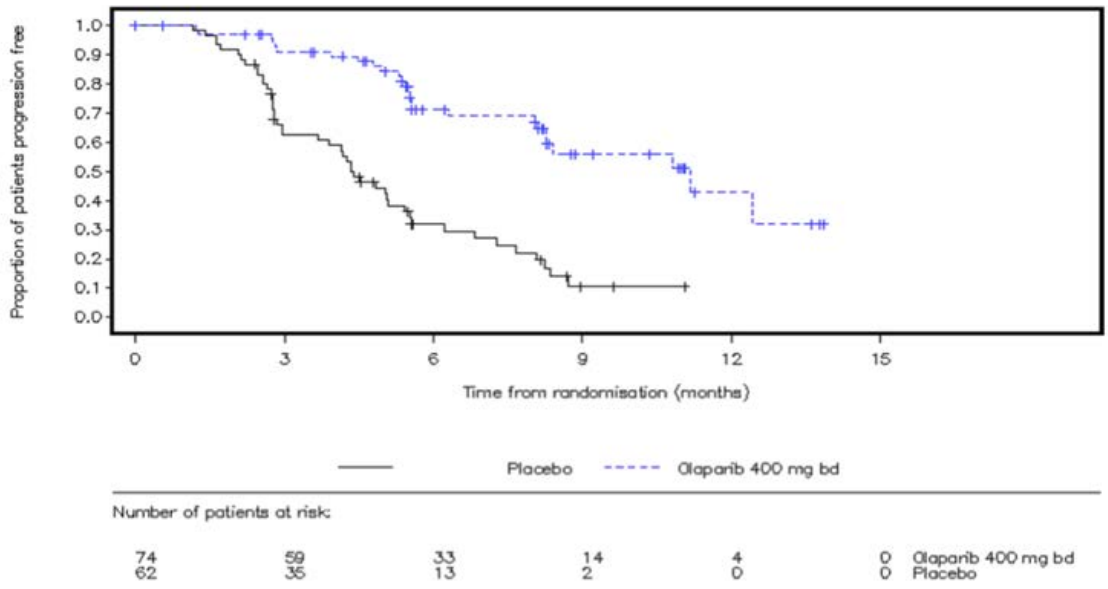
The sponsor combined available data for germline BRCA mutation status and tumour BRCA mutation status provided from the various sources and re-classified the data into the categories listed below to define the subgroups for analysis:

1. BRCA mutated: a deleterious or suspected deleterious mutation identified via germline testing, or in the tumour
2. BRCA wildtype/BRCA unknown (variant of unknown significance; VUS): not BRCA mutation-positive on germline or tumour testing
3. BRCA missing: patients who were not classified as BRCA mutated, BRCA wildtype/BRCA unknown (VUS) without a complete BRCA test report and did not have BRCA result recorded from tumour analysis or a BRCA result recorded in the case report form (CRF).

Progression free survival: Median PFS was 6.9 months longer in the olaparib arm compared with the placebo arm: 11.2 months in the olaparib group compared with 4.3 months in the placebo group (HR: 0.18; 95% CI: 0.18, 0.31; p < 0.00001).

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 to 0.40; p < 0.00001; median not reached versus 4.8 months).

Figure 3: Kaplan-Meier plot of progression free survival for the olaparib 400 mg BD and placebo groups; patients with BRCA mutation



Overall survival: The median OS in patients with BRCAm;[31] was not statistically significantly increased in an analysis performed at 52% maturity: 34.9 months for olaparib and 31.9 months with placebo.

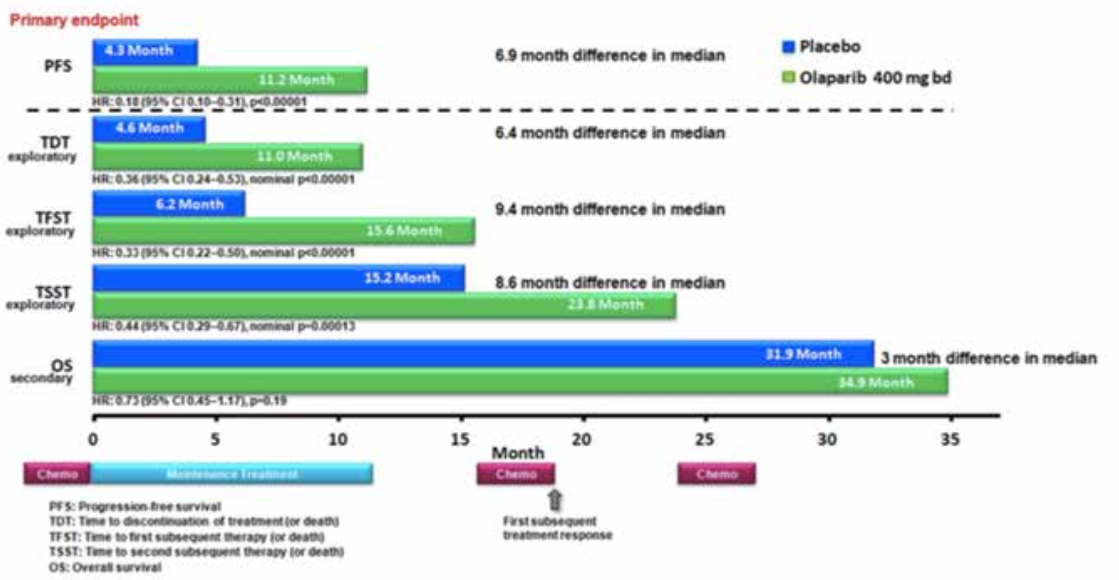
Discontinuation of olaparib/placebo treatment: The median time to discontinuation of olaparib/placebo treatment mirrored the PFS results: 11.0 months in the olaparib group and 4.6 months in the placebo group (HR of 0.36: 95% CI 0.24 to 0.53; p < 0.00001).

[31] BRCAm: gBRCA and/or tBRCA mutated

Consistent with progressive disease, the commencement of the next therapy followed soon after (the median time to first subsequent therapy was 15.6 months in the olaparib group and 6.2 months in the placebo group (HR 0.35: 95% CI 0.23 to 0.52; p < 0.00001).

Median time to second subsequent therapy or death was 23.8 months in the olaparib group and 15.3 months in the placebo group (HR 0.46: 95% CI 0.30 to 0.70; p = 0.00027).

Figure 4: Study 19; graphical summary of efficacy results in BRCA mutated patients



Quality of life: In patients with BRCA mutated tumours, there was a non-significant change in best response for Total FACT-O compared with the placebo group. Time to worsening on TOI was numerically longer for olaparib-treated patients than placebo treated patients, however there was no statistically significant difference between treatment groups (HR 0.8, 95% CI 0.48 to 1.34; p = 0.39521).

Table 16: 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%)

BRCA mutation is a rational choice as one potential biomarker for HRD but absolutely, there is a small proportion (136/265) with known status in this clinical trial, particularly for those with somatic BRCA-mutated tumours (n = 18). The data on this subgroup is not randomised. While there is an observational improvement in PFS, it is not accompanied by an improvement (or detriment) in OS. The quality of life measures do not indicate a significant benefit or a detriment. Beyond this population, in the absence of further known biomarkers at the time of the study, it is difficult to identify a population who might benefit from olaparib. This is reflected in the Delegate's modified indication.

In the 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 (SOLO-2) is ongoing with an expected completion of enrolment 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 (albeit an earlier population) and submission of this study for evaluation as soon as the CSR is available is a condition of registration (See Conditions of Registration).

For the majority of patients, the BRCA mutation was germline, and it could be postulated that ongoing benefit is more likely in this group than in the small proportion of patients with somatic BRCA mutations tumours, due to greater stability and persistence of the mutation and lesser intra and inter lesional heterogeneity with respect to BRCA status in the former. It is plausible that sBRCA mutated tumours will respond but the duration and degree of response is uncertain and needs further investigation. It is stated in the CHMP report that a randomised Phase III trial in this particular BRCA sub group of ovarian cancer patients is planned (Study SOLOIST). The sponsor is requested to provide an update on when this study is planned, and likely completion dates (See *Questions for sponsor*).

Additional efficacy studies

Study D0810C00009

Study D0810C00009 was a Phase II, open label, comparative, multicentre study to assess the efficacy and safety of olaparib at 2 dose levels in 58 patients with BRCA1 or BRCA2 associated ovarian cancer. Two sequential patient cohorts received continuous oral olaparib in 28 day cycles initially at 400 mg BD and subsequently at 100 mg BD.

Primary efficacy result: The ORR (RECIST) was 35.5% at 400 mg BD and 13.6% at 100 mg BD.

Secondary efficacy outcomes: Secondary efficacy outcomes: clinical benefit rate, duration of response, maximum change in tumour size, progression-free survival and patient-reported outcomes.

Overall clinical benefit rate (CR + PR + SD) was greater in the 400 mg BD group than in the 100 mg BD group (71.0% versus 45.5%). SD = stable disease for ≥ 8 weeks ± 1 week visit window.

The median 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 226.0 (105to 338) days in the 400 mg BD group and 62.5 (56 to 113) days in the 100 mg BD group.

This study demonstrates single agent activity of olaparib in a heavily pre-treated population, and gives support to dosing at 400 mg BD. The latter is important given the absence of PK, PD data to support the higher dose level.

Study D0810C00012

Study D0810C00012 was a Phase II, open label, randomised, comparative, multicentre study to compare the efficacy and safety of 2 different doses of olaparib (200 mg BD and 400 mg BD) versus liposomal doxorubicin in patients with BRCA1 or BRCA2 associated ovarian cancer who have failed previous platinum based chemotherapy; and half were platinum resistant. Treatment switching in to the doxorubicin arm to olaparib was permitted upon demonstrated radiological progression (14/32 patients did so during the study).

Primary efficacy result: For the primary endpoint, there was no statistically significant difference between olaparib monotherapy and liposomal doxorubicin (HR 0.88, 80% CI:

0.62 to 1.28, p = 0.6604). The median PFS was 8.8 months, 6.5 months and 7.1 months for olaparib 400 mg BD, 200 mg BD and liposomal doxorubicin respectively.

Secondary efficacy variables: 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 the olaparib group and the liposomal doxorubicin group for any of the parameters: objective response rate, disease control rate, duration of response, tumour size, CA 125 levels, overall survival, and quality of life.

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.

Study D0810C00020

Study D0810C00020 was a Phase II, open label, non-randomised correlative study of olaparib as a single agent given 400 mg BD to patients with recurrent triple negative breast or ovarian cancer. This study enrolled both patients with a BRCA 1 or BRCA2 mutation and non-carriers. 15/65 patients were enrolled with ovarian cancer had a BRCA mutation. The primary endpoint was OR. Secondary end points included identification of markers of olaparib efficacy through analysis of tumour material, PFS, safety and tolerability.

There are very few patients with a BRCA mutated ovarian cancer to inform regarding the proposed indication but the result for the primary endpoint in the ovarian cancer population is generally supportive of the propose usage: the response was 41.18% (95% CI 21.6, 64.0) for patients with a BRCA mutation and 24% (95% CI 13.9, 39.7) for patients without a BRCA mutation.

Study D0810C00041

Study D0810C00041 did not provide direct evidence of efficacy for the proposed usage as the study included treatment in combination with carboplatin and paclitaxel followed by maintenance olaparib, versus a carboplatin given at a different dose with paclitaxel and no olaparib and without maintenance; the maintenance phases are comparable for safety purposes although may be affected by prior treatment toxicities. A further limitation is that BRCA mutation status was only known or identified in 41/162 patients, thus limiting the conclusions that can be drawn to support the proposed usage.

Study D810C000042

Study D810C000042 was a Phase II, open label, non randomised, non comparative, multicentre study to assess the efficacy and safety of olaparib in patients with advanced cancers who had a confirmed BRCA1 and/or BRCA2 mutation. Patients received olaparib 400 mg BD and continued until disease progression. In total 317 patients were recruited, 298 received treatment, 193 with ovarian cancer. The primary endpoint is RR. Secondary endpoints include: ORR, PRS, OS, DoR, DCR.

Primary efficacy result: For the ovarian cancer group 60/193 patients responded (including 6 patients who had a CR), giving an ORR of 31.1% (95% CI 24.64, 38.13). The PFS in this study for the ovarian cancer group was 7.03 months. The response rate data were varied according to the malignancy, with highest response rates in the BRCA mutated prostate cancer patients and the lowest in breast cancer and the 'other cancer' group.

Secondary efficacy results: The secondary efficacy results were more difficult to interpret given there was no control group.

The statistics are descriptive in nature due to the non randomised nature of the data but the response rate in a platinum-refractory/resistant population with a poor likelihood of response to standard therapy lends support to the efficacy of olaparib monotherapy in BRCA mutated ovarian cancer.

Safety data

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; of these, 735 had received 400 mg BD schedule, including 397 women with BRCA mutated ovarian cancer (a further 20 had received monotherapy following chemotherapy in Study 41(Study D0810C00041). Randomised data are available from patients in Study 19 and the maintenance phase of Study 41, with subsets of these patients.

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. Overall the incidence of AEs of any kind was very similar between the safety set and the BRCAm population. The age range exposed was from 21 to 89 years.

The majority of patients had ovarian cancer, with 54% also having a BRCA mutation (proposed population); but the safety information from the other malignancies is also relevant in informing of the risks associated with treatment.

Of note, it is the capsule formulation being assessed here so the relevance and generalisability of this safety set for the tablet formulation currently being used in Phase III trials which the sponsor reports is not bioequivalent, could be undermined.

The median duration of treatment (see Table 15) is between 3 and 6 months in the general safety set, but longer in the BRCAm ovarian cancer patients (9 to 12 months in Study 19; see Table 16) likely reflecting the benefit in this group as well as in the natural history of the disease in this subpopulation compared with, for example, pancreatic and gastric cancers. Issues such as treatment discontinuation rates, median duration of exposure will thus only be considered in the BRCAm ovarian cancer population.

Table 15: 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

Olaparib is reasonably well tolerated as evidenced by the median duration of treatment, although dose reductions were required as indicated by the lower median duration at starting dose. Little can be determined about long term tolerability due to progression of the disease although the range extends to 1331 days in the BRCAm subgroup.

Table 16: Duration of treatment; Study 19, Safety analysis set

	All patients		mBRCA	
	Olaparib 400mg bd	Placebo	Olaparib 400mg 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 (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 (std 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.

Adverse events

Treatment emergent adverse events were common and spread across a range of systems, consistent with the advanced stage of cancer being treated. Rates of AEs among those receiving olaparib were comparable regardless of BRCA mutation status. In Study 19, 89.7% of events were attributed to olaparib compared with 72.7% in the placebo arm. The most common adverse events reported were predominantly gastrointestinal (nausea, vomiting, diarrhoea and constipation) or haematological (anaemia) and fatigue. The most frequent Grade 3/4 AEs can be seen in Table 17 with the most common being haematological with anaemia (when including the term 'haemoglobin decreased') occurring in 15.3%. The gastrointestinal events could be related to the study drug as well as the underlying condition.

Similar patterns of adverse events occurred in the maintenance phase of the Study 41. In this study 2 patients in the olaparib arm developed myelodysplastic syndrome compared with one in the control arm.

The Precautions section of the PI does not adequately inform regarding the potential severity or frequency of the anaemia observed (5.1% Grade 3 or 4 in the treatment arm in Study 19). This is inconsistent with the Adverse Drug Reactions table.

Table 17: 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.

Table 18: 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

Treatment-related adverse events (adverse drug reactions)

When standardised against duration of exposure in Study 19, the following occurred more frequently in the treatment arm compared with the placebo arm: nausea, vomiting,

anaemia, upper abdominal pain, dyspepsia and dysgeusia. Fatigue, decreased appetite, headache and dizziness were reported more frequently with olaparib treatment compared with placebo during the first 0 to 3 months and/or 3 to 6 months on study, although the numbers affected by these were small in each arm. 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 program (Study 12 (Study D0810C00012) and 41). Stomatitis occurred more frequently on olaparib, as did muscle spasms (9.6% versus. 3.9%).

Table 19: 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

AEs of special interest

MDS/AML

As of the data cut-off (DCO) of 1 October 2014, 21 reports of MDS/AML (22 stated in the FDA Clinical Reviewer report, accessed on FDA website, 14 December 2015) have been received out of a total of 3020 patients estimated to have received olaparib, giving an estimated cumulative incidence of 0.7% for MDS/AML. One additional report of MDS has been received from a blinded study in which the treatment of the patient (olaparib or placebo) is unknown, and if this patient were to have been on olaparib, the estimated incidence would be 0.73%. Of these 22 cases, 18 patients died, with MDS/AML listed as a primary or secondary cause of death in 12 cases. The duration of therapy ranged from less than 6 months to more than 2 years.

16 (17 in the FDA Report) of the cases were in patients with BRCA 1 or 2 mutations, with all but 5 reported to be fatal. In randomised trials, the cumulative incidence in patients with BRCA mutations was 1.1% compared with 0.6% for control arms.

A causative or contributing role for olaparib cannot be excluded, but these patients had all received chemotherapy with DNA damaging agents, which is an independent risk factor. It is plausible that the combination of DNA damaging agents, germline BRCA deficiency, followed by a pathway repair blocking agent act synergistically resulting in the development of MDS/AML. This is the subject of active pharmacovigilance (see conditions of registration) and is listed as an important potential risk. Randomised controlled data from the SOLO-2 trial will help clarify, although these patients will have received much less chemotherapy due to it being a trial of olaparib maintenance after first line chemotherapy.

The PI does not currently accurately convey the risk of death associated with this complication, nor are the rates of MDS/AML in patients with germline BRCA mutations mentioned. See PI Changes, and equivalent information should be included in the CMI.

Second malignancy

As of the DCO of 1 October 2014, 23 events (in 21 patients) of new malignant tumours have been received out of a total of 3020 patients estimated to have received olaparib, giving an estimated cumulative incidence of 0.71%. One additional report of a second malignant tumour has been reported in the placebo arm of Study 19 (1/128 [0.78%]). In the randomised controlled studies, 5 reports of new primary malignancy have occurred in the olaparib arm and 1 in the placebo arm.

No clear pattern in these second malignancies allows attribution of causality to olaparib, especially considering the enrichment for those with a BRCA mutation and the associated increase in risk for further cancers. No PI statement is required at this stage, and this is listed as an important potential risk in the RMP.

Pneumonitis

As of the DCO of 1 October 2014, 13 patients have reported pneumonitis out of a total of 3020 patients estimated to have received olaparib, giving an estimated cumulative incidence of 0.43%. Three additional reports of pneumonitis have been received from 2 blinded studies, where the treatment of the patients is unknown. If these patients were considered to have been on olaparib treatment, the estimated cumulative incidence would be 0.53%. There were 2 deaths from pulmonary insufficiency. The majority of these events occurred early in treatment with the greatest number occurring with < 3 months and almost all < 6 months of treatment with olaparib (or placebo).

The PI statements are appropriate.

Discontinuation due to adverse events

Discontinuation due to adverse events were uncommon in both arms of Study 19: 4.4% and 1.6% of patients receiving olaparib and placebo, respectively.

This indicates that olaparib was relatively well tolerated, and would suggest that clinical management strategies for the adverse events encountered is effective.

Deaths, serious adverse events

Two deaths in Study 19 were attributed to olaparib have occurred as a result of an AE: one case of haemorrhagic stroke with thrombocytopaenia, and MDS. Of the remaining 14 deaths reported in the pooled dataset, there were other potential contributing factors.

The PI Precautions section needs to state the fatality in the Haematological toxicity section due to thrombocytopaenia (see PI changes).

As with Study 19, the most common system organ class (SOCs) reported for serious adverse events (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% versus 18.4% in the overall population; 27.7% versus 21.6% in the BRCAm subgroup), this could reflect the more advanced stage of disease and inherently poorer prognosis of patients included in the pool (data cut-off 26 November 2012).

In the Study 41, serious AEs were reported in 10.6% of patients treated with olaparib compared with 7.3% in the placebo group. This included 3 MDS were observed in the olaparib arm, one resolved and 2 unresolved; one fatal case of DIC (disseminated intravascular coagulation) in a patient also having MDS was considered as related to study drug.

Table 20: Study D0810C00019 Deaths and SAE

Category	Olaparib 400mg bd N=136	Placebo N=128	BRCAm Olaparib 400mg bd N=74	BRCAm Placebo N=62
Total deaths	86 (63.2)	93 (72.7)	42 (56.8)	41 (66.1)
Death from disease under investigation	77 (56.6)	87 (68.0)	37 (50.0)	37 (59.7)
AE with outcome= death	1 (0.7)	0	1 (1.4)	0
Death related to disease and an AE with outcome = death	1 (0.7)	0	0	0
Other deaths	7 (5.1)	6 (4.7)	4 (5.4)	4 (6.5)
SAE	25 (18.4)	11 (8.6)	16 (21.6)	6 (9.7)

Clinical laboratory tests

Haematological abnormalities were very common and are discussed above. There were no changes to suggest that olaparib causes liver injury, and there were mild changes in creatinine which should be monitored.

Special groups

There is limited experience in the elderly with only 34/735 patients being over 75 and 114/735 being 65 to 74.

Safety and efficacy are not established in men and this needs to be stated in the PI.

There are currently no data to provide prescribing advice for patients with renal or hepatic impairment.

Electrocardiograph/cardiovascular

The studies were carried out with the 300 mg tablet formulation which is neither the formulation nor the dose proposed here. This study did not identify that olaparib is associated with QT prolongation although a single case of QT prolongation was noted in combination with itraconazole, emphasising the need to avoid concomitant use with strong CYP3A4 inhibitors.

Safety discussion

The safety of olaparib is supported by the overall low rates of study withdrawals and the mild to moderate severity of most of the AEs. Many of the AE are transient, mild and able to be managed with simple supportive measures. The most common side effects attributable to olaparib include anaemia, nausea, fatigue / asthenia, diarrhoea, anorexia, dyspepsia, upper abdominal pain, stomatitis, headache, dysgeusia and dizziness. However, the fatality secondary to thrombocytopaenia in Study 19 indicates the importance of close monitoring. A major potential safety signal, particularly in those with a germline BRCA mutation, is MDS/AML. Although there have been other potentially confounding factors, 17/22 cases occurred in patients with a germline mutation and of the 22 cases, most were fatal. Other potentially fatal complications of treatment include pneumonitis.

Given this is a maintenance treatment; there is relatively limited long term follow up data. Further information will become available when the SOLO-2 randomised controlled trial reports and submission for evaluation is a condition of registration.

Risk management plan

A number of recommendations for the RMP have been provided by the RMP evaluator and the sponsor should address these matters in the Pre-ACM Response and follow up where appropriate with the TGA.

Risk-benefit analysis

Delegate's considerations

Advanced ovarian cancer is an incurable for which there are limited treatment options. Olaparib offers a plausible mechanism of action for delaying progression of disease in those with a BRCA mutation, which is the population for whom registration is sought. There is a lack of randomised controlled data in support of the proposed indication; however, the totality of the data supports there being efficacy in BRCA mutated ovarian cancer patients. Additional information for both safety and efficacy will be provided from the SOLO-2 trial. There is some uncertainty about the treatment response rates and duration of response in those with somatic BRCA mutations compared with germline mutations and studies are planned to address this (SOLOIST). Overall the treatment was well tolerated with most side effects manageable.

There is a limited understanding of the pharmacokinetics and pharmacodynamics to provide specific information to prescribers about the benefit of dose reductions or delays

in managing these. There is wide inter-individual variability, and lesser but still clinically relevant intra individual variability in the PK and PD data presented, which significantly limits the utility and generalisability of the data obtained. This may well limit the generalisability of any PK data from studies in those with renal or hepatic impairment. Given the degree of variability, it is anticipated that there would need to be large numbers of each patient group, with individual data collected serially over time, and correlated with clinical parameters. This is likely to be more informative of the benefit-risk in these populations than pharmacokinetic predictions based upon a single dose administered.

Serious adverse events include the development of MDS/AML and there is some uncertainty about the role of olaparib in the observed increase in cases in the clinical trials. It is plausible that an agent blocking DNA repair would increase the risk of deleterious mutations causing transformation to a malignant phenotype, especially during or following chemotherapy with DNA damaging agents or radiation therapy. It is unclear whether the risk would increase with more lines of therapy prior to initiation of olaparib maintenance therapy or if this were re-introduced following relapse after first usage; thus, the optimal timing of olaparib usage has not been determined. Pharmacovigilance and further randomised studies will help clarify this, but given the seriousness of the disease under treatment, the risk is considered acceptable if patients are informed. The PI information is adequate in this regard.

There are currently no data on the use of olaparib as maintenance treatment for patients who are in response (complete or partial) following just one cycle of platinum based chemotherapy, as the inclusion criteria for the pivotal trial required two prior treatments. The sponsor's current indication would allow introduction in an earlier line of treatment without any efficacy or safety data to support this usage; it is noted there is a Phase III trial underway; SOLO-1 with ClinicalTrials.gov identifier number NCT01844986, to assess the benefits and risks in this population, using the 300 mg tablet formulation given twice daily. Thus the Delegate proposes modification of the proposed indication to reflect the evidence currently presented, and on which the decision was based. Results from SOLO-1 may support an extension of the currently supported indication to use after first line chemotherapy in the future.

Both the sponsor's and the Delegate's proposed indications are restricted already to a pre-specified subgroup of the original study population, that is, those with ovarian cancer associated with a BRCA mutation. This represents a group where a clinical benefit was identified, and the proposed mechanism of action is plausible. The small numbers in the clinical trials are consistent with the orphan designation of the drug, and there are confirmatory trials underway in this population, and in subsets of the target population (for example those with somatic BRCA mutations) to inform further the benefit-risk equation.

Subject to incorporation of the proposed PI changes which provide more detailed information for prescribers, agreement to the proposed conditions of registration and subject to the TGA having no outstanding issues with the pharmaceutical chemistry, the Delegate considers there to be a positive benefit risk for the patient group described in the Delegate's modified indication, based on unmet clinical need.

Proposed action

The Delegate had no reason to say, at this time, that the application for olaparib should not be approved for the following modified indication:

> *Olaparib is indicated as monotherapy for the maintenance treatment of patients with platinum-sensitive relapsed BRCA-mutated (germline or somatic) high grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response*

(complete response or partial response) after platinum based chemotherapy. Prior treatment must have included at least 2 courses of platinum based regimens.

Data deficiencies/limitations

1. There are no randomised, controlled data in support of the proposed indication.
2. There have been no studies reported for those with renal or hepatic impairment. The planned trials appear to be testing a single dose of 300 mg; given the wide inter individual variability in PK parameters, it is anticipated that there would need to be large numbers of patients and that clinical parameters may be more informative of the benefit-risk in these populations than predictions based upon dose administered. It is recommended therefore, that if no significant adverse events are reported in these limited studies, that such patients be included in clinical trials where efficacy and safety endpoints as well as PK and PD data are used to gather more meaningful information regarding the use of olaparib in such patients.
3. Given the failure of the population PK modelling, this would not be considered a suitable method of providing information, particularly for special populations.
4. There are no data to support retreatment with olaparib as maintenance following progression on that treatment. This must be stated in the PI, and it is appropriate to include this in both the Clinical Trial section and the Dosage and Administration section.

Questions for the sponsor

1. Olaparib inhibited multidrug resistance protein 1 (MDR1) and clinical interactions through inhibition of biliary or GI tract efflux of MDR1 substrates are possible. Olaparib also inhibited hepatic uptake transporters (OATP1B1 and OCT1) and renal uptake transporters (OCT2, OAT3, MATE1 and MATE2K) in vitro suggesting that drug interactions with substrates of these transporter proteins (for example statins, metformin, or creatinine) could be possible. Clinical studies to investigate the magnitude of such an interaction have not been performed. The sponsor is requested to state what trials are underway to investigate this further, when they are likely to be completed.
2. The sponsor is requested to provide 95% confidence intervals for the median PFS in those with BRCA mutated tumours.
3. The sponsor is requested to provide an update on when the randomised Phase III trial in these patients with sBRCA mutated ovarian cancer patients is planned and likely to be completed (Study SOLOIST).

Conditions of registration

The following are proposed as conditions of registration:

1. Implementation of the RMP (Version 5, dated 3 November 2014, data lock point 20 May 2014) with Australian Specific Annex (Version 1, dated 5 November 2015) and any future updates as a condition of registration.
2. Submission of the following clinical trial(s) as Category 1 submissions within 6 months of completion which were designed to evaluate:
    a. the progression free survival (PFS) and overall survival (OS) analyses with datasets from clinical trial D0818C00002
    b. the progression free survival (PFS) and overall survival (OS) analyses with datasets from clinical trial D0816C00010
    c. the 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 (SOLO-2)

3. Collect and analyse all cases of acute myelogenous leukaemia/ myelodysplastic syndrome identified in patients treated with Lynparza (olaparib), on an annual basis. These interim reports should summarise all cases identified up until that reporting date (new cases and those reported in previous years), and should include patients treated with Lynparza on clinical trials and outside of clinical trials (including spontaneous safety reports) to provide an accurate assessment of the long term incidence and risk of AML/MDS. These should be submitted to the TGA pharmacovigilance branch.
4. At the time of submission of the final reports to the FDA, the sponsor is required to submit to the TGA:
    a. The same final report for Trial D0816C00006 entitled, 'An open-label, non-randomised, multicentre, comparative, and Phase I study of the pharmacokinetics, safety and tolerability of olaparib following a single oral 300 mg dose to patients with advanced solid tumours and normal renal function or renal impairment'.
    b. The same final report for Trial D0816C00005 entitled, '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 dose to patients with advanced solid tumours and normal hepatic function or mild or moderate hepatic impairment."

Request for ACM advice

The Delegate did not refer this application to the Advisory Committee on Medicines (ACM) for advice.

Response from sponsor

The sponsor received the Delegate's overview for the above submission on 15 December 2015. Please see our responses to the requests below.

Question 1

Olaparib inhibited multidrug resistance protein 1 (MDR1) and clinical interactions through inhibition of biliary or GI tract efflux of MDR1 substrates are possible. Olaparib also inhibited hepatic uptake transporters (OATP1B1 and OCT1) and renal uptake transporters (OCT2, OAT3, MATE1 and MATE2K) in vitro suggesting that drug interactions with substrates of these transporter proteins (for example statins, metformin, or creatinine) could be possible. Clinical studies to investigate the magnitude of such an interaction have not been performed. The sponsor is requested to state what trials are underway to investigate this further, when they are likely to be completed.

Sponsor response

There are ongoing discussions regarding other studies, but currently there are no trials ongoing to investigate this further.

Question 2

The sponsor is requested to provide 95% confidence intervals for the median PFS in those with BRCA mutated tumours.

Sponsor response

Please refer to Table 21 which reports the interval as 8.3 – not calculated (NC) for olaparib and 3.0 – 5.4 for placebo. 'NC' means that the number was not calculated as it was not reached at the time of data analysis.

Table 21: Median and 95% CI (months) for PFS, TFST, TSST, OS and TDT; Full analysis set, Study 19

From IEMT 294:

AstraZeneca D0810C00019
IEMT request for Lancet publication
Table 1 Median and 95% CI (months) for PFS, TFST, TSST, OS and TDT
Full Analysis Set

Endpoint	Subgroup		Olaparib	Placebo
PFS	Full Analysis Set	Total number of patients	136	129
		Total number of events	60	94
		Median (months) [a]	8.4	4.8
		95% confidence interval [a]	7.4, 11.5	4.0, 5.5
	BRCA mutant	Total number of patients	74	62
		Total number of events	26	46
		Median (months) [a]	11.2	4.3
		95% confidence interval [a]	8.3, NC	3.0, 5.4

Question 3

The sponsor is requested to provide an update on when the randomised Phase III trial in these patients with sBRCA mutated ovarian cancer patients is planned and likely to be completed (Study SOLOIST).

Sponsor response

The sponsor would like to provide an update on the requested Study D0816C00009 (SOLOiST trial). The current proposed fist subject in date is second quarter 2016, with the study report being available in the first quarter 2019.

Conditions of registration

The sponsor accepts the proposed conditions of registration. However we make the following requests regarding conditions 2a, 2c and condition 3.

Condition 2a

Condition 2a refers to clinical trial D0818C00002. The sponsor has not conducted a trial with that code. Reference to this trial was made in the FDA approval letter (attached for reference) but this is a typographical error. The sponsor is however conducting trial D0816C00002, which is the SOLO-2 study. Thus it appears that Condition 2a and Condition 2c may refer to the same clinical trial and therefore one of the two conditions should be deleted.

Condition 2c

- At this time it is unclear when the first Category 1 submission should be made for the SOLO-2 trial given there is an interim PFS analysis in Q2/2016 and the final report with OS analysis in Q3 2019 (see dates in FDA approval letter). If the Delegate's intention is that a category 1 submission be done with the SOLO-2 trial interim PFS data, this has implications for ensuing extension of indication (EOI) submissions for advanced breast cancer (ABC) and first line ovarian cancer (1L OC).
  - The SOLO-2 study is conducted with Lynparza tablets (not capsules) and thus a SOLO-2 submission will be a new product application as well as a Clinical Trials update. As studies for ABC (Study OLYMPIAD) and 1L OC (Study SOLO-1) are also to be conducted with the tablets, the Lynparza tablets (via the SOLO-2 submission) would have to be approved before EOI submissions could be started;

  - Given current projected timings for completion of Studies SOLO-2, OLYMPIAD and SOLO-1, delays to EOI submissions for ABC and 1L OC would be in the vicinity of 6 to 12 months, thus delaying availability of Lynparza for those patients (please note that this is an approximation as all studies concerned are event driven).

- The sponsor understands the importance of the SOLO-2 study in confirming PFS seen in Study 19. With this in mind, but also taking into account the wish to make Lynparza available to ABC and 1L OC patients as soon as possible, we propose to the Delegate that the sponsor provides the SOLO-2 interim PFS analysis to the TGA at the same time that it is provided to the FDA but not as a category 1 application. On TGA review of the SOLO-2 trial PFS data, we accept that a submission could be subsequently requested by the TGA and we would undertake such a submission if requested.
- Alternatively, an allowance of 18 months instead of 6 months would be beneficial (this could be in addition to provision at the same time as FDA provision as in 2.).
- If the Delegate is agreeable to the proposal in 2 and 3, this would allow the sponsor to submit the SOLO-2 trial PFS interim analysis as part of a larger Category 1 extension of indications submission with the OLYMPIAD and SOLO-1 trials approximately 6 to 12 months later.
- If the Delegate's intention was a Category 1 submission based on the SOLO-2 trial final report in Q3 2019, this will not create the difficulties outlined above.

Whilst the sponsor requests the Delegate to consider our proposals outlined in 2 and 3 above, the sponsor does not wish to delay registration and so will accept a condition of registration that requests a category 1 application containing the SOLO-2 trial interim PFS analysis within 6 months of its availability.

Condition 3

Condition 3 reflects a similar condition applied in the USA (see attached FDA approval letter). The FDA condition is however time-limited such that the last report is due in 2020. The sponsor requests the same time limit for provision of data to the TGA.

Product information and consumer medicine information

The sponsor accepts the proposed PI and CMI changes with some minor editorial changes in the PI which can be seen in comments in the right hand margin of the annotated documents. A clean copy of each is also provided.

The sponsor proposes a more significant change in relation to the changes requested (addition of actual number of cases) for MDS/AML. The sponsor proposes the following text instead:

> *Myelodysplastic syndrome/Acute Myeloid Leukaemia (MDS/AML) have been reported in a small number of patients (< 1%) and the majority of reports have been fatal. The reports were typical of secondary MDS/cancer therapy-related AML. The duration of therapy with olaparib in patients who developed secondary MDS/AML varied from < 6 months to > 2 years. The majority of reports were in patients with a germline BRCA mutation.*

The sponsor considers it more appropriate to give a percentage figure rather than an actual number of cases (22) because the actual number of cases is constantly changing as more data accrue in ongoing studies. The percentage figure (< 1%) importantly gives the proportion of patients affected (providing better context) and secondly may also remain an accurate approximation as data accrue, thus potentially removing the need for updates should there be a significant change as data accrue. The percentage affected is reported in Summary of Clinical Safety (provided) as 0.7%, however, reporting of this exact figure is also not preferred as the exact figure may also change as data accrue. Other changes in the

paragraph include using 'majority' instead of 'most' and again the avoidance of using absolute numbers in the final sentence.

The sponsor also notes to the Delegate that the nonclinical PI changes were all incorporated in our PI provided with our response, except for the change to the value of in vitro protein binding which we have now accepted as ~ 90%.

Annotated and clean copies of the PI and CMI are provided.

Advisory Committee Considerations

The Delegate did not refer this application to the Advisory Committee on Medicines (ACM) for advice.

Delegate review of sponsor's response to delegate's overview

After further consideration of the conditions of registration, the Delegate proposed to remove submission of the interim results for PFS and OS from Study/Trial DO816C00010 as this is a different use of olaparib, more suited as the basis for an extension of indication in the future if positive. It does not, per se, inform regarding the proposed usage, and any safety information generated would be notified to the TGA under the general requirement to do so.

The Delegate noted the CSR for Study D0816C00009 (SOLOiST) clinical trial is likely to be ready in the first quarter of 2019. Given the relevance of this to the proposed usage, submission of this for evaluation as a Category 1 submission for evaluation is important and is a condition of registration. It would be acceptable to submit this at the same time as provided to the EMA. The SOLO-2 trial updates (interim and final) are considered key to support the proposed usage and thus submission of both as a Category 1 submission for evaluation is a condition of registration (The Delegate removed the duplication in the Conditions of Registration).

The Delegate reviewed the second round quality report, and noted the concern that the levels of olaparib hydroxymethyl increase with storage, particularly in conditions of high temperature and humidity; and that these were not toxicologically qualified. Given these conditions are particularly relevant to the Australian climate, this should be addressed when the new tablet formulation is submitted, particularly if the proposed usage is for maintenance treatment at an earlier stage. Given the currently proposed usage is for the treatment of an advanced malignancy, albeit as maintenance with a potentially long duration, after discussion with the nonclinical and pharmaceutical chemistry evaluators agree that this is not considered of sufficient concern to delay registration.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Lynparaza olaparib 50 mg capsule for oral administration, indicated for:

> *Olaparib is indicated as monotherapy for the maintenance treatment of patients with platinum sensitive relapsed BRCA-mutated (germline or somatic) high grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) after platinum based chemotherapy. Prior treatment must have included at least 2 courses of platinum based regimens.*

Specific conditions of registration applying to these goods

- The Lynparza RMP (Version 5, dated 3 November 2014, data lock point 20 May 2014) with Australian Specific Annex (Version 1, dated 5 November 2015) and any future updates, as agreed with the TGA will be implemented in Australia.
- Submission of the following clinical trial(s) as Category 1 submissions within 6 months of completion which were designed to evaluate:
  - the interim progression-free survival (PFS) and overall survival (OS) analyses with datasets from the Phase I/II randomised double blind placebo controlled multicentre study to assess the efficacy of o1aparib as maintenance monotherapy in patients with BRCAm platinum sensitive relapsed (PSR) high grade serous ovarian cancer (Study SOLO-2/SOLO-2 trial)
  - the results of the Phase IV, open label, single arm, non-randomised, multicentre study (Study 'SOLOiST') 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).
- Collect and analyse all cases of acute myelogenous leukaemia/ myelodysplastic syndrome identified in patients treated with Lynparza (olaparib), on an annual basis. These five annual interim reports (commencing December 2015 with a final sixth report due in June 2020) should summarise all cases identified up until that reporting date (new cases and those reported in previous years), and should include patients treated with Lynparza on clinical trials and outside of clinical trials (including spontaneous safety reports) to provide an accurate assessment of the long-term incidence and risk of AML/MDS. These should be submitted to the TGA Pharmacovigilance branch.
- At the time of submission of the final reports to the FDA, the sponsor is required to submit to the TGA for evaluation as Category 1 submissions:
  - The same final report for Trial DO-816C00006 entitled, 'an open-label, non-randomised, multicentre, comparative, and Phase I study of the pharmacokinetics, safety and tolerability of olaparib following a single oral 300 mg dose to patients with advanced solid tumours and normal renal function or renal impairment'.
  - the same final report for Trial DO-816C00005 entitled 'An open-label, nonrandomised, multicentre, comparative, phase i study to determine the pharmacokinetics, safety and tolerability of olaparib following a single oral 300 mg dose to patients with advanced solid tumours and normal hepatic function or mild or moderate hepatic impairment'.

Attachment 1. Product Information

The PI for Lynparza approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at < https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au