22 March 2018
EMA/CHMP/238139/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Rubraca

International non-proprietary name: rucaparib

Procedure No. EMEA/H/C/004272/0000

Note

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

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List of abbreviations

AE	adverse event
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios
AESI(s)	adverse event(s) of special interest
ALT	alanine aminotransferase
AML	acute myeloid leukaemia
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{0-12}	area under the concentration versus time curve from time zero to 12 hours postdose
AUC_{0-24}	area under the concentration versus time curve from time zero to 24 hours postdose
$AUC_{0-24.5}$	area under the concentration versus time curve from time zero to 24.5 hours postdose
AUC_{ss}	dose-averaged model-predicted steady-state area under the concentration-time curve
$AUC_{ss,avg}$	further adjusted $AUC_{ss,avg}$
AUC_{last}	area under the plasma concentration-time curve
BCRP	breast cancer resistance protein
BID	twice daily
BRCA	breast cancer gene
BRCA1	breast cancer gene 1
BRCA2	breast cancer gene 2
CA-125	cancer antigen-125
CDx	companion diagnostic test (validated test)
CFU	colony forming units
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL	clearance
CMA	Conditional Marketing Authorization
C_{max}	maximum observed plasma concentration
C_{min}	minimum observed plasma concentration
$C_{min,ss}$	minimum observed plasma concentration at steady-state
$C_{min,ss,avg}$	minimum observed plasma concentration at steady-state
CPP	critical process parameter
CQA	critical quality attribute
CR	complete response
CrCL	creatinine clearance
CSR	clinical study report
CTA	clinical trial assay
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	lowest concentration of a drug just before the next dose
CV%	coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DSB	double-strand breaks
DSC	differential scanning calorimetry
DVS	dynamic vapour sorption
EC	European Commission
ECG(s)	electrocardiogram(s)
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EOC	epithelial ovarian cancer
ESMO	European Society for Medical Oncology
EU	European Union
EU-RMP	European Union Risk Management Plan
FDA	Food and Drug Administration
FeSSIF	Fed state simulated intestinal fluid

FFPE	formalin-fixed, paraffin-embedded
FMI	Foundation Medicine, Inc
FPI	first patient in
gBRCA	germline mutations in BRCA (BRCA1 and BRCA2)
GC	Gas Chromatography
GCIG	Gynecologic Cancer Intergroup
GCP	Good Clinical Practice
GI	gastrointestinal
HDPE	high density polyethylene
HGSOC	high-grade serous ovarian cancer
HPLC	high-performance liquid chromatography
HRD	homologous recombination deficiency
HR	Hazard ratio
IC_{50}	half maximal inhibitory concentration
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
INN	International Nonproprietary Name
IPC	in-process control
IR	infrared
IRR	independent radiological review
IV	intravenous
KF	Karl Fischer titration
LDPE	low density polyethylene
LPI	last patient in
MAA	Marketing Authorization Application
MAH	marketing authorization holder
MATE	multidrug and toxin extrusion transporter
MHRA	Medicines and Healthcare products Regulatory Agency
MDR1	multidrug resistance protein 1
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mo	month(s)
N or n	number of patients
NA	not assessable
NE	not evaluable
NCI	National Cancer Institute
NLT	not less than
NMT	not more than
NOR	normal operating range
NR	not reported
OCT	organic cation transporter
ORR	objective response rate
OS	overall survival
P-gp	P-glycoprotein
PAR	proven acceptable range
PARP	poly(adenosine diphosphate[ADP]-ribose) polymerase
PDE	permitted daily exposure
Ph. Eur.	European Pharmacopoeia
PP	polypropylene
PPC	primary peritoneal cancer
PD	progressive disease
PFI	progression-free interval
PFS	progression-free survival
PK	pharmacokinetic
PLD	pegylated liposomal doxorubicin
PopPK	population pharmacokinetics
PPIs	proton pump inhibitors
PR	partial response
PT	Preferred Term

QD	once daily
QTc	corrected QT interval
QTcB QT	interval corrected using Bazett's formula
QTcF QT	interval corrected using Fridericia's method
RECIST	Response Evaluation Criteria in Solid Tumours
RH	relative humidity
RMP	Risk Management Plan
SAE	serious adverse event
SAG	Scientific advisory group
sBRCA	somatic mutations in BRCA (BRCA1 or BRCA2)
SD	stable disease
SmPC	Summary of Product Characteristics
SOC(s)	System Organ Class(es)
SSB	single-strand break
StD	standard deviation
$T_{1/2}$	half-life
tBRCAmut	tumour tissue alteration in BRCA1/2, including gBRCA and sBRCA mutations
TEAE(s)	treatment-emergent adverse event(s)
T_{max}	time from dosing at which C_{max} occurred
TOPO	topotecan
TTP	time to progression
ULN	upper limit of normal
UK	United Kingdom
US	United States
USAN	United States Adopted Name
vs.	versus
V_{ss}	volume of distribution at steady state
Wks	weeks
XRPD	x-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Clovis Oncology UK Ltd submitted on 1 November 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Rubraca, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 July 2015.

Rubraca was designated as an orphan medicinal product EU/3/12/1049 on 10 October 2012 in the following condition: Treatment of ovarian cancer.

The initially applied indication for Rubraca was:

Rubraca is indicated as monotherapy treatment of advanced ovarian cancer in adult patients with deleterious BRCA-mutated tumours, inclusive of both germline BRCA and somatic BRCA mutations, and who have been treated with two or more prior lines of chemotherapy.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Rubraca as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European public assessment reports.

The legal basis for this application refers to:

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

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

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) CW/1/2011 and CW/0001/2015 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Applicant's request(s) for consideration

Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional marketing authorisation in accordance with Article 14(7) of the above mentioned Regulation.

Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

New active Substance status

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

Scientific Advice

The applicant received Scientific Advice from the CHMP on 18 October 2012, 13 March 2013 and 18 February 2016. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Jorge Camarero Jiménez/ Co-Rapporteur: Greg Markey

- The application was received by the EMA on 1 November 2016.
- The procedure started on 24 November 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 22 February 2017. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 9 February 2017. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 27 February 2017
- During the meeting on 23 March 2017, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 12 July 2017.
- The following GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:
  - A GCP inspection at two clinical investigator sites located in Spain and USA and at the CRO (PRA International) in USA were conducted during March-April 2017 in connection with the conduct of pivotal trial with protocol number CO-338-017. The outcome of the inspection carried out was issued on 07 June 2017.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 25 August 2017.
- During the PRAC meeting on 01 September 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 14 September 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP 1st List of Outstanding Issues on 09 October 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 26 October 2017.
- During the CHMP meeting on 8 November 2017, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the CHMP meeting on 9 November 2017, the CHMP agreed on a 2nd list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 17 November 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 1 December 2017.
- During the CHMP meeting on 14 December 2017, the CHMP agreed on a 3rd list of outstanding issues to be sent to the applicant
- The applicant submitted the responses to the 3rd CHMP List of Outstanding Issues on 22 January 2018.
- During a meeting of a SAG on 13 February 2018, experts were convened to address questions raised by the CHMP. The CHMP considered the views of the SAG as presented in the minutes of this meeting.
- During the CHMP meeting on 22 February 2017, the CHMP agreed on a 4th list of outstanding issues to be sent to the applicant
- The applicant submitted the responses to the 4th CHMP List of Outstanding Issues on 27 February 2018.
- During the meeting on 19-22 March 2018, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a conditional marketing authorisation to Rubraca on 22 March 2018.
- The CHMP adopted a report on similarity for Rubraca on similarity with Yondelis and Zejula on date 22 March 2018 (Appendix 1)

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The applied indication for Rubraca, was as monotherapy in the treatment of advanced ovarian cancer in adult patients with deleterious BRCA mutated tumours, inclusive of both germline BRCA and somatic BRCA mutations, and who have been treated with two or more prior lines of chemotherapy.

The approved indication is as monotherapy treatment of adult patients with platinum sensitive, relapsed or progressive, BRCA mutated (germline and/or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with two or more prior lines of platinum based chemotherapy, and who are unable to tolerate further platinum based chemotherapy.

2.1.2. Epidemiology and risk factors / prevention

Ovarian cancer (OC) is the seventh most commonly diagnosed cancer among women in the world. Epithelial OC is the most predominant pathologic subtype, with five major histotypes that differ in origination, pathogenesis, molecular alterations, risk factors, and prognosis. Genetic susceptibility is manifested by rare inherited mutations with high to moderate penetrance. Genome-wide association studies have additionally identified 29 common susceptibility alleles for OC, including 14 subtype-specific alleles. Several reproductive and hormonal factors may lower risk, including parity, oral contraceptive use, and lactation, while others such as older age at menopause and hormone replacement therapy confer increased risks. These associations differ by histologic subtypes (histotype), especially for mucinous OC, likely reflecting differences in aetiology. The prevalence of ovarian cancer is currently estimated at 4.7 in 10,000. Ovarian cancer is the leading cause of death attributed to gynaecological cancer in the developed world (World Cancer Report 2014, WHO, Chapter 5.12).

2.1.3. Biologic features

Nearly all benign and malignant ovarian tumours originate from one of three cell types: epithelial cells, stromal cells, and germ cells. In developed countries, more than 90% of malignant ovarian tumours are epithelial in origin, 5%–6% of tumours constitute sex cord-stromal tumours (e.g., granulosa cell tumours, thecomas, etc.), and 2%–3% are germ cell tumours (e.g., teratomas, dysgerminomas, etc.). Epithelial OC reflects a heterogeneous disease with histotypes that differ in their cellular origin, pathogenesis, molecular alterations, gene expression, and prognosis. Malignant OC, also known as carcinomas, are comprised of five main histotypes: high-grade serous (HGSOC; 70%), endometrioid (ENOC; 10%), clear cell (CCOC; 10%), mucinous (MOC; 3%), and low-grade serous (LGSOC; <5%). Rare high penetrant mutations in breast cancer gene 1 (BRCA1) and breast cancer gene 2 (BRCA2) greatly increase lifetime risk and account for the majority of hereditary cases and 10%–15% of all cases (Reid et al, Cancer Biol Med 2017. doi: 10.20892). Poly (ADP-ribose) polymerase (PARP) enzymes, including PARP-1, PARP-2, and PARP-3, play critical roles in single-strand break (SSB) deoxyribonucleic acid (DNA) repair. BRCA1 and BRCA2 play an important role in

repairing double-strand breaks (DSB) in DNA. The inhibition or inactivation of both SSB and DSB repair pathways by administration of a PARP inhibitor in the context of an underlying genetic defect such as a BRCA1/2 mutation results in tumour cell death through accumulation of unrepaired DNA damage (Jayson et al, 2014, Lancet 384 (9951): 1376–88).

2.1.4. Clinical presentation, diagnosis and stage / prognosis

Early stage ovarian cancer is often asymptomatic and therefore difficult to detect. For women who do experience symptoms in the early stages, ovarian cancer is sometimes misdiagnosed because the majority of symptoms are nonspecific. These symptoms may overlap those of gastrointestinal and other diseases, and as a result, many patients may be treated incorrectly for months or years. Thus, ovarian cancer is often first detected in advanced stages when prognosis is poor. Because of delayed presentation and diagnosis, almost 75% of women with ovarian cancer are diagnosed with stage III/IV disease and 75% of women with advanced stage disease ultimately relapse or die from their disease, despite treatment. After initial therapy, most women will have a progression-free interval (PFI) of approximately 1.5 to 2 years, depending on the extent of post-operative residual disease and response to chemotherapy. However, relapse still occurs in the majority of cases, and only 10% to 30% of women experience long-term survival. Advanced stage disease is associated with a 5-year survival rate of only 30% to 40% (Doubeni et al, American Family Physician Volume 93, Number 11, 2016, pg 937-944).

2.1.5. Management

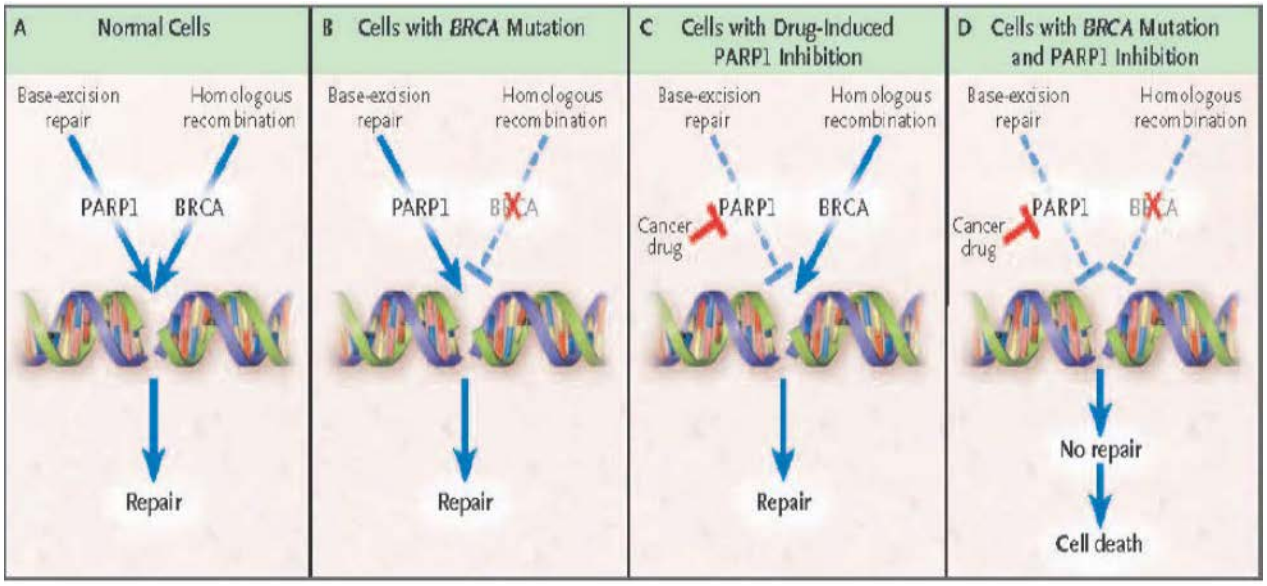
The standard approach to treatment of advanced HGSOC is cytoreductive surgery (either at time of diagnosis or interval debulking), with the goal of minimizing residual tumour to no visible residual disease, a major prognostic indicator for improved survival. Six to 8 cycles of platinum- and taxane-based chemotherapy is the global standard of care. Despite a 70% to 80% initial response rate, most women have disease relapse. The choice of treatment for relapsed disease is based on the treatment-free interval relative to last platinum therapy administered. Platinum-based regimens dominate ovarian cancer therapy and define treatment groups. In general, patients whose disease progresses during treatment with a platinum-based regimen are considered to have platinum-refractory disease; patients whose disease relapses within 6 months after the last platinum agent was administered are considered to have platinum-resistant disease; and patients whose disease relapses more than 6 months after last platinum-based therapy was administered are considered to have platinum-sensitive disease. Those with an interval of equal to 6 months or higher and up to 12 months are considered to have partially platinum-sensitive disease, while those with an interval equal to 12 months or higher are considered to have fully platinum-sensitive disease. (European Society for Medical Oncology [ESMO] guideline update, Ledermann et al, 2016)

Patients with platinum-sensitive disease are typically retreated with platinum-based therapy until they no longer respond to or can no longer tolerate such treatment. Trabectedin with PLD or paclitaxel can be used for platinum-sensitive patients who cannot tolerate further platinum. Patients with platinum-resistant disease have more limited treatment options, such as bevacizumab in combination with chemotherapy (paclitaxel, pegylated liposomal doxorubicin [PLD], or topotecan) or single-agent treatment with PLD, topotecan, gemcitabine, or weekly paclitaxel. There are no therapies specifically approved for use in the third-line setting and beyond (ie, after 2 or more prior therapies) for platinum-resistant disease. In addition, there is a lack of well-controlled studies of new or existing agents in later line settings.

Recently, PARP inhibitors, which have demonstrated clinical activity in patients with a BRCA1/2 mutation, have emerged as a new therapeutic option for treatment of relapsed ovarian cancer. In the EU, olaparib is approved as monotherapy for the maintenance treatment of adult patients, with platinum-sensitive relapsed ovarian cancer, who are in response to platinum-based chemotherapy. Another PARP inhibitor, niraparib, is indicated in a similar setting as maintenance treatment in platinum-sensitive patients who are in response to platinum-based chemotherapy.

About the product

Rucaparib is a potent, oral small molecule inhibitor of PARP enzymes, including PARP-1, PARP-2, and PARP-3, which play critical roles in single-strand break (SSB) deoxyribonucleic acid (DNA) repair. The BRCA1 and BRCA2 play an important role in repairing DSB in DNA, and rucaparib has been shown to have anti-tumour activity in BRCA-mutant models. The inhibition or inactivation of both SSB and DSB repair pathways by administration of a PARP inhibitor, such as rucaparib, in the context of an underlying genetic defect such as a BRCA1/2 mutation results in tumour cell death through accumulation of unrepaired DNA damage (below figure).



The indication for Rubraca initially proposed by the applicant was as follows:

“Rubraca is indicated as monotherapy in the treatment of advanced ovarian cancer in adult patients with deleterious BRCA mutated tumours, inclusive of both germline BRCA and somatic BRCA mutations, and who have been treated with two or more prior lines of chemotherapy.”

The final indication as approved by the CHMP following review of the application is:

“Rubraca is indicated as monotherapy treatment of adult patients with platinum-sensitive, relapsed or progressive, BRCA mutated (germline and/or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with two or more prior lines of platinum-based chemotherapy, and who are unable to tolerate further platinum-based chemotherapy.”

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

The recommended dose for Rubraca is 600 mg taken twice daily, equivalent to a total daily dose of 1,200 mg, until disease progression or unacceptable toxicity.

Type of Application and aspects on development

Rubraca was granted orphan drug designation on 10 October 2012, for which the number in the community register of orphan medicinal products is EU/3/12/1049.

A Paediatric Investigation Plan is not applicable as the indication has an agreed class waiver (CW/1/2011) confirmed on 17 August 2012 (EMA/502695/2012).

The applicant made a request for an accelerated assessment based on the fact that an effective treatment in a setting of relapsed ovarian cancer could be considered an unmet medical need, there is no PARP inhibitor approved, and there is a lack of specific treatments for BRCA-mutated patients in the relapsed setting.

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest and more mature data were not expected to be available for the initial phase of the assessment.

The applicant requested a conditional marketing authorisation based on the following reasons:

- The applicant claimed that the benefit-risk balance is positive:

Rucaparib has been well characterised in both nonclinical and clinical studies and has demonstrated meaningful efficacy in BRCA-mutated advanced ovarian cancer patients with an ORR that is reasonably likely to translate into clinical benefit. The unfavourable effects of rucaparib are acceptable within the context of the disease.

- It is likely that the applicant will be able to provide comprehensive data:

The applicant will submit data from Study CO-338-043 post-approval in order to provide confirmatory controlled data. Study CO-338-043 (ARIEL4) is a Phase 3 multicentre, open-label, randomized study of rucaparib versus chemotherapy in patients with BRCA-mutant or BRCA-like relapsed, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer. These data will further define the benefit-risk of rucaparib in the proposed indication.

- Unmet medical needs will be addressed:

There is a need of more active treatments capable of prolonging the life expectancy of these patients. In spite of high response-rates that could be achieved on platinum-based therapy, the majority of ovarian cancer patients will eventually recur. Effective and tolerable agents that can delay the recurrence of ovarian cancer and further chemotherapy treatment in these patients are highly awaited. The fact that it is a question of time that all patients will ultimately develop platinum-resistant disease justifies the unmet medical need.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required:

In a disease setting of BRCA-mutated relapsed ovarian cancer with poor long-term survival, significant co-morbidity, and decreasing clinical benefit despite repeated chemotherapy regimens, making rucaparib available on the market, offers an oral alternative therapy to patients for whom intravenous standard of care is

increasingly less well tolerated and less effective after multiple regimens. There has been slow progress in improving the outcome of ovarian cancer with chemotherapy over the last decade which has led to research into targeted therapies to offer women more effective and better tolerated options. PARP inhibitors represent a new step in the management of ovarian cancer and rucaparib can provide an important new molecularly targeted treatment option for patients with BRCA mutant ovarian cancer if it can be made immediately available.

Clovis Oncology United Kingdom (UK) Limited sought Scientific Advice from the Committee for Medicinal Products for Human Use (CHMP) in 2012 on the overall non-clinical program and for studies CO-338-010 (Study 10) and CO-338-014 (ARIEL3); follow-up Protocol Assistance (following the orphan designation) was sought in 2013 on the demonstration of significant benefit in the maintenance (study CO-338-014 (ARIEL3)) and in 2015 on the overall regulatory submission strategy for the proposed treatment indication.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 200, 250 or 300 mg of rucaparib (as camsylate salt) as active substance.

Other ingredients are:

Tablet core: microcrystalline cellulose, sodium starch glycolate (Type A), colloidal anhydrous silica and magnesium stearate.

Film-coating: polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol 4000 (E1521), talc (E553b), brilliant blue FCF aluminium lake (E133, 200 mg tablet only), indigo carmine aluminium lake (E132, 200 mg tablet only) and iron oxide yellow (300 mg tablet only).

The product is available in high density polyethylene (HDPE) bottles with polypropylene (PP) induction seal closures as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of rucaparib camsylate is 8-fluoro-2-{4-[(methylamino)methyl]phenyl}-1,3,4,5-tetrahydro-6*H*-azepino[5,4,3-cd]indol-6-one ((1*S*,4*R*)-7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methanesulfonic acid salt corresponding to the molecular formula $C_{19}H_{18}FN_3O.C_{10}H_{16}O_4S$. It has a relative molecular mass of 555.67 g/mol and the following structure:

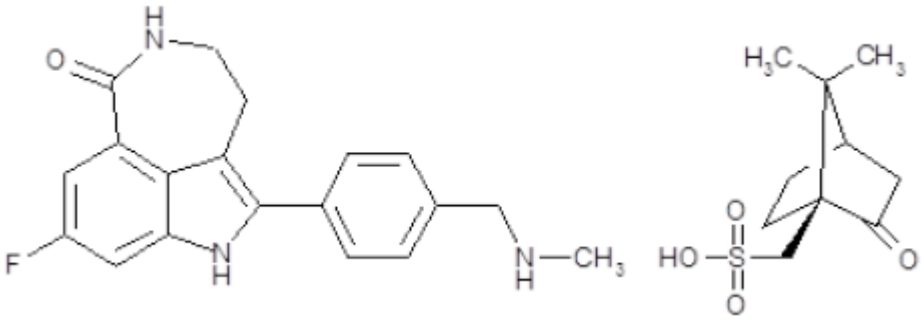


Figure 1: structure of rucaparib camsylate

The chemical structure of rucaparib camsylate was elucidated by a combination of ^{1}H, ^{13}C and ^{19}F nuclear magnetic resonance spectroscopy, mass spectrometry, elemental analysis and infrared spectroscopy. The solid state properties of the active substance were measured by differential scanning calorimetry (DSC), dynamic vapour sorption (DVS) and x-ray powder diffraction (XRPD).

The active substance is a white to pale yellow, non-hygroscopic, crystalline powder. It is slightly soluble in aqueous media between pH 3 and 7, with significantly reduced solubility above pH 9.5. Two enantiotropic polymorphic forms are known, the chosen commercial form being the most thermodynamically stable form.

Rucaparib itself has no chiral centres, although the camphorsulfonic acid counter ion does contain 2 stereocentres which are controlled in the raw material by a test for specific optical rotation.

Manufacture, characterisation and process controls

Rucaparib camsylate is synthesized by a single manufacturer from a single starting material with acceptable specifications. The final crystallization step controls both polymorphic form and particle size of the isolated active substance.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, the starting material and reagents have been presented. Set-points and normal operating ranges (NORs) have been defined for raw material inputs and reaction parameters, along with proven acceptable ranges (PARs) where justified by experimental data. Critical process parameters (CPPs), which impact the active substance critical quality attributes (CQAs) have been defined, and the overall control strategy is considered suitable.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. Relevant elemental impurities are controlled by the process to acceptable levels.

Rucaparib is indicated for the treatment of advanced cancer and is itself clastogenic. Therefore, in line with ICH S9 and M7, limits for impurities, including those which are potentially mutagenic, are set in accordance with ICH Q3A(R2). Nonetheless, genotoxicity of the single specified impurity was assessed *in silico* which indicated no additional structural alerts relative to the active substance. Other potential genotoxic impurities theoretically present based on the synthetic process were found not to form in any detectable amount, except for a potential by-product used in the synthesis of the starting material. It was argued by the applicant that its presence is unlikely, given the ability of the processing to purge impurities. Nonetheless, the applicant committed to developing an analytical method capable of detecting and quantifying the relevant compound.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Only minor changes to the process have been made in order to improve the efficiency of the process and quality of the active substance. These have been presented in sufficient detail and justified.

The active substance is packaged in LDPE bags, stored within HDPE drums. The material of the primary packaging complies with EC directives 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for appearance, identity (IR), assay (HPLC), assay of camphorsulfonic acid (ion chromatography), related substances (HPLC), residual solvents (GC), water content (KF), particle size (Ph. Eur.), and inorganic impurities (residue on ignition, Ph. Eur.).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set. The limit for one manufacturing impurity will be re-assessed by the applicant once sufficient production scale manufacturing experience is gathered and tightened if warranted. The active substance specifications are based on the active substance CQAs and are deemed acceptable. Omission of tests for other parameters was justified based on the information submitted.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from 15 pilot to production scale batches of the active substance made using the proposed commercial process (some with minor modifications to the filtration equipment) were provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from three batches of active substance from the proposed manufacturer stored in the intended commercial primary package for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Two batches were manufactured on production scale using an earlier iteration of the manufacturing process, although differences are considered unlikely to impact active substance quality. The third batch was manufactured on pilot scale using the proposed commercial route. Samples were tested for appearance, assay, related substances, water content, polymorphic form (XRPD) and microbiological evaluation (Ph. Eur.). The analytical methods used were the same as for release for those tests common to both specifications, and for the others, properties were suitably validated. No significant changes to any of the measured parameters were observed under either storage condition.

Photostability testing following the ICH guideline Q1B was performed on one batch. A slight yellowing and increase in degradation products was observed. Although the active substance is slightly photosensitive, the opaque container closure system provides sufficient protection from light.

Forced degradation studies were carried out on one batch, exposed to heat, heat and humidity, aqueous acid, aqueous base and aqueous oxidant. A small amount of degradation was observed in acid, base and at high temperature, whereas significant degradation occurred under oxidative conditions. The results indicate that the HPLC method is stability indicating.

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

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

Rubraca film-coated tablets contain rucaparib camsylate, equivalent to either 200, 250 or 300 mg of rucaparib freebase. The different strengths are made from a common blend which are then pressed and coated to form tablets distinguishable by colour, shape and debossing.

The aim was to develop an immediate-release oral dosage form with adequate quality for the intended indication.

A risk assessment was carried out in order to evaluate the potential of active substance properties, (solubility, polymorphic form, stability, hygroscopicity, flow properties and particle size), to impact the finished product manufacturability and CQAs. Based on knowledge of the active substance properties, the risk was considered low.

The active substance is a stable, non-hygroscopic crystalline solid which is slightly soluble in biologically-relevant aqueous media. Solubility decreases below pH 3 as less soluble salts can form with the counter ions of stronger acids (e.g. HCl and H_2SO_4), but is enhanced in biorelevant media such as fed state simulated intestinal fluid (FeSSIF).

Compatibility with most of the selected excipients was demonstrated using studies on binary mixtures of active substance with each chosen excipient under stressed conditions (50 ^{o}C / 75% RH). Given the stability of the active substance and prior clinical formulations, drug-excipient compatibility with the rest of the excipients, colloidal silicone dioxide and film-coating, is considered demonstrated. All excipients, including the individual ingredients in the film-coating mixture, are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in section 2.1.1 of this report.

Several different formulations were used in early clinical trials. The commercial formulation was introduced during phase 2 clinical trials. All three strengths are made from a common blend and, apart from the film-coat, are qualitatively identical and quantitatively proportional.

The amounts of active substance and different excipients were optimised to allow formulation of a robust tablet. The manufacturing process was chosen to address the properties of the active substance. The likely impact of individual process steps on the finished product CQAs was assessed and CPPs identified experimentally. Set-points and PARs were defined for CPPs in several manufacturing steps.

Development of the dissolution method took into account the properties of the active substance including its low aqueous solubility. The discriminatory power of the chosen method, as well as some of the other dissolution media, was evaluated against batches of finished product manufactured with meaningful changes in composition and manufacturing process parameters. The test is deemed acceptable as a quality control method and suitable specifications have been set.

The primary packaging is an HDPE bottle, with a PP induction seal closure. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of six main steps: blending of active substance with intra-granular excipients and sieving; roller compaction; blending with extra-granular excipients; compression; film-coating; packaging. The process is considered to be a standard manufacturing process.

It has been demonstrated during production of clinical and development batches that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. A process validation scheme has been provided which is deemed acceptable. Process validation will be carried out on a minimum of three commercial scale batches of each tablet strength prior to commercialization. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including appearance, identity (IR), assay (HPLC), degradation products (HPLC), dissolution (Ph. Eur.), uniformity of dosage units (Ph. Eur.), water content (KF) and microbial limit (Ph. Eur.). In line with ICH Q3D, a risk assessment was carried out to determine the likelihood of metal contaminants being present in the finished product. Furthermore, analysis data from multiple batches of finished product showed that no class 1 or 2a elemental impurities, not palladium, were present above 30% of the permitted daily exposure (PDE) levels. The absence of tests for elemental impurities is considered justified.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for three pilot scale batches of the 200 and 300 mg tablets manufactured at the previous manufacturing site, (not registered for commercial production), as well as two batches each of the 200 and 300 mg tablets, and one 250 mg batch, manufactured at slightly lower than planned production scale at the commercial site. The results confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from three pilot scale batches each of the 200 and 300 mg strengths of finished product was provided. All three strengths are made from a common blend, and, apart from the film-coat, are qualitatively identical and quantitatively proportional. The different strengths are packed in HDPE bottles of different sizes. However, the ratio of tablet mass to container volume is comparable from strength to strength. Therefore, this bracketing approach is acceptable. The batches were produced by a different manufacturer using a process which simulates the proposed commercial process and had the same composition as the proposed commercial tablets. They were packed in the primary packaging proposed for marketing (other than the white colourant used in the bottles) and were stored for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines. In addition, one

batch of each strength manufactured at the proposed commercial site at slightly less than production scale and stored in the proposed commercial primary packaging was stored for up to 12 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH). The batches of medicinal product are considered representative of the commercial product.

Samples were tested for appearance, assay, degradation products, dissolution, water content and microbial limits. The analytical procedures used are stability indicating. No significant variability in any of the measured parameters was observed, save for a small increase in water content, which was within the proposed specification limits and is not likely to have a significant effect on efficacy and safety of the product when used according to the directions in the SmPC.

In addition, one batch each of the 200 and 300 mg tablets produced by the previous manufacturer, and one batch of each strength produced by the commercial manufacturer were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Results indicate that the product is not photosensitive.

Based on available stability data, the proposed shelf-life of 36 months, with no special storage conditions, as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

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

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendations for future quality development

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

- The limits for impurities should be re-assessed by the applicant once sufficient production scale manufacturing experience is gathered and tightened if warranted.
- The applicant should develop an analytical method capable of confirming the absence of a potential manufacturing impurity to levels below the ICH qualification threshold defined in ICH Q3A (R2).

2.3. Non-clinical aspects

2.3.1. Introduction

Rucaparib has been characterised in a series of non-clinical studies conducted to support the use of rucaparib as an oral monotherapy for patients with BRCA1/2 mutation positive advanced cancers.

The primary and secondary pharmacology studies were not conducted in accordance with GLP. However, the main/pivotal toxicity studies with safety pharmacology endpoints and stand-alone safety pharmacology studies were conducted in accordance with GLP regulations.

The toxicity studies were performed in rats and dogs with duration of up to 6 months for IV administration and up to 92 days for oral administration. The non-clinical toxicology program was designed initially to support intravenous dosing but was supplemented with additional studies to support oral dosing.

Scientific Advice was sought on aspects of the nonclinical development program, and specifically, on the toxicology program.

2.3.2. Pharmacology

The pharmacology of rucaparib was studied in vitro and in vivo in order to demonstrate its activity as a potent inhibitor of PARP enzymes, including PARP-1, PARP-2, and PARP-3.

Primary pharmacodynamic studies

Pharmacodynamics - *in vitro* studies

The inhibition of rucaparib on the activity of recombinant human PARP-1 and mouse PARP-2 was determined in an enzymatic assay measuring the incorporation [32P]-NAD^+ into ADP-ribose polymers. Rucaparib was a potent inhibitor of PARP-1 and PARP-2 with an inhibition constant (Ki) of 1.4 ± 0.2 and 0.17 ± 0.05 nM, respectively. Crystallographic analysis showed that rucaparib bound to the active (NAD+ binding) catalytic site of PARP-1.

Biochemical profiling of twelve PARP family members using an enzymatic assay measuring the incorporation of biotinylated NAD^+ to activated DNA showed that rucaparib is a potent inhibitor of PARP-1, PARP-2, and PARP-3 enzymes with IC_{50} values of 0.8, 0.5, and 28 nM, respectively (Table 1).

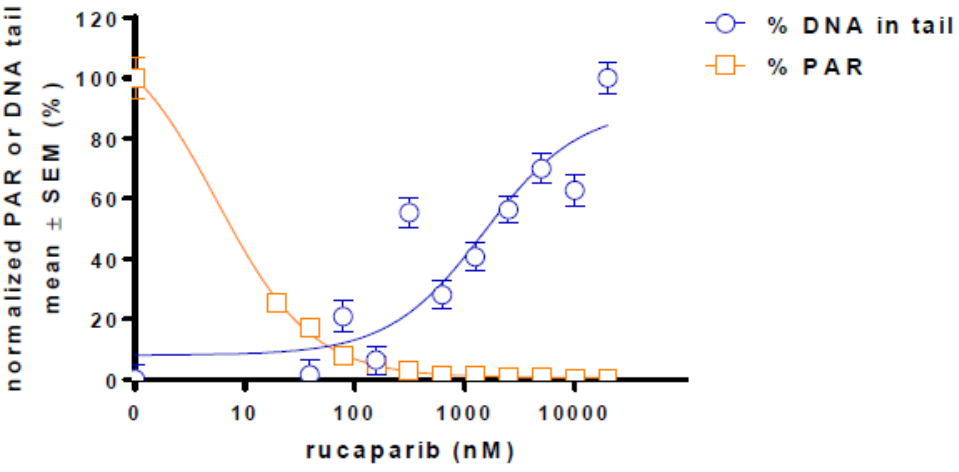
Table 1 Inhibitory Effects of Rucaparib on PARP Enzymes

Enzyme	IC_{50} (nM)
PARP-1	0.8
PARP-2	0.5
PARP-3	28
TNKS1 (PARP-5a)	796
TNKS2 (PARP-5b)	486
PARP-6	24000
PARP-7	5300
PARP-8	> 100000
PARP-10	1900
PARP-11	5800
PARP-12	2300
PARP-15	19800

The potency and mechanism of action of rucaparib were assessed in the UWB1.289 (BRCA1 mutant) and UWB1.289+BRCA1 (BRCA wild-type) isogenic cell line pair. Cell viability data showed that the UWB1.289 cell line was more sensitive (IC_{50} of 375 nM) to rucaparib treatment than the BRCA1 restored UWB1.289+BRCA1cell line (IC_{50} of 5430 nM). The 14-fold lower IC_{50} in the UWB1.289 cell line is consistent with the concept of synthetic lethality.

The impact of rucaparib on PARP inhibition was determined *in vitro* in the BRCA1 mutant UWB1.289 cell line by measuring the incorporation of biotinylated PAR onto histone proteins using an ELISA assay. Rucaparib inhibited formation of PAR in a dose-dependent manner, with an IC_{50} of 2.8 nM after 24 hours of treatment. The accumulation of SSBs was also evaluated in the UWB1.289 cell line using an alkaline Comet assay which detects single and double-stranded breaks based on the DNA "comet" tail shape and migration pattern by epifluorescence microscopy. Rucaparib increased DNA damage in a dose-dependent manner, with an EC50 of 1.5 µM after 24 hours of incubation.

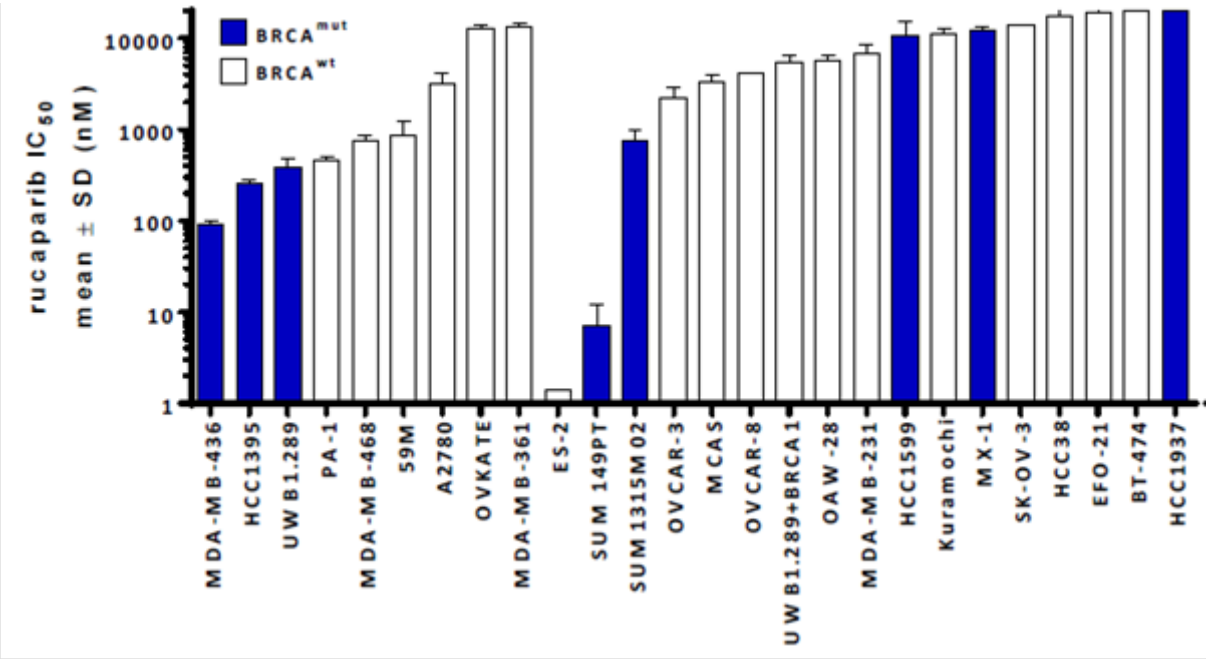
Figure 2: Rucaparib Treatment in BRCA1 Mutant UBW1.289 Cells Results in Dose-dependent Inhibition of PAR and Induction of DNA Damage



Additional mechanism of action studies using UBW1.289 cell line showed a concomitant and dose-dependent increase in DNA damage and an inverse relationship between rucaparib doses as compared to cell viability and caspase 3/7 levels. Taken together, these data suggest rucaparib treatment of the BRCA1 mutant UBW1.289 cell line results in DNA damage, apoptosis and cell death.

Rucaparib sensitivity was assessed in a panel of 12 breast and 14 ovarian cancer lines (figure below). Rucaparib treatment decreased the viability of several BRCA1/2 mutant cell lines, for example the IC_{50} of rucaparib in the BRCA mutant MDA-MB-436, HCC1395 and UWB1.289 cell lines was 91, 254, and 375 nM, respectively. In addition, cell lines with a defective HRR phenotype, as defined by the fold induction of γH2AX/RAD51 foci formation, had a statistically significant lower median rucaparib IC^{50} compared to HRR-proficient cells.

Figure 3: Rucaparib Sensitivity in a Panel of Breast and Ovarian Cancer Cell Lines



As an assessment of the *in vitro* activity of rucaparib in HRR deficient cells, a series of siRNA knock down (KD) experiments were performed. Gene KD by siRNA was used to model the impact of functional inactivation (i.e., deleterious mutation on one allele and loss of the wild type allele) of BRCA1/2. Knock down of BRCA1/2 increased rucaparib cytotoxicity in pancreatic, ovarian, and breast cancer cell lines. The IC_{50} of rucaparib in the pancreatic ductal adenocarcinoma (PDAC) Panc 10.05 cell line with reduced levels of BRCA1 or BRCA2 was 4564 and 356 nM, respectively. This represented a 2.8-fold and 35.3-fold increase in rucaparib sensitivity when BRCA1 and BRCA2 expression was reduced, respectively, compared to Panc 10.05 cells transfected with a non-targeting (NT4) control siRNA.

Genomic alterations in non-BRCA HRR genes may also render cells sensitive to PARP inhibitors. To test whether defects in non-BRCA HRR genes can induce sensitivity to rucaparib in vitro, 31 genes were individually knocked down by transient siRNA transfection in four different ovarian cancer cell lines (SK-OV-3, OVCAR-3, UWB1.289+BRCA1 and OAW-28 cell lines). BRCA1/2 KD increased the *in vitro* potency of rucaparib. The KD of 7 individual genes (BRCA1, BRCA2, RAD51, FANCM, PALB2, ATR, and BARD1) also increased rucaparib sensitivity compared to the NT4 transfected control. These results confirmed the synthetic lethal interaction

between rucaparib and BRCA1/2 mutations, and were consistent with the hypothesis that reduced levels of non-BRCA HRR related genes may confer sensitivity to rucaparib in ovarian cancer cell lines.

In addition to catalytic inhibition of the enzymatic activity, PARP inhibitors may also function by "trapping" PARP-1 and PARP-2 enzymes at damaged DNA. Avian B lymphoblast DT40 and human prostate DU145 cell lines were treated with 3 compounds including rucaparib, and PARP-DNA complexes were assessed by Western blot analyses of chromatin-bound fractions. A dose-dependent accumulation of PARP-DNA complexes was observed in rucaparib-treated cells suggesting that the mechanism of action of rucaparib may include DNA trapping.

Pharmacodynamics - *in vivo* studies

A series of PK, PK/PD, and efficacy studies were performed to evaluate the efficacy and MOA of rucaparib in subcutaneous and orthotopic MDA-MD-436 (BRCA1 mutant) triple negative breast cancer (TNBC) xenograft mouse models. The MDA-MB-436 cell line has a BRCA1_p.K1780_splice mutation and loss of the other BRCA1 allele.

Rucaparib Efficacy in the MDA-MB-436 (BRCA1 Mutant) Subcutaneous Breast Cancer Xenograft Model

In vivo, the anti-tumour activity of rucaparib was initially evaluated in the subcutaneous BRCA1 mutant MDA-MB-436 TNBC model. Oral rucaparib dosing at 150 mg/kg on QD or BID schedules, or 250 mg/kg QD, resulted in > 100% TGI after 17 days of dosing. Following cessation of rucaparib administration at Day 21, the tumour response in the rucaparib-treated groups was maintained until Day 45 with partial responses (PR) or complete responses (CR) being observed in all of the mice in the rucaparib-treated groups.

Plasma PK Parameters of Rucaparib Following a Single Oral Dose to Female NOD/SCID Mice

This was a single oral dose PK study performed in non-tumour bearing NOD/SCID mice to determine the plasma PK parameters of rucaparib following single oral gavage administration of rucaparib camsylate at 2, 5, 15, 50, and 150 mg/kg. It revealed that rucaparib was detected in the plasma of all animals up to 12 hours and T_{max} was at 1 to 2 hours post-dose. Rucaparib $T_{1/2}$ ranged from 1 to 3 hours. Exposures (C_{max} and AUC_{0-12}) were approximately dose proportional from 2 to 15 mg/kg, but were greater than dose proportional at 50 and 150 mg/kg as compared to 2 mg/kg.

PK/PD Assessment of Rucaparib in the MDA-MB-436 (BRCA1 Mutant) Orthotopic Breast Cancer Xenograft Model

In a PK/PD study in the BRCA1 mutant MDA-MD-436 TNBC orthotopic xenograft model, mice were given 5 doses of rucaparib at 2, 5, 15, 50, or 150 mg/kg. A dose-dependent inhibition of PAR was observed from 2- 150 mg/kg BID. Administration of 15, 50, and 150 mg/kg BID rucaparib resulted in statistically significant inhibition of 45%, 86%, and 96% respectively. There was an inverse and dose-dependent correlation between PAR and rucaparib levels in the plasma and tumour. Although the tumour to plasma (T/P) ratio was lower at higher doses of rucaparib, the levels of rucaparib in the tumour were consistently higher than the levels of rucaparib in plasma. A further PK/PD study was performed in the subcutaneous MDA-MB-436 xenograft model. Animals were treated with a single dose of 150 or 250 mg/kg rucaparib, or with 2 doses of 150 mg/kg rucaparib administered 8 hours apart. There was a higher T/P ratio at all time points evaluated.

Rucaparib Efficacy in the MDA-MB-436 (BRCA1 Mutant) Orthotopic Breast Cancer Xenograft Model

The anti-tumour activity of rucaparib at doses of 2, 5, 15, 50, and 150 mg/kg BID was evaluated in the orthotopic BRCA1 mutant MDA-MB-436 TNBC xenograft model. Rucaparib administration resulted in dose-dependent and statistically significant reduction in mean tumour volumes on the last day of dosing (Day 28) in all rucaparib treated groups, with > 100% TGI observed at 50 and 150 mg/kg BID. At study termination (Day 39) there was a dose-dependent and statistically significant TGI in all rucaparib treated groups.

Dose, Exposure and Response Relationship of Rucaparib in the MDA-MB-436 (BRCA1 Mutant) Orthotopic Breast Cancer Model

The dose, exposure and response relationship of rucaparib was evaluated in the studies performed in the orthotopic MDA-MB-436 TNBC xenograft model. In mice treated with rucaparib at a dose of 50 and 150 mg/kg BID, PAR was inhibited by 86% and 96%, respectively. Administration of rucaparib at 50 and 150 mg/kg BID resulted in TGI of 105% and 112%, respectively. Thus in this rucaparib sensitive model, ≥ 86% PAR inhibition in the tumour resulted in > 100% TGI. In contrast, dosing at 15 mg/kg BID resulted in only 45% PAR inhibition and lower anti-tumour activity, with a TGI of 58%. Direct correlations were observed between rucaparib plasma exposure (C_{max} and AUC_{0-12}), tumour rucaparib levels, and TGI. Comparing the exposures in mice treated with 50 mg/kg rucaparib BID and patients treated with 600 mg rucaparib BID, the estimated human-to-mouse ratio of unbound rucaparib AUC_{0-12} was 1.9. Thus, the exposures of unbound rucaparib in patient plasma are higher than that required for significant and durable anti-tumour responses in nonclinical models.

Rucaparib Efficacy in the HBCx-17 (BRCA2 Mutant) TNBC PDX Model and in the HBCx-6 (BRCA Wild-type) TNBC PDX Models

The anti-tumour effects of rucaparib as a single agent were evaluated in the BRCA2 mutant HBCx-17 and BRCA wild-type HBCx-6 TNBC PDX models. Both models have mutated TP53. Rucaparib was administered at doses of 50 mg/kg QD, 150 mg/kg QD and 150 mg/kg BID for 24 and 28 days in the HBCx-17 and HBCx-6 models, respectively. Rucaparib treatment at all doses evaluated resulted in significant reduction in tumour growth, with mean tumour/control (T/C) volumes ranging from 7.0-15.2% and 0.6-14.7% in the HBCx-17 and HBCx-6 models, respectively. In both studies, tumours were monitored for 13-15 days after rucaparib dosing was discontinued. In the HBCx-17 model, 50% of the mice treated with 150 mg/kg BID rucaparib had a PR or CR, whereas in the HBCx-6 model 100% of the mice treated with 150 mg/kg QD or 300 mg/kg BID rucaparib had a PR or CR.

Rucaparib Efficacy in 3 BRCA2 Mutant Pancreatic PDX Models

The efficacy of 150 mg/kg BID rucaparib was evaluated in the PAXF 1876, PAXF 2005 and PAXF 2094 pancreatic PDX models that have deleterious BRCA2 frame shift mutations On Day 28 of dosing, rucaparib showed differential sensitivity in the 3 models, with a T/C of 4.5%, 26.1%, and 55.6% for the PAXF 2005, PAXF 2094, and PAXF 1876 models, respectively.

Secondary pharmacodynamic studies

Secondary pharmacology assays included the off-target activity of rucaparib in radioligand binding assays, the potency of rucaparib against 530 wild type and mutant kinases by functional enzymatic profiling, and the follow-up profiling against 15 recombinant kinases and cellular reporter assays against three PIM family kinases.

The potential for off-target pharmacological activity of rucaparib was evaluated against 39 primary molecular targets, in a receptor screening assay that included transmembrane and soluble receptors, ion channels, and

monoamine transporters. At a concentration of 10 µM, rucaparib exhibited ≥50% inhibition against 2 targets, the non-selective sigma and sodium channel site 2. The IC_{50} values for these 2 receptors were 1.1 µM (Ki = 1.07 µM), and 2.67 µM (Ki = 2.39 µM), respectively. Functional tissue assays concluded that rucaparib showed neither agonist nor antagonist activity against the sodium channel 2, but showed weak functional antagonist activity (37%) against the non-selective sigma channel. The 30 µM concentration of rucaparib evaluated in the functional tissue assays was approximately 17-fold higher than the plasma rucaparib unbound C_{max} of 1.79 µM observed in patients at 600 mg BID. Rucaparib was also evaluated at a concentration of 10 µM against 5 endocrine related targets in a focused screening assay. No significant inhibition (≥ 50%) of the oestrogen receptor α (2 separate assays), oestrogen receptor β, progesterone receptor B, testosterone (2 separate assays) or thyroid receptor was noted. This concentration (10 µM) of rucaparib was approximately 6-fold higher than the plasma rucaparib unbound C_{max} of 1.79 µM observed in patients at 600 mg BID.

The selectivity of rucaparib against 384 wild-type and 146 mutant recombinant human kinases was evaluated at 1 µM using functional biochemical assays. A total of 3 enzymes demonstrated ≥70% inhibition by rucaparib: cyclin-dependent kinase (CDK) 16 (86%), the PIM3 protooncogene (PIM3, 83%), and CDK17 (70%). Additional biochemical profiling demonstrated that the IC_{50} of rucaparib against 11 kinase targets (including PIM1 and PIM3) was lower than the unbound mean plasma C_{max} (1.79 µM) observed in patients treated with 600 mg BID rucaparib. However, the IC_{50} of rucaparib for PIM1, PIM2, and PIM3 in cellular reporter assays was > 40 µM. These data suggested that rucaparib is not likely to have activity against PIM1 and PIM3 at exposures achieved in patients.

Safety pharmacology programme

As part of the development program for rucaparib, several stand-alone safety pharmacology studies were conducted. Additionally, cardiovascular, respiratory and central nervous system (CNS) safety pharmacology endpoints were incorporated into study designs for the pivotal repeat-dose toxicity studies in rat and dog. This approach is consistent with ICH S9, which specifies that stand-alone safety pharmacology studies are not generally required to support studies in patients with advanced cancer. The cardiac safety of rucaparib was evaluated in an *in vitro* assay for hERG activity, in a safety pharmacology study using conscious telemetry-instrumented dogs given rucaparib IV, and by monitoring ECGs in these dog studies: PO repeat-dose toxicity studies of 30 and 91 days and the 5-day IV repeat-dose toxicity study.

The IC_{50} for the inhibitory effects of rucaparib on hERG potassium currents was 22.6 µM which is approximately 13-fold higher than the mean unbound plasma C_{max} (1.79 µM) observed in patients treated with 600 mg BID rucaparib.

No adverse cardiovascular effects were noted in conscious telemetry-instrumented dogs that received rucaparib IV at up to 15 mg/kg. This dose corresponded to a C_{max} of 2542 ng/mL, which is 1.3-fold higher than the total plasma C_{max} (1940 ng/mL) observed in patients treated with 600 mg BID rucaparib. In the repeat-dose studies in dogs given rucaparib orally, no ECG changes were observed at doses up to 75 mg/kg/day (30-day repeat-dose study) and 20 mg/kg/day (91-day study) as well as no alterations in haemodynamic parameters or vital signs noted in the 91-day repeat-dose study. At 75 mg/kg, the C_{max} of 1680 and 2460 ng/mL for male and female dogs, respectively, was similar to the C_{max} bound plasma concentration (1940 ng/mL) observed in patients treated with 600 mg BID rucaparib.

Conversely, when rucaparib was given IV at 40 mg/kg for 5 days, ECG abnormalities described as persistent sinus tachycardia, atrioventricular nodal rhythm, were recorded in the dog. From the ECG tracings, the veterinary cardiologist concluded that nodal and ventricular arrhythmias identified in one dog indicated a

potential for rucaparib to induce arrhythmias and suggested that arrhythmia may have been related to the death of two dogs that died immediately post-dosing on Day 1.

Cardiac lesions were observed in rats and dogs following IV but not after PO dosing of rucaparib. In ten PO general toxicity studies (rat and dog combined) cardiac changes were not identified. Conversely, 4 GLP IV toxicity studies (rat and dog combined) were conducted and cardiac microscopic changes (myocardial degeneration (rat) and endocardial haemorrhage (dog)) were detected in two of these studies. Exposure data indicated that cardiac lesion development following IV dosing was likely C_{max} driven as cardiac effects were correlated to high C_{max} values after IV dosing.

In the repeat-dose toxicity studies in dog given rucaparib orally, there were no abnormalities in ECGs at doses up to 75 mg/kg/day (30-day repeat study), which corresponded to a mean C_{max} of 2070 ng/mL (C_{max} of 1680 and 2460 ng/mL for male and female dogs, respectively). Measurements of external ECGs, as well as vital signs (heart rate, body temperature, pulse oximetry, and respiratory rate), were also evaluated in the 91-day repeat-dose study in dog, with no findings at doses up to 20 mg/kg/day (C_{max} of 416 and 377 ng/mL for males and females, respectively). ECG abnormalities described as persistent sinus tachycardia and atrioventricular nodal rhythm were recorded when rucaparib was administered IV at a dose of 40 mg/kg for 5 days in dog. Therefore, it is concluded that rucaparib induce abnormal arrhythmias at IV doses of 40 mg/kg/day and 75 mg/kg/day in dog and rat, respectively.

Cardiac effects were observed in rats and dogs treated with rucaparib, but after IV administration at high doses, ≥ 75 mg/kg/day in rats and ≥ 40 mg/kg/day in dogs. In addition, microscopically, cardiac changes were described as myocardial degeneration in rat and a higher incidence of endocardial haemorrhage in dog when administered IV. No effects were observed with oral dosing of rucaparib to dog (75 mg/kg) and to rat (500 mg) in repeat-dose toxicity studies. However, the C_{max} exposure in these animals showed safety margins of 1.0 and 0.9 respectively. Therefore, a potential risk for humans cannot be discounted.

There were no rucaparib-related effects on functional observation battery and motor activity parameters measured as part of the 91-day repeat-dose study in rat at doses up to 100 mg/kg/day.

Exposures of rucaparib in the brain were not measured in the 91-day study in rat. However, in the [^{14}C]rucaparib rat study radioactivity was non-detectable or very low in the brain and spinal cord in rats following a single oral dose of 150 mg/kg (400 µCi/kg) rucaparib. No rucaparib-related clinical signs which were considered to be CNS-related were noted in the 91- day repeat-dose study in dog. Based on *in vitro* human transporter studies rucaparib is a substrate of human P-glycoprotein (P-gp) and breast cancer resistant protein (BCRP), both present in human blood-brain-barrier. The potential for rucaparib to elicit effects on respiratory function was evaluated by incorporating vital signs in the 91-day repeat-dose study in beagle dogs. Rucaparib administration at any dose level had no effect on respiration rate. The dose of 20 mg/kg was the NOEL for respiratory function in this study, which corresponded to a C_{max} of 416 and 377ng/mL in male and female dogs, respectively.

Pharmacodynamic drug interactions

No pharmacodynamic drug interactions study was submitted which was considered acceptable (see discussion on nonclinical aspects).

2.3.3. Pharmacokinetics

Liquid chromatography-tandem mass spectrometry (LC-MS/MS) assays were developed for PK and TK studies and were further validated in both rat and dog plasma and used to determine the concentrations of rucaparib in GLP toxicity studies.

A total of 9 studies were performed to evaluate the PK or TK of rucaparib following single IV and PO administration in the mouse, rat, and dog. In addition, the repeat PO dose TK of once daily rucaparib was examined in a 7-day non-GLP toxicology study in SD rats, two 7-day non-GLP toxicology studies in beagle dogs, 28-day and 91-day GLP toxicology studies in SD rats, and 30-day and 91-day GLP toxicology studies in beagle dogs. The TK of PO rucaparib was also assessed in a non-GLP dose range finding (DRF) embryo-foetal development study in pregnant SD rats.

Absorption

The absolute oral bioavailability of rucaparib was 17%, 22%, and 74-75% in mice, rats, and dogs respectively. Rucaparib showed moderate plasma protein binding and a high distribution volume with V_{ss} of 6.14, 6.5, and 15.2 L/kg in mouse, rat and dog, respectively. This is consistent with the preferential rucaparib distribution in RBCs with RBC-to-plasma ratios of 2 to 5.21 in animal species and wide tissue distribution in rats. The terminal elimination half-life ($T_{1/2}$) following IV dosing was 1.3, 3.5, and 4.5 hours in mice, rats, and dogs, respectively.

Following repeat oral administration, T_{max} was variable in both rat and dog, ranging from 2 to 8 and 1 to 7 hours, respectively. In rats, systemic exposure, as measured by peak plasma concentration (C_{max}) and area under the plasma concentration-time curve from 0 to 24 hours postdose (AUC_{0-24}), increased approximately dose proportionally between 10 and 40 mg/kg/day and less than dose proportionally in the tested dose range of 40 to 1000 mg/kg/day. In dogs, systemic exposure, as measured by C_{max} and AUC_{0-24}, were slightly less than dose proportional in the tested dose range of 10 to 80 mg/kg/day. There were generally no sex-related differences in the exposure to rucaparib. Following repeated dosing, there was no apparent accumulation of rucaparib and $T_{1/2}$ was not changed.

Following once daily 30-min IV infusion of rucaparib phosphate in rats for 5 days, 10 days, and 6 months, and in dogs for 5 days, the C_{max} and AUC from time 0 to 24 hours after the end of a 30-min infusion (AUC_{0-24}) increased approximately dose proportionally in the tested dose range of 1 to 75 mg/kg/day in rats and 15 to 40 mg/kg/day in dogs. No apparent sex-related difference was observed in rats or dogs.

Distribution

Rucaparib showed moderate plasma protein binding. The average protein binding in mouse, rat, dog, and human plasma was 61.9%, 56.4%, 66.8%, and 70.2%, respectively. At 100 µM in dog and human plasma, rucaparib protein binding was 49.5% and 54.6%, respectively, less than that observed at lower concentrations. Rucaparib showed high distribution volume with V_{ss} of 6.14, 6.5, and 15.2 L/kg in mouse, rat and dog, respectively. The V_{ss} values correspond to 8.5, 9.7, and 25.2 times total body water in respective species. This is consistent with the preferential rucaparib distribution in RBCs (RBC-to-plasma ratios of 2.26 to 5.85 in mice, 4.37 in rats, and 5.21 in dogs) and wide tissue distribution in rats.

The [14C]rucaparib-derived radioactivity was well distributed in most tissues in rats following an oral dose of [14C]rucaparib with tissue concentrations higher than blood at all time-points, consistent with the large distribution volume of rucaparib. The tissues with the highest concentrations were cecum, kidney medulla, adrenal gland medulla, stomach, liver, and small intestine. The tissues with [14C] concentrations similar to blood were Harderian gland, eye uvea, mammary gland region, blood, bone, testis, white adipose, and eye lens.

Spinal cord and brain had very low [14C] concentrations, suggesting minimal passage of rucaparib-derived radioactivity through the blood-brain barrier. Tissue concentrations in male and female SD rats decreased steadily and the concentrations in most tissues were BLQ at 72 hours post-dose, except for excretory organs (liver and kidney), adrenal gland, testis, uterus, and ovary. The concentrations in those tissues were low and near the LLOQ, which indicated that complete elimination was expected.

Following a single PO dose of [14C]rucaparib in male pigmented LE rats, the radioactivity distribution pattern in pigmented and albino rats was qualitatively similar, with the exception of the uveal pigment of the eyes and the pigmented skin where a higher concentration of radioactivity was observed, suggesting an association of radioactive drug-related material with melanin. At 168 hours (7 days) and 1200 hours (50 days, last time-point) after dosing, radioactivity was still detectable in the pigmented skin and uveal pigment of the eyes, respectively. However, rucaparib was not phototoxic (eye and skin evaluated) following 5-day repeat PO dose administration to LE pigmented rats at 750 mg/kg/day.

Metabolism

"*In vitro*", rucaparib showed greater metabolic stability in human (67% remaining), monkey (94% remaining), and rat (97 % remaining) liver microsomes compared with those of the mouse (NA) and dog (57% remaining). In an *in vitro* CYP phenotyping study, recombinant human CYP2D6, and to a lesser extent CYP1A2 and CYP3A4, contributed to the oxidative metabolism of rucaparib. The main metabolite identified *in vitro* in human hepatocytes, M324 (Phase I deamination and oxidation product), was also present in rat, dog, and monkey hepatocytes. The metabolites of rucaparib were profiled in Sprague-Dawley (SD) rats and beagle dogs following a single PO dose of [14C]rucaparib. No marked sex-related difference was observed. In rats, M324 and rucaparib were the major species, accounting for 48.0% and 32.9-40.8% of total radioactivity in pooled plasma, respectively; 27.2-34.4% and 60.9-72.8% in pooled urine, respectively; and 10.9-11.4% and 82.3-89.1% in pooled faeces, respectively. In pooled bile from BDC rats, Phase II metabolites (sulfation and glucuronidation products) and M324 were the major species, accounting for approximately 52.1-64.1% and 30.7-40.0% of total recovered radioactivity, respectively. In dogs, rucaparib and M309 (N-demethylation product) were the main species in the plasma and urine, accounting for 36.5-39.0% and 37.3-63.5% of total radioactivity in pooled plasma, respectively; and 46.9-58.1% and 30.9-41.8% in pooled urine, respectively. M324 was a relatively minor species in plasma and urine. In faeces, M324 and rucaparib were the major species, accounting for 41.8-53.8% and 28.8-29.0% of total radioactivity in pooled faeces, respectively. In patients with a solid tumour, preliminary metabolite profiling following repeated PO doses of 600 mg rucaparib BID (no 14C isotope label) suggested that rucaparib, M324, and M338 (phase II metabolite, subsequent N-methylation product of M324) were the major species in the plasma, accounting for 43.5-55.1%, 16.8-20.0%, and 12.8-24.9% of total rucaparib-related peak areas in the pooled plasma samples, respectively.

Excretion

Following oral administration of [14C]rucaparib, radioactivity was almost completely excreted in 7 days with the majority excreted in the first 24-48 hours. Faecal excretion was the major elimination pathway, with the mean dose recovery of 93.9% and 89% in rats and dogs, respectively, and urinary excretion was a minor pathway (approximately 6% in the rat and dog). Bile excretion accounted for 21.5-32.0% of the radioactive dose in male and female BDC rats, respectively.

Pharmacokinetics Drug Interactions

In vitro, rucaparib reversibly inhibited CYP1A2, CYP2C9, CYP2C19, and CYP3A, and to a lesser extent CYP2C8, CYP2D6, and UGT1A1. Rucaparib induced CYP1A2, and down-regulated CYP2B6 and CYP3A4 in human hepatocytes at clinically relevant concentrations.

In vitro, rucaparib is a substrate of P-gp and BCRP, but not a substrate of hepatic uptake transporters OATP1B1 and OATP1B3, or renal uptake transporters OAT1, OAT3, and OCT2.

Rucaparib is a potent inhibitor of MATE1 and MATE2-K, and a moderate inhibitor of OCT1. Also, rucaparib has the potential to inhibit P-gp in the gut and BCRP in the gut, liver and kidney. At clinical exposures, rucaparib did not inhibit MRP2, MRP3, BSEP, OATP1B1, OATP1B3, OAT1 or OAT3. Rucaparib inhibits MRP4 with an IC_{50} of 242 µM which is ~1/3 of the C_{max} reached in the gut. This IC_{50}/Cmax for MRP4 inhibition is clinically relevant. This information has been included in the section 5.2 of the SmPC.

Inhibition of MRP3 and MRP2 transporters by rucaparib was tested up to 300 µM. However, this concentration is lower than the C_{max} reached in the gut of patients. In an additional *in vitro* study evaluating the potential of rucaparib to inhibit MRP2 and MRP3 at higher rucaparib concentrations, the effects of rucaparib at concentrations up to 4 mM on MRP2 and MRP3-mediated transport of β-estradiol-17-β-D-glucuronide (E217βG) were tested using inside-out vesicles expressing human MRP2 and MRP3. Rucaparib showed biphasic effects on MRP2 activity. At lower concentrations (148 to 1333 µM), mild increase in MRP2 activity was observed (up to 77% increase at 444 µM). At the top concentration of 4 mM, mild (48%) inhibition was observed. The theoretically calculated rucaparib concentration in the gut is high following a 600 mg dose (0.24 mg/ml or 0.742 mM) assumed total dissolution in 250 mL intestinal fluid. Rucaparib showed concentration-dependent inhibition of MRP3 with an IC_{50} determined to be 899.5 µM (0.29 mg/ml). As rucaparib concentration in enterocytes is expected to be lower, the in vitro inhibition study suggested no interaction of rucaparib with MRP3 at relevant clinical exposure. Rucaparib inhibits MRP4 with an IC_{50} of 242 µM which is ~3 fold lower than the C_{max} reached in the gut. These results have been adequately included in the SmPC, section 5.2.

Additionally, rucaparib inhibited OCT2 with an IC_{50} of 31 µM suggesting potential in vivo OCT2 inhibition.

2.3.4. Toxicology

Single dose toxicity

Administration of rucaparib camsylate via oral gavage was generally well-tolerated in rats given 100, 500, or 2000 mg/kg as a single dose. No rucaparib-related deaths or clinical signs occurred. However, body weight gain and correlating food consumption were negatively affected, especially in females at 2000 mg/kg. Consequently, 2000 mg/kg/day was considered an unacceptable dose level. Rucaparib phosphate was given to male dogs as a single dose via oral gavage in an escalating dose regimen at 5, 30, 60, 125, and 250 mg/kg. At ≥60 mg/kg, clinical signs were emesis and abnormal faeces (non-formed, discoloured, mucoid or watery). In addition, the dog given 250 mg/kg was cold to the touch. Haematological changes included increased reticulocyte counts at all doses. A subsequent GLP single-dose study was conducted in which the mid and high doses were lowered and TK was evaluated. Rucaparib phosphate was given via oral gavage at 5, 20, and 75 mg/kg. It was generally well tolerated at doses up to 75 mg/kg with findings of abnormal faeces and emesis. There were no changes in body weight or food consumption, clinical pathology parameters, including troponin I, or anatomic pathology. The highest tested dose, 75 mg/kg, was defined as the NOAEL, which corresponded to a mean combined male and female C_{max} of 1530 ng/mL and AUC_{0-24} of 8750 ng·hr/mL.

Repeat dose toxicity

Oral administration

In repeat-dose toxicity studies conducted in rat there were no deaths following a single PO dose of 2000 mg/kg/day (approximately 92% of the human AUC) and rucaparib was generally well tolerated. Decreased body weight gain that correlated with lower food consumption was evident at 2000 mg/kg/day. After 7 days of treatment, there was one death at 1000 mg/kg/day that was potentially rucaparib related. Decreased body weight gain that correlated with lower food consumption was noted at ≥ 500 mg/kg/day in males. Haematologic changes as well as tissue alterations involving bone marrow and lymphoid tissues were observed. In the 28-day study, there was a death at 150 mg/kg/day (potentially rucaparib related) and two deaths at the high dose of 500 mg/kg/day (approximately 58-82% of human AUC). Deaths at 500 mg/kg were attributed to marked anaemia based on haematologic and histologic data and were attributed to rucaparib treatment. Reversible clinical signs at ≥ 150 mg/kg/day included thinning hair coat and pale eyes. Decreased body weight gain that correlated with lower food consumption was seen at ≥ 50 mg/kg, but was only considered adverse at 500 mg/kg. No clinical signs in the 13-week study occurred at doses up to 100 mg/kg/day. Decreases in mean body weight and body weight gain at ≥ 40 mg/kg/day correlated with lower food consumption. By the end of the recovery period, mean body weight remained lower at ≥ 40 mg/kg/day. At ≥ 40 mg/kg/day, findings similar to those from the 28-day study were observed, including reversible haematologic changes and tissue alterations involving bone marrow and lymphoid tissues. In these repeat-dose studies all haematopoietic cell lineages of the bone marrow were affected by rucaparib administration, with the erythroid lineage altered the most consistently.

In the dog, rucaparib associated moribund sacrifice occurred at 40 mg/kg/day (which is approximately 12% of human AUC) on Day 18 in the 91-day study. The common clinical presentation in all single and repeat dose studies was abnormal faeces. Emesis was also seen in conjunction with abnormal faeces in the single dose (75 mg/kg/day) and 7-day (80 mg/kg/day) studies. In an initial 7-day in which rucaparib was given as a suspension by oral gavage, no effects on body weight or food consumption were observed. In a subsequent 7-day study in which rucaparib was given orally by capsules, body weight loss and reduced food consumption were noted at 80 mg/kg/day. The high dose in the follow-up 30-day study was set at 75 mg/kg/day. Body weight loss was present early in the dosing phase, but not at study termination, even though food consumption was decreased at 75 mg/kg/day. In the 91-day study, body weight loss and inappetence occurred at the high dose of 40 mg/kg/day. These findings, coupled with a death at 40 mg/kg/day, led to dose reduction to 20 mg/kg/day on Day 27.

The profile of haematologic changes in all repeat-dose studies in the dog was comparable to that seen in the rat. A consistent signal indicating a rucaparib-related effect on haematopoietic tissue was reductions in reticulocytes. Like the rat, all haematopoietic cell lineages of the bone marrow were affected by rucaparib administration, with erythropoietic tissue being affected most consistently. These haematologic changes correlated with histologic findings that revealed bone marrow hypocellularity and lymphocyte depletion involving one or more lymphoid tissues. The main target organs identified for both species in the general toxicology oral program involved the gastrointestinal, haematopoietic and lymphopoietic systems.

Intravenous administration

In the GLP 5-day IV study, rats were given daily 30-minute IV infusions of rucaparib phosphate at 5, 15, or 75 mg/kg/day. Rucaparib-related effects included dose-related clinical signs (decreased activity, weakness, lateral recumbency, laboured breathing, swelling, poor tail condition) and transient, slight reductions in body temperature (75 mg/kg/day). Haematology effects observed at 75 mg/kg/day on Day 6 included increased neutrophils and decreased lymphocytes, monocytes and erythroid parameters (RBC counts, reticulocytes, haemoglobin, haematocrit). Males given 75 mg/kg/day also had decreased platelet counts on Day 6. Decreased albumin and increased globulin levels, accompanied by decreased albumin/globulin ratios, were noted at 75 mg/kg/day on Day 6. These changes were related to the tissue injury at the infusion site in both main study and recovery animals, which was observed primarily at 75 mg/kg/day. Dose-related microscopic findings included bone marrow hypocellularity, lymphoid atrophy in the mandibular and mesenteric lymph nodes, and thymic atrophy (correlated with decreased thymic weights at 75 mg/kg/day). Minimal to moderate myocardial degeneration, necrosis, and fibroplasia usually located at the apex of the heart were observed in males at 75 mg/kg/day. No associated changes in troponin T levels were noted on Day 6. The NOAEL for rucaparib in this study was considered to be 5 mg/kg/day, which corresponded to a mean combined male and female C_{max} and $AUC_{0-24.5}$ of 672 ng/mL and 992 ng·hr/mL, respectively.

Administration of rucaparib was well-tolerated clinically up to 15 mg/kg/day when administered via 30-minute IV infusion to rats for two repeat-dosing cycles of 5 consecutive days of dosing each. Rucaparib-related adverse effects on body weight, body weight gain, and food consumption were noted in males given 45 mg/kg/day. The moribund sacrifice of one TK female given 45 mg/kg/day was of uncertain relationship to rucaparib. Also at 45 mg/kg/day, rucaparib-related, adverse tissue injury at the catheter and/or infusion sites and decreased erythropoiesis in bone marrow were noted at necropsy and persisted in some animals following the recovery phase. In addition, rucaparib-related adverse (but reversible) depletion of lymphocytes in the thymus was noted in animals given 45 mg/kg/day and correlated with decreased thymic weights. The NOAEL was 15 mg/kg/day, which corresponded to a mean combined male and female and C_{max} and $AUC_{0-24.5}$ from Day 12 of the dosing phase of 2670 ng/mL and 6560 ng·hr/mL, respectively.

IV infusion of rucaparib to rats over 30 minutes at 1, 5, or 15 mg/kg/day once daily for 5 consecutive days, followed by a rest period of 23 days, for 6 treatment cycles, was associated with a decrease in reticulocyte count in both sexes at 15 mg/kg/day, a decrease in lymphocyte count in males at 15 mg/kg/day, a slight decrease in thymus weights at ≥ 5 mg/kg/day in males and at 15 mg/kg/day in females and a minimal generalized depletion of the bone marrow in males at 15 mg/kg/day, on completion of the 6th treatment cycle (Day 145). None of these changes was evident in the animals euthanized after the 23-day rest period (Day 169), indicating complete recovery. The NOEL in this study was considered 5 mg/kg/day, which corresponded to a mean combined male and female C_{max} of 578.9 ng/mL and AUC_{0-24} of 882 ng·hr/mL.

In a repeat-dose GLP study, dogs were infused IV for 30-minutes over 5 consecutive days at 15, 25, or 40 mg/kg/day of rucaparib phosphate followed by 24 days of recovery. Deaths occurred at 40 mg/kg/day. Dose-related clinical observations included; decreased activity, defecation, increased respiratory rate, lateral recumbency, salivation, retching, vomiting, tremors and red skin discoloration. At 40 mg/kg/day, ECG abnormalities (persistent sinus tachycardia, atrioventricular nodal rhythm) were noted. Dose-related reversible reductions in platelets and reticulocytes were seen. Thymus weights were decreased across all groups. Dark discoloration in the left ventricular endocardium correlated with endocardial haemorrhage detected microscopically with a higher incidence in animals at 40 mg/kg/day. These cardiac changes were reversible. Reversible, dose-related (≥ 25 mg/kg/day) bone marrow hypocellularity, thymic atrophy and lymphoid atrophy of GALT were additional histologic changes. Although infusion site injury detected across all groups was related

to experimental procedure, infusion site thrombosis at ≥ 25 mg/kg/day was rucaparib-related. A NOAEL was not established. Effects on Day 5 at 15 mg/kg/day, which corresponded to a mean C_{max} of 3602 and 3956 ng/mL and $AUC_{0-24.5}$ of 4724 and 5917 ng·hr/mL for males and females, respectively, were generally mild and well tolerated.

Genotoxicity

Rucaparib was not genotoxic in four *Salmonella typhimurium* and *Escherichia coli* strains, but was a weak bacterial mutagen in a single strain, TA98, in the absence of metabolic activation. Rucaparib induced chromosomal aberrations in cultured human lymphocytes, with or without metabolic activation.

Type of test / study ID / GLP	**Test system**	**Concentrations / Concentration range / Metabolising system**	**Results Positive / negative / equivocal**
Gene mutations in bacteria	Salmonella strains TA 98, TA 100, TA1535, TA1537 E. coli strain WP2uvrA	5.00, 16.0, 50.0, 160, 500, 1600, 5000 µg/plate (-S9) 5.00, 16.0, 50.0, 160, 500, 1600, 5000 µg/plate (+S9)	Negative
In vitro chromosomal aberration assay	Human peripheral lymphocytes	3-hr assay (-S9) 10.8, 15.4,16.8 µg/ml 3-hr assay (+S9) 20.5, 25.6, 32.0 µg/ml 24-hr assay (-S9) 2.41, 3.76, 5.88 µg/ml	Positive

Carcinogenicity

No carcinogenicity study was submitted which is acceptable (see discussion on non-clinical aspects)

Reproduction Toxicity

Male reproductive assessment was included as part of the 3-month repeat-dose studies in rat and dog. In these studies, there were no rucaparib-related effects on sperm total count, density, motility, or morphology in either species at 100 mg/kg/day in the rat (approximately 29% of human AUC) and 20 mg/kg/day in the dog (approximately 9% of human AUC). Thus exposures at the tolerated doses of rucaparib used in the 91-day toxicity studies in rat and dog may be inadequate to assess the effects on spermatogenesis in humans. In three repeat-dose studies equivocal microscopic testicular changes were observed in the rat at 1000 mg/kg/day and at all doses (5 to 80 mg/kg/day) in the dog, as well as some of the control dogs. The female reproductive organs were not identified as target organs in the repeat-dose studies with rucaparib in dog or rat. However, the exposures showed in these studies do not provided sufficient safety margin. Therefore, based on the animal studies, impact on fertility associated with the use of rucaparib cannot be ruled out. Moreover, based on published studies rucaparib, as a PARP inhibitor, has the potential to impair spermatogenesis and reduce fertility at clinically relevant exposures in patients treated with 600 mg BID.

Rucaparib caused maternal toxicity in rats at ≥ 500 mg/kg/day in a dose range finding embryo-foetal development study. Pregnancy occurred in all rats and dose groups. There was a 100% post-implantation loss in all rucaparib-treated groups (100% early resorptions) even at the lowest dose of 50 mg/kg/day. Rucaparib is a developmental toxicant as it was embryotoxic at ≥ 50 mg/kg/day. Rucaparib effects on embryo-foetal survival are an expected outcome, consistent with the pharmacologic blockade of PARP-1 and PARP-2. Thus rucaparib has the potential to cause embryo or foetal harm when administered to a pregnant woman. Rucaparib should not be used during pregnancy. Appropriate warnings and precautions regarding use during pregnancy or breast-feeding are provided in the SmPC (Section 4.6). Females of childbearing potential are advised to use effective contraception during treatment with rucaparib and for 6 months after the final dose. The findings of embryo-toxicity have been included in section 5.3 (Preclinical safety data) of the SmPC.

As per ICH S9, pre-and postnatal toxicology studies are generally not warranted to support marketing of pharmaceuticals for the treatment of patients with advanced cancer.

Juvenile toxicity investigations are not applicable for rucaparib, since relapsed ovarian cancer is unlikely to occur in the paediatric population.

Toxicokinetic data

Following repeat oral administration, T_{max} was variable in both rat and dog, ranging from 2 to 8 and 1 to 7 hours, respectively. In rats, systemic exposure, as measured by C_{max} and AUC_{0-24}, increased approximately dose proportionally between 10 and 40 mg/kg/day and less than dose proportionally in the tested dose range of 40 to 1000 mg/kg/day. In dogs, systemic exposure, as measured by C_{max} and AUC_{0-24}, were slightly less than dose proportional in the tested dose range of 10 to 80 mg/kg/day. There were generally no sex-related differences in the exposure to rucaparib. Following repeated dosing, there was no apparent accumulation of rucaparib and $T_{1/2}$ was not changed.

Following once daily 30-min IV infusion of rucaparib phosphate in rats for 5 days, 10 days, and 6 months, and in dogs for 5 days, the C_{max} and AUC_{0-24} after the end of a 30-min infusion increased approximately dose proportionally in the tested dose range of 1 to 75 mg/kg/day in rats and 15 to 40 mg/kg/day in dogs. No apparent sex-related difference was observed in rats or dogs.

Local Tolerance

Since the clinical route of administration of rucaparib is oral, the oral tolerance of rucaparib was evaluated in the repeat-dose toxicity studies in rat and dog. In the dog, emesis and abnormal stools occurred at doses from 60 to 80 mg/kg in single-dose and 7-day studies and non-formed faeces in males given ≥3 mg/kg/day in the 91-day study.

Other toxicity studies

Immunotoxicity

According to ICH S8 guideline the potential immunotoxicity of rucaparib has been investigated in the repeat-dose toxicity studies in rats and dogs. Changes in the haematopoietic and lymphopoietic systems were observed. Furthermore, these effects on the immune system were reversible based on detailed haematologic and histologic assessments of haematopoietic and lymphopoietic tissues. Importantly, the rucaparib-related

nonclinical findings on the immune system have been predictive of effects associated with immunosuppression and consequent adverse effects in patients.

Metabolites

The major metabolite observed in all the species was the oxidative deamination product M324. However metabolite M338, which is a Phase II N-methylated product of M324, was tentatively identified in patient plasma only. In patients with a solid tumour (Study CO-338-010), preliminary metabolite profiling following repeated PO doses of 600 mg rucaparib BID (no 14C isotope label) suggested that rucaparib, M324, and M338 (phase II metabolite, subsequent N-methylation product of M324) were the major species in the plasma, accounting for 43.5-55.1%, 16.8-20.0%, and 12.8-24.9% of total rucaparib-related peak areas in the pooled plasma samples, respectively. Taking into account the preliminary metabolite profiling results from Study CO-338-010, where patients received repeated oral doses of 600 mg rucaparib BID without [14C] label, the exposures of M324 and M338 metabolites could result greater than 10% of total drug-related exposure in human plasma. Therefore, these metabolites should be characterized. The metabolism of rucaparib is being further assessed in an ongoing definitive [14C]rucaparib study in cancer patients. Once the results of the mass balance and metabolite profiling study in patients are available it is recommended that the applicant submits them and assesses if further investigation of rucaparib metabolites is warranted. *Impurities*

One process related impurity was observed using the commercial manufacturing process for rucaparib camsylate. This impurity was present in toxicology batches of rucaparib camsylate at levels of 0.2% to 0.3% a/a and in early clinical batches in the range of 0.1% to 0.2% a/a. As per ICH S9 and ICH Q3A guidelines, establishing alternative impurity acceptance criteria is justified by considering the patient population and the disease being treated. Based on this approach, the process related impurity was qualified at 0.1% in female dogs in the 91-day study. ICH guideline Q3A also states that the level of any impurity present in a new drug substance that has been adequately tested in clinical studies is considered qualified. The impurity was present in a drug product batch at a level of 0.18% and used in clinical study CO-338-010; thus a level of 0.18% is considered qualified based on clinical exposure. In addition, based on the comparative DEREK (Q)SAR assessment of rucaparib and impurity, the impurity should be considered to present no additional or qualitatively different risk of genotoxicity.

Phototoxicity

A phototoxicity study of rucaparib was conducted in Long-Evans (LE) pigmented rats given rucaparib camsylate via oral gavage for 5 days at a dose of up to 750 mg/kg/day, using a study design consistent with guidance ICH S10 “Photosafety Evaluation of Pharmaceuticals”. Administration of rucaparib and control article to LE pigmented rats elicited no skin reactions or ocular reactions indicative of phototoxicity. The lack of ocular reactions was confirmed by histopathological evaluation. The group of rats administered the comparator article, 8-MOP, showed skin reactions (erythema, oedema and/or flaking) and ocular observations (bilateral diffuse corneal oedema, internal structures were not visible, confirmed by histopathological evaluation) indicative of phototoxicity.

Rucaparib camsylate was not found to be phototoxic in this study. The mean plasma rucaparib concentration was 1513 ng/mL. This was 78% of the mean steady-state C_{max} in patients following 600 mg rucaparib BID, at which photosensitivity has been reported in <15% of patients.

2.3.5. Ecotoxicity / environmental risk assessment

In the Phase I screening environmental risk assessment for rucaparib, the refined PECSURFACEWATER for rucaparib was calculated as 13.8 ng/L, using a refined Fpen for the target patient population. The Fpen has been recalculated using ovarian cancer prevalence data and population for Latvia, the member state with the highest prevalence of the disease for the year 2012. As the action limit of 0.01 µg/L is exceeded, further risk assessment in Phase II of the procedure is required. The Applicant has decided to initiate a Phase II Tier A assessment.

The octanol-water partition coefficient (Kow) was estimated using a validated and recognized method "Shake Flask Method" according to the OECD 107. The log Kow value presented by the applicant for rucaparib is 0.71, which is below the trigger value of 4.5 for conducting a PBT assessment (see table 2 below).

Table 2: Summary of main study results

Substance (INN / Invented Name): Rucaparib			
CAS-number (if available): 1859053-21-6			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	0.71	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}		B/not B
	BCF		B/not B
Persistence	DT50 or ready biodegradability		P/not P
Toxicity	NOEC or CMR		T/not T
PBT-statement :	The compound is not considered as PBT or vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$ refined (e.g. prevalence, literature)		13.8 ng/L	> 0.01 µg/L threshold (Y)

As a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of rucaparib to the environment.

The applicant is recommended to perform the ERA phase II studies as follow-up measure.

2.3.6. Discussion on non-clinical aspects

Rucaparib is an oral small molecule inhibitor of PARP enzymes, including PARP-1, PARP-2, and PARP-3, which is developed as an oral monotherapy for patients with advanced ovarian cancer who have been identified as having a mutation in the BRCA1 or BRCA2 gene based on analysis of DNA extracted from tumour tissue.

In vitro and *in vivo* primary pharmacology studies showed that rucaparib is a selective, small molecule inhibitor of PARP enzymes, including PARP-1, PARP-2, and PARP-3. Consistent with the concept of synthetic lethality, rucaparib showed *in vitro* activity as a single agent in BRCA1/2 mutant cell lines by inhibiting proliferation and *in vivo* activity, in mouse xenograft models. PARP inhibition of mutant BRCA cells is associated with PAR inhibition, with a concomitant increase in DNA damage, caspase 3/7 levels, and cell death. Overall, *in vitro* studies have shown that the mechanism of action of rucaparib involves PARP enzyme inhibition and PARP-DNA complex formation or trapping.

The results from the cancer cell lines studies confirm rucaparib's activity in BRCA mutant cancers, and are consistent with nonclinical and clinical studies showing that BRCA1/2 mutations confer sensitivity to PARP inhibitors in multiple cancer types.

PK/PD studies were performed in subcutaneous and orthotopic MDA-MD-436 (BRCA1 mutant) TNBC xenograft models. The results of these studies suggest that the mechanism of action of rucaparib may include high and/or sustained rucaparib levels in the tumour. Significant anti-tumour efficacy was observed in 4 out of 5 xenograft models with BRCA1 or BRCA2 mutations (MDA-MB-436, HBCx-17, PAXF 2005, and PAXF 2094). In addition, significant anti-tumour activity was observed in the BRCA wild-type HBCx-6 model.

Taken together, rucaparib showed durable *in vivo* efficacy in multiple BRCA1/2 mutant models. Rucaparib was also active in a BRCA wild-type model, consistent with *in vitro* data suggesting that rucaparib is active in cells with other deficits in HRR through synthetic lethality.

The results from the secondary PD studies suggest that rucaparib has a limited potential for off-target effects in humans.

Safety pharmacology studies suggest oral dosing of rucaparib poses a low risk of causing cardiac, neurobehavioral, or respiratory function effects in patients. However, safety pharmacology endpoints were incorporated into study designs for the pivotal repeat-dose toxicity studies in rat and dog. Based on data of pivotal studies cardiovascular effects associated to rucaparib oral treatment in patients cannot be ruled out (see discussion below). Data from the safety pharmacology suggest that rucaparib exposures in the brain of patients are expected to be low.

The results of pharmacology studies are consistent with the proposed mechanism of action of rucaparib and support its use as an oral monotherapy for patients with BRCA1/2 mutation-positive advanced cancers.

The rat and dog were considered relevant species for the general toxicology studies which was supported by in vitro data with cryopreserved hepatocytes showing that the metabolite profiles in SD rats, beagle dogs, and humans were similar.

The absolute oral bioavailability of rucaparib was 17%, 22%, and 74-75% in mice, rats, and dogs respectively. Rucaparib showed moderate plasma protein binding and a high distribution volume with in mouse, rat and dog. This is consistent with the wide tissue distribution in rats. The terminal elimination half-life ($T_{1/2}$) following IV dosing was 1.3, 3.5, and 4.5 hours in mice, rats, and dogs, respectively.

Following daily repeat oral administration, the T_{max} was variable in both rat and dog and ranged from 2 to 8 and 1 to 7 hours, respectively. In rats, the systemic exposure (as measured by C_{max} and AUC_{0-24}), increased approximately dose proportionally between 10 and 40 mg/kg/day but less than dose proportionally between 40 to 1000 mg/kg/day. In dogs, the systemic exposure was slightly less than dose proportional between 10 to 80 mg/kg/day. There were generally no gender related differences in the exposure to rucaparib. Following repeated dosing, there was no apparent accumulation of rucaparib and $T_{1/2}$ was unchanged.

Following a single PO dose of [14C]rucaparib in male and female SD rats, rucaparib-derived radioactivity was well distributed into tissues with concentrations higher than that in blood at all monitored time points. Concentrations in most tissues were below or near the lower limit of quantification by 7 days post-dose (last time-point). Rucaparib showed minimal penetration of rucaparib-derived radioactivity through the blood-brain barrier. Rucaparib appeared to preferentially distribute into tumours in a cancer xenograft model.

In vitro data suggested slow metabolism by CYP enzymes, with CYP2D6 and to a lesser extent CYP1A2 and CYP3A4 contributed to the metabolism of rucaparib. In vivo metabolite profiling in rats, dogs, and patients

showed that a carboxylic acid metabolite (M324) is a common major metabolite in all three species. A Phase II N-methylated metabolite of M324 (M338) was only observed in patients. Consequently this entity has not been tested for general toxicity or genotoxicity in the non-clinical studies. It is acknowledged that in the intended patient population a separate non-clinical evaluation of metabolites is generally not warranted. However, taking into account the preliminary metabolite profiling results from Study CO-338-010, where patients received repeated oral doses of 600 mg rucaparib BID without [14C] label, the exposures of M324 and M338 metabolites could result greater than 10% of total drug-related exposure in human plasma and, based on the structure of the metabolite an assessment of its potential toxicity should be made. The metabolism of rucaparib is being further assessed in an ongoing definitive [14C]rucaparib study in cancer patients. Once the results of the mass balance and metabolite profiling study in patients are available the Applicant is recommended to submit the results of the mass balance and metabolite profiling study and assess if further investigation of rucaparib metabolites is warranted

Following oral administration, faecal excretion was the major route of elimination in the rat and dog. The majority of drug related radioactivity was recovered 24 hours (rat) or 48 hours (dog) following drug administration.

In vitro, rucaparib reversibly inhibited CYP1A2, CYP2C9, CYP2C19, and CYP3A, and to a lesser extent CYP2C8, CYP2D6, and UGT1A1. Rucaparib induced CYP1A2, and down-regulated CYP2B6 and CYP3A4 in human hepatocytes at clinically relevant exposures.

In vitro, rucaparib is a substrate of P-gp and BCRP, but not a substrate of hepatic uptake transporters OATP1B1 and OATP1B3, or renal uptake transporters OAT1, OAT3, and OCT2.

Rucaparib is a potent inhibitor of MATE1 and MATE2-K, and a moderate inhibitor of OCT1. Also, rucaparib has the potential to inhibit P-gp in the gut and BCRP in the gut, liver and kidney. At clinical exposures, rucaparib did not inhibit MRP2, MRP3, BSEP, OATP1B1, OATP1B3, OAT1 or OAT3. For MRP4 inhibition, the IC_{50}/C_{max} is clinically relevant. This information has been included in the section 5.2 of the SmPC.

No interaction with MRP2 or MRP3 was observed in vitro at the clinical exposure of rucaparib, however, mild bi-phasic activation and inhibition of MRP2 and concentration dependent inhibition of MRP3 were observed at concentrations higher than observed plasma C_{max} of rucaparib.

Additionally, rucaparib inhibited OCT2 with an IC_{50} of 31 µM suggesting potential in vivo OCT2 inhibition.

No drug-drug interaction studies with metabolites have been submitted. Once the results of the mass balance and metabolite profiling study in patients are available interaction studies should be performed with all metabolites observed at exposures greater than 10% of total drug-related exposure.

Based on repeated-dose oral toxicity studies in the rat and dog, the non-clinical toxicity of rucaparib was characterised and determined to be similar in both test animal species. Target organs of toxicity involved the haematopoietic, lymphopoietic and GIT systems. In general, the toxicities induced in rats and dogs reversed after a four week period of rucaparib withdrawal. Importantly, no additional targets were identified in animals following prolonged oral dosing (3 months).

The toxicology findings were compared to the adverse events (AEs) observed in patients treated with 600 mg BID rucaparib. The AEs in patients treated with rucaparib involved the haematopoietic, lymphopoietic, and gastrointestinal systems and demonstrated that findings from toxicology species were generally predictive for humans. Gastrointestinal effects in the dog manifested principally as clinical signs (emesis, diarrhoea), but were not dose-limiting and did not affect the general health of the animals. Similarly, nausea, vomiting, and diarrhoea were observed in 74.8%, 45.2%, and 33.7% of patients treated with rucaparib, respectively. Decreases in body

weight and food consumption occurred in the rat and dog. Consistent with these findings, decreases in appetite were also observed in patients. In toxicology studies, haematologic and histopathologic findings demonstrated hypocellularity of the bone marrow. In general, reduction in cellularity of haematopoietic and lymphopoietic tissues correlated with changes in haematologic parameters and thus these effects can be readily monitored clinically. Considering the dog and rat data collectively, it was evident that all cell lineages could be affected by rucaparib administration, but that erythroid tissues were most susceptible to rucaparib effects. Marked anaemia was noted in rats at 500 mg/kg. Similarly anaemia and/or low/decreased haemoglobin were reported in 24.9% of patients treated with 600 mg BID rucaparib. In addition, thrombocytopenia and neutropenia were reported in 3.2% and 5.4% of patients, respectively. The potential for rucaparib to induce changes in the cardiovascular system was assessed non-clinically in vitro and in vivo. Cardiovascular effects were observed in rats and dogs treated with rucaparib after intravenous administration. Taking into account that C_{max} and AUCs reached after oral administration in animals do not suppose a safety margin for patients at clinically relevant doses, cardiovascular effects associated to rucaparib oral treatment cannot be ruled out.

Rucaparib was not mutagenic in an Ames assay and was clastogenic in vitro. The latter result is consistent with the mechanism of action of rucaparib.

Carcinogenicity studies using rucaparib were not submitted in accordance with ICH S9.

Male reproductive assessment was included as part of the 3-month repeat-dose studies in rat and dog. In these studies, there were no rucaparib-related effects on sperm total count, density, motility, or morphology in either species at 100 mg/kg/day in the rat (approximately 29% of human AUC) and 20 mg/kg/day in the dog (approximately 9% of human AUC). Thus exposures at the tolerated doses of rucaparib used in the 91-day toxicity studies in rat and dog may be inadequate to assess the effects on spermatogenesis in humans. In three repeat-dose studies equivocal microscopic testicular changes were observed in the rat at 1000 mg/kg/day and at all doses (5 to 80 mg/kg/day) in the dog, as well as some of the control dogs. The female reproductive organs were not identified as target organs in the repeat-dose studies with rucaparib in dog or rat. However, the exposures showed in these studies do not provided sufficient safety margin. Therefore, based on the animal studies, impact on fertility associated with the use of rucaparib cannot be ruled out. Moreover, based on published studies, rucaparib, as a PARP inhibitor, has the potential to impair spermatogenesis and reduce fertility at clinically relevant exposures in patients treated with 600 mg BID.

Rucaparib caused maternal toxicity in rats at ≥ 500 mg/kg/day in a dose range finding embryo-foetal development study. Pregnancy occurred in all rats and dose groups. There was a 100% post-implantation loss in all rucaparib-treated groups (100% early resorptions) even at the lowest dose of 50 mg/kg/day. Rucaparib is a developmental toxicant as it was embryotoxic at ≥ 50 mg/kg/day. Rucaparib effects on embryo-foetal survival are an expected outcome, consistent with the pharmacologic blockade of PARP-1 and PARP-2. Thus rucaparib has the potential to cause embryo or foetal harm when administered to a pregnant woman. Rucaparib should not be used during pregnancy. Appropriate warnings and precautions regarding use during pregnancy or breast-feeding are provided in the Summary of Product Characteristics (Section 4.6). Females of childbearing potential are advised to use effective contraception during treatment with rucaparib and for 6 months after the final dose. The finding of embryo-toxicity has been included in section 5.3 Preclinical safety data of the SmPC (SmPC text: In an embryo-foetal development study in rats, rucaparib was associated with post-implantation loss at exposures of approximately 0.04 times the human AUC at the recommended dose).

As per ICH S9, pre-and postnatal toxicology studies were not submitted.

Juvenile toxicity investigations are not applicable for rucaparib, since relapsed ovarian cancer is unlikely to occur in the paediatric population.

The lack of phototoxicity in LE pigmented rats could have been due to lower exposures. Considering the photosensitivity that has been reported in <15% of patients, a risk of phototoxicity cannot be ruled out in human at doses clinically relevant. In addition, using the search criteria that includes the MedDRA HLT (higher level term) of Photosensitivity and photodermatosis conditions, and the preferred terms of Photodermatosis, Photosensitivity reaction, Polymorphic light eruption, Solar dermatitis, and Sunburn, a total of 43 patients (10.5%) in the overall safety population and 15 patients (10.5%) with BRCA mutant ovarian cancer experienced photosensitivity (See clinical safety).

Environmental Risk

The log Kow value presented by the applicant for rucaparib is below the trigger value for conducting a PBT assessment.

Further risk assessment in Phase II of the procedure is required and the Applicant has decided to initiate a Phase II Tier A assessment. The applicant is recommended to perform the ERA phase II studies.

Implications of the assessment of non-clinical data for the Safety Specification of the Risk Management Plan (RMP)

The main safety concerns identified in the non-clinical documentation include myelosuppression, nausea and vomiting.

Risk of development of cardiac lesions in patients cannot be ruled out when rucaparib is given orally.

A risk of phototoxicity cannot be ruled out.

2.3.7. Conclusion on the non-clinical aspects

Rucaparib is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP-1, PARP-2, and PARP 3, which play a role in DNA repair. In vitro studies have shown that rucaparib-induced cytotoxicity involves inhibition of PARP enzymatic activity and the trapping of PARP-DNA complexes resulting in increased DNA damage, apoptosis, and cell death.

Rucaparib has been shown to have in vitro and in vivo anti-tumour activity in BRCA mutant cell lines through a mechanism known as synthetic lethality, whereby the loss of two DNA repair pathways is required for cell death.

The findings in nonclinical toxicology studies performed with oral rucaparib were generally consistent with the adverse events observed in clinical studies. In repeat-dose toxicity studies of up to 3 months duration in rats and dogs, the target organs were the gastrointestinal, haematopoietic, and lymphopoietic systems. These findings occurred at exposures below those observed in patients treated at the recommended dose, and were largely reversible within 4 weeks of cessation of dosing.

Although no cardiac effects were observed following oral dosing, based on the findings in the intravenous studies and safety margins, cardiac effects in patients cannot be excluded when rucaparib is given orally.

No effects on male and female fertility were observed general toxicology studies in rats and dogs. However, a potential risk on human fertility cannot be ruled out based on the safety margin observed, and according to rucaparib's mechanism of action (SmPC 4.6).

Based on its mechanism of action and preclinical data, rucaparib may cause foetal harm when administered to a pregnant woman. Relevant wording in the SmPC states that rucaparib should not be used during pregnancy unless the clinical condition of the woman requires treatment with it (SmPC 4.6).

The CHMP considers the following measures necessary to address the non clinical issues:

The Applicant is recommended to provide a complete environmental assessment and submit the updated ERA accordingly as soon as it is available.

2.4. Clinical aspects

2.4.1. Introduction

GCP

No concern was raised during the assessment about compliance with GCP or related regulatory and ethical requirements. The applicant states that the clinical trials were conducted according to GCP and meet the ethical requirements of Directive 2001/20/EC.

Tabular overview of clinical studies

Table 3: Clinical Studies contributing Clinical Pharmacology data

Study Title	Rucaparib treatments	Key Clinical Pharmacology Analyses
A4991014: Parallel arms safety, PK and PD study of rucaparib in combination with several chemotherapeutic regimens in adult patients with advanced solid tumours	Iv single 12-40mg Oral, single, 12 – 360mg Oral QD, 80-360mg	Single dose iv PK Single dose oral PK Steady state oral PK PopPK
CO-338-010: Phase 1/2, open-label, safety, PK and preliminary efficacy study of oral rucaparib in patients with gBRCA mutation ovarian cancer, or other solid tumour	Oral, single 40-500mg Oral, QD, 40-600mg Oral, BID, 240-840mg	Single dose oral PK Steady state oral PK Trough (C_{min}) PK PK of different tablet strengths Food effect Metabolite profiling QTc PopPK/ER
CO-338-017: Phase2, open-label study of rucaparib in patients with platinum-sensitive, relapsed, high grade epithelial ovarian, fallopian tube or primary peritoneal cancer	Oral, BID, 600mg	Trough (C_{min}) PK PopPK/ER
CO-338-044: Phase 1, open-label, multiple probe drug-drug interaction study to determine the effect of rucaparib on PK of caffeine, S-warfarin, omeprazole, midazolam and digoxin in patients with advanced solid tumours	Oral, BID, 600mg	DDI
CO-338-045: Phase 1, single-dose study of the disposition of [14-C]-radiolabelled rucaparib in patients with advanced solid tumours	Oral, single, 600mg	Mass balance Metabolite profiling

Table 4: Clinical Efficacy Studies

Study ID	No. of centres/ locations	Design	Posology	Objective	Subjs entered/ compl.	Duration	Gender Median Age	Diagnosis Incl. criteria	Primary Endpoint
CO-338-010	13 sites, US, UK, Spain, Israel, Canada	Phase 1/2, 3 part, open label, **Part 1 + 2** = non-randomised; **Part 3** = single-dose, 2-period, crossover design	**Part 1**: Escalating doses of 40 -500 mg QD & 240 - 840 mg BID oral rucaparib camsylate **Parts 2A and 3**: 600 mg BID oral rucaparib camsylate in 21-day cycles	**Part 1:** evaluate safety, determine MTD + RP2D, PK **Part 2:** Evaluate ORR in OC population with BRCA mutation **Part 3:** PK	124 pts **Part 1:** 56 pts **Part 2A:** 42 pts **Part 3:** 26 pts Parts 1, 2A and 3 enrolment completed; 5 pts ongoing in Parts 2A and 3	Pts continue until meet protocol defined criteria for removal	**Part 1:** 51F, 5M 51.0 yrs **Part 2:** 42F, 0M 56.5 yrs **Part 3:** 21F, 5M 59.5 yrs	gBRCA mutation ovarian cancer or other advanced solid tumours	**Part 1:** Incidence of Grade 3/4 AEs or lab abnormalities defined as DLTs, PK parameters **Part 2:** ORR per RECIST **Part 3:** PK parameters
CO-338-017	64 sites, N. America, Europe, Australia	Phase 2, non-randomised, open label	600mg oral rucaparib BID for continuous 28-day cycles	**Part 1:** Determine PFS in pts with relapsed platinum-sensitive OC grouped by HRD signature **Part 2:** Estimate ORR in in heavily pre-treated pts with relapsed OC grouped by HRD signature	Study ongoing **Part 1:** 204 pts **Part 2:** 111 pts 19 + 21 pts ongoing at data cut-off	Pts continue until meet protocol defined criteria for removal	**Part 1:** 204F, 0M 64.5 yrs **Part 2:** 111F, 0M 61.0 yrs	Platinum sensitive (Part 1) & heavily pre-treated platinum resistant/ sensitive (Part 2) Pts with relapsed, high-grade OC classified into subgroups by a defined HRD signature	**Part 1:** Investigator assessed disease progression by RECIST 1.1 or death from any cause in molecularly defined HRD subgroups **Part 2:** ORR by RECIST 1.1 in molecularly defined HRD subgroups

2.4.2. Pharmacokinetics

Rucaparib has been formulated in a film-coated tablet containing rucaparib camsylate and is available in 200, 250, and 300 mg tablet strengths. The recommended clinical dose is 600 mg BID.

The drug substance has an equilibrium solubility of 1.4 mg active/mL in water at 25°C, 1.7 mg active/mL in water at 37°C. Aqueous solubility is not pH-dependent between pH 3 to 7. Solubility is lower at pH 1 and 2 and is dependent on the type of acid used to adjust solution pH. Drug solubility in vitro was reduced by the presence of chloride ions. Solubility is higher in biorelevant media with a significant increase in fed state intestinal fluid (FeSSiF) media.

Rucaparib showed moderate/low permeability across a Caco-2 monolayer. Rucaparib showed higher permeability in the B-A direction than in the A-B direction, with ER values evaluated >2, indicating that there was active efflux of this compound in Caco-2 cell at all investigated concentrations.

Rucaparib has a half-life of 11- 30 hours. The accumulation ratio following BID dosing is 3.5 to 6.2, consistent with the elimination half-life.

Pharmacokinetic data is available from 3 studies: an open-label dose escalation Phase 1 study of rucaparib in combination with chemotherapeutic regimens in adult patients with advanced solid tumours (Study A4991014), a Phase 1/2 study in patients with germline breast cancer gene (gBRCA) mutation cancers (Study CO-338-010) and a Phase 2 open-label study in patients with platinum-sensitive, relapsed, high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer (Study CO-338-017 [ARIEL2]).

Methods

The plasma concentration of rucaparib was determined using a validated high-performance liquid chromatography (HPLC) with tandem mass spectrometry (LC-MS/MS) method.

Absorption

Bioavailability

In Study A4991014, the mean absolute oral bioavailability following a single oral dose of 12 to 120 mg rucaparib was 36% (ranged 30.1% to 45.3%).

In Study CO-338-010 Part 3, following 600 mg rucaparib BID dosing, the mean steady-state C_{max} and AUC_{0-12} were 1,940 ng/mL and 16,900 ng·hr/mL, respectively. Median T_{max} was 1.92 hour. The C_{max}/ lowest concentration of a drug just before the next dose (C_{trough}) ratio was approximately 1.2. Steady state rucaparib exposures were achieved after approximately 1 week of rucaparib dosing.

Bioequivalence

During development, tablets of 12 mg, 40 mg, 60 mg, 120 mg, 200 mg, and 300 mg tablet strengths (as active free base) encompassing 4 different formulations, and 12 mg phosphate powder, a sterile injectable formulation, were used in clinical studies. Tablets of 120 mg, 200 mg, 250 mg, and 300 mg strengths are currently available. Only the 200 mg, 250 mg, and 300 mg tablet strengths are intended for commercialization.

Table 2.7.1-2. Tablets and Formulations Used in Clinical Studies

Dosage Strength	Formulation [a]	Dosage Form	Drug Substance	Clinical Study [b]
12 mg/vial	A	powder for injection	rucaparib phosphate	A4991014
12 mg	B	tablet	rucaparib camsylate	A4991014
40 mg	C	film-coated tablet	rucaparib camsylate	A4991014 CO-338-010
60 mg	C	film-coated tablet	rucaparib camsylate	A4991014 CO-338-010 CO-338-017
120 mg	D	film-coated tablet	rucaparib camsylate	CO-338-010 CO-338-017
200 mg	E	film-coated tablet	rucaparib camsylate	CO-338-010 CO-338-017 CO-338-044 CO-338-045
250 mg	E	film-coated tablet	rucaparib camsylate	Planned
300 mg	E	film-coated tablet	rucaparib camsylate	CO-338-010 CO-338-017 CO-338-044 CO-338-045

[a] Formula composition are described in Table 2.7.1-3.
[b] Clinical study information can be found in Synopses of Individual Studies (Section 2.7.6).

Table 2.7.1-3. Formula Composition of Formulations Used in Clinical Studies

Ingredient	Quality Standard	Function	Amount (% w/w) per Unit Formulation				
			A Powder for Injection, 12 mg Clinical	B Tablet, 12 mg Clinical	C Tablet, 40 mg & 60 mg Clinical	D Tablet 120 mg Clinical	E Tablet 200 mg, 250 mg, & 300 mg Clinical & Commercial
Core Tablet or Vial Fill							
Rucaparib Phosphate[1]	In-house	Active	7.20				
Mannitol	Ph.Eur	Diluent	92.80				
Water for Injection[2]	Ph.Eur	Process Aid	---				
Nitrogen[2]	Ph.Eur	Process Aid	---				
Rucaparib Camsylate[1]	In-house	Active		17.18	17.18	32.22	73.65
Dicalcium Phosphate	Ph.Eur	Diluent		26.27	26.27	19.16	
Microcrystalline Cellulose	Ph.Eur	Diluent		52.55	52.55	45.08	17.60
Sodium Starch Glycolate	Ph.Eur	Disintegrant		3.00	3.00	2.81	6.00
Colloidal Silicon Dioxide	Ph.Eur	Glidant					1.00
Magnesium Stearate	Ph.Eur	Lubricant		1.00	1.00	0.73	1.75
	%Total per Core Tablet or Vial		100.0	100.0	100.0	100.0	100.0
Coating							
Opadry II White (33G285230)	Vendor	Film-Coat			3.0		
Opadry II Orange (33G13726)	Vendor	Film-Coat				3.0	
Opadry II Blue (85F120057)[3]	Vendor	Film-Coat					3.5[3]
Opadry II White (85F18422)[3]	Vendor	Film-Coat					3.5[3]
Opadry II Yellow (85F105111)[3]	Vendor	Film-Coat					3.5[3]
Water for Pharmaceutical Use[2]	Ph.Eur	Process Aid			---	---	---

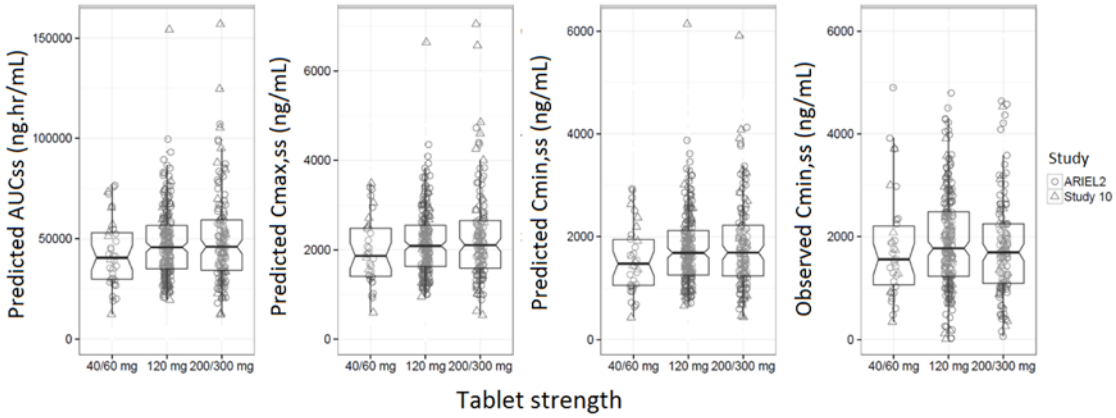
Source: Table 3.2.P.2.2.2 in Drug Product Section (3.2.P.2.2).
Abbreviations: mg = milligram; Ph. Eur. = European Pharmacopoeia
[1] Assumes drug substance assay is 100%. Theoretical potency of rucaparib camsylate is 58.2% w/w. Theoretical potency of rucaparib phosphate is 77.2% w/w
[2] Ingredient is a processing aid which is removed during manufacturing and present in minute amounts in the finished drug product.
[3] Opadry II blue is used to coat the 200 mg strength tablet, Opadry II white is used to coat the 250 mg strength tablet, and Opadry yellow is used to coat the 300 mg strength tablet to a target weight gain of 3.5% w/w.

Tablets of 12, 40, 60, and 120 mg strengths produced during development of rucaparib achieved greater than 85% dissolution within 15 minutes, and tablets of 200 mg, 250 mg, and 300 mg strengths proposed for commercialization achieved greater than 95% dissolution within 15 minutes. Importantly, the 200 mg and 300 mg strength tablets produced and tested by 2 different manufacturers achieved 97 to 103% release within 15 minutes.In Study A4991014, administration of oral rucaparib using 12 mg (Formulation B), and 40 mg and 60 mg strength tablets (Formulation C) did not appear to affect rucaparib PK, as demonstrated by similar T_{max}, and dose-proportional increases in C_{max} and AUC_{0-24}.

Similarly, in Study CO-338-010, rucaparib exposures as measured by C_{max}, and AUC, increased approximately proportionally following QD (40 to 500 mg) and BID (240 to 840 mg) dosing using 40 mg (Formulation C), 60 mg (Formulation C), and 120 mg (Formulation D) strength tablets.

The effect of tablet strength (40/60 mg, 120 mg, 200/300 mg) and formulation on rucaparib PK was assessed by PopPK analysis. Based on model-predicted exposures and observed $C_{min,ss}$, there did not appear to be an effect of tablet strength on rucaparib exposures at the 600 mg rucaparib BID. The “notched” regions of the boxplots are overlapping, suggesting the medians may not be significantly different.

Figure 2.7.1-5. Model-predicted and Observed Steady-state Exposures Stratified by Tablet Strength at 600 mg BID



Source: Figure 14, Report QS-CLV-06, Section 5.3.3.5
Abbreviations: AUCss = area under the curve at steady state; BID = twice daily; Cmax,ss = maximum plasma concentration at steady-state; Cmin,ss = minimum plasma concentration at steady-state; mg = milligram; mL = milliliter; ng = nanogram; Study 10 = CO-338-010; ARIEL2 = CO-338-017

Influence of food

According to results of part 3 of Study CO-338-010, at the proposed clinical dose of 600 mg rucaparib, a high-fat meal increased the C_{max} and AUC_{0-24} of rucaparib by approximately 20% and 38%, respectively, and delayed the T_{max} by a median of 2.5 hours.

Table 2.7.1-8. Summary of Analysis for Effect of a High-fat Meal on C_{max} and AUC_{last} of Rucaparib at 600 mg (Study CO-338-010 Part 3)

PK Parameter (Units)	N	Geometric Least Square Means			90% CI		ISCV (%)
		Fed	Fasted	Fed/Fasted Ratio (%)	LCL	UCL	
C_{max} (ng/mL)	26	757.35	630.15	120.18	99.05	145.83	42.38
AUC_{last} (ng·hr/mL)	26	10918.51	7919.71	137.87	117.05	162.37	35.42

Source: Table 3-6 and Table 14.2.7.1 in Appendix 16.1.17 of CO-338-010 CSR, Section 5.3.4.2
Abbreviations: AUC_{last} = area under the plasma concentration versus time curve from time zero to the last measurable concentration; CI = confidence interval; C_{max} = maximum observed plasma concentration; hr = hour; ISCV = intra-subject coefficient of variation; LCL = lower confidence limit; mL = milliliter; mg = milligram; N = number of patients; ng = nanogram; UCL = upper confidence limit
AUC was calculated based on PK sampling up to 24 hours postdose.

Figure 1. Typical PK Profiles Demonstrating Effects of Fasted Dosing and Dosing After a High-fat or Patient-selected Meal on day 1 and at Steady-state After 600 mg Rucaparib BID

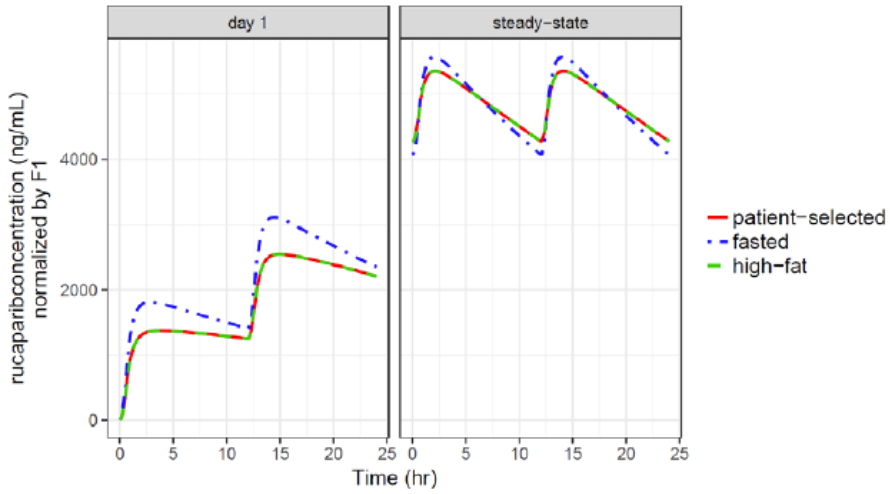
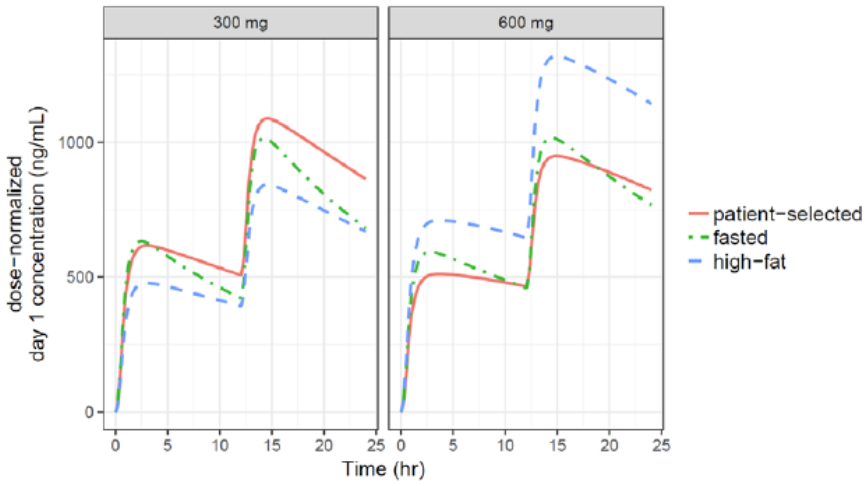


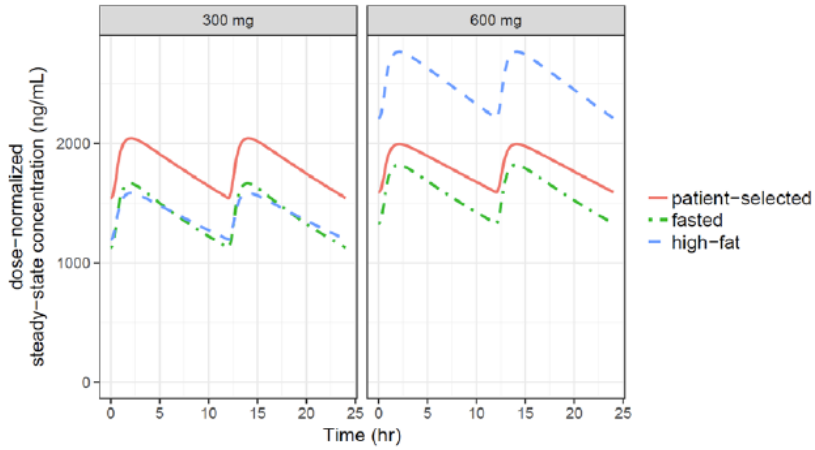
Figure 2. Typical PK Profiles on Day 1 after 300 or 600 mg Rucaparib BID Dosing



The effect of food on rucaparib PK was also assessed in the PopPK analyses. The oral bioavailability of rucaparib at doses > 480 mg with a high-fat meal, under fasted conditions, and with a meal of patient's choice was 51.7%, 32.6%, and 37.2%, respectively. The oral bioavailability of rucaparib at doses ≤ 480 mg with a high-fat meal or under fasted conditions was 29%. According to Figure 2, the impact of food effect on fasted and patient-selected meal groups is similar between 300 and 600 mg rucaparib BID, but higher exposures are achieved in the high-fat meal group at 600 mg relative to 300 mg.

There is an increase (14.5%) on the bioavailability in the high-fat meal group with dose greater than 480 mg, vs patient's choice group. However, there is an opposite effect (decrease of 8.2%) on bioavailability in the high-fat meals group with dose lower than 480 mg, vs patient's choice group.

Figure 3. Typical PK profiles at Steady-state after 300 or 600 mg Rucaparib BID Dosing



Distribution

In vitro, rucaparib has moderate plasma protein binding of 70.2% at clinical exposures and [14C]rucaparib preferentially distributed into red blood cells (RBCs) with a blood-to-plasma ratio of 1.83. Rucaparib showed large steady state volume of distribution with V_{ss} of 113 to 262 L following a single IV dose of 12 mg to 40 mg rucaparib, suggesting distribution to tissues.

Elimination

Excretion

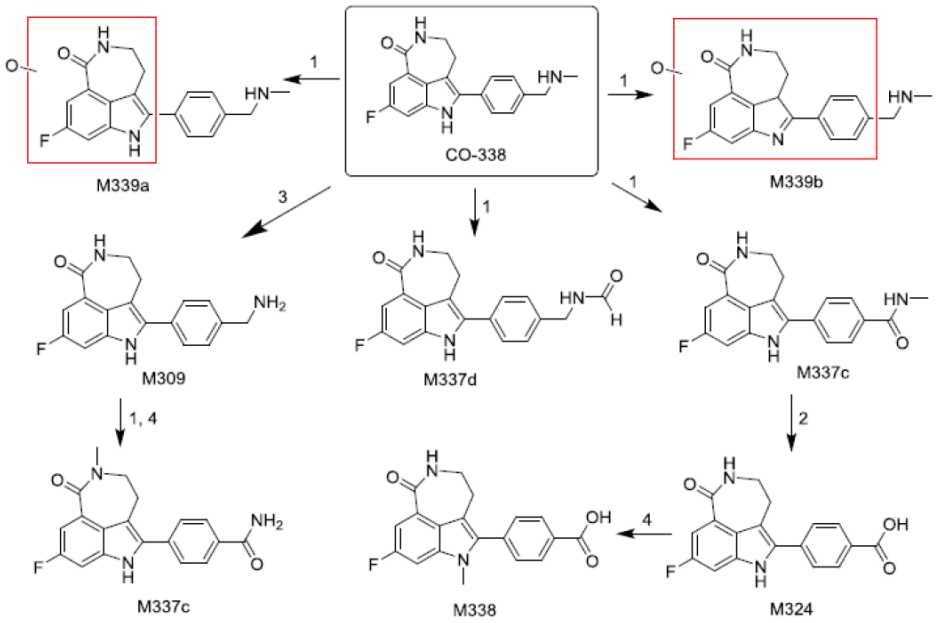
Following a single IV dose of 12 to 40 mg rucaparib, the clearance (CL) ranged from 13.9 to 18.4 L/hr with a half-life of 17 hours. No data is available on V_{ss} and CL following a single oral dose of 600 mg rucaparib. The mean half-life ($T_{1/2}$) was 17 to 19 hours, following a single dose of rucaparib 600 mg.

Metabolism

In vitro data suggested slow metabolism by CYP enzymes, with CYP2D6 and to a lesser extent CYP1A2 and CYP3A4 contributing to the metabolism of rucaparib.

Preliminary metabolite profiling was performed using steady state plasma samples collected from 3 patients in Study CO-338-010 treated with 600 mg rucaparib BID. The biotransformation pathways for rucaparib have been characterised as hydroxylation or oxidation, N-demethylation, deamination, and phase II methylation. Preliminary in vivo metabolite profiling in patient plasma suggested a carboxylic acid metabolite (M324, 32% to 46% of rucaparib) and a Phase II N methylated metabolite of M324 (M338, 23% to 57% of rucaparib) as major metabolites. Metabolites M337c and M337d were proposed as oxidation, N-demethylation, and/or N-methylation products. Metabolites M339a and M339b were identified as hydroxylation or oxidation products. Metabolite, M309, was identified as N-demethylated rucaparib.

Figure 2.7.2-6. Proposed Biotransformation Pathway of Rucaparib in Cancer Patients



Source: Figure 1, Report 130808.03 (Appendix 16.1.18 to CSR CO-338-010)
Note: 1. Hydroxylation or oxidation; 2. Deamination; 3. N-demethylation; 4. Phase II methylation
Two metabolites (M337c) had the same HPLC retention time.
Red box for M339a and M339b indicates uncertainty of the oxidation site.

Table 2.7.2-14. Study CO-338-010 - Relative Amount of Detected Metabolites and Rucaparib from Pooled Plasma following 600 mg Rucaparib BID Dosing for 2 Weeks (Part 3)

Metabolite	Mean%	%CV
M339a	1.41%	13.83%
M339b	0.53%	32.17%
M309	0.81%	29.52%
M337c	2.19%	6.21%
M337d	8.10%	13.84%
M324	18.40%	8.70%
M338	18.03%	34.45%
Rucaparib	50.53%	12.23%

Source: Table 3, Report 130808.03 (Appendix 16.1.18 to CSR CO-338-010)
Abbreviations: BID = twice daily, CV = coefficient of variation n = 3

The relative abundance of each metabolite was estimated by comparing the metabolite's peak area with the sum of all rucaparib-related peak areas.

Genetic polymorphism

Study CO-338-017 (ARIEL2 study) collected different individuals with CYP2D6 and CYP1A2 phenotypes. The phenotypes data were evaluated in Population PK modelling as covariate. These covariates were not statistically significant during covariate analysis.

Population	Predicted AUC_{ss} (ng.hr/mL)	Predicted $C_{max,ss}$ (ng/mL)	Predicted $C_{min,ss}$ (ng/mL)	Observed $C_{min,ss}$ (ng/mL)
CYP 1A2 genotype				
Normal	43513 (37%) N=28	1998.9 (35%) N=28	1589.2 (41%) N=28	1503.4 (110%) N=28
Hyperinducer	43246 (37%) N=136	1987.9 (35%) N=136	1578.2 (41%) N=136	1691.2 (61%) N=133
Not collected	45244 (45%) N=208	2083 (42%) N=208	1650.6 (48%) N=208	1485.2 (98%) N=198
CYP 2D6 genotype				
Poor	39219 (37%) N=9	1815.1 (34%) N=9	1418.9 (41%) N=9	1603.2 (41%) N=9
Normal	42831 (35%) N=76	1969.6 (33%) N=76	1562.2 (39%) N=76	1686.1 (58%) N=75
Intermediate	44741 (41%) N=71	2052.6 (38%) N=71	1637.1 (45%) N=71	1720.2 (63%) N=69
Ultra-rapid	36840 (32%) N=4	1711.7 (29%) N=4	1326.1 (35%) N=4	1633.3 (62%) N=4
Not collected	45209 (44%) N=212	2081.2 (42%) N=212	1649.3 (48%) N=212	1462.5 (100%) N=202

Source: Table 10 in Report QS-CLV-006, Section 5.3.3.5.
Abbreviations: AUC_{ss} = area under the concentration time curve at steady state, BID = twice a day, $C_{max,ss}$ = maximum plasma concentration at steady state, $C_{min,ss}$ = minimum plasma concentration at steady state, CV = coefficient of variation, NA = not available

Post- hoc estimates of rucaparib CL were compared among patients with different CYP1A2 and CYP2D2 phenotypes. For CYP1A2, the CL values were comparable between normal metabolizers (n = 28) and hyper-inducers (n = 136). For CYP2D6, the CL values were largely overlapping among poor metabolizers (n = 9), intermediate metabolizers (n = 71), normal metabolizers (n = 76), and ultra-rapid metabolizers (n = 4).

Dose proportionality and time dependencies

Following rucaparib administration at 40 to 500 mg QD and 240 to 840 mg BID, the plasma exposures of rucaparib was approximately dose proportional.

Table 10-7 Rucaparib Dose Proportionality Test (Part 1, Cycle 1 Day 15)

Dosing Frequency	Y	Log Y= $\beta_0+\beta_1$*Log Dose			R^2
		β_1(SE)	90%CI_low for β_1	90%CI_upper for β_1	
QD	C_{max}	0.92 (0.129)	0.69	1.15	0.795
	AUC_{last}	0.98 (0.147)	0.72	1.25	0.775
BID	C_{max}	1.03 (0.353)	0.42	1.63	0.261
	AUC_{0-12}	1.04 (0.366)	0.42	1.67	0.253

Programming note: Excluding food effect cohort. AUC_{0-12} was calculated using extrapolated concentration at 12 h.
Source data: T_14_2_4_1and T_14_2_4_2

Following BID administration of 240 mg to 840 mg rucaparib, the mean accumulation of C_{max} and AUC were in the range of 2.6 to 4.9 for C_{max}, 3.5 to 6.2 for AUC_{last}, and 1.47 to 5.44 for AUC_{0-12}. Data provided do not allow comparison of different structural PK parameters (ka, CL, V1, etc) across time.

Table 2.7.2-9. Study CO-338-010 - Single Dose and Steady State Plasma PK Parameters of Rucaparib following QD or BID Administration

Dosage	N	Day	C_{max} (ng/mL)	T_{max} (hr)	$AUC_{0-\tau}$ (ng·hr/mL)	CL_{ss}/F (L/hr)	AR	$T_{1/2}$ (hr)
40 mg QD	3	1	129 (28)	2.5 (1-4)	915[b]	NR	NA	13.9 (57)
		15	138 (36)	4 (1-4.05)	1810 (44)	26.7 (59)	1.68[b]	25.7 (23)
80 mg QD	3	1	114 (41)	1.5 (1-2.5)	800 (27)	NR	NA	11.0[b]
		15	175 (37)	2.5 (2.5-2.57)	1740 (20)	47.5 (23)	2.33 (42)	19.5[b]
160 mg QD	4	1	261 (51)	4.0 (4-6.05)	3050 (51)	NR	NA	19.9 (21)
		15	288 (29)[c]	3.75 (2.5-4)[c]	4110 (33)[c]	41.6 (29)[c]	1.84 (31)[c]	33.6 (12)[c]
300 mg QD	3	1	629 (37)	2.5 (1-4.08)	5740 (38)	NR	NA	15.2 (72)
		15	693 (76)	2.53 (2.5-8)	9610 (83)	46.7 (63)	1.6 (53)	29.8[b]
500 mg QD	3	1	949 (52)	4 (4-4)	11000 (61)	NR	NA	15.0 (32)
		15	1390 (23)	4 (4-4.17)	19900 (41)	27.8 (35)	1.94 (17)	20.8 (38)
240 mg BID	3	1	219 (72)	6 (4.05-6)	2800[a]	NR	NA	NR[h]
		15	971 (49)	1.5 (1-4)	10700[b]	27.3[b]	5.44[a]	
360 mg BID	8	1	666 (58)	3.23 (1.5-6)	4860 (58)[f]	NR	NA	
		15	1300 (43)[f]	3.3 (0-6.33)[f]	9430[b]	40.4[b]	4.08[b]	
480 mg BID	9	1	1150 (57)	2.5 (1.5-4)	8810 (63)[g]	NR	NA	
		15	3170 (69)[g]	1.51 (0-6)[g]	26300 (73)[f]	26.2 (63)[f]	3.97 (38)[e]	
600 mg BID	7	1	1030 (61)	4 (2.42-10)	7200 (66)[d]	NR	NA	
		15	2420 (45)	4 (2.53-10)	21400 (61)[d]	58.6 (123)[d]	3.23 (66)[d]	
840 mg BID	3	1	1380 (69)	4 (2.5-8)	13200[b]	NR	NA	
		15	3030 (NR)[b]	4.04 (4-4.07)[b]	29000[a]	29[a]	1.47[a]	

Source: Table 10-3. Study CO-338-010 CSR, Appendix 16.1.17
Abbreviations: AR = accumulation ratio based on AUC; $AUC_{0-\tau}$ = area under the plasma concentration-time curve from 0 to the end of dosing interval (τ=24 hr for QD; τ=12 hr for BID; for BID dosing, concentration at 12 hr was calculation by extrapolation from last observed concentration in the same dosing interval); BID = twice daily; CL_{ss}/F = apparent steady state clearance; C_{max} = maximum plasma concentration; NA = not available; NR = not reportable; QD = once daily; $T_{1/2}$ = half-life; T_{max} = time of occurrence of C_{max}.
Arithmetic mean (CV%) for all PK parameters except median (range) for T_{max}.
[a] n = 1; [b] n = 2; [c] n = 3; [d] n = 4; [e] n = 5; [f] n = 6; [g] n = 8;
[h] $T_{1/2}$ is too long to allow for accurate estimate in BID dosing.

Intra- and inter-individual variability

Inter-individual variability on CL, estimated for all patients, was 48.8%. Inter-individual variability on Ka and D1, for patients in Study CO-338-010 Part 1 and Part 3, and study A4991014, were 63.5% and 111%, respectively. Proportional residual error was 38.2% and two different additive residual errors for intensive (0.83 ng/mL) or sparse sampling (378.9 ng/mL) were estimated.

Pharmacokinetics in target population

The clinical pharmacology investigation has been performed in patients. No investigations have been conducted in healthy volunteers.

Population PK model

The PK model with sequential zero-order and first-order absorption and first-order elimination was selected. The initial model (run011) included estimates of inter individual variability (IIV) on clearance (CL/F), the absorption rate (Ka), the duration of the zero-order absorption (D1), and the relative bioavailability (F1). Relative bioavailability was fixed at 1 in the initial model. Assessment of rucaparib PK in cancer patients showed approximately dose-proportional exposure after QD or BID dosing, absorption with C_{max} achieved within 1.5 to 6 hours, and a large volume of distribution. The oral bioavailability was approximately 36% at 12 to 120 mg and $T_{1/2}$ ranged from 11 to 29.8 hours. Rucaparib was moderately bound to human plasma proteins in vitro.

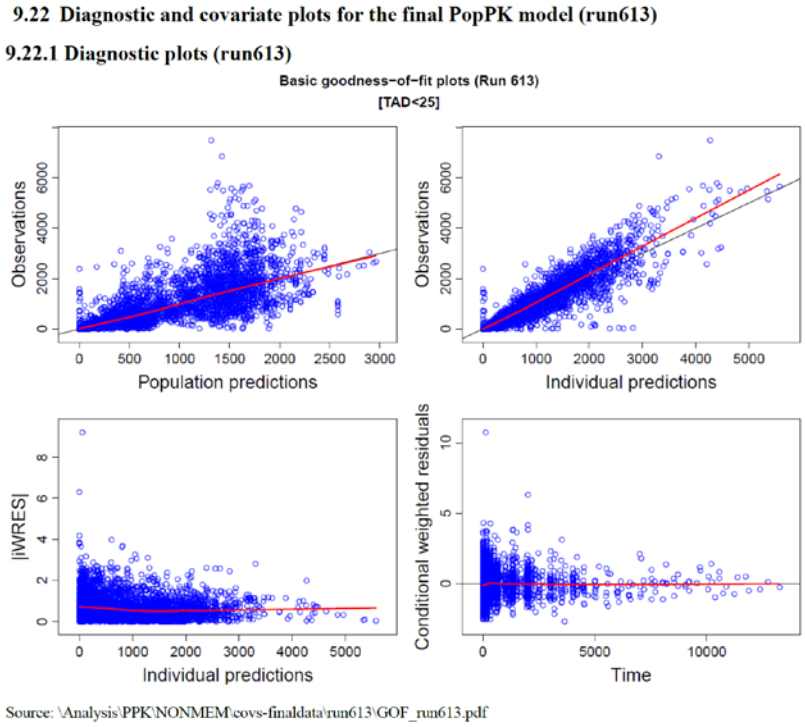
Table 9. Model parameter estimates for the final PPK model

Description	NONMEM Estimate	Bootstrap Estimate	Bootstrap 95% CI	%CV	Shrinkage
θ_1 CL, L/hr	10.26	10.36	(8.573, 12.82)	48.8	8.84
θ_2 Vc, L	16.92	16.98	(13.73, 20.33)	-	-
θ_3 Q, L/hr	17.44	17.9	(14.55, 22.96)	-	-
θ_4 Vp, L	165.9	164.7	(132.5, 199.7)	-	-
θ_5 Ka, hr^{-1}	0.07175	0.0732	(0.05712, 0.0891)	63.5	5.21
θ_6 D1, hr	0.6188	0.6195	(0.4771, 0.812)	111	11.8
θ_7 LF1	-0.5234	-0.5175	(-0.828, -0.1276)	-	-
F1	0.3720	0.3734	(0.3041, 0.4681)	-	-
θ_8 ResErr(Prop), all patients	0.3821	0.3772	(0.3573, 0.3991)	-	-
θ_9 ResErr(Add), intensively sampled patients	0.8314	0.8364	(0.5435, 3.082)	-	-
θ_{10} ResErr(Add), sparsely sampled patients	378.9	377.2	(269.1, 458)	-	-
θ_{11} F1, fasted or a high-fat meal, ≤480 mg	-0.3802	-0.3768	(-0.7392, -0.09048)	-	-
θ_{12} F1, fasted, >480 mg	-0.2017	-0.2686	(-0.7004, 0.1833)	-	-
θ_{13} F1, high-fat, >480 mg	0.5903	0.5518	(0.05534, 1.086)	-	-
θ_{14} Ka, fasted	0.4009	0.4501	(0.1151, 1.072)	-	-
θ_{16} dose on Ka	-0.3249	-0.3012	(-0.4082, -0.1776)	-	-
θ_{17} albumin on CL	0.7202	0.7226	(0.2873, 1.159)	-	-
θ_{18} CLCR on CL	0.3130	0.3213	(0.1969, 0.4463)	-	-
η_1 IIV D1, intensively sampled patients	1.241	1.192	(0.9131, 1.608)	-	-
η_2 IIV KA, intensively sampled patients	0.4035	0.3975	(0.2809, 0.5237)	-	-
η_3 IIV CL, all patients	0.2386	0.2332	(0.1692, 0.3357)	-	-

CL = clearance, CV = coefficient of variation, D1 = duration of the zero-order absorption, F1 = absolute bioavailability, IIV = inter individual variability, LF1 = logit of bioavailability, Ka = absorption rate, Vc = central volume of distribution, Q = inter-compartmental clearance, ResErr(Prop) = proportional residual error, ResErr(Add) = additive residual error, Vp = peripheral volume

Source: .\Analysis\PPK\NONMEM\covs-finaldata\run613\bs\run613.thetas.with.bootstrap.results.csv

Figure 4: Final goodness-of-fit plots



Special populations

No formal studies have been performed with rucaparib neither in patients with renal impairment nor in patients with hepatic impairment.

In the PopPK analyses, 147 (40%) patients had normal renal function (creatinine clearance [CrCL] ≥ 90 mL/min); however, 40% (N = 149) and 20% (N = 76) had mild (CrCL 60 to 89 mL/min), and moderate (CrCL 30 to 59 mL/min) renal function impairment. No measures of kidney function other than CrCL were taken in the clinical study. Following continuous 600 mg BID rucaparib dosing, the model-estimated steady-state AUC for patients with mild and moderate renal impairment was 15% and 33% higher than that of patients with normal renal function, respectively and no starting dose adjustment is required in patients with mild or moderate renal impairment.

The pharmacokinetic characteristics of rucaparib in patients with CrCL less than 30 mL/min or patients on dialysis are unknown. Rucaparib is not recommended for use in patients with severe renal impairment.

In the PopPK analyses, most patients had normal hepatic function (91%, N = 337); however, 9.0% (N = 34) of patients had mild hepatic impairment. Following continuous 600 mg BID rucaparib dosing, the model-estimated steady-state AUC for patients with mild hepatic impairment was 9.3% smaller than that of patients with normal hepatic function therefore no starting dose adjustment is required in patients with mild hepatic impairment.

Gender effect on PK was not conclusive as the majority of patients were female (96%).

In the population of patients treated at 600 mg rucaparib BID, each non-White race was present at < 10% of the population, with 14 Asian patients and 8 Black patients treated. Following continuous 600 mg BID rucaparib

dosing, the model-estimated steady-state AUC for Asian and Black patients was 0.8% and 38.8% higher than that of White patients, respectively. The small sample size prevents any meaningful conclusions.

Baseline body weight (41 to 171 Kg) and BMI (17.3 to 58.5 Kg/m^2) show no relationship with exposure.

Age (20 to 86 years old) showed an apparent impact on exposure. However, no statistically significant effect of age was identified during the covariate search.

Rucaparib is not indicated in children and adolescents. No data are available in this population.

Table 1. PK Parameters Categorized by Age

	Age <65 (Younger subjects number/total number)	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Total N	218/372 (58.6%)	114/372 (30.6%)	39/372 (10.5%)	1/372 (0.3%)
Study CO-338-010	51/372 (13.7%)	15/372 (4.0%)	6/372 (1.6%)	0
Study CO-338-017	167/372 (44.9%)	99/372 (26.6%)	33/372 (8.9%)	1/372 (0.3%)
PK parameter	Geometric mean (%CV)			
AUC_{ss} (ng·hr/mL)	43043 (42%)	45193 (43%)	49637 (35%)	52611
$C_{max,ss}$ (ng/mL)	1984.7 (40%)	2075.6 (40%)	2267.1 (32%)	2381.2
$C_{min,ss}$ (ng/mL)	1566.4 (45%)	1652.3 (46%)	1827.3 (38%)	1958.0
$C_{min,obs}$ (ng/mL)	1498.7 (89%)	1638.8 (72%)	1677.9 (110%)	1940.0

AUC_{ss}, steady-state AUC; $C_{max,ss}$, maximum concentration at steady-state; $C_{min,ss}$, minimum or trough concentration at steady state; $C_{min,obs}$, observed minimum concentration.

The Applicant provided the table with the PK parameters for each age group, as requested. Results from elderly +85 should be considered with caution as only one patient was enrolled in Studies CO-338-010 and CO-338-017.

There are limited clinical data in patients aged 85 or over.

Pharmacokinetic interaction studies

Effect of other medicinal products on rucaparib

In vitro:

In vitro data suggested slow metabolism by CYP enzymes, with CYP2D6 and to a lesser extent CYP1A2 and CYP3A4 contributing to the metabolism of rucaparib.

Rucaparib was shown to be a substrate of P-gp and BCRP, but not a substrate of renal uptake transporters organic anion transporter (OAT) 1, OAT3, and organic cation transporter (OCT) 2, or hepatic transporters organic anion transporting polypeptide (OAPT) 1B1 and OATP1B3.

In Silico - Population Pharmacokinetic:

Pharmacokinetic (PK) drug-drug interaction (DDI) modelling for rucaparib was performed using in vitro parameters and the mean steady state C_{max} of rucaparib (6.0 µM) following 600 mg rucaparib twice daily (BID).

Concomitant usage of strong P-gp, CYP1A2, or CYP2D6 inhibitors did not appear to impact rucaparib PK.

During treatment with 600 mg rucaparib BID, patients who had concomitant use of proton pump inhibitors (PPIs) showed slightly higher (approximately 15% higher F1), but largely overlapping, exposures as compared with the other patients; the effect was deemed clinically insignificant.

Insufficient data were available for other classes of concomitant drugs, including strong CYP3A4 inhibitors and inducers, and strong BCRP inhibitors.

In vivo:

No formal in vivo drug interactions with rucaparib as a victim were conducted.

Effects of rucaparib on other medicinal products

In vitro:

In vitro, rucaparib reversibly inhibited CYP1A2, CYP2C19, CYP2C9, and CYP3A, and to a lesser extent CYP2C8, CYP2D6, and UGT1A1. Rucaparib induced CYP1A2, and down regulated CYP2B6 and CYP3A4 in human hepatocytes at clinically relevant exposures. Rucaparib is an inhibitor of multidrug and toxin extrusion transporter (MATE) 1 and MATE2-K, OCT1 and OCT2. Weak inhibition was observed at 300 µM for multidrug resistance associated protein MRP (4), OATP1B1, OATP1B3, OAT1, and OAT3. That concentration is considered supra-therapeutic for OATP1B1, OATP1B3, OAT1 and OAT3, but not for MRP4. Thus, inhibition of MRP4 in vivo in the gut cannot be ruled out. Rucaparib did not interact with MRP2, MRP3 or bile salt export pump (BSEP) at rucaparib concentrations up to 300 µM. That concentration is considered supra -therapeutic concentration for BSEP, but not for MRP2 and MRP3. For MRP2 and MRP3 this concentration is lower than the C_{max} reached in the gut of patients. Therefore, as requested, an additional in vitro study was performed to evaluate the potential of rucaparib to inhibit MRP2 and MRP3 at higher rucaparib concentrations. This study showed mild bi-phasic activation and inhibition of MRP2 and concentration dependent inhibition of MRP3. The clinical relevance MRP2 and MRP3 interaction in the gut is not known. In vitro, rucaparib is an inhibitor of the BCRP and P-gp efflux transporters with IC50 values suggesting a potential for P-gp and BCRP inhibition in the gut and potential for BCRP inhibition also in the liver and renal.

In silico - Mechanistic static modelling:

The DDI potential of rucaparib through CYP interaction was assessed by calculating the ratio of AUC (AUCR) of CYP probe drugs in the presence and absence of rucaparib coadministration at target clinical exposures using mechanistic static modelling. Hepatic CYP interaction with CYP probe drugs was modelled except for CYP3A4, where reversible inhibition in both the liver and the gut were considered using midazolam as the probe, and for CYP1A2, where a net effect based on both reversible inhibition and induction by rucaparib was modelled.

According to the classification of in vivo inhibitors of CYP enzymes, the DDI potential for rucaparib was moderate for CYP3A (AUCR = 5.0), CYP1A2 (AUCR = 2.9), CYP2C8 (AUCR = 2.6), and CYP2D6 (AUCR = 2.3); but appeared to be strong (AUCR > 5) for CYP2C19 (AUCR = 11) and CYP2C9 (AUCR = 5.2). Given that CYP3A down-regulation was not considered in the current modelling, AUCR for CYP3A could further increase.

In vivo:

Based on the in vitro results, the effects of rucaparib coadministration on the PK of sensitive substrates of CYP1A2, CYP2C9, CYP2C19, CYP3A, and P-gp has been assessed in the ongoing cocktail-based drug-drug interaction study in patients (Study CO-338-044). The PK of CYP cocktail probes (caffeine [CYP1A2], S-warfarin [CYP2C9], omeprazole [CYP2C19]), and midazolam [CYP3A4]) and a P-gp probe (digoxin) were assessed with and without rucaparib treatment. Patients received single doses of CYP drug cocktail (caffeine, warfarin, omeprazole, and midazolam) on Day 1 and Day 12, and single doses of digoxin on Day 2 and Day 13. Continuous treatment with rucaparib 600 mg BID started on Day 5 and lasted until at least Day 16 of Part I. PK samples of the CYP probes were collected up to 96 hr for the CYP probes and digoxin. Vitamin K was given with warfarin on Days 1 and 12, and if clinically necessary, on Days 2 and 13 to mitigate bleeding risk. The patients were genotyped for CYP2C9 and CYP2C19. Based on the genotyping results poor metabolizers of CYP2C9 (n = 2) were excluded from the S-warfarin DDI assessment.

Pharmacokinetics using human biomaterials

Presented above in various sections (mainly as “in vitro”).

2.4.3. Pharmacodynamics

Mechanism of action

Rucaparib (CO-338) is a potent, oral small molecule inhibitor of PARP enzymes, including PARP-1, PARP-2 and PARP-3. The putative rucaparib metabolites M324 and M338 were synthesized, and preliminary in vitro characterization was performed. Data suggest that metabolites M324 and M338 have limited enzymatic and cellular activity against PARP-1, PARP-2, and PARP-3.

Primary and Secondary pharmacology

Dose justification

Rucaparib doses up to 840 mg BID were tested during the dose-escalation phase in Study CO-338-010, but the maximum tolerated dose (MTD) was not reached. The justification for the recommended rucaparib dose of 600 mg BID with or without food is based on the cumulative safety and efficacy evaluations in ovarian cancer patients at the proposed dosage. Selection of 600 mg rucaparib, instead of a lower starting dose, is supported by the exposure-efficacy analysis with higher IRR assessed Response Evaluation Criteria in Solid Tumours (RECIST) response rate at higher exposures.

QT prolongation

The effects of oral rucaparib on QTc prolongation were evaluated in Study CO-338-010 Part 1. ECG data (pre –dose and at 2 and 7 hours post- dose) were centrally read by Cardiocore. The ECG study population comprised 56 patients. The primary endpoint for analyses of QTc was change from baseline (Day -1 prior to Cycle 1) in QTcF (ΔQTcF). The mean values for change of QTcF in Cycle 1 ranged from 5.0 to 14.0 ms. Of the 56 patients enrolled, there were baseline and post-dose ECG measurements for 55 patients. Of these, 6 (11%) patients had at least one post baseline QTcF measurement >450ms and 10 (18%) had increase in QTcF >30ms from

baseline. One patient receiving 480 mg BID rucaparib had a QTcF ≥ 480 msec and it was determined that this patient was receiving citalopram, a medication with known potential to cause QT prolongation that was not prohibited per protocol. This patient continued to receive monotherapy rucaparib at a dose of 480 mg BID with no further QTcF measurement ≥ 480 msec. One patient of 56 had a QTcF increase from baseline > 60 msec and it was subsequently determined that this patient had a history of QT prolongation prior to study entry and received 1 dose of rucaparib before discontinuing from the study due to eligibility violation.

Table 5. Percent of patients with Outlier Findings by Rucaparib Dose level

	Rucaparib dose (mg)									
Criterion	**40 QD (N=6)**	**80 QD (N=3)**	**160 QD (N=4)**	**300 QD (N=9)**	**500 QD (N=4)**	**240 BID (N=3)**	**360 BID (N=8)**	**480 BID (N=7)**	**600 BID (N=3)**	**840 BID (N=3)**
QTcF Interval >450 msec	0	0	0	0	0	33	13	22	29	0
QTcB Interval >450 msec	33	33	75	11	25	67	50	56	57	33
QTcF Interval >480 msec	0	0	0	0	0	0	13	0	0	0
QTcB Interval >480 msec	0	0	0	11	25	0	0	11	29	0
QTcF Interval >500 msec	0	0	0	0	0	0	0	0	0	0
QTcB Interval >500 msec	0	0	0	0	0	0	0	0	0	0
Increase from Baseline of QTcF Interval >30 msec	40	0	0	22	25	0	13	22	0	67
Increase from Baseline of QTcB Interval >30 msec	40	0	0	44	25	0	0	22	14	33
Increase from Baseline of QTcF Interval >60 msec	0	0	0	0	25	0	0	0	0	0
Increase from Baseline of QTcB Interval >60 msec	0	0	0	0	25	0	0	0	0	0
PR >200 msec and an Increase from Baseline >25%	0	0	25	0	0	0	0	0	0	0
QRS >110 msec and an Increase from Baseline > 25%.	0	0	0	0	0	0	0	0	0	0

Source: Table 9, Cardiovascular Safety Report of the Study CO-338-010 CSR (Section 5.3.4.2)
Abbreviations: ECG = electrocardiogram, PK = pharmacokinetics

It seems that there is an increasing rucaparib concentration associated with increasing QTcF from baseline. Additionally, an exposure-QTc analysis has been conducted. The projected drug-related median QTcF prolongation from baseline following 600 mg rucaparib BID was 11.5 msec (90% CI of 8.77 to 14.2 msec), with the upper bound of the two-sided 90% confidence interval of 17.2 msec (90% CI of 12.6 msec to 21.7 msec).

Companion Diagnostic

Clovis has collaborated with Foundation Medicine, Inc (FMI) to develop a Companion Diagnostic (CDx) test. Central testing in the clinical studies was initially performed using the clinical trial assay (CTA) and subsequently bridged to the CDx. Tumour specimens from 79 patients in the primary efficacy (PE) population were received for central BRCA mutation testing at FMI; there was a high positive agreement between local and central BRCA results. The CTA and CDx results appeared consistent. The CDx test does not distinguish between germline and somatic BRCA mutations. The FoundationFocus™ CDxBRCA test was CE marked on 19 January 2017. The FoundationOne® test will be made available in each member state in the EU.

Exposure-Response analyses

Steady-state average PK parameters ($AUC_{avg,ss}$, $C_{minss,avg}$, $C_{max,avg,ss}$) were utilized for exposure-response analysis. For efficacy analysis, the primary variable was $AUC_{avg,ss}$, and $C_{min,ss,avg}$ was explored in a sensitivity analysis. For safety analysis, the primary variable was $C_{max,avg,ss}$, although $AUC_{avg,ss}$ was also explored in the sensitivity analysis. The additional exposure-efficacy analyses tested four endpoints: investigator assessed confirmed response according to RECIST v1.1, independent radiology review (IRR) assessed confirmed response according to RECIST v1.1, maximum percent change from baseline in sum of diameters of tumour target lesions (per RECIST v1.1) from the investigator assessed dataset, and maximum percent change from baseline in serum cancer antigen-125 (CA-125). Investigator and IRR confirmed response, and the best change from baseline in sum of diameters of target lesions were analysed only in the efficacy subset of patients with measurable disease (measurable tumour at baseline). The maximum percent change from baseline in sum of diameters of tumour target lesions is derived from investigator assessments.

The efficacy dataset (N=121) comprised ovarian cancer patients with a deleterious BRCA1 or BRCA2 mutation with at least two prior chemotherapies who received at least 1 dose of rucaparib (40-1680 mg/day). It did not cover a large range of doses with the majority of patients (n=110) receiving 600 mg BID. $AUC_{avg,ss}$ was selected as the exposure metric based on the population PK model and actual doses for each patients.

Investigator-confirmed RECIST Version 1.1 response rate (n = 118, p = 0.201) and the RECIST/CA-125 composite response rate (n = 118, p = 0.137) did not significantly increase with increasing daily dose. No statistically significant relationship was observed between $AUC_{ss,avg}$ and investigator-confirmed RECIST Version 1.1 response rate (n = 114, p = 0.169), maximum change from baseline in SDTL (n = 114, p = 0.136) or RECIST/CA-125 response rate (n = 114, p = 0.396). The response vs. $AUC_{ss,avg}$ regression lines suggested similar responses over the tested dose range and over the 90% confidence interval of $AUC_{ss,avg}$ with a starting dose of 600 mg BID (20145 to 65136 ng·hr/mL). Therefore, clinically observed PK variability is not expected to significantly impact clinical efficacy. Kaplan-Meier survival curves stratified by exposure quartile showed no consistent improvement in PFS or DOR with increasing rucaparib exposures.

Longer PFIs correlated with better efficacy. Patients with PFI < 6 months had a RECIST Version 1.1 response rate of 20.7% compared with 74.2% in patients with PFI > 12 months. For PFS and DOR, compared to patients with a PFI of 6-12 months, patients with a PFI greater than 12 months had a relative risk of 0.42 and 0.45 respectively and patients with a PFI < 6 months had a relative risk of 1.33 and 1.88 respectively, with confidence intervals that overlap 1.

Similarly, in the second set of analyses, no significant exposure-efficacy correlation was observed for confirmed investigator-assessed objective response (n = 114, p = 0.738), maximum percent change from baseline in sum of diameters of target lesions (n = 112, p = 0.297) or maximum percent change from baseline in serum CA-125 (n = 115, p = 0.705). Covariate analysis was also consistent with the first set of analysis. PFI was the only statistically significant covariate affecting independent radiology review (IRR) assessed RECIST response. In

patients with PFI < 6 months, the observed IRR response rate was low [11% (3/27)], while the response rates in patients with PFI of 6-12 months and ≥ 12 months categories were similar and >50% (28/52 for 6 to 12 months and 13/23 for ≥ 12 months). Higher exposure was associated with higher IRR (but not investigator) assessed RECIST response rate, and the correlation was statistically significant in patients with PFI ≥ 6 months (n = 75, p = 0.017).

The small sample sizes in these analyses do not allow definitive conclusions. Further exposure efficacy analyses are warranted with emerging data from ongoing clinical studies.

Exposure-Safety analyses

In total, exposure-safety analysis was conducted with data from 393 ovarian cancer patients. Daily C_{max} was selected as the exposure metric, and individual C_{max} values were calculated from a population PK analysis. The exposure-safety analysis population included ovarian cancer patients who received at least one dose of rucaparib (N=375). The exposure-safety response modelling allows a reasonable understanding of the safety considerations with rucaparib dosing. From a safety viewpoint, changes in liver function, renal function, haematological parameters and asthenia/ fatigue correlated with rucaparib exposure. After accounting for covariates, Grade ≥ 3 alanine aminotransferase (ALT) (p = 0.033), Grade ≥ 3 aspartate aminotransferase (AST) (p = 0.027), Grade ≥3 platelet decrease (p=0.04), maximum haemoglobin change-from-baseline (p<0.001), Grade ≥2 increased creatinine (p<0.001) and Grade ≥3 fatigue/asthenia (p=0.029) had a statistically significant exposure-response relationship. At the median C_{max} following 600 mg rucaparib BID (1774 ng/mL), the mean haemoglobin decrease was 2.5 g/dL with 5^{th} to 95^{th} percentile confidence intervals of 2.2 to 2.6 g/dL. Following 600 mg rucaparib BID, the model-projected incidences were 30.1% for Grade ≥2 creatinine, 13.8% for Grade ≥3 ALT, 4.4% for Grade ≥3 AST, 6.3% for Grade ≥3 platelets, and 11.7% for Grade ≥3 fatigue/asthenia. The effect on creatinine is due to inhibition of MATE 1 and 2k without a change in GFR.

2.4.4. Discussion on clinical pharmacology

A mass balance study (CO-338-045) is ongoing. This study will further elucidate distribution, mean pathways of metabolism, routes of elimination and potential interactions of rucaparib and its metabolites. This data will also allow to confirm the mean absolute oral bioavailability at the 600 mg dose and to clarify the reasons of low bioavailability. The applicant is recommended to submit the results.

Additionally, a dedicated hepatic impairment study in patients with advanced cancer (CO-338-078) is ongoing, which is required for further investigating the impact of moderate hepatic impairment on rucaparib (considered as missing information). Patients with normal hepatic function and moderate hepatic impairment will be included. The Part I CSR of Study CO-338-078 is estimated to be available in Q3 2019. (See RMP)

Solubility of rucaparib is low (1.4 mg active/mL in water at 25°C, 1.7 mg active/mL in water at 37°C). It is expected that 600 mg of rucaparib will be administered with 250 ml of water (2.4 mg/ml). Rucaparib showed a lower solubility at pH of 1 and 2, which suggests a potential impact of food and PPIs effects on PK of rucaparib (see SmPC 4.5).

Rucaparib showed moderate/low permeability across a Caco-2 monolayer. Rucaparib showed higher permeability in the B-A direction than in the A-B direction, with ER values evaluated >2, indicating that there was active efflux of this compound in Caco-2 cell at all investigated concentrations. Ka reflects the coefficient for the total rucaparib amount at the absorption site that transited by a zero-order release kinetics, from the administration compartment. Therefore, due to rucaparib shows a low solubility, Ka would be reduced at higher doses.

Absorption

The Applicant described different modelling approaches to characterize the delayed onset of absorption of rucaparib PK observations. Different models were adopted but all accounted for a delay in the absorption as a consequence of drug disintegration, dissolution, gastric emptying, etc but none of them considered the likely process of precipitation. The Applicant is recommended to provide clear evidence of other absorption models that might reduce IIV on absorption parameters (ka and D1) and better explain the food effect on dose and bioavailability, which could be related to the modest in vitro solubility of rucaparib. Other structural models, incorporating mechanistic absorption processes are recommended to be submitted in a proper population PK report.

Dose has been selected as a significant covariate on ka parameter, decreasing the ka value as dose increases. The influence of dose on any PK parameter is purely empirical and is related to non-linear processes. In the intestinal wall, different transporters are involved in the uptake or efflux of xenobiotics.

Bioavailability

The mean absolute oral bioavailability provided on report is based on much lower doses (≤120 mg) than the one recommended. Considering that dose seems to have impact on Ka and that there are differences between food effect on lower and higher dose than 480 mg, results from the ongoing mass-balance study, which is recommended, are awaited in order to confirm the absolute oral bioavailability at the 600 mg dose and to clarify the reasons of low bioavailability.

Bioequivalence

Different strength and formulations have been used in the pivotal clinical studies. The compositions of strengths with the same formulation are considered proportional. Additionally, these tablets achieved greater than 85% dissolution within 15 minutes. Therefore, bioequivalence study is not considered necessary between doses with the same formulation.

Although a tablet of 250 mg - formulation E has not been used in any clinical study, no further studies are considered necessary because its composition is considered proportional to tablets of 200 mg and 300 mg, formulation E and they achieved greater than 95% dissolution within 15 minutes.

Influence of food

The effect of food on bioavailability of rucaparib appears complicated.

Food intake would enhance the drug absorption as the absorption of rucaparib is incomplete and deemed to be driven by its solubility. However, in the population PK analysis there is an increase in the ka value in fasted conditions (0.1 h-1) compared to patient-selected and high-fat meal (0.072 h-1).

There is an absolute increase (14.5%) on the bioavailability in patient-receiving high-fat meal (dose greater than 480 mg) group vs patient of choice group. However, there is an opposite effect (decrease of 8.2%) on bioavailability in patients receiving high-fat meals (dose lower than 480 mg) group vs patient of choice group.

The influence of high-fat meal was not adequately addressed, considering that high-fat meal increases oral bioavailability at 600 mg (51.7% vs 37.2%), whereas decreases at dose levels below 480 mg (29%). It leads to almost 59% higher exposures in the high-fat meal group vs. the others (patient-selected and fasted). It should be noted that with these results rucaparib apparently showed non-linear pharmacokinetics under high-fat meal conditions, which could have an impact on dose adjustments.

There was limited meal information collected in order to establish any relationship between food and incidence of nausea/vomiting.

Variability seems very similar between high-fat meal and fasted groups, indicating a lack of relationship that would require any food recommendation. However, the IIV on PK of the patient-selected group is missing. The applicant is recommended to further evaluate additional population PK models in order to explain any dose-dependent food effect.

Metabolism

The main metabolites, carboxylic acid (M324) and a Phase 2 N-methylated metabolite of M324 (M338) have been preliminary identified. Pharmacokinetics of the main metabolites were not described by the Applicant. Results from the mass balance study are awaited. The mass-balance study should allow to identify the contribution of the metabolites in the PK of rucaparib. The applicant is encouraged to monitor M324 and M338 metabolites plasma levels in patients after repeated administration and assess if potential for accumulation of these metabolites could be excluded. Considering the relative abundance of metabolites M324 and M338, they should be properly characterised (pharmacodynamic, pharmacokinetic, interactions). Characterisation of M324 and M338 should be performed based on the results of the studies CO-338-045 (mass-balance) and CO-338-078 (hepatic patients). This information is recommended to be provided as soon as the results of these studies become available.

Genetic polymorphism

Enzymes responsible for rucaparib metabolism have not been identified. Based on in vitro data, CYP2D6, and to a lesser extent CYP1A2 and CYP3A4, were able to metabolize rucaparib. In population PK analysis, patients with different CYP2D6 or CYP1A2 genotypes showed comparable rucaparib PK. However, impact of genotypes on pharmacokinetic cannot be fully ruled out based only on population PK analysis. It should be noted that several relevant subgroups of phenotypes have limited representation, especially for CYP2D6.

Dose proportionality and time dependency

Rucaparib appears to be almost proportional to the dose in the range of 40 to 500 mg QD and 240 to 840 mg BID, which includes the recommended dose (600 mg BID).

In population PK model, dose has been selected as a significant covariate on Ka parameter, this fact suggests non-linear pharmacokinetics. However, probably due to long $T_{1/2}$, no-linearity on Ka is not reflected in exposure.

Data provided do not allow comparison of different structural PK parameters (Ka, CL, V1, etc) across time. However, the observed trough PK data do not show time-dependent PK and model evaluation through prediction-corrected visual predictive check from Part 1 (Day 1 and 15) and Part 3 (Day 1 and 15) showed the adequacy of the model to describe the experimental data for each food group of patients, assuming time-independent parameters. As consequence, clinically significant auto-inhibition or auto-induction related to CYP2D6, CYP1A2 or CYP3A4 seem to be unlikely.

Intra- and inter-individual variability

The model selected for inter-individual variability in the population PK model seems acceptable. The estimated variability in the absorption parameters (Ka and D1) appears to be high. After the inclusion of significant covariates, the inter-individual variability did not decrease in a significant manner. Table 9 (model parameter estimates for the final PPK model) does not report the RSE (relative standard error) of the inter-individual variability obtained with the bootstrap analysis. Instead, 95% CIs were reported for the bootstrap estimates of the inter-individual variability to assess the precision of the parameter estimation. The use of a proportional

residual error model is adequate. The use of two additive components regarding the different sampling frequency is reasonable. However, 38% of residual error is extremely high, which can be related to a bias in the structural model selection (see comments on population PK model).

Population PK model

The population model development analysis is acceptable in terms of data handling, and missing data. However, several points need to be clarified:

In the population pharmacokinetic model, the Ka generally decreased at higher dose levels. A zero-order release step was incorporated in the model to describe the delayed absorption. Sequentially, the absorption was described with the first-order kinetics where the rate of absorption is proportional to the amount of drug "released" by the zero-order step with Ka as the rate constant. Two distribution compartments were included assuming linear inter-compartment and elimination clearances.

Other mechanistic models and the inclusion of a third distribution compartment will be assessed from available PK data from Study CO-338-014 that the applicant is recommended to submit.

The effect of high fat meal would be related to a solubility-limited oral absorption of rucaparib. Rucaparib bioavailability is slightly increased in patients with no food restriction (37.2%) and greater increased in high-fat meal patients (51.7%) compared to fasted patients (32.6%), which represents for high-fat meal patients an increase of 58.6% in rucaparib bioavailability over fasted patients. However, the cumulative clinical PK, safety and efficacy data indicate that this effect is not clinically meaningful.

The covariate analysis does not reduce the variability on the PK parameters. The clinical relevance of CLCr on CL was low at the extreme 10th and 90th percentiles (13% reduction and 13.3% increase, respectively). No clinical information was provided for the other covariates-parameter relationships.

Taking into account the pharmacokinetics of Rubraca (partition coefficient blood-to-plasma approximately 2), its side effects (anaemia, reduction in haematocrit) and the cancer disease, red blood cell (RBC) and haematocrit (HCT) should be considered to be included in the PopPK model. The applicant explained that only data for HCT is available and showed that this does show a correlation with volume of distribution and clearance. However, the correlation with clearance is stated to be unexpected and it is suggested that it is due to a correlation of HCT with albumin and CrCL which are already included in the model. This is accepted. It is suggested that all the effects are not clinically significant but the lack of clinical significance of HCT on volume of distribution was not adequately discussed. A more adequate explanation about the lack of clinical significance of HCT on volume of distribution and C_{max} was provided in the following round of responses. The applicant suggests that the testing of HCT as a time varying covariate is more robust, this is agreed and a large effect is not expected at steady state.

The following comments should be also noted:

-Final goodness-of-fit plots show an underprediction of the model at higher concentrations, which is related to a model misspecification on the C_{max}. This could reflect an inadequate absorption model that requires further improvement.

-The large variability that it is associated to the absorption parameters did not decrease after the inclusion of Dose and Food as covariates. Moreover, the use of dose as covariate reflects non-linear absorption process, which has not been explored during model development process.

Special populations

Regarding special populations analysis, no formal investigations have been performed in renal and hepatic impaired patients so far. A dedicated study, which is required for further investigating the impact of moderate hepatic impairment on rucaparib (considered as missing information), including patients with advanced cancer and normal hepatic function or moderate hepatic impairment (CO-338-078) is planned (see RMP). According to the provided protocol, C_{max} and AUC will be the primary PK parameters in this study; however $T_{1/2}$, which is a secondary parameter, could also be important to inform dose frequency. On the other hand, no reliable information could be derived from the population-PK analysis since very limited data collected in moderate/mild insufficient patients were part of the analysed dataset. Considering that the mass-balance study is still ongoing, the results are still preliminary. The PK assessment on these population groups has not been properly assessed and any dose recommendation is accepted based on available data but is still provisional.

The relationship between age, BMI and weight, and these exposure metrics were evaluated. Neither baseline BMI nor body weight showed relationships with observed or model-predicted exposure metrics, including AUC_{ss} and $C_{max,ss}$.

Results from elderly +85 should be considered with caution as only one patient was enrolled in Studies CO-338-010 and CO-338-017.

Current smokers had 22.8-29.9% lower PK exposures compared to non-smokers. This covariate effect was properly assessed covariate searching, but no statistically significant results were obtained in order to incorporate smoking status into the model, due to this effect is partially explained by the inclusion of CLCr covariate on CL. Higher CLCr values were correlated to current smokers, decreasing in the former smokers and non-smokers groups. This fact could be relation with CYP1A2 as enzyme responsible for rucaparib metabolism. It should be noted that smoking is a potent inducer of CYP1A2 enzyme activity. The number of current smoker is limited (n=16). Therefore, the clinical relevance of CYP1A2 as enzyme responsible for rucaparib metabolism cannot be fully ruled out.

Due to the unbalanced Asian and Black proportion of patients, no conclusion could be made regarding the influence of race on rucaparib PK's.

Around 10 cases of AML/MDS (myelodysplasia) was reported out of 1077 treated with Rubraca. Therefore, AML/MDS are considered as adverse events of special interest (AESIs). A summary of the PK data in AML/MDS patients comparing to non-AML/MDS patients and an analysis in the PopPK model showed that the exposure is broadly similar.

The expected changes in albumin by renal and hepatic function and that of the albumin effect in the PopPK model are small and in the reverse direction to that that would be expected. In addition, it is noted that the ppb of Rubraca is relatively low so unlikely to change significantly with changes in albumin.

Interactions:

Effects of other medicinal products on rucaparib (as a victim drug)

The effects in vivo of other medicinal products on rucaparib have been only investigated on the population PK. Results of the population PK should be considered as exploratory because dose administered and time of exposure of the concomitant drug is unknown.

In vitro data suggested slow metabolism by CYP enzymes, with CYP2D6 and to a lesser extent CYP1A2 and CYP3A4 contributing to the metabolism of rucaparib. Rucaparib was shown to be a substrate of P-gp and BCRP. If results of Study CO-338-045 (mass balance) support the in vitro results, the effects of strong inhibitors of CYP2D6, P-gp and BCRP on rucaparib pharmacokinetic would have to be investigated in dedicated in vivo drug-drug interaction studies. Additionally, the effects of strong inhibitors and strong inducers of CYP1A2 and CYP3A4 on rucaparib pharmacokinetic could have to be investigated in dedicated in vivo drug-drug interaction studies. It should be noted that the number of active smokers (n=16) and poor CYP2D6 (n=10) in the dataset included in the population PK is limited.

With the available data, a significant contribution of CYP3A4 cannot be excluded. CYP3A4 was less important in vitro, but the relative/quantitative contribution of different CYPs in vivo cannot be determined from in vitro data. CYP3A4 is highly abundant in vivo, and could contribute to a high degree of first-pass metabolism. The MAH states that no restrictions on inhibitors/inducers of CYPs or other enzymes are required in ongoing clinical rucaparib safety/efficacy studies. However, according to the study report for study CO-338-017, concomitant use of strong inhibitors and inducers of CYP1A2 or 3A4 was excluded in this study. In the dose-escalation study CO-338-010, inhibitors or inducers of CYP1A2 or 3A4 were to be avoided. Therefore, from the safety data currently available, it appears that no conclusions on the safety of concomitant use of strong CYP1A2 or CYP3A4 inhibitors can be drawn.

As CYP3A4 inhibition or induction can lead to very large effects on exposure of a CYP3A4 substrate, e.g. if there is a large degree of first-pass metabolism, a warning against use of strong CYP3A4 inhibitors and inducers has been included in the SmPC, awaiting data from the mass-balance study and, if necessary, further DDI studies. (CYP1A2 inhibition may be of less concern as the effects are seldom as large as what can be observed with CYP3A4 inhibition).

Firm conclusions cannot be drawn from the population PK analysis about PPIs because dose given and time of administration has not been documented for PPIs. However, the risk for a clinically relevant effect of PPIs is likely small. The anticipated effect would be an increase in exposure. However, rucaparib could be administered with food in the efficacy/safety studies, and it is considered unlikely that a PPI would induce a larger increase in exposure than that seen with a high-fat meal.

Effects of rucaparib on other medicinal products pharmacokinetic (as a perpetrator drug)

The effects of rucaparib coadministration on the PK of sensitive substrates of CYP1A2, CYP2C9, CYP2C19, CYP3A, and P-gp was assessed in the cocktail-based drug-drug interaction study in patients (Study CO-338-044). The Applicant has provided the results from Study CO-338-044 Part 1, where rucaparib showed moderate inhibition of CYP1A2, weak inhibition of CYP2C9, CYP2C19, and CYP3A4, and marginal inhibition of P-gp.

It should be noted that rucaparib is an inhibitor of the P-gp efflux transporters with IC50 values suggesting a potential for P-gp inhibition in the gut. However, the study has been conducted with digoxin instead of dabigatran etexilate, which seems to be more sensitive to intestinal P-gp inhibition than oral digoxin. Therefore, results with digoxin could be underestimating the effect on P-gp in the gut. Results by genotypes for CYP1A2,

CYP2C9 and CYP2C19 have not been provided yet. For time-dependent interaction (CYP3A down-regulation), the maximum effect is expected when a new steady state level of the affected enzyme has been obtained. To better estimate the % steady state of potential CYP3A4 regulation achieved following 7 days rucaparib treatment, an indirect effect pharmacokinetics/pharmacodynamics model was developed. Based on this model, the study cannot be considered at steady state for cytochrome effects as the Kdeg is quite high (Kdeg = 0.00962 hr-1 in liver) and even with this value the calculation is only 80% for hepatic CYP3A4, therefore perhaps the effects seen are not maximal. The applicant has provided an updated assessment of CYP3A4 downregulation using a mechanistic model, where oral and intravenous route of administration have been discussed separately. Using different conservative approaches, it seems that the magnitude of the effect is still between the range ≥1.25 but <2 fold, which suggest that the effect would be weak in all tested scenarios. Therefore, although perhaps the effects seen are not maximal, this issue is not further pursued.

If a metabolite is responsible for the enzyme inhibition, steady state of the metabolite should have been reached. However, the mean metabolites have not been fully characterized. When characterization of metabolites is available their impact on this DDI study should be discussed and the results of this DDI study could be re-assessed.

A justification that probe drugs combined in the cocktail do not interact in vivo with other was provided and considered acceptable. The Cooperstown 5+1 cocktail has been validated. Study CO-338-044 used a modified cocktail that included 4 of the 5 cocktail probes. Digoxin is not part of the validated cocktail, and was thus dosed separately. Taking into account the $T_{1/2}$ of caffeine (1 – 4 hours), warfarin (31-40 hours), omeprazole (1 hour) and midazolam (1.5-2.5 hours), only warfarin would not be eliminated when digoxin is administered. However, taking into account the metabolism and route of elimination/excretion of warfarin and digoxin no interaction is expected between them.

The applicant was requested to discuss plans to further investigate in dedicated in vivo drug-drug interaction studies inhibition of UGT 1A1, CYP 2D6, BCRP, OCT1, OCT2, MATE1 and MATE2k (with e.g. with metformin, dofetilide) and induction of CYP 2B6,CYP1A2 and CYP3A4. This issue was discussed for:

UGT1A1 inhibition:

Considering that available data suggests rucaparib has a limited potential to cause clinically meaningful UGT1A1 inhibition together with the fact that a UGT1A1 probe for DDI studies is not clearly identified and rucaparib cannot be administered to healthy volunteers, the applicant's justification for not conducting a clinical study to evaluate UGT1A1 inhibition by rucaparib is acceptable. A statement is included in the SmPC to reflect that special caution should be paid when it is co-administered with UGT1A1 substrates (i.e. irinotecan) to in patients with UGT1A1*28 (poor metabolizer).

CYP2D6 and CYP2C8 inhibition:

As rucaparib, in vivo, showed moderate or weak inhibition of CYPs (CYP1A2, CYP2C9, CYP2C19, and CYP3A4) which were higher reversibly inhibited by rucaparib in vitro than CYP2D6 and CYP2C8, the in vitro weak CYP2D6 and CYP2C8 inhibition by rucaparib, is unlikely to result in clinically significant drug-drug interactions in vivo. Considering that rucaparib cannot be administered to healthy volunteers, the applicant's justification for not conducting a dedicated DDI study is accepted, although it should be noted that CYP1A2 with AUCR=2.9 in the mechanistic static modelling (the third lowest AUCR after CYP2C8, AUCR=2.6 and CYP2D6, AUCR =2.3) showed the higher inhibition in vivo study.

BCRP:

The proposed text included in Section 4.5 of the SmPC is acceptable. However, further assessment of the in vivo BCRP inhibition by rucaparib is recommended (see RMP). It should be noted that in vitro, IC50 for BCRP (55 µM) is lower than for P-gp (169 µM). These IC50 suggested a potential inhibition for P-gp and BCRP in gut but also for BCRP in liver and kidneys. Data of in vivo study with P-gp substrate (rucaparib marginally inhibits P-gp in the gut) cannot be considered a worst scenario for efflux transporters in the gut because the IC50 is lower for BCRP and the DDI study of P-gp has been conducted with digoxin instead with dabigatran etexilate. Additionally, rucaparib can inhibit BCRP in liver and kidneys. It should be also pointed out that an interaction with statin drugs (competitive inhibitors of HMG-CoA reductase) as BCRP substrate drugs has high clinical relevance. Therefore, an additional study to assess in vivo BCRP inhibition by rucaparib will be conducted. (See RMP)

OCT1, OCT2, MATE1, MATE2-K:

Rucaparib is a potent inhibitor of MATE 1 and MATE2-K, and a moderate inhibitor of OCT1, and OCT2. The rapid increase in serum creatinine following the start of rucaparib treatment in patients, indicates that rucaparib is an inhibitor of renal transporters in vivo, and is likely to affect the pharmacokinetics of medicines which are actively excreted in the urine. Thus, irrespective if rucaparib is transported for more than 25% in urine, a in vivo interaction study would be recommended in this case (e.g. with metformin, dofetilide) to estimate the effect size of the interaction. However, as DDI studies will need to be carried out in cancer patients, an effect can already be expected based on the creatinine elevations observed with rucaparib treatment and the number of known substrates for which clinically relevant changes can be expected is low, this issue has been considered as resolved listing these substrates as examples (i.e. metformin) in a specific warning in the SmPC.

Induction of CYP1A2, CYP2B6, and CYP3A4:

The potential in vivo dual effect on CYP1A2 (reversible inhibition and induction) and CYP3A4 (reversible inhibition and down regulation) were investigated in clinical study CO-338-044. As rucaparib did not inhibit CYP2B6 and the CYP2B6 down regulation by rucaparib was less than for CYP3A4, the potential for clinically meaningful DDI with rucaparib as a CYP2B6 perpetrator is unlikely. Therefore, no evaluation in vivo of the effect of rucaparib on CYP2B6 is considered acceptable.

Considering that rucaparib is a potential human teratogen and might be used in a population including fertile women, a DDI study with an oral contraceptive steroid is planned (see RMP). The results from Study CO-338-044 suggest that steady state rucaparib is likely to have a limited impact on the exposure of oral contraceptives. In addition, because rucaparib inhibits CYP3A, the interaction would not be expected to result in decreased exposures, and thus reduced efficacy, of oral contraceptives. However, as the Guideline on the investigation of drug interaction (CPMP/EWP/560/95/Rev. 1 Corr. 2**) mentions, there may still be mechanisms of induction which presently are unknown. Therefore, a potential human teratogen (Definition given in EMEA/CHMP/203927/2005) needs to be studied in vivo for effects on contraceptive steroids if the drug is intended for use in fertile women, regardless of the in vitro induction study results. Consequently, although justification for rucaparib as a CYP3A perpetrator is reasonable, an in vivo study will be conducted since there may still be mechanisms of induction which presently are unknown. This is also reflected in the SmPC.

Dose justification

Dose justification has been properly assessed in the Efficacy section. Dose adjustments under section 4.2 in the SmPC are based on the rucaparib clinical experience. With available data, the proposed dose adjustments seem to be appropriated to manage the AEs. The applicant is encouraged to collect further data from clinical experience to review and improve the proposed dose adjustment in the future.

Secondary pharmacology – QT prolongation

A relationship between QTcF and rucaparib exposure at 600 mg BID was shown. The projected drug-related median QTcF prolongation from baseline following 600 mg rucaparib BID was 11.5 msec (90% CI of 8.77 to 14.2 msec), with the upper bound of the two-sided 90% confidence interval of 17.2 msec (90% CI of 12.6 msec to 21.7 msec). Consequently, the concentration-response analysis showed an upper bound of the two-side 90% CI for the QTc effect > 10 ms at the highest clinically relevant exposure with a mean prolongation <20 ms.

There were 5 cases of cardiac or related events potentially associated with QT prolongation (1 patient with SAE of grade 4 arrhythmia secondary to congenital QTC syndrome, 2 patients with SAE of cardiac arrest, and 2 patients with SAE of syncope) were identified in patients (n = 1077) that have been exposed to oral rucaparib in Clovis-sponsored studies as of 10 April 2017. A review of the 5 cases from the search indicated other possible/likely causality for each specific reported event, including pre-existing cardiac history in 2 of the patients. Additionally, a total of 3 events of seizure have been reported in the 1077 patients exposed to rucaparib in Clovis-sponsored studies as of 10 April 2017, although none of them were attributed to potential cardiac abnormalities, and there was no documented evidence of arrhythmia.

For all above, the potential effect on cardiac repolarization has been established as low for the moment. QT prolongation has been included as an Important Potential Risk in the RMP, along with details on monitoring events of QT prolongation, their subsequent review and management. Additionally, information on potential effect on cardiac repolarization has been reflected in the SmPC and RMP.

2.4.5. Conclusions on clinical pharmacology

Clinical pharmacology has been characterized overall. However, several relevant issues should be addressed.

Results of the Study CO-338-045 (mass balance), which is a recommended study, will be submitted in order to elucidate distribution, the main metabolism pathways and routes of excretion/elimination. Additionally, main metabolites should be properly characterized with results from the recommended study, Study CO-338-045 (mass balance) and Study CO-338-078 (hepatic impairment) in the RMP. Without this data, it is difficult to properly assess interactions. For the moment, interactions can be considered properly discussed and justified according to the available data. Further DDI studies with substrates of BCRP and contraceptives will be conducted (see RMP). Additional studies could be required when further data on metabolism pathways and metabolites profile are available.

The study CO-338-078 in patients with hepatic impairment is part of the RMP and a report on other structural models of population pharmacokinetics is recommended to be submitted.

2.5. Clinical efficacy

Clinical efficacy data came from a group of patients enrolled in two Phase 2 open-label studies that evaluated rucaparib as open-label treatment for relapsed ovarian cancer. The primary efficacy population comprises 106 ovarian cancer patients harbouring a deleterious BRCA mutation who received 2 or more prior regimens of chemotherapy.

2.5.1. Dose response studies

Study CO-338-010: A Phase I/II open-label, safety, PK and preliminary efficacy study of oral rucaparib in patients with gBRCA mutation ovarian cancer or other solid tumours.

Study CO-338-010 is an ongoing 3-part, multi-centre, multi-national, Phase 1/2, open-label, safety, pharmacokinetics (PK), and efficacy study of oral rucaparib administered daily for continuous 21-day cycles. Patients enrolled in to one specific part of the study only. There were no control groups. Rucaparib tablets (40mg, 60mg, 120mg, 200mg or 300mg) were taken without reference to food intake, except Day -7 and Day 1 of the food effect portion of the study. A new treatment cycle could begin if ANC ≥1.0 x 10^9/L, platelet count ≥75.0 x 10^9/L and non-haematologic toxicities returned to baseline or ≤ Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 severity (or ≤CTCAE Grade 2 severity at the investigator' s discretion).

From the 3 parts of the study (1, 2A and 2B and 3), Part 1 served as the basis for dose finding.

Part 1 evaluated the safety and PK of escalating doses of rucaparib and determined the MTD and RP2D in patients with advanced solid tumours. There was a RP2D expansion cohort in patients with a deleterious gBRCA mutation by local BRCA testing of DNA extracted from blood or buccal samples. No dose reductions were permitted in Cycle 1.

Part 2A evaluated the overall investigator-assessed response rate (ORR) of rucaparib by RECIST Version 1.1 in patients with relapsed, platinum-sensitive high grade serous or endometrioid epithelial ovarian cancer who had received between 2 and 4 prior treatment regimens, with a maximum of 1 non-platinum regimen. Patients had to harbour a deleterious gBRCA mutation as determined by a local laboratory test. Archival formalin-fixed paraffin-embedded tumour tissue samples were retrospectively requested to confirm the presence of BRCA mutations utilizing the FMI validated tests (CTA then CDx).

Part 2B evaluated ORR of rucaparib by RECIST V1.1 in patients with high-grade epithelial ovarian cancer with evidence of a deleterious BRCA mutation (germline or somatic) who received 3 to 4 prior chemotherapy regimens. Patients may have been sensitive, resistant or refractory to their most recent platinum regimen and have had a documented treatment – free interval (TFI) ≥6 months following the first chemotherapy regimen received. No patients had been enrolled in Part 2B as of the cut-off date (1 October 2015).

Part 3 evaluated PK and safety at the RP2D of rucaparib in patients with any advanced solid tumour (including lymphoma), who had a known deleterious BRCA mutation (gBRCA or sBRCA) as determined by a local laboratory. There was no requirement for type or number of prior treatments received and patients could have received prior PARP inhibitor treatment, provided it was not the last treatment or received in the last 6 months. Efficacy data were immature at the time of the CSR and will be reported at study completion.

Results

Part 1: a total of 56 patients received at least 1 dose of rucaparib between December 2011 and October 2013. Dose escalations ranged from 40 to 500mg once daily followed by cohorts receiving 240 to 840mg BID for one or two 21-day cycles. All 56 patients have discontinued treatment, primarily due to PD by RECIST Version 1.1.

Table 6: Dose Limiting Toxicities (DLTs) Reported by Dose Level in Cycle 1 of Phase 1

Starting Dose	N Evaluated	N with DLT	Description of Event
40 to 500 mg QD	26	0	-
240 mg BID	3	0	No patients initiating rucaparib at 240 mg BID experienced a DLT, although dose modifications were required [a]
360 mg BID	8	1 (11.1%)	One patient experienced Grade 3 nausea.
480 mg BID	9	0	No patients initiating rucaparib at 480 to 840 mg BID experienced a DLT, although dose modifications were required [a]
600 mg BID	7	0	
840 mg BID	3	0	

Source: Listing 16.2.7.6

[a] All dose modifications occurred after Cycle 1, with the exception of one patient who initiated rucaparib at 840 mg BID. This patient reduced her dose to 7 tablets once (420 mg QD) or twice daily (420 mg BID) starting 3 days after initiating treatment due Grade 2 events of nausea, vomiting, anxiety, and dysgeusia, as well as the inability to swallow the required number of tablets to achieve the starting dose (fourteen 60 mg tablets). Dose modifications were handled per protocol.

No patient at any QD dose level evaluated experienced a DLT. Only 1 DLT was observed (Grade 3 nausea in a patient at 360mg BID), so a MTD per protocol specified definition was not determined. Myelosuppression was observed in later cycles of treatment with rucaparib at higher BID dose levels. At the 600 mg BID dose level all 3 patients initially treated achieved steady state levels at least 2 times the desired target C_{min} of 2 µM (650 ng/mL); there was no further increase in rucaparib trough level observed at the 840 mg BID dose.

The DLT-evaluable population consisted of all patients who received at least 17 complete days of rucaparib and completed Cycle 1 of treatment or who experienced a DLT in Cycle 1 (N=49). No patient at any QD dose level evaluated experienced a DLT. Only 1 DLT was observed (Grade 3 nausea in a patient at 360mg BID), so a MTD per protocol specified definition was not determined. Myelosuppression was observed in later cycles of treatment with rucaparib at higher BID dose levels. At the 600 mg BID dose level all 3 patients initially treated achieved steady state levels at least 2 times the desired target C_{min} of 2 µM (650ng/mL). No further increase in rucaparib trough level was observed at the 840 mg BID dose.

A dose of 600mg BID was selected as the RP2D, as this was within the range of efficacious doses, within the approximate dose proportional linearity for rucaparib exposure at steady state and considered to be the highest dose with an acceptable safety profile for continuous administration.

The efficacy-evaluable population consisted of all patients who met eligibility criteria, received at least 1 dose of rucaparib, had measurable tumour lesions at baseline and had at least 1 post-baseline disease assessment (N=48). A confirmed response was recorded in 8 patients; 2 achieved a CR (both gBRCA1) and 6 achieved a PR (1 with gBRCA1, 3 with gBRCA2 and 2 with indeterminate germline/ somatic BRCA1). A best response of stable disease (SD) was recorded in 22 patients (11 with gBRCA 1 and 7 with gBRCA2). Data presented include 124 patients enrolled in Part 1, Part 2A and Part 3 of the study.

Part 2A: 42 platinum-sensitive patients were enrolled between February 2014 and April 2015; 36 patients discontinued treatment, mainly due to progressive disease (n=25). Two patients discontinued treatment due to an AE 4 and 10 days after initiating rucaparib; neither had a post-baseline disease assessment. ORR was evaluated in the efficacy evaluable population as the primary efficacy endpoint (n=40). Efficacy is presented in the safety population, consisting of patients who received at least 1 dose of rucaparib (n=42).

Table 7: Study CO-338-010 Part 2A: Investigator-assessed Confirmed Objective Response Rate by RECIST Version 1.1 in the Safety Population (N = 42)

	600 mg BID (N = 42)
Confirmed ORR (CR + PR) n (%) [95% CI, %]	25 (59.5) [43.3, 74.4]
Best Overall Confirmed Response n (%)[a]	
CR	4 (9.5)
PR	21 (50.0)
SD	12 (28.6)
Completed study	12
Ongoing with single response	0
Ongoing without response	0
PD	2 (4.8)
NE	3 (7.1)
Response by RECIST or GCIG CA-125 (n [%])	
Yes [95% CI]	35 (83.3) [68.6, 93.0]
No	5 (11.9)
Unevaluable	2 (4.8)

Source: Table 14.2.1.1.1 of the Study CO-338-010 CSR.
Abbreviations: BID = twice daily; CA-125 = cancer antigen-125; CI = confidence interval; CR = complete response; GCIG = Gynaecologic Cancer InterGroup; CSR = clinical study report; N or n = number of patients; NE = not evaluable; ORR = objective response rate; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours; SD = stable disease.
[a] Assessed by RECIST or if no assessments were done, by reason for discontinuing study.

The ORR was broadly similar in patients with gBRCA1 (19/25, 65.5%, 95% CI 45.7-82.1%) and gBRCA2 (6/11, 54.5%, 95% CI 23.4-83.3%) mutations. Most patients had a PFI of ≥6 to 12 months following their last dose of platinum (ORR 17/30, 56.7%, 95% CI 37.4-74.5%); the ORR appeared higher in patients with a PFI > 12 months (8/10, 80%, 95% CI 44.4-97.5%).

Duration of response was censored at the date of the last post-baseline scan for 8 patients. At the visit cut-off date, 5 responders (3 with CR & 2 with PR) were ongoing. The median duration of response in the 25 patients with a confirmed investigator- determined CR or PR was 270 days (95% CI 170-344 days) or approximately 8.9 months (95% CI 5.6 -11.3 months) using Kaplan-Meier methodology. The median duration of response should be presented for all patients, not just those with a confirmed CR or PR, and those with no response assigned a duration of zero.

Of the 40 efficacy-evaluable patients, 19 (47.5%) had a decrease of ≥50% in the sum of diameters of target lesions (SDTL). Over half of the responders (14/25, 56.0%) did so by week 8 (cycle 2); all 25 responded by week 20 (cycle 6).

Part 2B: Data were not presented for this part in the application as no patients had enrolled as of the 01 October 2015 cut-off.

Part 3: Characterisation of the PK, including the effect of food, of a higher dose strength (300 mg) rucaparib tablet in advanced solid tumour patients with a BRCA mutation. Efficacy data were immature at the time of the CSR and will be reported at study completion.

2.5.2. Main studies

Clinical efficacy data come from a group of patients enrolled in **two Phase 2 open-label studies** that evaluated rucaparib as open-label treatment for relapsed ovarian cancer. The primary efficacy population

comprises 106 ovarian cancer patients harbouring a deleterious BRCA mutation who received 2 or more prior regimens of chemotherapy.

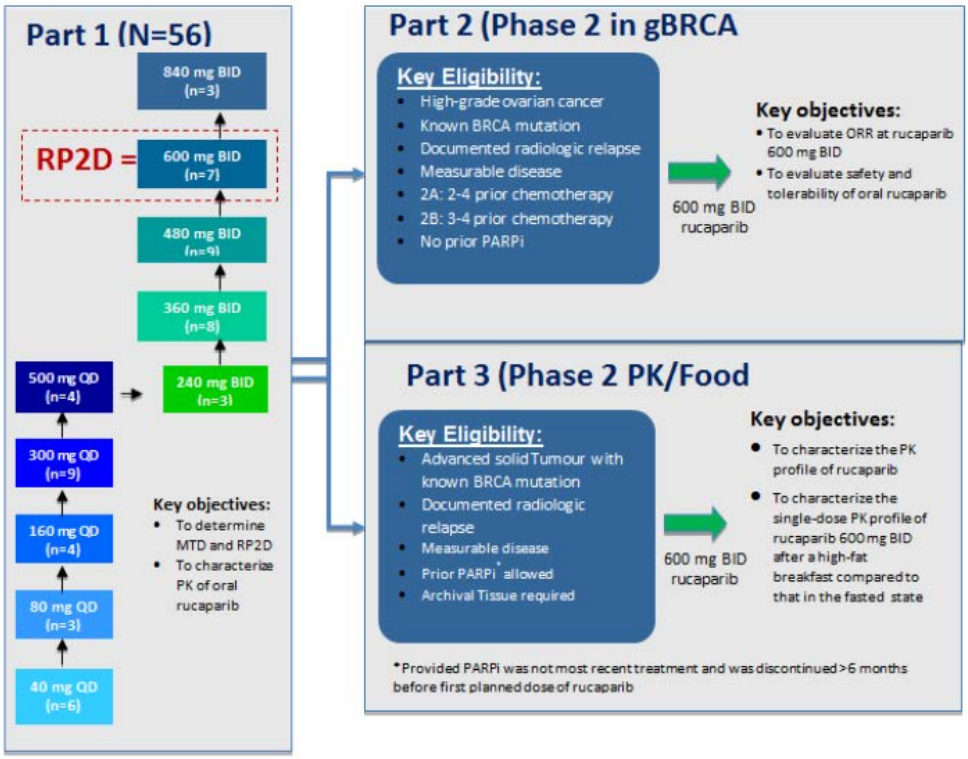
Table 8. Summary of Efficacy Data Cut-off Dates

Rucaparib Dose	Study	SCE Includes Data from Patients Enrolled by:	Includes All Visits Up Until:
600 mg BID	CO-338-010 Part 2A	Enrollment completed in April 2015; all enrolled patients included	29 April 2016
	CO-338-017 Part 1	Enrollment completed in October 2014; all enrolled tBRCA mutation patients included	29 April 2016
	CO-338-017 Part 2	1 October 2015 (enrollment ongoing at data cut-off)	29 April 2016

Abbreviations: BID = twice daily; SCE = Summary of Clinical Efficacy; tBRCA = tumor tissue alteration in breast cancer gene 1/2, includes germline BRCA (gBRCA) and somatic BRCA (sBRCA).

Study CO-338-010 is an ongoing 3-part, Phase 1/2, open-label, safety, pharmacokinetics (PK), and efficacy study of oral rucaparib administered daily for continuous 21-day cycles. Efficacy data are only provided from the **part 2A**, which enrolled patients with relapsed, platinum-sensitive disease who received 2 to 4 prior treatment regimens and were known to harbour a gBRCA mutation based on results from local testing. Data are not included for patients in Part 2B as no patients were enrolled as of the enrolment cut-off date (1 October 2015)

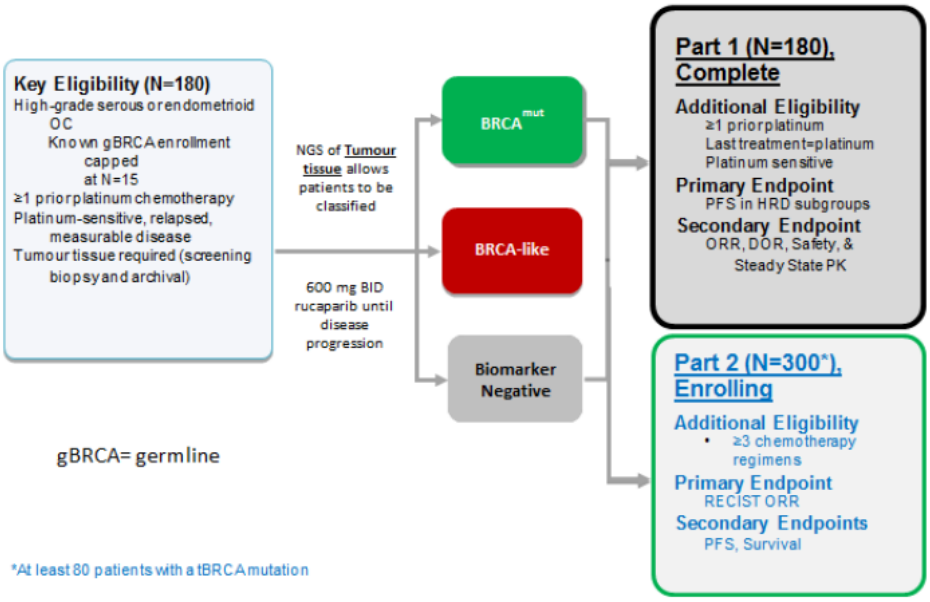
Figure 5: Study 10 Schematic



CO-338-017 (ARIEL2) is an ongoing 2-part, Phase 2, open-label, efficacy study of oral rucaparib in patients with relapsed high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer. All patients took 600 mg BID rucaparib with or without food in continuous 28-day treatment cycles. Patients continued to receive rucaparib until disease progression, unacceptable toxicity, patient or investigator request

to discontinue, or death. Efficacy data are only provided from patients who enrolled on or before 01 October 2015, with relapsed, platinum-sensitive disease who had received ≥ 2 prior chemotherapy regimens and were known to have a BRCA mutation (germline or somatic).

Figure 6: ARIEL2 Study Schematic



Note: the ARIEL2 study schematic was taken on July 2015

In addition, Clovis proposes to submit data from **2 additional studies post-approval**, in order to support the conditional approval. Placebo-controlled, safety and efficacy data from a larger patient population within the same condition will be available first from Study CO-338-014 (ARIEL3). Comparator-controlled data in the proposed treatment indication will be provided from Study CO-338-043 (ARIEL4) later. These data will likely form the basis of specific obligations that will further confirm a positive benefit:risk of rucaparib.

- **Study CO-338-014 (ARIEL3)** is an ongoing randomized, international, double-blind, placebo-controlled Phase 3 study evaluating rucaparib versus placebo as maintenance treatment following response to platinum-based therapy in patients with platinum-sensitive ovarian cancer. The primary endpoint is progression-free survival (PFS) by RECIST Version 1.1, as assessed by the investigator. The target enrolment of 540 patients was completed in May 2016; data analyses were conducted in June2017. This study is considered to be supportive and potentially confirmatory to demonstrate clinical benefit of rucaparib for the following reasons: i) it is a randomized, placebo-controlled study where the benefit:risk profile of rucaparib can be assessed; ii) the study includes patients who achieved a complete response (CR) or partial response (PR) to platinum-based therapy; patients with a PR and residual disease may have further disease control or tumour reduction with rucaparib. Rucaparib as a maintenance treatment in these patients may therefore provide further evidence of safety and efficacy in an advanced disease setting.
- **Study CO-338-043 (ARIEL4)** is a Phase 3, multicentre, open-label, randomized study evaluating Rucaparib versus chemotherapy for treatment of relapsed tBRCAmut (tumour tissue alteration in BRCA1/2, including gBRCA and sBRCA mutations) ovarian cancer. During the protocol assistance procedure concluded in February 2016, the CHMP agreed that Study CO-338-043 could serve as the

confirmatory study to support conditional approval and provided initial comments on the study design based on information provided by Clovis within the meeting background materials. The study will enrol patients with relapsed, high grade epithelial serous or Grade 2 or Grade 3 endometrioid, ovarian, fallopian tube, or primary peritoneal cancer who have a deleterious BRCA1/2 mutation in the tumour (tBRCAmut). All patients will be required to have received at least 2 prior chemotherapy regimens. Study CO-338-043 enrolment (N=345) is anticipated to be complete in Q3 2020with interim data including the primary endpoint of PFS anticipated to be available by Q3 2021.

Methods

Study Participants

Study CO-338-010 - Part 2A

Inclusion criteria

Standard: age ≥ 18 years, life expectancy ≥ 3 months, Eastern Cooperative Oncology Group (ECOG) performance status 0-1, adequate organ function [ANC ≥1.5 x 10^9/L, platelets >100 x 10^9/L, haemoglobin ≥9 g/dL; AST & ALT ≤3 x ULN (if liver metastases ≤5 x ULN), bilirubin ≤ 1.5 x ULN; serum creatinine ≤ 1.5 x ULN]

Patients with ovarian cancer who had received 2 to 4 prior treatment regimens and were known to harbour a deleterious gBRCA mutation.

The deleterious gBRCA mutation was determined by a local laboratory test. No tumour tissue sample was required to have been submitted prior to enrolment or treatment with rucaparib. The applicant requested archival tumour samples to retrospectively confirm the BRCA mutation in tumour tissue using the proposed validated test (Foundation Medicine, Inc. [FMI] companion diagnostic test [CDx].

The last treatment received must have been a platinum-based regimen to which the patient must have been sensitive (ie, disease progression occurred at least 6 months after last dose of platinum was administered).

Exclusion criteria

- Prior treatment with a PARPi
- Untreated or symptomatic CNS metastases
- Treatment (including chemotherapy, radiation, antibody therapy, gene or vaccine therapy) within 14 days prior to 1st rucaparib dose or ongoing AEs >NCI CTCAE Grade 1
- Strong CYP1A2 or CYP3A4 inhibitor ≤7 days from 1st scheduled dose of rucaparib
- Pre-existing duodenal stent or any GI disorder that would, in the opinion of the Investigator, interfere with absorption of rucaparib
- Non –study related minor surgical procedure ≤ 5 days or major surgical procedure ≤21 days prior to 1st rucaparib dose
- Impaired cardiac function or clinically significant cardiac disease
- History of clinically significant abnormal 12-lead ECG, QTcF >450msec (males) or >470 msec (females), PR interval >240 msec or QRS >110 msec [removed in Amendment 5]February 2015]

- Pregnant/ breast feeding females; fertile patients who refused to use effective contraception during the period of the trial and for 6 months after the last dose of oral rucaparib

Study CO-338-017

Inclusion criteria

Part 1 enrols patients with relapsed ovarian cancer who had received at least 1 prior platinum-based regimen and had platinum-sensitive disease following their most recent platinum regimen, and Part 2 enrols patients who have received at least 3, and no more than 4, prior chemotherapy regimens bewho were resistant or refractory, as well as sensitive, to their last platinum-based regimen. Patients who were resistant or refractory to the last platinum-based regimen may also have received subsequent treatment with additional non-platinum based chemotherapy before initiating treatment with rucaparib.

All patients in Part 1 were required to have undergone a biopsy of tumour tissue prior to enrolment and have the tumour tissue confirmed by central laboratory (FMI) as being of adequate quality. Submission of archival formalin-fixed, paraffin-embedded (FFPE) tumour tissue was also required. For enrolment in Part 2, patients known to harbor a BRCA mutation were allowed to enrol without a biopsy provided that archival FFPE was available and was submitted to FMI for analysis. Based on the analysis of a screening biopsy and/or archival tumour tissue sample, patients were prospectively classified into 1 of 3 molecularly-defined HRD subgroups as defined by the clinical trial assay (CTA). The presence of a deleterious BRCA1 or BRCA2 mutation in tumour tissue resulted in classification into the tBRCA mutation subgroup. Patients without a BRCA mutation were classified into 1 of 2 other subgroups based on the level of tumour genome-wide loss of heterozygosity (LOH) observed. These groups are referred to as non-BRCA/LOH+ and non-BRCA/LOH-. In Part 1, enrolment of patients known to harbour a deleterious gBRCA mutation was limited to 15 in order to ensure sufficient power for the comparison of the non-BRCA HRD subgroups. In other words, patients in this study can be classified as:

BRCA: Patients whose tumour had a BRCA1/2 mutation, irrespective of genomic LOH measurement

Non-BRCA LOH+: Patients whose tumour did not have a BRCA1/2 mutation and had a tumour genomic LOH measurement ≥ 14% (Part 1) or ≥ 18% (Part 2)

Non-BRCA LOH-: Patients whose tumour did not have a BRCA1/2 mutation and had a tumour genomic LOH measurement < 14% (Part 1) or < 18% (Part 2)

Unknown: Patients without a BRCA mutation and indeterminate for genomic LOH.

However, and having said that, since the company is applying for an indication only in those patients with deleterious BRCA-mutated tumours, inclusive of both germline BRCA (gBRCA) and somatic BRCA (sBRCA) mutations, and who have been treated with 2 or more prior lines of chemotherapy, the primary efficacy population will comprise 106 ovarian cancer patients harbouring a deleterious BRCA mutation who received 2 or more prior regimens of chemotherapy.

Exclusion criteria

- Active second malignancy- history of malignancy permitted if all chemotherapy completed >6 months prior/ bone marrow transplant > 2 years prior to first dose
- Prior PARP inhibitor treatment (previous iniparib allowed)
- Symptomatic and/ or untreated CNS metastases

- Pre-existing duodenal stent and/or any GI disorder that would, in the opinion of the investigator, interfere with absorption of rucaparib
- Pregnant / breast feeding
- Ongoing requirement for / administration of strong CYP1A2 or 3A4 inhibitors ≤7 days from first dose

Treatments

In study CO-338-010 part 2A patients received oral rucaparib 600 mg BID for 21-day cycles. Patients in Part 2A using 60 and 120 mg tablets had their dose of oral rucaparib modified as needed.

In study CO-338-017 all patients received oral (PO) rucaparib at 600 mg BID in continuous 28-day cycles. Patients enrolled into Part 1 of the study initially received 60 mg or 120 mg tablets. Patients enrolled into Part 2 of the study initially received 300 mg tablets. Tablets of 200 mg dose strength were also available for patients in Part 2 to enable dose reductions in 100 mg increments.

Objectives

Study CO-338-010 part 2A

Main objective

To evaluate overall response rate (ORR) in patients with relapsed, high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer associated with a BRCA mutation

Study CO-338-017

Main objectives

To determine FS in patients with relapsed platinum-sensitive ovarian cancer classified into molecularly-defined subgroups by a prospectively defined HRD signature (Part 1)

To estimate ORR in heavily pre-treated patients with relapsed ovarian cancer classified into molecularly-defined subgroups by a prospectively defined HRD signature (Part 2)

Outcomes/endpoints

Study CO-338-010 Part 2A

The primary efficacy endpoint in Part 2A was ORR defined as best confirmed response according to RECIST Version 1.1.

Study CO-338-017

Part 1: The primary efficacy endpoint was PFS according to RECIST Version 1.1, as assessed by the investigator, or death from any cause, in molecularly defined HRD subgroups.

Part 2: The primary efficacy endpoint was ORR by RECIST Version 1.1 in molecularly defined HRD subgroups.

Sample size

Study CO-338-010 Part 2A

Up to 41 evaluable patients with platinum-sensitive, relapsed, high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer associated with a gBRCA mutation were planned to be enrolled into Part 2A with an ORR of 20% set as the target.

Study CO-338-017

Part 1: It was anticipated that approximately 180 patients would be required in order to ensure each subgroup of patients (BRCA, non-BRCA/LOH+, and non-BRCA/LOH-) would contain an adequate number of patients.

Part 2: The objective of Part 2 was to estimate the ORR in each of the HRD subgroups (BRCA, non-BRCA LOH+, non-BRCA LOH-, and unknown) in a more heavily pretreated patient population (at least 3, but no more than 4, prior chemotherapy regimens). Overall, there is a need for new treatments and alternatives to chemotherapy for heavily pre-treated ovarian cancer patients with advanced, relapsed disease. Based on the promising response rate seen in Part 1, ORR was chosen as a primary endpoint with the following sample size assumption. Up to 300 patients were to be enrolled in Part 2 of the study in order to enrol at least 80 patients in each HRD subgroup. A total of 300 patients would be sufficient assuming an approximate 33.3% allocation to each HRD subgroup in the enrolment population.

Randomisation

Both studies are non-randomised.

Blinding (masking)

Both studies are open label studies.

Statistical methods

Study CO-338-010 Part 2A

The primary efficacy endpoint was evaluated in the efficacy-evaluable population in Part 2A of the study. The ORR was summarized with frequencies and proportion together with 95% CI of the proportion using Clopper-Pearson methodology.

Efficacy-evaluable Population consisted of all patients who met eligibility criteria, received at least 1 dose of rucaparib, had measurable tumour lesions at baseline, and had at least 1 post- baseline disease assessment.

DOR for any confirmed RECIST CR or PR was measured from the date of the first response until the first date that PD is documented. DOR was summarized as a time to event variable. For patients who continue treatment post-progression, the first date of progression was used for the analysis. Any patients with an ongoing response were censored at the date of the last post- baseline scan. The Kaplan-Meier methodology was used to summarize DOR. If able to be estimated, the 50th (median) percentile together with a 95% CI, was presented. The number of patients with PD events and the number of censored patients were also presented

Study CO-338-017

Efficacy-evaluable Population consisted of all patients who received at least 1 dose of rucaparib, had at least 1 measureable tumour lesion at baseline, and had at least 1 post-baseline tumour scan assessment using RECIST Version 1.1

Data were summarized separately for Parts 1 and 2 of this study and were pooled as appropriate.

The summary tables were presented for all treated patients and by the subgroups defined by HRD status (BRCA, non-BRCA LOH+, non-BRCA LOH-, and unknown).

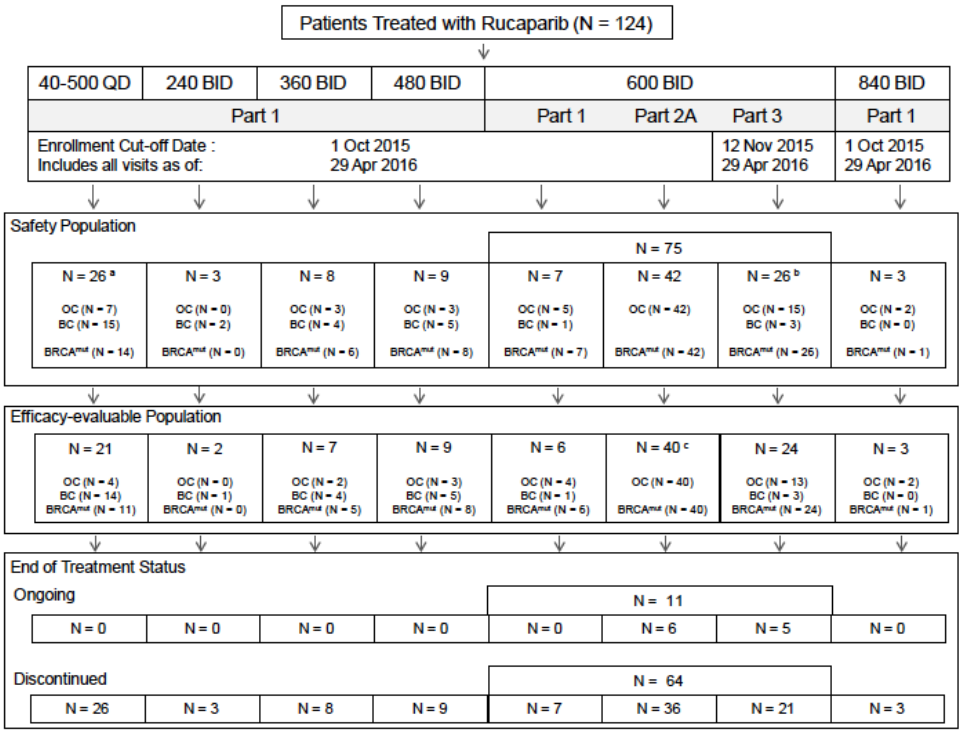
Quantitative variables were summarized using frequencies and percentages for appropriate categorizations and could also be summarized using descriptive statistics. For variables summarized with descriptive statistics, the following were presented: N, mean, standard deviation, median, minimum and maximum. Categorical variables were presented using frequencies and percentages.

The Kaplan-Meier methodology was used to any time to event endpoint. If estimable, the 50th (median) together with a 95% CI together with range was presented. The number of patients with events and the number of censored patients were also presented.

Results

Participant flow

Study CO-338-010



Abbreviations: BC = breast cancer; BID = twice daily; BRCA^{mut} = breast cancer gene mutation; N = number of patients; OC = ovarian cancer; QD = once daily.

[a] Includes N = 6 (40 mg QD, food-effect cohort); N = 3 (80 mg QD); N = 4 (160 mg QD); N = 9 (300 mg QD; food-effect cohort); and N = 4 (500 mg QD).

[b] All 26 patients were included in the food-effect cohort.

[c] Includes N = 31 patients in the GCIG CA-125 evaluable population.

Study CO-338-017

Part 1

	BRCA (N = 40)	Non-BRCA/LOH+ (N = 82)	Non-BRCA/LOH- (N = 70)	Unknown (N = 12)	Overall (N = 204)
Patient Population (n [%])					
Investigator tumor evaluable population	40 (100.0)	79 (96.3)	69 (98.6)	12 (100.0)	200 (98.0)
GCIG CA-125 evaluable population	29 (72.5)	54 (65.9)	46 (65.7)	8 (66.7)	137 (67.2)
End of Treatment Status (n [%])					
Ongoing	11 (27.5)	7 (8.5)	0	1 (8.3)	19 (9.3)
Discontinued	29 (72.5)	75 (91.5)	70 (100.0)	11 (91.7)	185 (90.7)
Primary Reason for Discontinuation of Rucaparib[a] (n [%])					
Progressive disease	24 (82.8)	56 (74.7)	57 (81.4)	8 (72.7)	145 (78.4)
Clinical progression	2 (6.9)	5 (6.7)	2 (2.9)	1 (9.1)	10 (5.4)
Adverse event	0	7 (9.3)	7 (10.0)	1 (9.1)	15 (8.1)
Death	0	0	0	0	0
Withdrawal by patient	3 (10.3)	6 (8.0)	1 (1.4)	1 (9.1)	11 (5.9)
Physician decision	0	0	2 (2.9)	0	2 (1.1)
Other	0	1 (1.3)	1 (1.4)	0	2 (1.1)

Source: Table 14.1.1.1

Abbreviations: BRCA = breast cancer gene; GCIG = Gynecologic Cancer Intergroup; LOH = loss of heterozygosity.

[a] Percentages based on the number of patients who discontinued rucaparib.

Part 2

	BRCA (N = 38)	Non-BRCA/LOH+ (N = 30)	Non-BRCA/LOH- (N = 36)	Unknown (N = 7)	Overall (N = 111)
Patient Population (n [%])					
Investigator tumor evaluable population	37 (97.4)	30 (100.0)	35 (97.2)	7 (100.0)	109 (98.2)
GCIG CA-125 evaluable population	30 (78.9)	25 (83.3)	24 (66.7)	5 (71.4)	84 (75.7)
End of Treatment Status (n [%])					
Ongoing	16 (42.1)	1 (3.3)	2 (5.6)	2 (28.6)	21 (18.9)
Discontinued	22 (57.9)	29 (96.7)	34 (94.4)	5 (71.4)	90 (81.1)
Primary Reason for Discontinuation of Rucaparib[a] (n [%])					
Progressive disease	13 (59.1)	21 (72.4)	23 (67.6)	4 (80.0)	61 (67.8)
Clinical progression	2 (9.1)	2 (6.9)	4 (11.8)	0	8 (8.9)
Adverse event	5 (22.7)	5 (17.2)	2 (5.9)	1 (20.0)	13 (14.4)
Death	0	0	0	0	0
Withdrawal by patient	1 (4.5)	0	5 (14.7)	0	6 (6.7)
Physician decision	1 (4.5)	0	0	0	1 (1.1)
Other	0	1 (3.4)	0	0	1 (1.1)

Source: Table 14.1.1.2
Abbreviations: BRCA = breast cancer gene; GCIG = Gynecologic Cancer Intergroup; LOH = loss of heterozygosity.
[a] Percentages based on the number of patients who discontinued rucaparib.

For the purpose of this application, the primary analysis population is patients who met the criteria specified below. As patients in Study CO-338-010 Part 2A and Study CO-338-017 Parts 1 and 2 met these criteria, they were considered appropriate (according to the company) for pooling of efficacy results.

1. Had a diagnosis of high-grade ovarian cancer (inclusive of primary peritoneal and fallopian tube cancer);

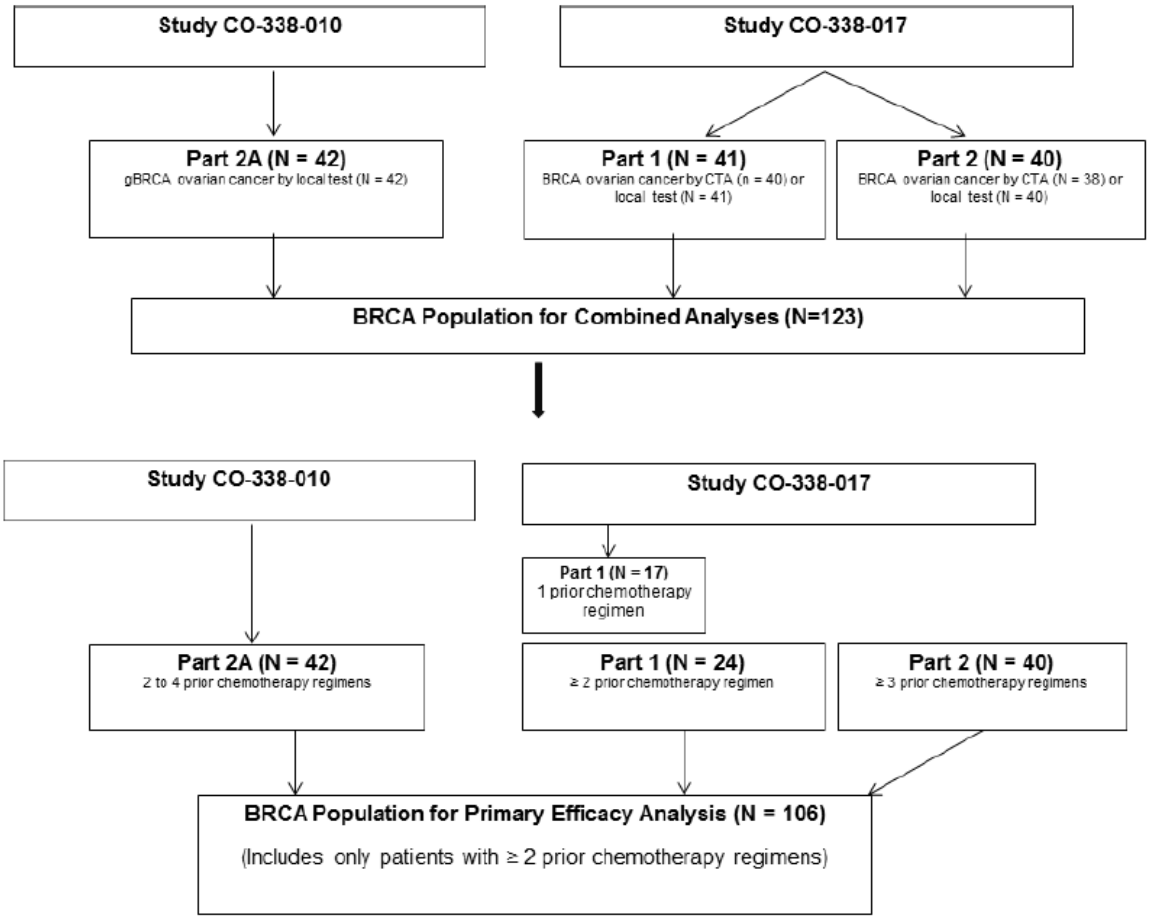
2. Received ≥ 2 prior chemotherapy regimens, including at least 2 platinum-based regimens;

3. Had a deleterious gBRCA or sBRCA mutation as detected by the CTA or a local laboratory test;

4. Were enrolled in a CO-338-010 or CO-338-017 study portion where ORR by RECIST Version 1.1 was the primary or a key secondary efficacy endpoint; and

5. Received at least 1 dose of rucaparib (600 mg).

Figure 7. Flow Diagram of Patients Included in the Primary Analysis and Combined Analyses



Abbreviations: BRCA = breast cancer gene; CTA = clinical trial assay; gBRCA = germline BRCA.

Recruitment

Both studies are ongoing. The visit cut-off dates for efficacy analyses are shown below:

Dose Group	Study	N	FPI Date	LPI Date	Enrollment Cut-off Date	Visit Cut-off Dates:
600 mg BID ovarian cancer (including BRCA mutant)	CO-338-010 Part 1	5	14 December 2011	17 September 2013	All patients enrolled	29 April 2016
	CO-338-010 Part 2A	42	5 February 2014	28 April 2015	All patients enrolled	29 April 2016
	CO-338-010 Part 3	15	27 April 2015	12 November 2015	All patients enrolled	29 April 2016
	CO-338-017 Part 1	204	30 October 2013	19 December 2014	All patients enrolled	29 April 2016
	CO-338-017 Part 2	111	13 March 2015	1 October 2015	1 October 2015	29 April 2016

Conduct of the study

Baseline data

In the part 2A of the study CO-338-010, the median age was 56.5 years (range, 42.0 to 84.0 years). The median time since cancer diagnosis was 43.1 months (range, 6.3 to 177.9 months). All 42 patients had high-grade ovarian cancer, which was classified as serous in 88.1% of patients. All 42 patients had a gBRCA mutation (assessed locally) as required for study eligibility: 30 patients had a gBRCA1 mutation and 12 patients had a gBRCA2 mutation. All 42 patients in Part 2A had at least 2 prior anticancer therapies, per protocol inclusion criteria. The median number of prior anticancer therapies and prior chemotherapies was 2 (range, 2 to 4). A majority of patients (64.3%) received 2 prior chemotherapy regimens. Two patients (4.8%) received prior hormonal therapies (1 or 2 prior regimens) in additional to their prior chemotherapy and platinum regimens. All 42 ovarian cancer patients received at least 2 prior platinum-based therapies and, as required for eligibility, their last treatment was platinum-based to which they were sensitive. The median PFI from the last platinum-based regimen was 8.0 months (range 6-116 months).

Within the subgroup of BRCA in the part 1 of the study CO-338-017, the median age was 58.5 years (range, 33-78 years). The majority of patients had epithelial ovarian cancer (95.0% BRCA) and most patients had serous histology (97.5% BRCA). The median time since diagnosis was 37.1 months in the BRCA subgroup. Approximately one-third of patients had received 2 prior chemotherapy regimens (35.0% BRCA), including 2 platinum-based regimens (37.5% BRCA). Germline BRCA was detected in 20 patients whereas somatic BRCA was reported in 19 patients (there was one patient with unknown status). BRCA1 and BRCA2 were 29 and 11 subjects respectively.

In part 2 (BRCA subgroup), the median age was 60.5 years. The majority of patients had epithelial ovarian cancer (81.6% BRCA) and most patients had serous histology (92.1% BRCA). Germline BRCA was detected in 30 patients whereas somatic BRCA was reported in only 4 patients (there were 4 patients with unknown status). BRCA 1 and BRCA2 were 16 and 22 subjects respectively The median time since diagnosis was longer than for patients in Part 1, with 51.7 months in the BRCA subgroup. Over one-fourth of patients had received 4 prior chemotherapy regimens (26.3% BRCA). Approximately 74% had received 3 prior platinum-based regimens (BRCA subgroup). By inclusion criteria, all patients were required to have received at least 3 but no more than 4 prior chemotherapy regimens. The median PFI from the last platinum-based regimen was notably shorter for patients in Part 2 compared to those in Part 1, with 4.1 and 10.7 months for the BRCA subgroup in part 2 and part 1 respectively. Only 31.6% of BRCA subgroup had platinum-sensitive disease vs 100% in the part1. The remaining patients were platinum-resistant (52.6% BRCA) or platinum-refractory (15.8% BRCA).

In the light of baseline characteristics, the pool of both studies (only BRCA positive) is characterised by a population mainly platinum sensitive (92 patients out of 120) with a median of 2 prior platinum therapies and with germline BRCA (90 patients). Having said that and considering only the target population (≥ 2 prior chemotherapy regimens, including at least 2 platinum-based regimens and BRCA positive; 106 patients), the baseline characteristics of this subgroup (target population) are defined a group of patients previously treated with 2 or 3 prior platinum regimens and mainly platinum-sensitive, with only 7 patients (6.6%) considered platinum-refractory and 21 (19.8%) platinum-resistant. Eighty-eight patients were germline BRCA (83%) and 13 (12.3%) somatic BRCA (there were 5 patients with unknown status). Sixty-seven were BRCA1 and thirty-nine were BRCA2.

Both studies are ongoing.

Study CO-338-010 Part 2A

Table 9. Disease History: Safety Population

	600 mg BID (N=42)
Time Since Cancer Diagnosis (months)	
Mean (StD)	58.8 (35.9)
Median	43.1
Min, Max	6.3, 177.9
Type of Cancer (n [%])	
Ovarian cancer [a]	42 (100.0)
Histological Classification (n [%])	
Serous	37 (88.1)
Mixed	3 (7.1)
Endometrioid	1 (2.4)
Clear cell	1 (2.4)
Histological Grade (n [%])	
High grade	42 (100.0)
Local HRD Group (n [%])	
BRCA mutation detected	42 (100.0)
Local BRCA Classification (n [%])	
Germline BRCA mutation detected	42 (100.0)
Local BRCA Mutation (n [%])	
BRCA1	30 (71.4)
BRCA2	12 (28.6)

	600 mg BID (N=42)
Number of Prior Anticancer Therapies	
Mean (StD)	2.4 (0.6)
Median	2.0
Min, Max	2.0, 4.0
Number of Prior Chemotherapy Regimens	
Mean (StD)	2.4 (0.6)
Median	2.0
Min, Max	2.0, 4.0
Number of Prior Platinum Regimens	
Mean (StD)	2.3 (0.5)
Median	2.0
Min, Max	2.0, 4.0
Progression-free Interval Since Last Platinum (months)	
Mean (StD)	12.6 (17.6)
Median	8.0
Min, Max	6.0, 116.4
Platinum Status (n [%])	
Sensitive	42 (100.0)

Study CO-338-017

Table 10. Disease History: Safety Population – Part 1

	BRCA (N = 40)	Non-BRCA/LOH+ (N = 82)	Non-BRCA/LOH- (N = 70)	Unknown (N = 12)	Overall (N = 204)
Time Since Ovarian Cancer Diagnosis (months)					
Mean (StD)	47.1 (37.7)	43.6 (29.8)	41.2 (26.3)	27.1 (11.7)	42.5 (29.8)
Median	37.1	38.5	34.8	24.9	35.3
Range	12.0, 196.6	12.0, 171.1	12.6, 125.5	12.6, 49.2	12.0, 196.6
Type of Ovarian Cancer (n [%])					
Epithelial ovarian	38 (95.0)	68 (82.9)	49 (70.0)	9 (75.0)	164 (80.4)
Primary peritoneal	1 (2.5)	10 (12.2)	12 (17.1)	1 (8.3)	24 (11.8)
Fallopian tube	1 (2.5)	4 (4.9)	9 (12.9)	2 (16.7)	16 (7.8)
Histological Classification (n [%])					
Serous	39 (97.5)	80 (97.6)	66 (94.3)	12 (100.0)	197 (96.6)
Endometrioid	1 (2.5)	1 (1.2)	2 (2.9)	0	4 (2.0)
Mixed	0	1 (1.2)	2 (2.9)	0	3 (1.5)
Histological Grade (n [%])					
High grade	40 (100.0)	82 (100.0)	70 (100.0)	12 (100.0)	204 (100.0)
Low grade	0	0	0	0	0

Table 11. Disease History: Safety Population – Part 2

	BRCA (N = 38)	Non-BRCA/LOH+ (N = 30)	Non-BRCA/LOH- (N = 36)	Unknown (N = 7)	Overall (N = 111)
Time Since Ovarian Cancer Diagnosis (months)					
Mean (StD)	55.6 (23.9)	52.3 (21.3)	57.1 (29.9)	56.5 (45.0)	55.2 (26.6)
Median	51.7	51.6	48.5	34.3	50.2
Range	21.5, 124.1	20.8, 125.9	27.3, 151.8	30.8, 154.7	20.8, 154.7
Type of Ovarian Cancer (n [%])					
Epithelial ovarian	31 (81.6)	28 (93.3)	23 (63.9)	6 (85.7)	88 (79.3)
Fallopian tube	4 (10.5)	2 (6.7)	6 (16.7)	0	12 (10.8)
Primary peritoneal	3 (7.9)	0	7 (19.4)	1 (14.3)	11 (9.9)
Histological Classification (n [%])					
Serous	35 (92.1)	28 (93.3)	33 (91.7)	6 (85.7)	102 (91.9)
Endometrioid	1 (2.6)	0	2 (5.6)	1 (14.3)	4 (3.6)
Mixed	2 (5.3)	2 (6.7)	1 (2.8)	0	5 (4.5)
Histological Grade (n [%])					
High grade	38 (100.0)	30 (100.0)	36 (100.0)	7 (100.0)	111 (100.0)
Low grade	0	0	0	0	0

Table 12. Prior Anticancer Therapies: Safety Population – Part 1

	BRCA (N = 40)	Non-BRCA/LOH+ (N = 82)	Non-BRCA/LOH- (N = 69)	Unknown (N = 12)	Overall (N = 203)
Number of Prior Chemotherapy Regimens					
Mean (StD)	2.0 (1.1)	1.7 (1.0)	1.4 (0.7)	1.3 (0.6)	1.6 (0.9)
Median	2.0	1.0	1.0	1.0	1.0
Minimum, maximum	1.0, 5.0	1.0, 6.0	1.0, 3.0	1.0, 3.0	1.0, 6.0
0	0	0	0	0	0
1	17 (42.5)	45 (54.9)	49 (70.0)	10 (83.3)	121 (59.3)
2	14 (35.0)	21 (25.6)	14 (20.0)	1 (8.3)	50 (24.5)
3	4 (10.0)	12 (14.6)	7 (10.0)	1 (8.3)	24 (11.8)
4	4 (10.0)	2 (2.4)	0	0	6 (2.9)
5	1 (2.5)	1 (1.2)	0	0	2 (1.0)
> 5	0	1 (1.2)	0	0	1 (0.5)
Number of Prior Platinum Regimens					
Mean (StD)	1.9 (1.0)	1.6 (0.9)	1.4 (0.6)	1.3 (0.6)	1.6 (0.8)
Median	2.0	1.0	1.0	1.0	1.0
Minimum, maximum	1.0, 5.0	1.0, 5.0	1.0, 3.0	1.0, 3.0	1.0, 5.0
0	0	0	0	0	0
1	17 (42.5)	45 (54.9)	49 (70.0)	10 (83.3)	121 (59.3)
2	15 (37.5)	24 (29.3)	15 (21.4)	1 (8.3)	55 (27.0)
3	6 (15.0)	11 (13.4)	6 (8.6)	1 (8.3)	24 (11.8)
> 3	2 (5.0)	2 (2.4)	0	0	4 (2.0)
Progression-free Interval Since Last Platinum (months)					
< 6	0	1 (1.2)	0	1 (8.3)	2 (1.0)
≥ 6 to 12	23 (57.5)	37 (45.1)	31 (44.3)	5 (41.7)	96 (47.1)
> 12 to 24	14 (35.0)	28 (34.1)	25 (35.7)	5 (41.7)	72 (35.3)
> 24	3 (7.5)	16 (19.5)	14 (20.0)	1 (8.3)	34 (16.7)
Mean (StD)	12.6 (5.8)	15.7 (9.6)	17.8 (14.4)	14.0 (9.6)	15.7 (11.1)
Median	10.7	12.8	13.2	12.1	12.2
Minimum, maximum	6.1, 26.5	5.9, 46.7	6.0, 74.4	5.9, 39.2	5.9, 74.4
Sensitivity to Last Platinum (n [%])					
Sensitive	40 (100.0)	81 (98.8)	70 (100.0)	11 (91.7)	202 (99.0)
Resistant	0	1 (1.2)	0	1 (8.3)	2 (1.0)
Refractory	0	0	0	0	0

Source: Table 14.1.4.1
Abbreviations: BRCA = breast cancer gene; LOH = loss of heterozygosity; StD = standard deviation.

Table 13. Prior Anticancer Therapies: Safety Population – Part 2

	BRCA (N = 38)	Non-BRCA/LOH+ (N = 30)	Non-BRCA/LOH- (N = 36)	Unknown (N = 7)	Overall (N = 111)
Number of Prior Chemotherapy Regimens					
Mean (StD)	3.3 (0.5)	3.3 (0.5)	3.2 (0.4)	3.3 (0.5)	3.3 (0.5)
Median	3.0	3.0	3.0	3.0	3.0
Minimum, maximum	3.0, 4.0	2.0, 4.0	3.0, 4.0	3.0, 4.0	2.0, 4.0
0	0	0	0	0	0
1	0	0	0	0	0
2	0	1 (3.3)	0	0	1 (0.9)
3	28 (73.7)	19 (63.3)	29 (80.6)	5 (71.4)	81 (73.0)
4	10 (26.3)	10 (33.3)	7 (19.4)	2 (28.6)	29 (26.1)
5	0	0	0	0	0
> 5	0	0	0	0	0
Number of Prior Platinum Regimens					
Mean (StD)	2.6 (0.6)	2.4 (0.6)	2.4 (0.5)	2.6 (0.8)	2.5 (0.6)
Median	3.0	2.0	2.0	3.0	2.0
Minimum, maximum	2.0, 4.0	1.0, 3.0	1.0, 3.0	1.0, 3.0	1.0, 4.0
0	0	0	0	0	0
1	0	1 (3.3)	1 (2.8)	1 (14.3)	3 (2.7)
2	16 (42.1)	15 (50.0)	21 (58.3)	1 (14.3)	53 (47.7)
3	20 (52.6)	14 (46.7)	14 (38.9)	5 (71.4)	53 (47.7)
> 3	2 (5.3)	0	0	0	2 (1.8)
Progression-free Interval Since Last Platinum (months)					
< 6	26 (68.4)	24 (80.0)	26 (72.2)	6 (85.7)	82 (73.9)
≥ 6 to 12	8 (21.1)	5 (16.7)	5 (13.9)	1 (14.3)	19 (17.1)
> 12 to 24	4 (10.5)	0	3 (8.3)	0	7 (6.3)
> 24	0	1 (3.3)	2 (5.6)	0	3 (2.7)
Mean (StD)	5.3 (5.7)	4.0 (6.1)	5.9 (9.8)	2.1 (2.8)	4.9 (7.3)
Median	4.1	1.8	2.0	0.8	2.5
Minimum[a], maximum	-0.7, 21.4	-0.7, 31.9	-0.5, 49.7	-0.8, 6.4	-0.8, 49.7
Sensitivity to Last Platinum (n [%])					
Resistant	20 (52.6)	16 (53.3)	19 (52.8)	3 (42.9)	58 (52.3)
Sensitive	12 (31.6)	6 (20.0)	10 (27.8)	1 (14.3)	29 (26.1)
Refractory	6 (15.8)	8 (26.7)	7 (19.4)	3 (42.9)	24 (21.6)

Source: Table 14.1.4.2
Abbreviations: BRCA = breast cancer gene; LOH = loss of heterozygosity; StD = standard deviation.
[a] A negative value represents patients who were refractory and had disease progression before they stopped platinum therapy.

Pooled data from both studies in the target population.

Demographic data for all patients included in the primary efficacy analysis population (N = 106). The population includes 106 female patients with BRCA-mutant ovarian cancer who received ≥ 2 prior chemotherapy regimens and received at least 1 dose of 600 mg rucaparib. Overall, the majority of patients were White (78.3%). Patients had a median age of 59.0 years (range, 33.0-84.0 years). Patients were recruited at clinical sites in North America (53.8%), Europe (29.2%), and other regions (17.0%; Australia and Israel). All patients had an ECOG performance status of 0 or 1 at baseline. Patients were primarily nonsmokers (66.0%) or former smokers (28.3%).

The median time since diagnosis of ovarian cancer was 52.1 months (range, 6.3-196.6 months). The majority of patients had EOC (85.8%) and serous histology (91.5%). All patients had received ≥ 2 prior anticancer therapies (mean ± standard deviation [StD], 2.9 ± 0.86; range, 2.0-6.0). The mean ± StD number of prior platinum regimens was 2.5 ± 0.67 (range, 2.0-5.0), with 56.6%, 37.7%, and 5.7% of patients having received 2, 3, and > 3 prior platinum-based regimens, respectively. The median PFI following the most recent platinum

regimen was 7.9 months. Slightly more than half (51.9%) of all patients had a PFI of ≥ 6 to 12 months following their most recent platinum-based regimen, and 26.4% of patients had a PFI of < 6 months following their most recent platinum-based regimen. Of note, platinum-sensitivity was not required in Part 2 of Study CO-338-017 and the median PFI following the most recent platinum regimen was 2.5 months.

Numbers analysed

Study CO-338-010 Part 2A

The efficacy-evaluable population included 40 patients from Part 2A

A total of 42 patients in Part 2A received at least 1 dose of rucaparib, of whom 6 remained ongoing as of the 29 April 2016 visit cut-off date.

Study CO-338-017

The study is ongoing and the data presented herein are from patients enrolled up to 1 October 2015, with a visit data cutoff of 29 April 2016. There were 315 patients enrolled and with data available as of the cut-off date, and all patients initiated treatment with 600 mg BID of rucaparib.

Enrolment into Part 1 of CO-338-017 initiated in October 2013 and was completed in December 2014. A total of 204 patients were treated with rucaparib in this portion of the study. Of these, 40 were identified as having a deleterious BRCA mutation in their screening biopsy or archival tumour sample based on the results of the CTA. BRCA mutation analysis for a subset of these patients was subsequently performed using the validated FMI test (CDx).

Enrolment into Part 2 of Study CO-338-017 initiated in March 2015. A total of 111 patients were treated with rucaparib in this portion of the study as of the enrolment cut-off date of 1 October 2015 for this assessment report. Of these, 38 patients were identified as having a deleterious BRCA mutation in their screening biopsy or archival tumour sample based on the results of the CTA.

Outcomes and estimation

Efficacy analyses were performed for the safety population of ovarian cancer patients with a BRCA mutation, defined as all patients who received at least 1 dose of 600 mg rucaparib. The breakdown of patients included in the efficacy analyses are as follows:

- Study CO-338-010 Part 2A gBRCA (N = 42 patients with ≥ 2 prior chemotherapy regimens)
- Study CO-338-017 Part 1 BRCA subgroup (N = 24 patients with ≥ 2 prior chemotherapy regimens)
- Study CO-338-017 Part 2 BRCA subgroup (N = 40 patients with ≥ 3 prior chemotherapy regimens)

The visit cut-off dates allowed for the last patients enrolled to have ≥ 4 disease assessment scans (ie, ≥ 6 months on treatment).

Table 14. Confirmed Objective Response Rate Based on Investigator- assessed Response: Primary Efficacy Population

	600 mg BID (N = 106)
Confirmed ORR (CR + PR) (n [%])	57 (53.8)
95% CI (%)	43.8, 63.5
Best Overall Confirmed Response (n [%])	
CR	9 (8.5)
PR	48 (45.3)
SD	36 (34.0)
Completed study	29
Ongoing with single response	1
Ongoing without response	6
PD	9 (8.5)
NE	4 (3.8)
Response by RECIST or GCIG CA-125 (n [%])	
Yes	76 (71.7)
95% CI (%)	62.1, 80.0
No	27 (25.5)
Inevaluable	3 (2.8)

Source: Table 2.1.1 (Section 5.3.5.3).
Abbreviations: BID = twice daily; CA-125 = cancer antigen 125; CI = confidence interval; CR = complete response; GCIG = Gynecologic Cancer Intergroup; N or n = number of patients; NE = not evaluable; ORR = objective response rate; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

Confirmed ORR by RECIST Version 1.1 as assessed by central IRR was a supportive analysis. In the overall primary efficacy population, confirmed ORR by IRR (44.3% [95% CI, 34.7%-54.3%]) was lower than the confirmed ORR with investigator-assessed responses (53.8% 95% CI, 43.8%-63.5%]). Comparison of IRR versus investigator-assessed response in each study and part revealed a similar difference, though these data should be interpreted with caution due to the low number of patients in each study portion. The ORR by IRR was lower by 5%, 21%, and 8% in Study CO-338-010 Part 2A, Study CO-338-017 Part 1, and Study CO-338-017 Part 2, respectively, compared with investigator assessment of response.

The difference in response assessment of the individual cases between the investigator review and the independent review in Study CO-338-017 Part 1 was further explored. Overall, 11 of 24 patients in Study CO-338-017 Part 1 had a discordant best overall response assessment. This included 4 patients with a PR by investigator and SD by IRR, 3 patients with a CR by investigator and a PR by IRR, 2 patients with a PR by investigator and a CR by IRR, 1 patient with a PR by investigator and PD by IRR, and 1 patient with SD by investigator and PD by IRR. The scans for these 11 patients were provided to an external, independent peer reviewer at an earlier data cut-off date (29 February 2016) in order to assess the reasons for discordance. The peer reviewer found no error by either the investigator or IRR for the majority (7 of 11) of patients reviewed, including 2 patients that were assessed as having a response (PR in each case) by investigator, but not by IRR. In the remaining 4 patients the independent peer reviewer found 3 errors by the investigator, including lesion selection at screening, assessment of non-target lesion progression, or determination of date of progression, and 1 error by IRR, which was lack of identification of target at screening. In the latter case this resulted in a best overall response of SD by IRR as compared to PR by investigator. The reviewer also assessed scans for a 12th

patient with prolonged durable SD as assessed by both investigator and IRR assessment. In this case the independent reviewer noted that the target lesion selection by the investigator was in error; however, this did not affect the outcome and the overall assessment of SD by both investigator and IRR was correct. As there was no systematic issue identified, the discordance in the other study portions was not further investigated. Overall, the IRR results are consistent with response assessment by the investigators, both in the individual study parts and in the overall primary efficacy population. The variability observed between investigator and IRR assessed responses was considered to result from differences in target lesion selection rather than from assessment errors. Given the extent of non-measurable disease in advanced ovarian cancer, including the presence of ascites, the consistent selection of appropriate target lesions is often subjective between different individuals.

Table 15. Supportive Analysis - Confirmed Response Rate per Independent Reviewer (primary efficacy population)

	600 mg BID (N=106)
Confirmed Response Rate	47 / 106 (44.3%)
95% CI	34.7 - 54.3%
Best Overall Confirmed Response	
CR	8 / 106 (7.5%)
PR	39 / 106 (36.8%)
SD	35 / 106 (33.0%)
Discontinued	26
Ongoing	9
PD	19 / 106 (17.9%)
NE	5 / 106 (4.7%)
Response by RECIST or GCIG CA-125	
Yes	69 (65.1%)
95% CI	55.2 - 74.1%
No	33 (31.1%)
Inevaluable	4 (3.8%)

Table 16. Supportive Analysis - Overall Response per Independent Reviewer by Study Part (primary efficacy population)

	CO-338-010 (N=42)	**CO-338-017 Part 1 (N=24)**	**CO-338-017 Part 2 (N=40)**
Objective Response Rate (95% CI)	57.1% (41.0 - 72.3)	50.0% (29.1 - 70.9)	35.0% (20.6 - 51.7)
Confirmed Response Rate (95% CI)	54.8% (38.7 - 70.2)	50.0% (29.1 - 70.9)	30.0% (16.6 - 46.5)
Confirmed Response (CR or PR)	23 (54.8%)	12 (50.0%)	12 (30.0%)
CR	3 (7.1%)	2 (8.3%)	3 (7.5%)
PR	20 (47.6%)	10 (41.7%)	9 (22.5%)
SD	11 (26.2%)	8 (33.3%)	16 (40.0%)
PD	5 (11.9%)	4 (16.7%)	10 (25.0%)
NE	3 (7.1%)	0	2 (5.0%)

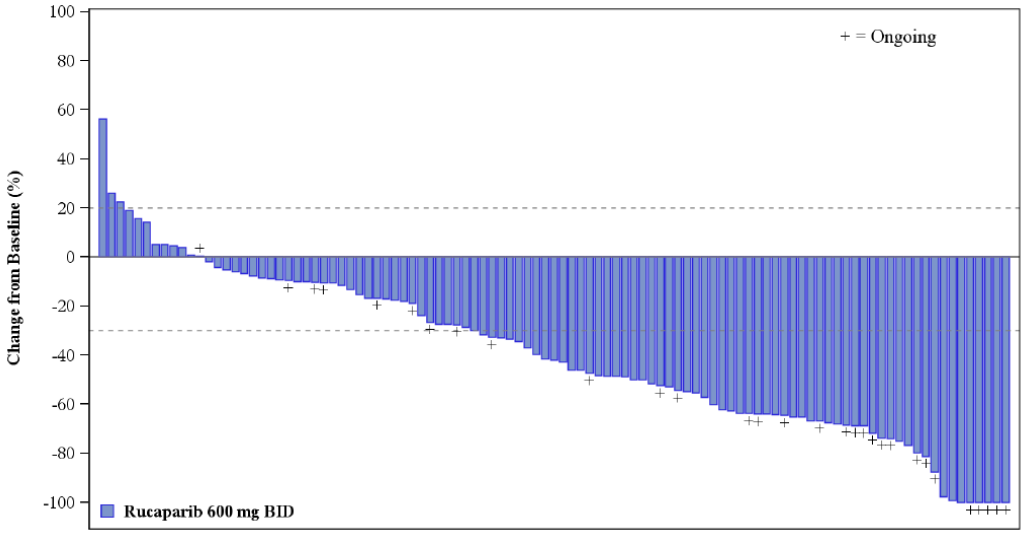
The median duration of response was 294.0 days (95% CI, 202-392 days), or approximately 9.7 months. Duration of response data were censored at the date of the last post-baseline scan for 24 patients; 16 of whom had an ongoing response at the time of data cut-off.

The median duration of response for patients with CR or PR as determined by IRR assessment is reported separately for each reader. The median duration of response for Radiologist 1 and Radiologist 2 was 231.0 days (95% CI, 168-not assessable [NA] days), or approximately 7.6 months and 231.0 days (95% CI, 169-659 days), or approximately 7.6 months, respectively. Duration of response was censored for 24 and 23 patients for Radiologist 1 and Radiologist 2, respectively.

The endpoint of ORR based on RECIST or GCIG CA-125 criteria is defined as the best confirmed response of CR or PR using RECIST Version 1.1 or a confirmed response per GCIG CA-125 criteria. The endpoint of CA-125 response rate is defined as a 50% reduction from baseline in CA-125 measurement as assessed by GCIG criteria.

The confirmed ORR by RECIST (with responses assessed by the investigator) or GCIG CA-125 criteria was 71.7% (95% CI, 62.1%-80.0%). Thirty-nine of 40 (97.5%) patients who achieved a radiologic response and were also evaluable for a GCIG CA-125 response, achieved a tumour marker response. In general, the GCIG CA-125 response tracked very closely with the RECIST response and in some cases preceded the radiologic response. In addition, 15 patients with a best overall response of SD achieved a GCIG CA-125 response. The confirmed ORR by RECIST (with responses assessed by IRR) or GCIG CA-125 criteria was 65.1% (95% CI, 55.2%-74.1%)

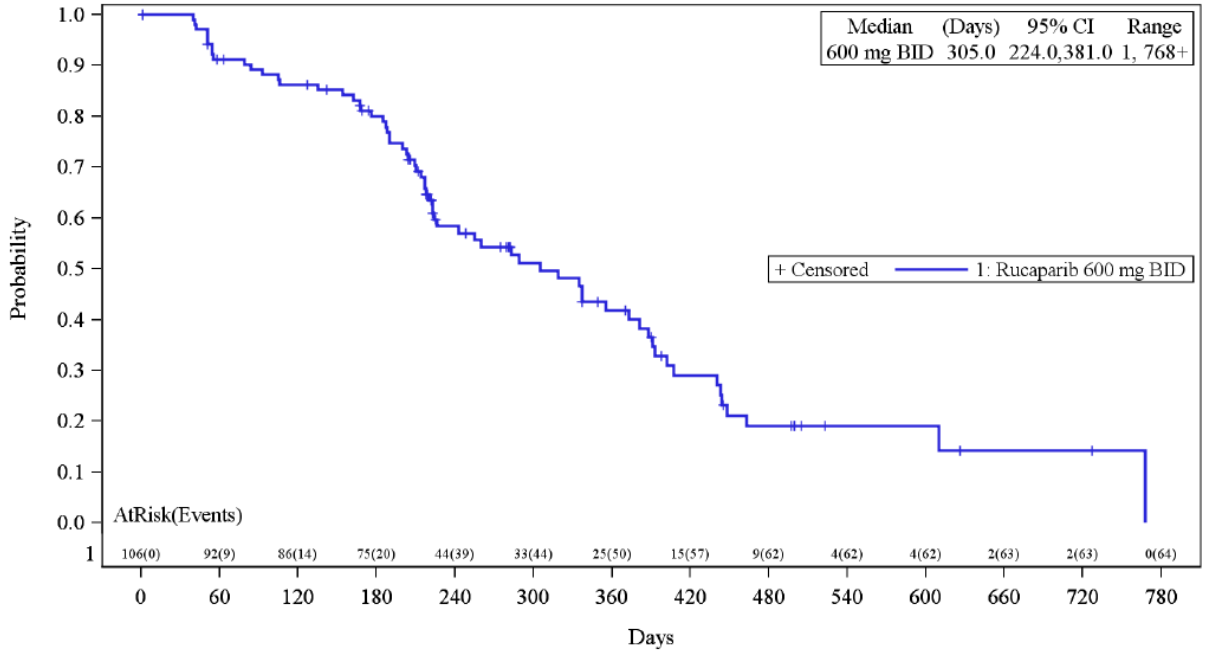
Figure 8. Investigator-assessed Best Response for Target Lesions in BRCA-mutant Patients with Measureable Disease: Primary Efficacy Population



Source: Figure 2.1.2 (Section 5.3.5.3).
Abbreviations: BID = twice daily; BRCA = breast cancer gene.
Note: Each bar represents a single patient. Patients with zero percent change from baseline are shown as 0.5% for visual clarity. Includes the best percent change from baseline up to and including the first overall response of progressive disease.

The median PFS for rucaparib by investigator assessment was 10.0 months (95% CI, 7.4-12.5 months). PFS data were censored at the date of the last visit for 42 patients, of whom 23 remained ongoing with rucaparib treatment.

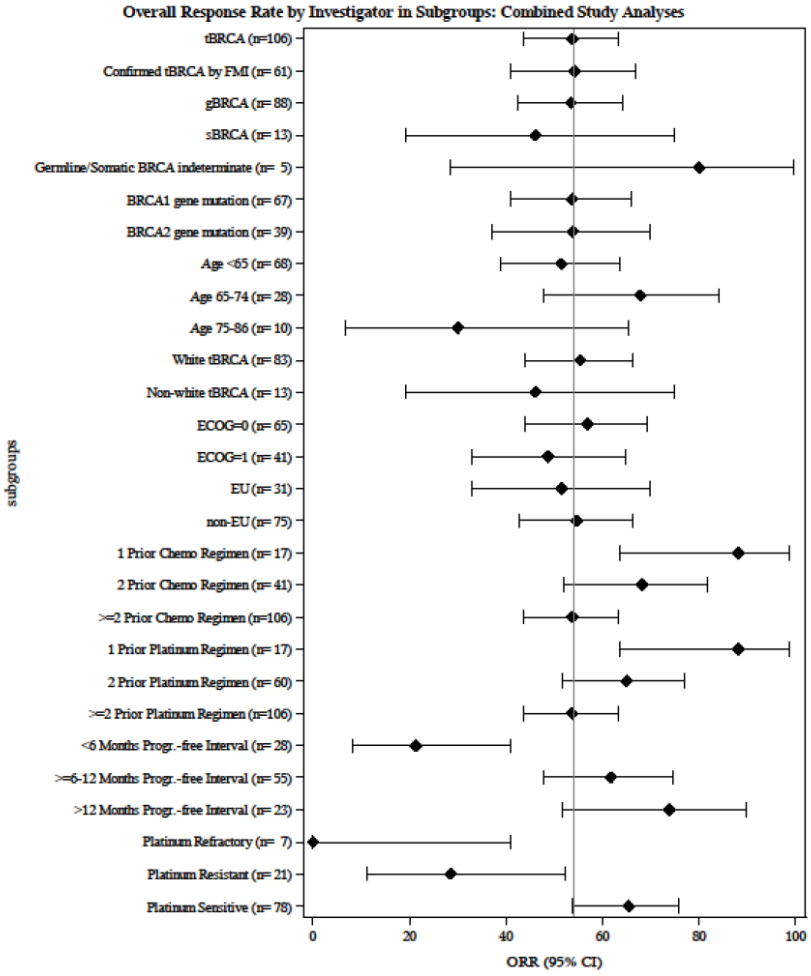
Figure 9. Investigator-assessed Progression-free Survival in the Primary Efficacy Population



Source: Figure 4.1 (Section 5.3.5.3).
Abbreviations: BID = twice daily; CI = confidence interval.

Comparison of Results in Sub-populations

Figure 10. Overall Response Rate by Investigator in Subgroups: Combined Study Analyses



Source: Figure 2.7.3-13.
Abbreviations: BRCA(1/2) = breast cancer gene(1/2); CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; EU = European Union; FMI = Foundation Medicine, Inc.; gBRCA= germline mutations in BRCA; ORR = objective response rate; sBRCA = somatic mutations in BRCA; tBRCA = tumor tissue alteration in BRCA1/2, including gBRCA and sBRCA.
Note: The vertical line represents the investigator-assessed confirmed ORR of 53.8% in the 106 patient efficacy population, as presented in Table 2.5.4-1.

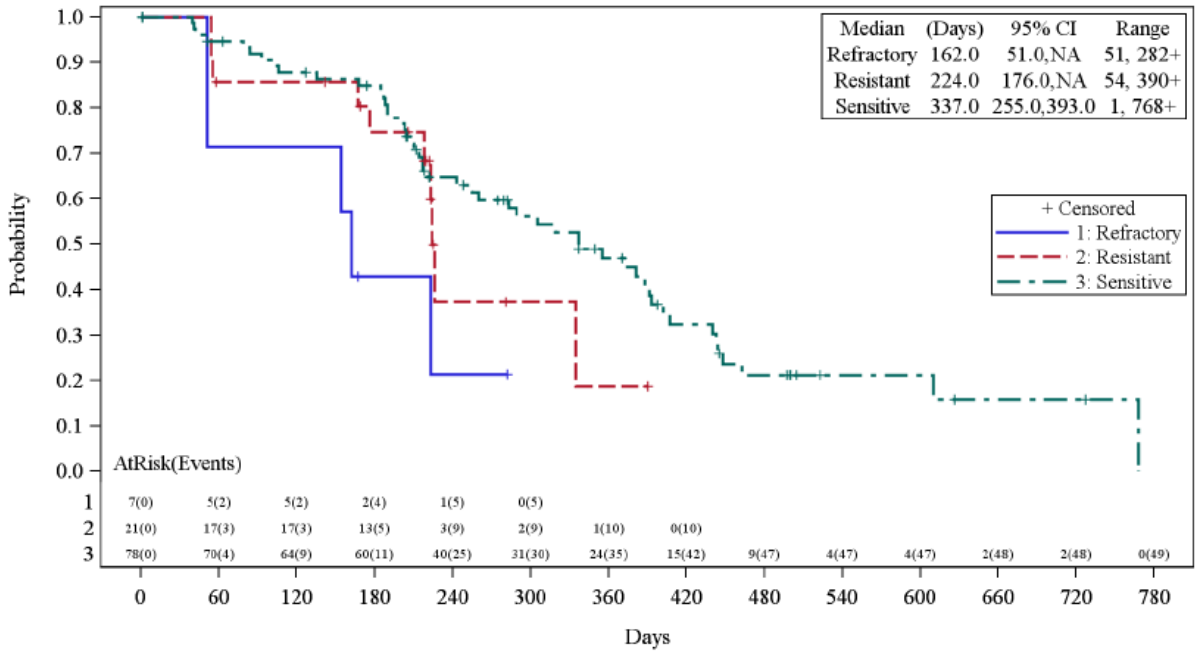
Confirmed ORR by investigator-assessed response: 88.2% [95% CI, 63.6%-98.5%, N = 17], 65.0% [95% CI, 51.6%-76.9%, N = 60], and 53.8% [95% CI, 43.8%-63.5%, N = 106] for patients with 1, 2, and ≥ 2 prior platinum-based chemotherapy regimens, respectively. The median duration of response was 224.0 days (approximately 7.4 months), 270.0 days (approximately 8.9 months), and 294.0 days (approximately 9.7 months), as assessed by the investigator, for patients with 1, 2, and ≥ 2 prior platinum chemotherapy regimens, respectively, as assessed by the investigator. Confirmed ORR by investigator-assessed response: 73.9% [95% CI, 51.6%-89.8%, N = 23], 61.8% [95% CI, 47.7%-74.6%, N = 55], and 21.4% [95% CI, 8.3%-41.0%, N = 28] for patients with a PFI of > 12 months, ≥ 6 to 12 months, and < 6 months, respectively. The median duration of response, as assessed by the investigator, was 414.0 days (approximately 13.6 months), 270.0 days (approximately 8.9 months), and 115.0 days (approximately 3.8 months), for PFI intervals of > 12 months, ≥

6 to 12 months and < 6 months, respectively. Confirmed ORR by investigator-assessed response: 65.4% [95% CI, 53.8%-75.8%, N = 78], 28.6% [95% CI, 11.3%-52.2%, N = 21], and 0% [95% CI, 0.0%-41.0%, N = 7] for platinum-sensitive, resistant, and refractory patients, respectively.

An additional subgroup analysis of PFS by platinum status (sensitive, resistant, or refractory) was performed. The median PFS was highest in platinum-sensitive patients (11.1 months [95% CI, 8.4-12.9, N = 78]). The median PFS in platinum-resistant patients was 7.4 months (95% CI, 5.8-NA, N = 21). Even though no patient with platinum-refractory disease achieved a RECIST response, the median PFS in this group was 5.3 months (95% CI, 1.7 – NA, N = 7). These data should be interpreted with caution due to the low number of platinum-refractory (N = 7) and platinum-resistant (N = 21) patients.

Among the platinum-sensitive patients (N=78), the majority (55/78, 70.5%) were partially platinum-sensitive (PFI from last platinum dose of 6 to 12 months) and the rest (N=23) were fully sensitive to platinum (PFI >12 months). The median PFS was longer in the fully platinum-sensitive group than the partially sensitive group (12.9 vs. 9.3 months).

Figure 11. Investigator-assessed Progression-free Survival by Platinum Status in the Primary Efficacy Population



Source: Figure 4.2 (Section 5.3.5.3).
Abbreviations: CI = confidence interval; NA = not assessable.

Results for each study (CO-338-010 and CO-338-017) are described individually in the clinical AR.

Updated efficacy analyses (visit cut-off 10 April 2017).

The initial MAA presented at least a 6 month follow up for all patients included in the primary efficacy analysis population (N=106). All patients were enrolled as of 01 October 2015, with a visit cut-off of 29 April 2016, allowing for up to 3 post-baseline tumour assessments to be performed for all patients. The updated analysis presented in response to the Day 120 LoQs includes up to an additional 11 months of data from a visit cut-off of 10 April 2017.

Summary of Studies and Cut-off Dates for the Primary Efficacy Analysis (N=106)				
Rucaparib Dose	**Study**	**n**	**Efficacy Data are from Patients Enrolled by:**	**Visit Cut-off Date**
600 mg BID	CO-338-010 Part 2A[a]	42	Enrollment completed in April 2015; all enrolled patients included	10 April 2017
	CO-338-017 Part 1	24	Enrollment completed in October 2014; all enrolled tBRCA mutation patients included	
	CO-338-017 Part 2	40	01 October 2015; 40 of the 95 patients were enrolled as of this cut-off date[b]	
Total number of patients		106		

Abbreviations: BID = twice daily; MAA = Marketing Authorisation Application; tBRCA = tumour tissue alteration in breast cancer gene 1/2, includes germline BRCA (gBRCA) and somatic BRCA (sBRCA).

[a] CO-338-010 Part 2B (not included in the application) was closed to enrollment on 01 July 2016. A total of 12 BRCA-mutant ovarian cancer patients with ≥ 2 prior chemotherapies were enrolled.

[b] CO-338-017 Part 2 was closed to enrollment on 29 July 2016. A total of 95 BRCA-mutant ovarian cancer patients with ≥ 2 prior chemotherapies were enrolled.

Comparison of efficacy data for the initial MAA and Day 120 Update show that confirmed ORR, DOR, and PFS for investigator-assessed responses are very similar **(Tables 17 ,18 and 19).**

The data are considered mature. There was a censoring rate of 42.1% for DOR at the time of the initial MAA visit cut-off; at the Day 120 Update the censoring rate was 29.3%. For PFS, the censoring rate was 39.6% and 21.7% at the time of the initial MAA and Day 120 Update visit cut-offs, respectively. Most the remaining censored patients discontinued the studies before a progression event was observed.

The studies remain ongoing and the Applicant plans to provide final analyses upon study completion.

Table 17. Investigator-assessed Confirmed Objective Response Rate: Comparison of Data in Initial MAA and Day120 Update

Parameter and Subgroup	N	Initial MAA (29 April 2016)	N	Day 120 Update (10 April 2017)
Primary Efficacy Analysis Population				
Confirmed ORR, n (%)	106	57 (53.8)	106	58[a] (54.7)
95% CI (%)		43.8-63.5		44.8-64.4
Best Overall Confirmed Response, n (%)				
CR		9 (8.5)		9 (8.5)
PR		48 (45.3)		49 (46.2)
Platinum Sensitivity Status Subgroup				
Confirmed ORR, Platinum-sensitive, n (%)	78	51 (65.4)	79[b]	51 (64.6)
95% CI (%)		53.8-75.8		53.0-75.0
Confirmed ORR, Platinum-resistant, n (%)	21	6 (28.6)	20[b]	7[a] (35.0)
95% CI (%)		11.3-52.2		15.4-59.2
Confirmed ORR, Platinum-refractory, n (%)	7	0	7	0
95% CI (%)		0.0-41.0		0.0-41.0
PFI from Last Platinum Dose Subgroup				
Confirmed ORR, PFI > 12 months, n (%)	23	17 (73.9)	24	17 (70.8)
95% CI (%)		51.6-89.8		48.9-87.4
Confirmed ORR, PFI 6-12 months, n (%)	55	34 (61.8)	55	34 (61.8)
95% CI (%)		47.7-74.6		47.7-74.6
Confirmed ORR, PFI < 6 months, n (%)	28	6 (21.4)	27	7 (25.9)
95% CI (%)		8.3-41.0		11.1-46.3

Source: Tables 2.30.1, 2.34.1, 2.35.1 (Day120 Update, Analysis of Efficacy, Section 5.3.5.3).

Abbreviations: CI = confidence interval; CR = complete response; ORR = objective response rate; [a] PFI = progression-free interval; PR = partial response.

There is 1 new responder in the platinum-resistant group. This patient had an initial response documented prior to the initial MAA visit cut-off; however, this response had not been confirmed at the time of the initial submission. This response was subsequently confirmed in June 2016.

[b] The platinum status of 1 patient changed from platinum-resistant to platinum-sensitive from the initial MAA to the Day 120 Update due to source data updates.

Table 1b. Supportive Analysis - Confirmed Response Rate per Independent Reviewer (Day 120 update)

	600 mg BID (N=106)
Confirmed Response Rate	47 / 106 (44.3%)
95% CI	34.7 - 54.3%
Best Overall Confirmed Response	
CR	13 / 106 (12.3%)
PR	34 / 106 (32.1%)
SD	34 / 106 (32.1%)
Discontinued	34
Ongoing	0
PD	19 / 106 (17.9%)
NE	6 / 106 (5.7%)

Table 18. Investigator-assessed Duration of Response in Responders: Comparison of Data in Initial MAA and Day120 Update

Parameter and Subgroup	N	Initial MAA (29 April 2016)	N	Day 120 Update (10 April 2017)
Primary Efficacy Analysis Population				
DOR, days (95% CI), Responders [a]	57	294 (202-392)	58[b]	288 (202-392)
Censoring, n (%)		24 (42.1)		17 (29.3%)
Platinum Sensitivity Subgroup				
DOR, days (95% CI), Platinum-sensitive subgroup	51	294 (232-393)	51	294 (224-393)
DOR, days (95% CI), Platinum-resistant subgroup	6	115 (113-NA)	7b	196 (113-NA)
DOR, days (95% CI), Platinum-refractory subgroup	0	not done	0	not done
PFI from Last Platinum Dose Subgroup				
DOR, days (95% CI), PFI > 12 months subgroup	17	414 (232-NA)	17	383 (232-709)
DOR, days (95% CI), PFI 6-12 months subgroup	34	270 (169-355)	34	270 (169-392)
DOR, days (95% CI), PFI < 6 months subgroup	6	115 (113-NA)	7	196 (113-NA)

Source: Figures 2.6.3.7, 2.7.3.7., 2.13.4 (Day120 Update, Analysis of Efficacy, Section 5.3.5.3). Figures 2.7.3.1, 2.8.3.1 (Initial MAA, Analysis of Efficacy, Section 5.3.5.3).

[a] DOR was analysed in the subgroup of patients who had measurable disease at baseline and a confirmed response by RECIST v1.1. DOR for any confirmed RECIST CR or PR was measured from the date of the first response until the first date that PD was documented. Any patients with an ongoing response were censored at the date of the last post-baseline scan.

[b] There is 1 new responder in the platinum-resistant group. This patient had an initial response documented prior to the initial MAA visit cut-off; however, this response had not been confirmed at the time of the initial submission. This response was subsequently confirmed in June 2016.

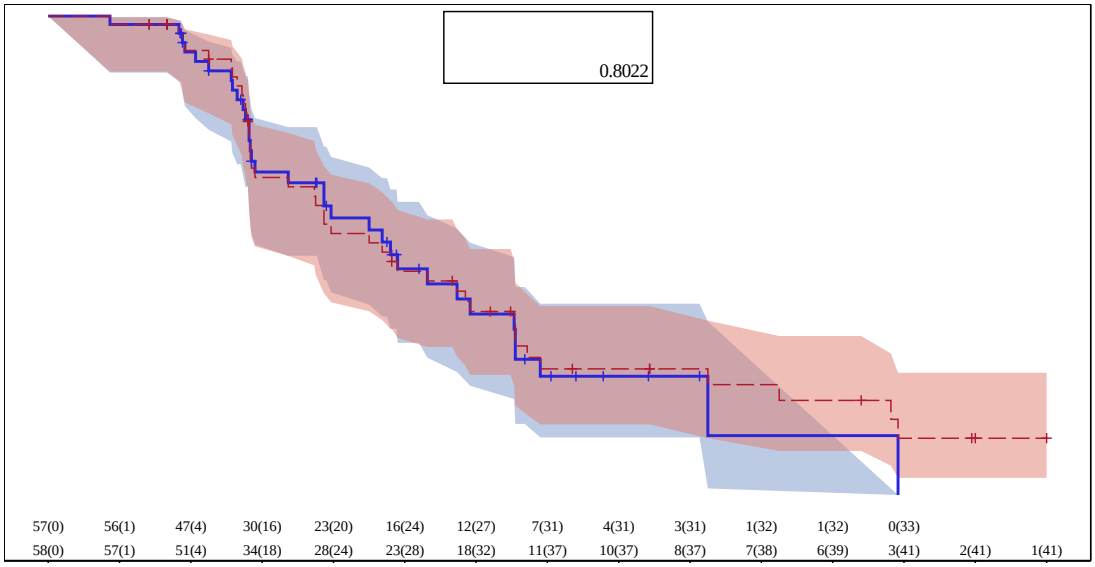
Table 19. Investigator-assessed Progression-free Survival: Comparison of Data in Initial MAA and Day120 Update

Parameter and Subgroup	N	Initial MAA (29 April 2016)	N	Day 120 Update (10 April 2017)
Primary Efficacy Analysis Population				
PFS, days (95% CI)	106	305 (224-381)	106	289 (226-337)
Censoring, n (%)		42 (39.6)		23 (21.7)
Platinum Sensitivity Subgroup				
PFS, days, Platinum-sensitive (95% CI)	78	337 (255-393)	79[a]	332 (255-391)
PFS, days, Platinum-resistant (95% CI)	21	224 (176-NA)	20[a]	282 (218-335)
PFS, days, Platinum-refractory (95% CI)	7	162 (51-NA)	7	162 (51-223)
PFI from Last Platinum Dose Subgroup				
PFS, days (95% CI), PFI > 12 months	23	not done	24[a]	391 (319-693)
PFS, days (95% CI), PFI 6-12 months	55	not done	55	279 (210-381)
PFS, days (95% CI), PFI < 6 months	28	not done	27[a]	224 (176-296)

Source: Figures 2.12.1, 2.12.2, 2.12.5 (Day120 Update, Analysis of Efficacy, Section 5.3.5.3). Figure 4.2 (Initial MAA, Analysis of Efficacy, Section 5.3.5.3).

[a] The platinum status of 1 patient changed from platinum-resistant to platinum-sensitive from the initial MAA to the Day 120 Update due to source data updates.

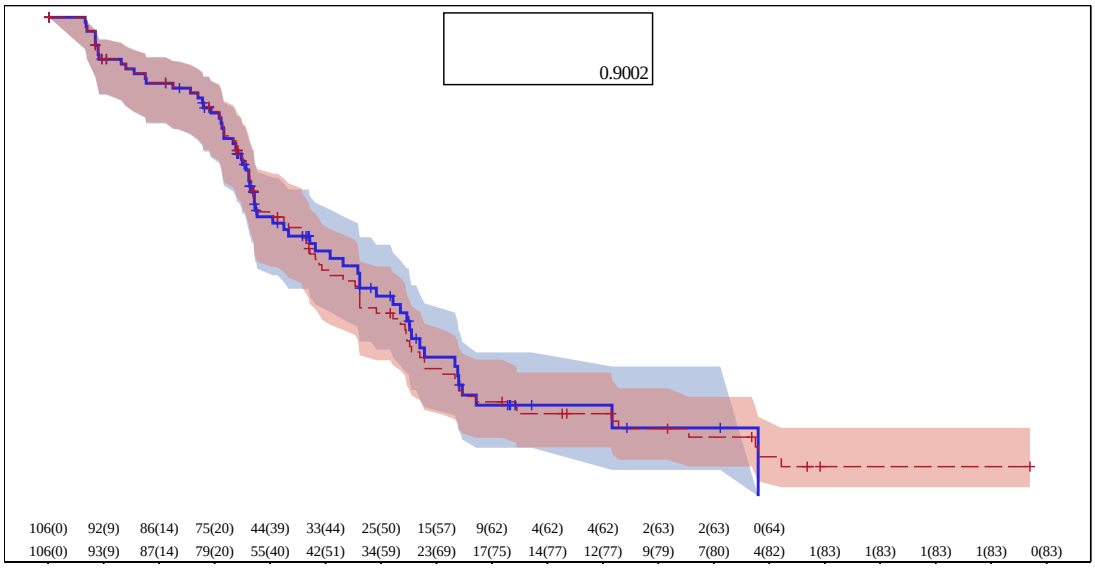
Figure 12. Duration of Response for Responders within the Primary Efficacy Analysis Population: Data in Initial MAA (N=57) Compared to Day 120 Update (N=58)



Source: Figure 2.13.4 (Day 120 Update, Analysis of Efficacy, Section 5.3.5.3).

Note: Shaded areas represent 95% confidence intervals.

Figure 13. Progression-free Survival for the Primary Efficacy Analysis Population (N=106): Data in Initial MAA Compared to Day 120 Update



Source: Figure 2.12.1 (Day 120 Update, Analysis of Efficacy, Section 5.3.5.3).
Note: Shaded areas represent 95% confidence intervals.

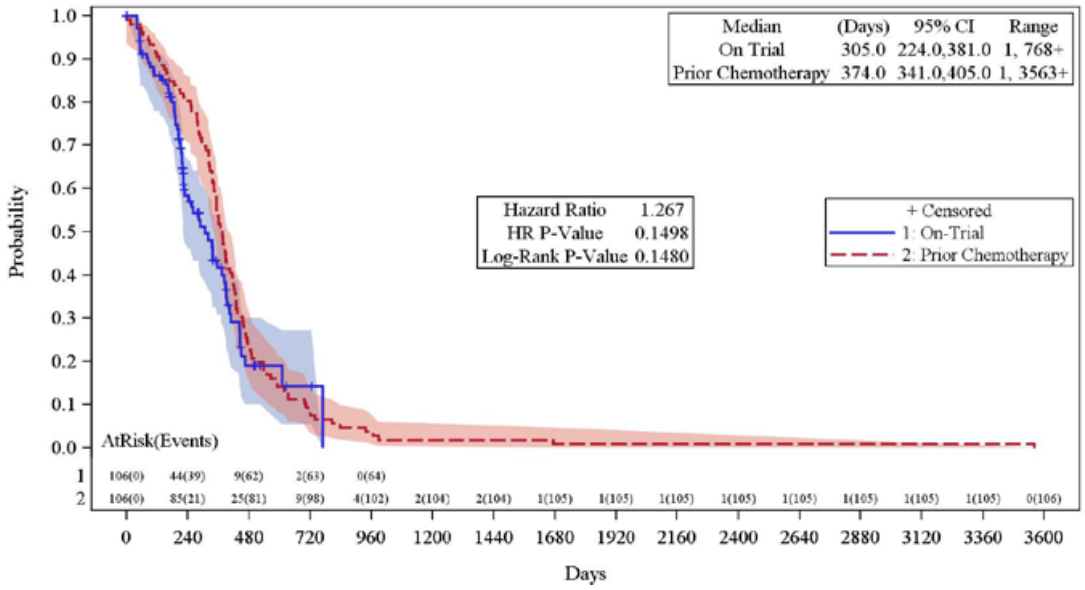
The Day 120 Update assessment of PFS continued to show that PFS did not differ significantly for rucaparib compared to PFS for the immediate prior line of chemotherapy **(Figure 14).** The median PFS for rucaparib was approximately 10.0 months (initial MAA) and 9.5 month (Day 120 Update).

Ancillary analyses

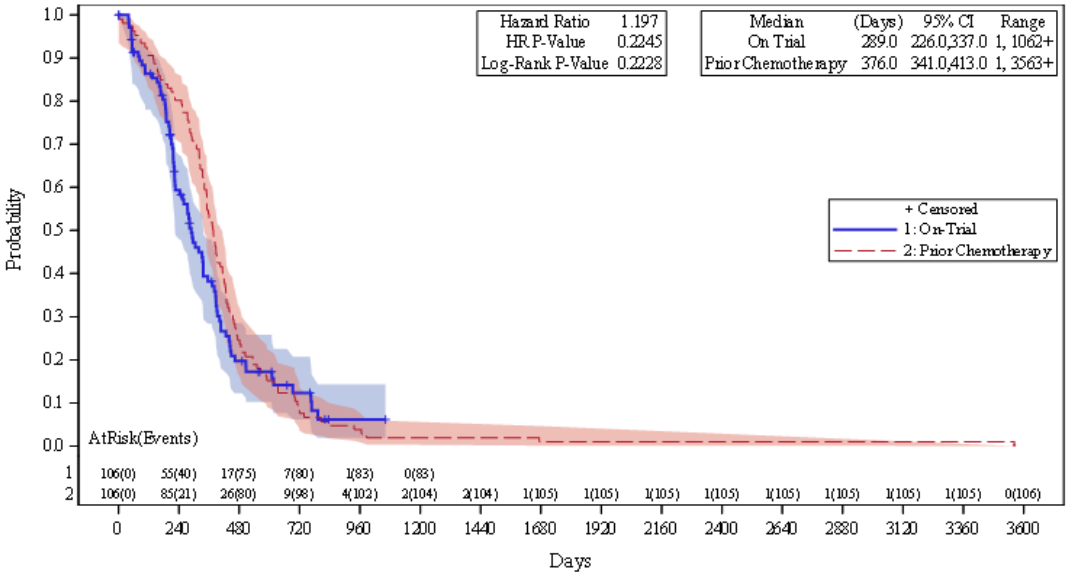
Given that the patients treated with rucaparib included in the efficacy analysis were enrolled in single-arm studies and no assessment against a comparator within the same patient population was possible, an exploratory analysis of PFS with rucaparib treatment versus that with the immediately preceding chemotherapy treatment was performed. Therefore, in this analysis, the efficacy cohort is used as a control cohort. The PFS for rucaparib (median, 9.5 months [95% CI, 7.4-11.1 months]) is similar to the PFS for the immediately preceding chemotherapy regimen (median, 12.4 months [95% CI, 11.2-13.6 months; hazard ratio [HR]: 1.197, log-rank p-value = 0.2228).

Figure 14. Progression-free Survival for Rucaparib Compared to Progression-free Survival for the Immediately Preceding Chemotherapy: Data in Initial MAA and Day 120 Update

Initial MAA

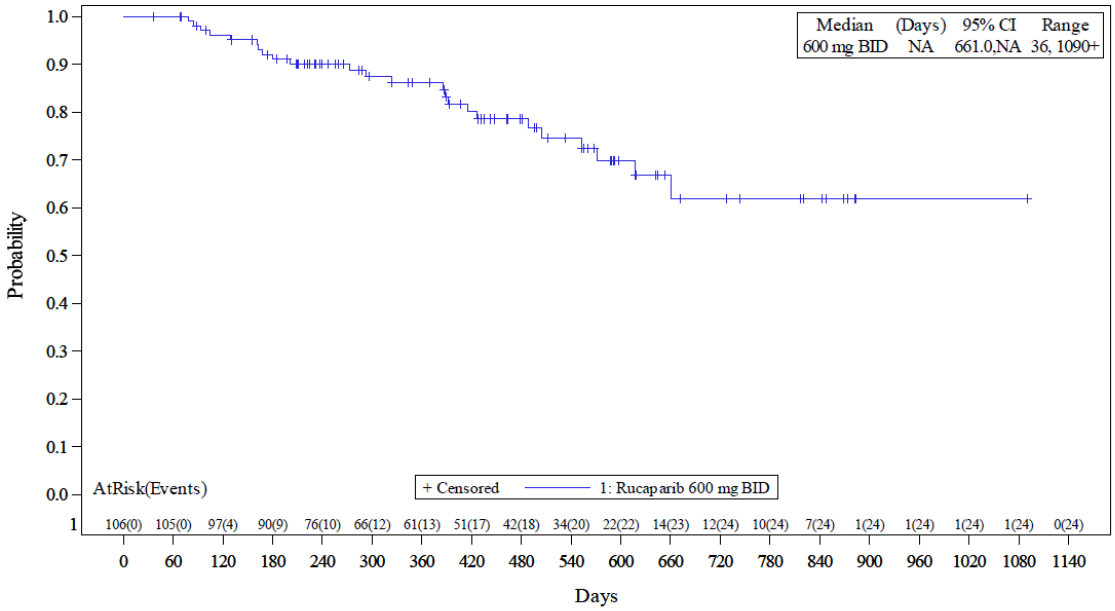


Day 120 Update



OS data were not presented in the initial MAA, as OS was not a primary or key secondary endpoint in the summary of clinical efficacy statistical analysis plan. Per protocol, post progression survival data are only being collected for patients enrolled in Study CO-338-010 Part 2B and Study CO-338-017 Part 2. Data for Study CO-338-010 Part 2B were not presented in the application as no patients had enrolled as of the 01 October 2015 cut-off. The Applicant has analysed available OS data from the primary efficacy analysis population (N=106) (**Figure 15**) and from the subset of patients from CO-338-017 Part 2 (N=40) (**Figure 16**). Patients were censored at the last date known to be alive.

Figure 15. Overall Survival for the Primary Efficacy Analysis Population (N=106): Data from Day 120 Update



Patients without progressive disease are censored at the last post-baseline scan

Source: Figure 2.12.3.8 (Day120 Update, Analysis of Efficacy, Section 5.3.5.3).

The median OS in the primary efficacy analysis population (N=106) has not yet been defined but the lower boundary of the 95% confidence interval is 21.7 months. Hanker et al reported a median OS ranging from 5 to 11 months in patients receiving third or later line therapy. Lorusso et al reported a median OS of approximately 18 months in a population with BRCA-mutated tumours or a BRCA-like clinical phenotype who had received 2 or more previous lines of chemotherapy. Sehouli et al reported a median OS of approximately 10 to 14 months in a 2-arm study of treosulphan in patients who had a median of 2 previous chemotherapy lines.

Most patients in CO-338-017 Part 2 (N=40) had platinum-resistant or refractory disease, and all were receiving rucaparib as fourth or fifth-line treatment. Median OS has not yet been defined but the lower boundary of the 95% confidence interval is 16 months. Lorusso et al reported median OS < 12 months in a platinum-resistant population with tumour BRCA (tBRCA) mutation or BRCA-like clinical phenotype.

Figure 16. Overall Survival for Patients from CO-338-017 Part 2 (N=40): Data from Day 120 Update

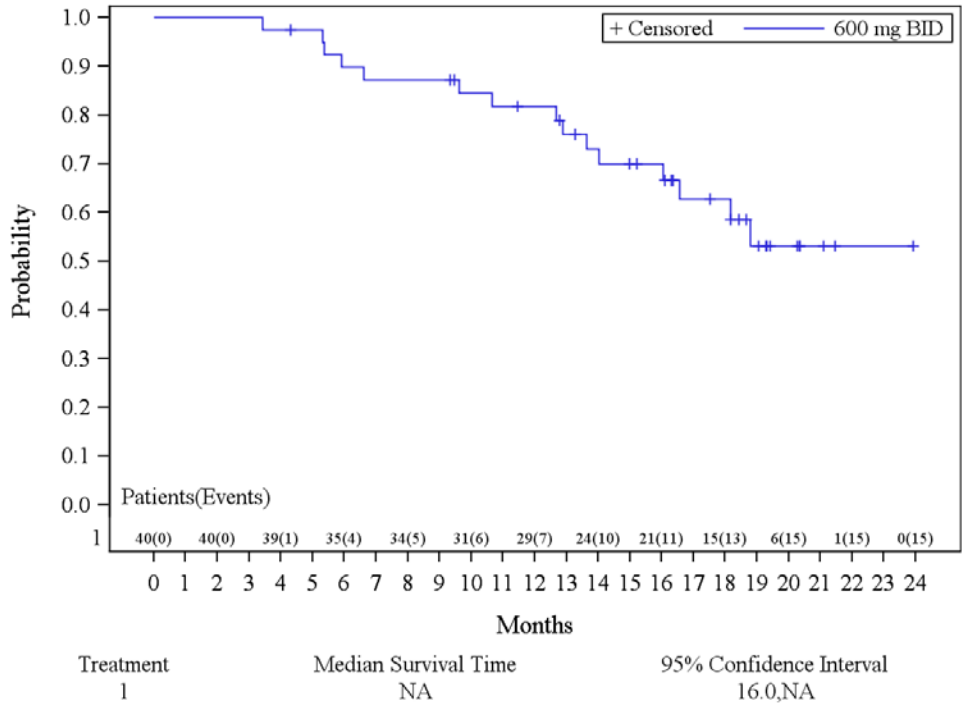
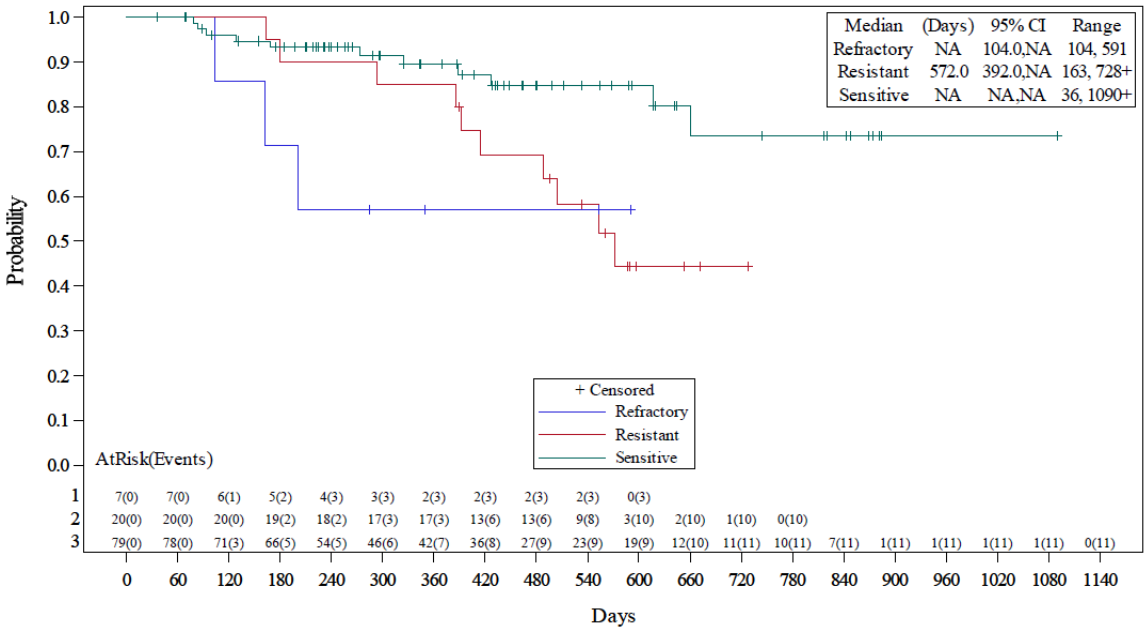


Figure 17. Overall Survival for the Primary Efficacy Analysis Population (N=106) by platinum sensitivity: Data from Day 120 Update



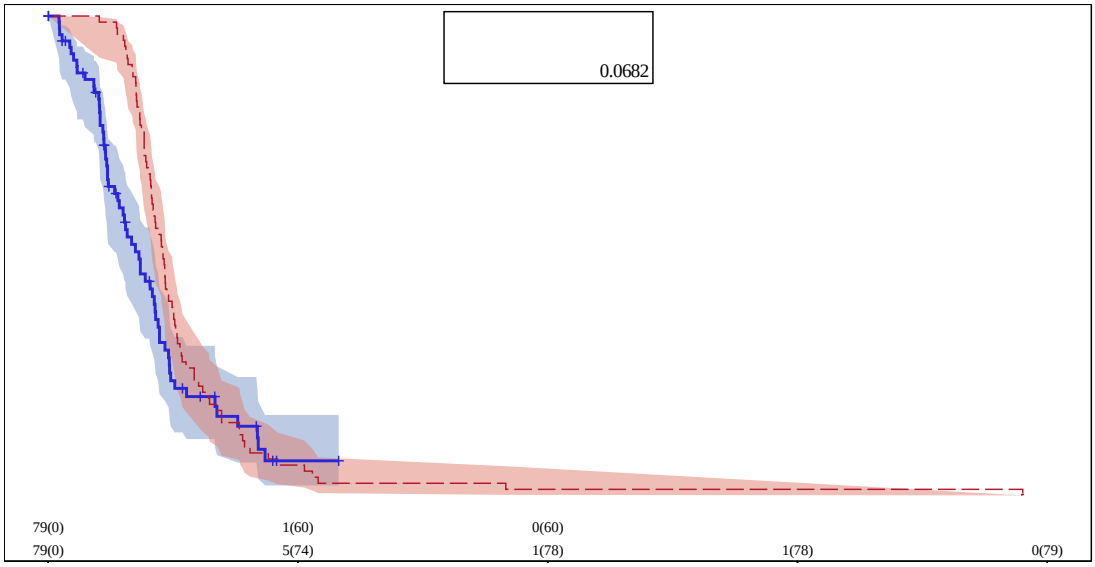
Patients without progressive disease are censored at last post-baseline scan.

Efficacy in platinum sensitivity subgroups

An analysis of PFS for rucaparib in platinum-sensitive patients vs the PFS for the immediately preceding chemotherapy regimen was also submitted at CHMP request.

Data for this endpoint was analysed from the Day 120 Update dataset.

Figure 18. PFS for Rucaparib Compared with PFS for the Immediately Preceding Chemotherapy (Day 120 Update): Platinum-sensitive Patients (N=79)

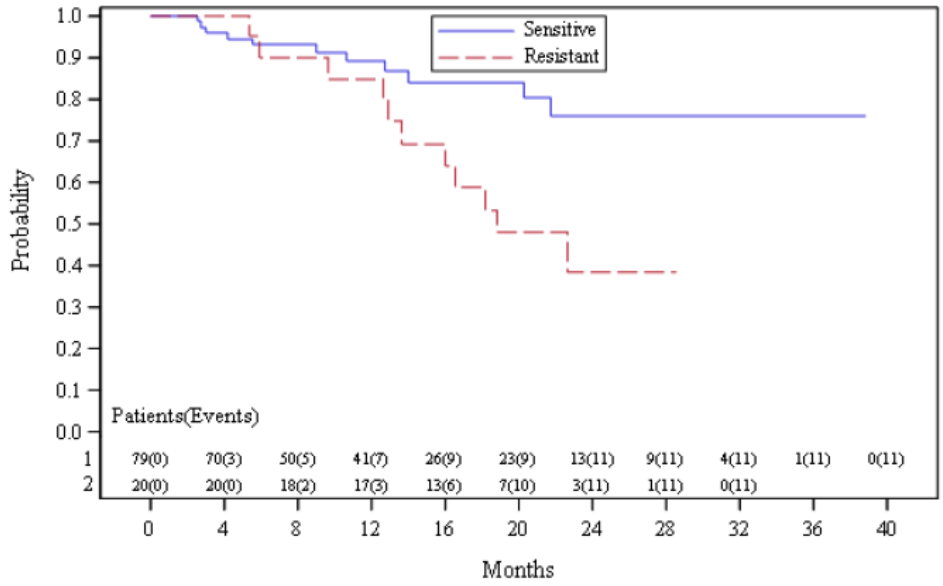


Source: Data cutoff Day 120 Update (10 April 2017) **Note:** Shaded areas represent 95% confidence intervals (CI)

An updated overall survival (OS) analysis of the primary efficacy population presented for the platinum-sensitive (n = 79) and platinum-resistant (n = 20) populations is provided in Figure 19 below with a cut-off date of 01 September 2017.

The median OS in the platinum-sensitive population has not yet been defined due to the high rate of censoring. Median OS in the platinum-resistant subgroup is 18.8 months (95% CI, 12.9-NA). The platinum-resistant patients were all enrolled in Part 2 of Study CO-338-017 and all had received rucaparib as a fourth or fifth line of treatment.

Figure 19. Overall Survival Update: MAA primary efficacy population (platinum-sensitive and platinum-resistant)



Updated data cutoff of 01 Sep 2017

The reasons for censoring are provided in Table 20.

Table 20. Summary of Death and Reason for Censoring

Reason	Platinum-resistant (n=20)	Platinum-Sensitive (n=79)	Overall (n=99)
Death	11	11	22
Censored at last study visit - No further follow up per protocol	0	51	51
Censored at last follow up visit during long term follow up	7[a]	9[b]	16
Censored at last visit and patient still ongoing with treatment	2	8	10

Note: Data cutoff 01 Sep 2107

[a] One patient withdrew consent from follow-up during the follow-up period so is no longer followed

[b] Three patients have withdrawn consent from follow-up during the follow up period and are no longer followed

Summary of main study(ies)

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

Table 21. Summary of Efficacy for the primary efficacy population.

Title: Pooled data from Part2A of Study CO-338-010 and Study CO-338-017 (ARIEL2)			
Study identifier	CO-338-010 (Eudra CT number: 2011-004250-26). CO-338-017 (Eudra CT number: 2013-000517-20)		
Design	Open label studies, no randomised.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Both studies ongoing; CO-338-010 data cut-off date of 10 April 2017. ARIEL2 data presented are for patients enrolled by 1 October 2015, with a visit data cut-off date of 10 April 2017
Hypothesis	N/A		
Treatments groups	Rucaparib		600 mg BID
Endpoints and definitions	Primary endpoint	Confirmed ORR by investigator (RECIST 1.1)	Proportion of patients with a confirmed CR or PR on subsequent tumour assessment
	Secondary endpoint	Duration of response	Duration of response in patients with a RECIST Version 1.1 CR or PR as determined by investigator assessment
	Secondary endpoint	PFS	Progression free survival
Database lock	10 April 2017		

Results and Analysis

Analysis description	**Primary Analysis**	
Analysis population and time point description	Primary efficacy analysis encompasses those patients from both studies with ≥ 2 prior chemotherapy regimens, including at least 2 platinum-based regimens and BRCA mutation positive.	
Descriptive statistics and estimate variability	Treatment group	Rucaparib
	Number of subject	106
	ORR (%)	54.7
	95% CI	44.8-64.4
	mDoR (days)	288
	95% CI	202-392
	PFS (median days)	289

	95% CI	226-337
Effect estimate per comparison	N/A	
Analysis description	**Subgroup analyses according to previous response to platinum-based therapy**	
Descriptive statistics and estimate variability	Treatment group	Rucaparib - Platinum-sensitive
	Number of subject	79
	ORR (%)	64.6
	95% CI	53.0-75.0
	mDoR (days)	294
	95% CI	224-393
	PFS (median days)	332
	95% CI	255-391
Effect estimate per comparison	N/A	
Descriptive statistics and estimate variability	Treatment group	Rucaparib - Platinum-resistant
	Number of subject	20
	ORR (%)	35.0
	95% CI	15.4-59.2
	mDoR (days)	196
	95% CI	113-NA
	PFS (median days)	282
	95% CI	218-335
Effect estimate per comparison	N/A	
Descriptive statistics and estimate variability	Treatment group	Rucaparib - Platinum-refractory
	Number of subject	7

	ORR (%)	0
	95% CI	0.0-41.0
	mDoR (days)	Not done
	95% CI	
	PFS (median days)	162 (51-223)
	95% CI	51-223
Effect estimate per comparison	N/A	

Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials	n/a	n/a	n/a
Non Controlled Trials	28	10	

Table 22: Confirmed Response Rate per Investigator by Age Group (Safety Population in Ovarian Cancer Patients with BRCAmut Tumours who received 600 mg BID, 2 or more prior chemotherapy regimens)

	Age <65 (N=68)	Age 65-74 (N=28)	Age 75-86 (N=10)
Confirmed Response Rate	35 / 68 (51.5%)	19 / 28 (67.9%)	3 / 10 (30.0%)
95% CI	39.0 - 63.8%	47.6 - 84.1%	6.7 - 65.2%
Best Overall Confirmed Response			
CR	5 / 68 (7.4%)	4 / 28 (14.3%)	0 / 10 (0.0%)
PR	30 / 68 (44.1%)	15 / 28 (53.6%)	3 / 10 (30.0%)
SD	26 / 68 (38.2%)	7 / 28 (25.0%)	3 / 10 (30.0%)
Discontinued or PD	22	5	2
Ongoing with single response	1	0	0
Ongoing without response	3	2	1
PD	7 / 68 (10.3%)	1 / 28 (3.6%)	1 / 10 (10.0%)
NE	0 / 68 (0.0%)	1 / 28 (3.6%)	3 / 10 (30.0%)
Response by RECIST or GCIG CA-125			
Yes	48 (70.6%)	24 (85.7%)	4 (40.0%)
95% CI	58.3 - 81.0%	67.3 - 96.0%	12.2 - 73.8%
No	20 (29.4%)	3 (10.7%)	4 (40.0%)
Inevaluable	0	1 (3.6%)	2 (20.0%)

- Age

For patients aged < 65 years, 65 to 74 years, and 75 to 86 years, the confirmed ORR by investigator-assessed response was 51.5% (95% CI, 39.0%-63.8%, N = 68), 67.9% (95% CI, 47.6%-84.1%, N = 28), and 30.0% (95% CI, 6.7%-65.2%, N = 10), respectively. The confirmed ORR by RECIST and GCIG CA-125 criteria was 70.6%, 85.7% and 40.0% for patients aged < 65 years, 65 to 74 years, and 75 to 86 years, respectively. Although response rates by both criteria were lower for patients aged 75 to 86 years, the data should be interpreted with caution given the low number of patients in this subgroup. In all 3 age groups, patients achieved a decrease in the sum of target lesions. For patients aged < 65 years and 75 to 86 years, the median duration of response, as assessed by the investigator, was 288.0 days (approximately 9.5 months) and 170.0 days (approximately 5.6 months), respectively; for the 65 to 74 years age group, at the data cut-off, the median duration of response was not calculable.

- Race

Analyses of efficacy data by race (White vs. non-White) should be interpreted with caution as only 13 patients were non-White compared to 83 patients who were White. The confirmed ORR by investigator-assessed response was 55.4% (95% CI, 44.1%-66.3%, N = 83) and 46.2% (95% CI, 19.2%-74.9%, N = 13), for White and non-White patients, respectively. The median duration of response, as assessed by the investigator, was 319.0 days (approximately 10.5 months) and 232.0 days (approximately 7.6 months), respectively.

2.5.3. Discussion on clinical efficacy

The applicant initially applied for rucaparib (as CMA) in an indication that encompasses the treatment of advanced ovarian cancer in adult patients with deleterious BRCA-mutated tumours, inclusive of both germline BRCA (gBRCA) and somatic BRCA (sBRCA) mutations, and who have been treated with 2 or more prior lines of chemotherapy.

In order to support this CMA two open label clinical studies have been submitted.

Study CO-338-010 is an ongoing Phase 1/2, open-label, safety, pharmacokinetic (PK), and efficacy study of oral rucaparib monotherapy in advanced gBRCA-mutant solid tumours and relapsed ovarian cancer.

Study CO-338-017 is an ongoing 2-part, open label Phase 2 study of oral monotherapy rucaparib in relapsed, high-grade ovarian cancer patients designed to identify ovarian cancer patients that are likely to respond to rucaparib.

These studies are ongoing and the Applicant is recommended to provide final data for the studies.

Design and conduct of clinical studies

Study CO-338-010 encompasses three (four) different parts. Part 1 evaluated escalating doses (from 40 mg once daily (QD) to 840 mg BID) of rucaparib in advanced gBRCA-mutant solid tumours and identified 600 mg BID as the recommended starting dose for subsequent studies. Part 2A enrolled patients with relapsed, platinum-sensitive disease who received 2 to 4 prior treatment regimens and were known to harbor a gBRCA mutation based on results from local testing. The last treatment received must have been a platinum-based regimen to which the patient must have been sensitive (ie, disease progression occurred at least 6 months after last dose of platinum was administered). Part 2B enrolled advanced ovarian cancer patients who received ≥3 prior chemotherapy regimens and have either a gBRCA or sBRCA mutation. Part 3 characterized the PK,

including the effect of food, of a higher dose strength (300 mg) rucaparib tablet in advanced solid tumour patients with a BRCA mutation. Only efficacy data from Part 2A has been submitted, since part 1 was a dose finding substudy and in Part 2B no patients were enrolled as of the enrolment cut-off date (1 October 2015).

Study CO-338-017 encompasses two different parts. Part 1 enrolled patients with relapsed, platinum-sensitive disease who had received ≥ 1 prior platinum regimen. Part 2 enrolled patients who have received at least 3, and no more than 4, prior chemotherapy regimens, and they can be resistant or refractory, as well as sensitive, to their last platinum-based regimen.

Population recruited

Based on the inclusion/exclusion criteria, the population recruited in the two clinical studies can be considered a broad ovarian cancer population, with both sensitive and resistant/refractory patients, BRCA1 and BRCA2 mutation, somatic and germline and with different number of previous treatment.

The primary efficacy population comprises 106 ovarian cancer patients harbouring a deleterious BRCA mutation who received 2 or more prior regimens of chemotherapy. Additionally, supportive efficacy data are also available for an additional 17 ovarian cancer patients with a BRCA mutation who received only 1 prior chemotherapy regimen.

Treatment

Patients in both studies (Part 2A of CO-338-010 and all parts of CO-338-017) received 600 mg BID, but the duration of the cycles is different. 21 and 28 day-cycles were defined in part 2A of CO-338-010 and all parts of CO-338-017 respectively. This difference may be relevant in the assessment of tumour progression, since these evaluations were carried out at different times according to the cycles' duration.

Endpoints

In the study CO-338-010, ORR by investigator was the primary endpoint. In the study CO-338-017 there were two primary endpoints, one in each part (PFS by investigator in part1 and ORR by investigator in part 2).

Efficacy data and additional analyses

In the light of baseline characteristics, the pool of both studies (only BRCA positive) is characterised by a population mainly platinum-sensitive (92 patients out of 120) with a median of 2 prior platinum therapies and with germline BRCA (90 patients). Considering only the target population (≥2 prior chemotherapy regimens, including at least 2 platinum-based regimens and BRCA positive; 106 patients), the baseline characteristics of this subgroup (target population) are defined a group of patients previously treated with 2 or 3 prior platinum regimens and mainly platinum-sensitive, with only 7 patients (6.6%) considered platinum-refractory and 20 (18.9%) platinum-resistant. Eighty-eight patients were germline BRCA (83%) and 18 (17.0%) somatic BRCA (there were 5 patients with unknown status). Sixty-seven were BRCA1 and thirty-nine were BRCA2.

Focusing on the target population (n=106; primary efficacy population) the use of rucaparib in the whole subset clearly shows an anti-tumour activity. Confirmed ORR by investigator was 54.7% **(95% CI, 44.8-64.4%)**, which seems to be durable given that the median duration of response was 288 days (95% CI, 202-392 days), or approximately 9.7 months. In the overall primary efficacy population, confirmed ORR by IRR was slightly lower, as can be expected (44.3% [95% CI, 34.7%-54.3%]). The median duration of the response by IRR was shorter (7.6 months) than the investigator.

Overall, the ORR observed in the primary efficacy population appears to be similar to that observed in Study 10 (59.5%) but dissimilar to ORR from Study CO-338-017 (Part1 ORR 80.0% in BRCA population; Part2 ORR 39.5% in BRCA population). This discrepancy is likely due to the different populations included in Study CO-338-017, where both patients with only 1 prior platinum-based therapy, and ≥ 2 platinum prior therapies were included.

One subgroup of interest was the germline/somatic BRCA and BRCA1/BRCA2. The analysis of the BRCA mutation was prospectively and centrally analysed at FMI in Study CO-338-017 (Parts 1 and 2) and retrospectively collected from patients in Study CO-338-010 Part 2A. Results in ORR according to the BRCA1 vs BRCA2 and sBRCA vs gBRCA do not reveal difference in the former (53.7% vs 53.8% respectively) and slightly differences in the latter (46.2% vs 53.4% respectively).

There was no important decrease in median PFS compared to immediate prior chemotherapy in the full population (N=106; Day 120 Update - 289 vs. 376 days). This holds true for the platinum-resistant and -refractory populations where PFS on rucaparib is numerically longer than prior chemotherapy (resistant-282 vs. 203 days; refractory – 162 vs. 105 days).

OS data by subgroups, although apparently immature and limited by the quite small sample size of some subgroups, show a marked difference in K-M curves for platinum-sensitive and platinum-resistant patients.

The results in **platinum-resistant** patients are not sufficient with regards to efficacy and this patient population is not considered further. The final indication population was revised to reflect this. It was also considered that the histological specification of "high-grade serous epithelial" is likely unnecessary according to current clinical practice.

ORR in **platinum-sensitive patients** was 64.6% by investigator and 53.2% by IRR, DOR was 9.1 and 8.8 months respectively. Differences in this subgroup are consistent with those previously seen and although could be of concern, in a worst case scenario 53.2% is still considered of compelling clinical relevance.

Acknowledging differences between study designs and importantly taking into account that rucaparib was administered in a later setting (3^{rd}-4^{th} line) an ORR of 64.6% (53.2% by IRR) was observed for the platinum-sensitive subset being even greater in the subset of patients that received rucaparib as 3^{rd} line therapy (ORR 68.3%, data not shown) which is considered clinically compelling for the setting of platinum-sensitive population. It is likely that an ORR of such magnitude could translate into long-term clinical benefit as further supported by preliminary OS data.

Focusing in the specific population of these 79 patients, the observed benefit appears consistent across the different PFI subgroups of platinum sensitivity.

The comparison of PFS for rucaparib in this subgroup of platinum-sensitive patients vs the PFS for the immediately preceding chemotherapy regimen showed a trend for differences between previous chemo and rucaparib, though not significant likely due to the sample size. A decline line after line is somehow acceptable for rucaparib, as pointed out by data from subgroups analysis for ORR according to treatment line and further supported by data from other PARPi, olaparib which showed a decrease in ORR line after line (Annals of Oncology 27: 1013–1019, 2016).

Data in the literature (CALYPSO and Oza et al.) showed response rates of around 60% for platinum doublets which could be considered below rucaparib findings (ORR 64.5% for the platinum-sensitive subset being even greater in the subset of patients that received rucaparib as 3rd line therapy (ORR 68.3%) if the fact that rucaparib patients were treated in later treatment lines were considered (≥3rd line vs 2nd-3rd line rucaparib vs comparators respectively).

There was not an outstanding effect for rucaparib as compared to the likely most active (most studied) alternative in this new setting, i.e. the combination of trabectedin+PLD (see tables below). The only data available in BRCAm come from only 24+17 patients retrospectively analysed from the OVA-301 study (Monk et al; Annals of Oncology 2015) that showed a median PFS of 13.6 months (versus 5.5 months in the PLD alone arm) in a population that had received at least 1 prior platinum treatment and was treated with trabectedin-PLD (platinum-sensitive). ORR for the overall population of BRCAm patients (irrespective of platinum sensitivity) in OVA-301 trial was 63% (15/24) in those treated with trabectedin+PLD and 29% (5/17) in those treated with PLD alone.

Table 2. Results from Prospective Studies in Platinum-Sensitive Disease that Include 3rd Line Treatment

Agent	Rucaparib	PLD[a]	PLD+Gem	PLD+Doce	Paclitaxel	Paclitaxel	Topotecan	Topotecan	Trabectedin
Source	MAA Day 120 data cut-off 10 April 2017	Pignata 2017[22]	D'Agostino 2003[23]	Koinis 2014[24]	Lorenz 1999[25]	Phillips 1995[26]	McGuire 2000[27]	Bookman 1998[28]	LoRusso 2016[11]
n	79	109	32	23	13	23	46	26	46
Line	3+	2-3	2+	2+	2+	2-4	2-3	2-3	3+
ORR	65%	43%	45%	30%	15%	15%	33%	20%	48%
DoR (mo)	9.7	NR	7	NR	NR	NR	11.2	NR	NR
PFS (mo)	10.9	5	NR	4.8	NR	NR	NR	NR	6

[a] 94% received PLD. 6% received other nonplatinum chemotherapy.

Abbreviations: Doce = docetaxel, DoR = duration of response, Gem = gemcitabine, mo = month, NR = Not Reported, ORR = objective response rate, PFS = progression-free survival, PLD = pegylated liposomal doxorubicin

Platinum sensitive population	**Trabectedin+PLD N=218**
Previous Treatments	1 previous treatment line only
ORR(%)	47.2
PFS(m)	9.4
OS(m)	27.0

Monk 2010

The proposed restricted population has limited efficacious treatment options, with worse expected toxicity than PARPi. All in all, if taking into account that rucaparib was studied in a later line setting it seems likely that even in a worst-case scenario, rucaparib findings could be comparable to those of trabectedin+PLD in terms of efficacy.

From a **mechanistic point of view**, the role of rucaparib in the platinum-sensitive population seems further supported given that sensitivity to platinum adducts indicate deficiency in HRD with reduced ability to repair DNA damage, which is closely linked to PARPi mechanism of action. Although this makes platinum-sensitive patients more likely to benefit from PARP inhibition it is possible that activity of rucaparib may not be limited to platinum-sensitive patients (ORR between 35-25% in platinum-resistant population).

There are no data to answer the question whether rucaparib could be used to treat a relapse in a patient previously treated with olaparib to maintain the remission. Rucaparib should not be used in patients who have previously progressed on PARPi treatment. Relevant information in this regard has been reflected in the SmPC.

Additional efficacy data needed in the context of a conditional MA

Efficacy has been established on the basis of durable ORR. The magnitude of this effect is such that it can be assumed that this will result in a favourable effect on long-term outcomes such as PFS and OS. Although the durable response in a high proportion of patients is considered a benefit, and the data observed for time-related endpoints are reassuring that the efficacy is adequate compared to available treatment options, there is a need to further quantify the efficacy of rucaparib in the therapeutic context of the approved indication in terms of time-related outcomes in a comparative trial.

Regarding the future submission of comprehensive data, study **CO-338-043 (ARIEL4)** is likely to confirm findings of rucaparib in the same population in which CMA is applied for (OC patients that has received at least 2 prior lines of therapy). The study will enrol a BRCA mutated population, irrespective of platinum-sensitivity. The applicant has detailed the support it intends to provide to sustain recruitment at the planned rate and report data in Q2 2023. Despite the increasing clinical use of PARP inhibitors, the applicant's calculations and assumptions regarding patient enrolment can be accepted. This trial is likely to provide comprehensive data suitable to confirm efficacy of Rubraca in the approved indication.

Additional expert consultation

A SAG-O meeting was held on February the 13th.

The SAG oncology was invited to provide its opinion on the following points:

1. **What are the available treatment options in this target population, to what extent are these regimens used in clinical practice, what is the expected efficacy and safety and to what extent are these documented in patients with BRCA mutant, platinum-sensitive ovarian cancer?**

The SAG discussed available options in patients with platinum-sensitive disease. The SAG agreed that as long as platinum-containing regimens (doublets; monotherapy) are an available option, these are the preferred options from an efficacy point of view. However, the SAG acknowledged that there is a group of patients in whom platinum-containing regimens are contraindicated (e.g., allergy). There is also a group of patients who, having discussed preferred options, may refuse further platinum-containing treatment, including single agent carboplatin, due to expected toxicity. In these two groups of patients, available options are limited. The regimen considered to be associated with highest activity is the (approved) combination of trabectedin+PLD. However, this regimen is not often used due to the considerable toxicity.

The SAG agreed that rucaparib has a much more favourable toxicity profile compared to chemotherapy including trabectedin+PLD. (Certain aspects though should be clarified for a better understanding of risks, like mechanisms behind the mostly transient liver enzyme elevation; toxicity of metabolites; transient or stable dynamics of most important toxicity; relationship between dose-intensity/PK and efficacy/toxicity; causal role in second malignancies based on molecular characterisation; generalisability of choice of treatment and compliance from the trial to real-life).

The SAG agreed that, in principle, having an additional (selective) option with a different toxicity profile and different route of administration in this restricted group of patients could be an important additional treatment option for some patients. However, the relevance of any advantage in safety needs to be assessed in the context of the efficacy data for rucaparib. A number of aspects related to the rucaparib development and results (patient, disease and treatment characteristics; dose-response relationships; plausibility of subgroup and statistical aspects including multiplicity) were discussed and uncertainties identified.

For instance, objective criteria for inclusion in the studies were lacking and information on subsequent (platinum-based) treatment was lacking, or information on how PFS before study entry correlated with the observed PFS after rucaparib (patient-level analysis) was not available. Due to the remaining uncertainty, the SAG views diverged on whether efficacy had been sufficiently established in these subgroups.

According to one (prevailing) view, fully acknowledging all the uncertainties (selection bias; lack of data on efficacy by prior treatments comparing PFS at study entry to PFS on-study; PFS2; lack of parallel comparative data; doubts about how many patients studied actually represent the target population; questions on generalisability) the activity shown in terms of objective response rate (ORR) and duration was high and convincing enough to rule out a significant detriment compared to trabectedin+PLD, on the basis of the observed effect of trabectedin+PLD (less than 2 months difference in median PFS compared to PLD alone for patients with platinum sensitive disease, and with a PFS of 13.5 months and a response rate of 63% for BRCA mutated platinum sensitive patients after second line chemotherapy; Monk et al. 2015), the high ORR associated with rucaparib in a more extensively pre-treated population compared to trabectedin historical control (even assuming a more pessimistic point estimate for rucaparib of 45% ORR to account for the retrospective selection of patients), and that the population studied was sufficiently representative. According to this view there were no significant concerns about potential detrimental effect (albeit, this would have to be confirmed post-approval even if indirectly) and rucaparib represents an additional option for some patients, which is a clear advantage.

According to an opposing view, the methodological flaws (including selection bias, retrospective analysis, lack of convincing comparative data, lack of generalisability) preclude any conclusion about the efficacy of rucaparib compared to trabectedin+PLD. According to this view, there are significant concerns about potential loss of efficacy in the absence of more definitive and direct comparative data. Furthermore, in many instances these patients would likely have been treated with PARP inhibitors in the maintenance setting making the target population somewhat theoretical. There were also concerns that patients could be misguided by apparent advantages in toxicity without due consideration to uncertainty about efficacy.

2. What is the clinical importance of the efficacy, safety (toxicity, tolerability), patient selection, and possibility of outpatient oral administration associated with rucaparib compared to available treatment options?

The SAG agreed on the clinical importance of safety and ease of administration, but that this needs to be assessed in the context of efficacy results and uncertainties. The SAG disagreed on whether sufficient efficacy had been demonstrated. See answer to question No. 1.

3. Is there a subset of patients in whom the unmet need/clinical importance could be greater compared to available treatment options (e.g., patients who cannot tolerate further platinum-containing regimen)?

The SAG agreed that the population for which there is a clear unmet need is the population of patients who cannot tolerate (allergy; patient preference) further platinum-containing regimens. The SAG views diverged about the extent to which there is sufficient evidence to conclude that rucaparib fulfils that unmet need (see answer to question No. 1).

Concerning the indication, it is important to mention that histological detail (high-grade serous epithelial) is likely unnecessary according to current practice. Thus, a potential indication could be worded like "…monotherapy treatment of adult patients with platinum sensitive, relapsed or progressive, BRCA mutated (germline and/or somatic), ~~high-grade serous epithelial,~~ ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with two or more prior lines of platinum based chemotherapy, and who ~~are not suitable for~~ cannot tolerate further platinum based chemotherapy.

It is also important to ensure that there is no misunderstanding about maintenance therapy (in the absence of further evidence being submitted and evaluated, rucaparib should not be used for maintenance treatment after platinum therapy), that rucaparib should not be used in patients who have been already treated with another PARP inhibitor, and that when treatment choice is left to patient preferences that patients are adequately informed about available treatment options and uncertainties (especially in terms of efficacy).

2.5.4. Conclusions on the clinical efficacy

A durable ORR of 53%-65% along with PFS results in the platinum-sensitive setting is considered clinically meaningful.

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

Study CO-338-043 (ARIEL4) is likely to provide comprehensive clinical data suitable to confirm the findings of rucaparib in the same population in which CMA is applied for (OC patients that has received at least 2 prior lines of therapy). ARIEL4 will recruit BRCA mutated OC patients that received at least 2 prior lines of therapy, including both platinum-sensitive and platinum-resistant patients.

2.6. Clinical safety

The most relevant data for the safety evaluation of rucaparib have been collected in 3 open-label clinical studies (Study CO-338-010, Study CO-338-017 [ARIEL2], and Study CO-338-023 [RUCAPANC]), in which patients with advanced ovarian cancer or other solid tumours received 600 mg BID rucaparib until disease progression or other reason for discontinuation. The safety population was defined as all patients who received at least 1 dose of rucaparib.

The primary safety analyses include 409 patients. Of these, 377 patients had advanced ovarian cancer, 143 of whom had a BRCA mutation. There were also 32 patients who had a solid tumour other than ovarian cancer.

At day 120 of the procedure an update of the safety profile was submitted (visit cut-off of 10 April 2017). New data are presented at the end of each section.

The list of the 5 clinical studies referenced in this SCS is provided in Table 23.

Table 23. Clinical Studies with Rucaparib Referenced in the Summary of Clinical Safety

Study Number	Study Design	Treatment	Number of Patients Enrolled / Number in Safety Analyses	Safety Assessments	Study Status (as of 29 April 2016)
CO-338-010[a] (Study 10)	Phase 1/2, 3-part, open-label study to assess the safety and pharmacokinetic (PK) of escalating doses (from 40 mg QD to 840 mg BID), establish the MTD and RP2D (Phase 1), to assess efficacy in relapsed, platinum sensitive high-grade serous or endometrioid epithelial ovarian, primary peritoneal, and fallopian tube cancer with a germline BRCA mutation (Phase 2)	Phase 1 Rucaparib: 40, 80, 160, 300, and 500 mg QD and 240, 360, 480, 600, and 840 mg BID PO on Days 1–21 of every 21-day cycle Phase 2 Rucaparib: 600 mg BID PO on Days 1–21 of every 21-day cycle	Phase 1 (Part 1) 56 enrolled/ **7 treated at 600 mg BID**[d] Phase 1 (Part 1) 40-500 mg QD PO 240-840 mg BID PO Phase 2 (Part 2A) 42 enrolled/ **42 treated** Phase 2 (Part 3) 26 enrolled/ **26 treated** Phase 2 (Part 2, Part 3) 600 mg BID PO	AEs, haematology, clinical chemistry, urinalysis, serum pregnancy, vital signs, 12-lead ECG, body weight and height, physical examinations, ECOG performance status	Phase 1 (Part 1) Completed Phase 2 (Part 2A, Part 2B, and Part 3) Ongoing
CO-338-017[a] (ARIEL2)	Phase 2, 2-part, open-label, single arm study to assess safety and efficacy in relapsed, platinum-sensitive high-grade serous or endometrioid epithelial ovarian, primary peritoneal, and fallopian tube cancer A Phase 2 open-label study of oral rucaparib monotherapy in relapsed, high-grade ovarian cancer	Rucaparib 600 mg BID PO on Days 1–28 of every 28-day cycle	Part 1 206 enrolled/ **204 treated** Part 2 111 enrolled/ **111 treated** Part 1 and Part 2 600 mg BID PO	AEs, haematology, clinical chemistry, urinalysis, serum pregnancy test, vital signs, 12-lead ECG, body weight and height, physical examinations, ECOG performance status	Ongoing
CO-338-023[a] (RUCAPANC)	Phase 2, open-label, single arm study to assess safety and efficacy in relapsed, locally advanced or metastatic pancreatic cancer associated with a deleterious BRCA mutation A Phase 2, single-arm, open-label study of oral rucaparib monotherapy as treatment for patients with previously treated locally advanced or metastatic pancreatic cancer and a known deleterious BRCA mutation	Rucaparib 600 mg BID PO on Days 1–28 of every 28-day cycle	19 enrolled/ **19 treated** 600 mg BID PO	AEs, haematology, clinical chemistry, urinalysis, serum/urine pregnancy test, vital signs, 12-lead ECG, body weight and height, physical examinations, ECOG performance status	Completed
CO-338-014[b] (ARIEL3)	A Phase 3, randomized, double-blind study of oral rucaparib monotherapy versus placebo as switch maintenance treatment in patients with platinum sensitive, relapsed, high-grade ovarian cancer who achieved a response to platinum-based chemotherapy	2:1 randomization 600 mg BID PO OR Placebo BID PO	N = 533, enrolment ongoing at the cut-off date of 29 April 2016. Note that this study completed enrolment after the cut-off date [on 19 July 2016] with 564 patients enrolled). This study is not included in this SCS.		Ongoing
A4991014[c]	A Phase 1, open-label, dose escalation study of IV and oral rucaparib administered with different chemotherapy regimens in patients with advanced solid tumours	12-40 mg (IV infusion) 80-360 mg QD PO	This study is not included in this SCS.		Completed
Total number of patients for all tumour types			**409 treated**		

Abbreviations: AE = adverse event; AESI = adverse events of special interest; BID = twice daily; BRCA = breast cancer gene; E gBRCA = germline breast cancer gene; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; IV = intravenous; MTD = maximum tolerated dose; PK = pharmacokinetic; PO = orally; QD = once daily; RP2D = recommended Phase 2 dose; SCS = Summary of Clinical Safety.

a Patients from these studies who received a starting dose 600 mg BID at the time of the data cut-off are included in the SCS.
b Complete safety analyses for Study CO-338-014 were not conducted as this study remains blinded to study treatment; however safety narratives for AESIs from all rucaparib studies are summarized in Table 2.7.4-23 and included in Section 5.3.5.1.
c Safety data are available in the Study A4991014 CSR (Section 5.3.4.2); data are not included in this SCS.

d The 7 patients who initiated treatment with 600 mg BID rucaparib are included in the combined safety analyses. Safety data from all 56 enrolled patients are presented in the CSR for this study.

Patient exposure

The applicant provided a summary of clinical safety (SCS) which included data on patients treated with rucaparib 600 mg BID collected in 3 open-label clinical studies: Studies CO-338-010 and CO-338-017 [ARIEL2], as previously mentioned, and Study CO-338-023 [RUCAPANC]) in patients with previously treated locally advanced or metastatic pancreatic cancer with a known deleterious BRCA mutation.

A total of 409 patients enrolled in Studies CO-338-010, CO-338-017, and CO-338-023 had initiated at least 1 treatment cycle with 600 mg BID rucaparib. Of these, 377 patients had advanced ovarian cancer, 143 of whom had a BRCA mutation and 234 non-BRCA. There were also 32 patients with various other types of tumours. In the group of 143 ovarian cancer patients with a BRCA mutation, 106 patients comprise the primary efficacy population; the remaining 37 patients received only 1 prior chemotherapy regimen and/or were enrolled into a part of Study CO-338-010 where PK and safety, but not efficacy, were the primary endpoints.

In the 409 patients with any type of tumour, the median duration of treatment was 168 days (range, 2-852 days), and the median number of cycles initiated was 6 (range, 1-31). Overall, 15.4% of patients received > 12 months of treatment, and 44.3% of patients received ≥ 6 months of treatment. The mean relative dose intensity was high (0.87), indicating that most patients received their intended dose throughout the study (Table 2.7.4-6).

The median duration of treatment was longer in the BRCA mutant ovarian cancer population than the non-BRCA and all ovarian cancer populations (224.0 days, range, 4-852 days, 112.5 days, range 3 – 680 and 168 days, range 3-852, respectively), although the dose intensity was slightly lower (mean [StD] 0.82 [0.19] vs. 0.91[0.13] and 0.87[0.16], respectively). Approximately 25% of patients with BRCA mutant ovarian cancer received > 12 months of treatment, and 69.2% of patients received > 6 months of treatment.

Of the 358 (87.5%) patients who discontinued in these studies, the most common primary reason for discontinuation of rucaparib was disease progression (radiologic or clinical; 79.6% overall, 79.8% of patients with BRCA mutant ovarian cancer). Approximately 10% of patients overall and in the BRCA mutant ovarian cancer population discontinued treatment due to AEs (all causality).

Demographic and Other Characteristics of Study Population

There were no notable differences in demographic characteristics between patients with BRCA mutant and non-BRCA mutant ovarian cancer.

In ovarian cancer patients, the median number of prior anticancer therapies of any type was 2.0 (range, 1-8), with 66.3% of patients receiving ≥ 2 prior chemotherapy regimens and 65.3% receiving ≥ 2 prior platinum-based regimens. In patients with BRCA mutant ovarian cancer, the median number of prior anticancer therapies of any type was 3.0 (range, 1-8), with 83.9% of patients receiving ≥ 2 prior chemotherapy regimens. These patients had received a median of 2.0 prior chemotherapy regimens containing platinum (range, 1-5), and 73.4% were sensitive (defined as disease progression ≥ 6 months after the last dose of platinum) to the last platinum-based regimen they received.

Updated data

The applicant provided a data update with the responses to Day 120 questions using a more recent visit cut-off of 10 April 2017 i.e., up to an additional 11 months of data in order to demonstrate maturity of the clinical data.

Table 1. Exposure: Comparison of Data in the Initial MAA and Day 120 Update (Safety Population)

	600 mg BID					
	Initial MAA			Day 120 Update		
	Ovarian Cancer BRCA^{mut} (N=143)	All Ovarian Cancer (N=377)	Overall Safety Population (N=409)	Ovarian Cancer BRCA^{mut} (N=143)	All Ovarian Cancer (N=377)	Overall Safety Population (N=409)
Number of Cycles Started						
Mean (StD)	10 (7.39)	7.8 (6.46)	7.6 (6.40)	12.0 (9.51)	8.7 (8.07)	8.3 (7.94)
Median	9.0	6.0	6.0	9.0	6.0	6.0
Min, Max	1, 31	1, 31	1, 31	1, 41	1, 41	1, 41
Duration of Treatment (days)						
Mean (StD)	269.9 (178.78)	209.4 (168.47)	203.1 (166.98)	320.7 (245.51)	236.3 (219.17)	227.9 (215.32)
Median	224.0	168.0	168.0	238.0	168.0	168.0
Min, Max	4, 852	3, 852	2, 852	4, 1090	3, 1090	2, 1090
Duration of Treatment (years)						
Mean (StD)	0.7 (0.49)	0.6 (0.46)	0.6 (0.46)	0.9 (0.67)	0.6 (0.60)	0.6 (0.59)
Median	0.6	0.5	0.5	0.7	0.5	0.5
Min, Max	0, 2	0, 2	0, 2	0, 3	0, 3	0, 3
Duration of Treatment, n (%)						
< 6 months of treatment	44 (30.8)	203 (53.8)	228 (55.7)	42 (29.4)	201 (53.3)	226 (55.3)
6-12 months of treatment	64 (44.8)	113 (30.0)	118 (28.9)	56 (39.2)	101 (26.8)	106 (25.9)
> 12 months of treatment	35 (24.5)	61 (16.2)	63 (15.4)	45 (31.5)	75 (19.9)	77 (18.8)

Source: Table 2.15 (Day 120 Update, Analysis of Safety, Section 5.3.5.3)
Abbreviations: BID = twice daily; BRCA = breast cancer gene; BRCA^{mut} = mutated breast cancer gene, MAA = Marketing Authorisation Application; N or n = number of patients; StD = standard deviation.
Notes: Initial MAA data are from combined studies with a visit cut-off as of 29 April 2016 for the ongoing Studies CO-338-010 and CO-338-017 and final data for Study CO-338-023. Updated MAA data are from combined studies with a cut-off as of 10 April 2017 for the ongoing Studies CO-338-010 and CO-338-017 and final data for Study CO-338-023.

Adverse events

A summary of treatment-emergent adverse event (TEAEs) is presented in Table 23.

In the overall patient population, all patients experienced at least 1 TEAE, with treatment-related TEAEs reported for 94.9% of patients. SAEs were reported for 29.6% of patients, with treatment-related SAEs occurring in 9.5% of patients. In total, 62.6% of patients experienced TEAEs of Grade 3 or higher. TEAEs led to treatment interruption and/or dose reduction in 64.1% of patients (treatment interruption = 58.2% of patients, dose reduction = 44.3%). TEAEs led to discontinuation of rucaparib in 18.8% of patients and treatment-related TEAEs led to discontinuation in 8.1% of patients. TEAEs with an outcome of death were reported in 3.4% of the study population; none of these was considered related to treatment.

In the ovarian cancer patient population, all patients experienced at least 1 TEAE, with treatment-related TEAEs reported for 95.5% of patients. SAEs were reported for 27.9% of ovarian cancer patients, with treatment-related SAEs occurring in 9.5% of ovarian cancer patients. In total, 61.5% of ovarian cancer patients experienced TEAEs of Grade 3 or higher. TEAEs led to treatment interruption and/or dose reduction in 65.0% of ovarian cancer patients (treatment interruption = 58.9% of patients, dose reduction = 45.9%). TEAEs led to discontinuation of rucaparib in 18.6% of ovarian cancer patients and treatment-related TEAEs led to discontinuation in 8.2% of ovarian cancer patients. TEAEs with an outcome of death were reported in 2.4% of ovarian cancer patients; none of these was considered related to treatment.

The TEAE profile in patients with BRCA mutant ovarian cancer was similar to that of the total safety population as well as the ovarian cancer population. In the BRCA mutant OC population, 97.9% of patients experienced TEAEs that were considered treatment-related. SAEs were reported for 31.5% of patients, with the incidence of treatment-related SAEs at 8.4%. In total, 65.7% experienced TEAEs of Grade ≥3. TEAEs led to treatment interruption and/or reduction in 71.3% of patients (treatment interruption = 60.8%, dose reduction = 50.3%).

TEAEs led to rucaparib discontinuation in 18.9% of patients; treatment-related TEAEs led to discontinuation in 5.6% of patients. TEAEs with an outcome of death were reported in 3.5% of patients with BRCA mutant ovarian cancer; none of these was considered related to treatment.

Table 23. Overall Summary of TEAEs: Safety Population (Combined Studies CO-338-010, CO-338-017, and CO-338-023)

	600 mg BID				
	Ovarian Cancer BRCA N = 143	Ovarian Cancer Non-BRCA N = 234	All Ovarian Cancer N = 377	Other Tumors N = 32	Overall N = 409
Number (%) of Patients with at Least 1:					
TEAE[a]	143 (100)	234 (100)	377 (100)	32 (100)	409 (100)
Treatment-related TEAE	140 (97.9)	220 (94.0)	360 (95.5)	28 (87.5)	388 (94.9)
Serious TEAE[a]	45 (31.5)	60 (25.6)	105 (27.9)	16 (50.0)	121 (29.6)
Treatment-related serious TEAE	12 (8.4)	24 (10.3)	36 (9.5)	3 (9.4)	39 (9.5)
≥ Grade 3 TEAE[a]	94 (65.7)	138 (59.0)	232 (61.5)	24 (75.0)	256 (62.6)
Treatment-related ≥ Grade 3 TEAE	71 (49.7)	107 (45.7)	178 (47.2)	13 (40.6)	191 (46.7)
TEAE with an outcome of death[a]	5 (3.5)	4 (1.7)	9 (2.4)	5 (15.6)	14 (3.4)
Treatment-related TEAE with an outcome of death	0	0	0	0	0
TEAE leading to discontinuation[a]	27 (18.9)	43 (18.4)	70 (18.6)	7 (21.9)	77 (18.8)
Treatment-related TEAE leading to discontinuation	8 (5.6)	23 (9.8)	31 (8.2)	2 (6.3)	33 (8.1)
TEAE leading to treatment interruption	87 (60.8)	135 (57.7)	222 (58.9)	16 (50.0)	238 (58.2)
Treatment-related TEAE leading to treatment interruption	69 (48.3)	119 (50.9)	188 (49.9)	11 (34.4)	199 (48.7)
TEAE leading to dose reduction	72 (50.3)	101 (43.2)	173 (45.9)	8 (25.0)	181 (44.3)
Treatment-related TEAE leading to dose reduction	69 (48.3)	98 (41.9)	167 (44.3)	8 (25.0)	175 (42.8)
TEAE leading to dose reduction or interruption	102 (71.3)	143 (61.1)	245 (65.0)	17 (53.1)	262 (64.1)
Treatment-related TEAE leading to dose reduction or interruption	88 (61.5)	129 (55.1)	217 (57.6)	12 (37.5)	229 (56.0)
TEAE leading to dose reduction or interruption or discontinuation	110 (76.9)	152 (65.0)	262 (69.5)	21 (65.6)	283 (69.2)
Treatment-related TEAE leading to dose reduction or interruption or discontinuation[a]	91 (63.6)	134 (57.3)	225 (59.7)	12 (37.5)	237 (57.9)

Source: Table 3.1.1 (Section 5.3.5.3)

Abbreviations: BID = twice daily; BRCA = breast cancer gene; N = number of patients; TEAE = treatment-emergent adverse event.

[a] Included events of disease progression.

Updated data

Table 2. Summary of Treatment Emergent Adverse Events (Safety Population)

	600 mg BID					
	Initial MAA			Day 120 Update		
	Ovarian Cancer BRCA^{mut} (N=143)	All Ovarian Cancer (N=377)	Overall Safety Population (N=409)	Ovarian Cancer BRCA^{mut} (N=143)	All Ovarian Cancer (N=377)	Overall Safety Population (N=409)
Number (%) of patients with at least 1						
TEAE[a]	143 (100.0)	377 (100.0)	409 (100.0)	143 (100.0)	377 (100.0)	409 (100.0)
Treatment-related TEAE	140 (97.9)	360 (95.5)	388 (94.9)	140 (97.9)	360 (95.5)	388 (94.9)
Serious TEAE	45 (31.5)	105 (27.9)	121 (29.6)	46 (32.2)	108 (28.6)	124 (30.3)
Treatment-related serious TEAE	12 (8.4)	36 (9.5)	39 (9.5)	13 (9.1)	37 (9.8)	40 (9.8)
≥ Grade 3 TEAE	94 (65.7)	232 (61.5)	256 (62.6)	96 (67.1)	236 (62.6)	260 (63.6)
Treatment-related ≥ Grade 3 TEAE	71 (49.7)	178 (47.2)	191 (46.7)	72 (50.3)	179 (47.5)	192 (46.9)
TEAE with an outcome of death	5 (3.5)	9 (2.4)	14 (3.4)	6 (4.2)	10 (2.7)	15 (3.7)
Treatment-related TEAE with an outcome of death	0	0	0	1 (0.7)	1 (0.3)	1 (0.2)
TEAE leading to discontinuation	27 (18.9)	70 (18.6)	77 (18.8)	27 (18.9)	70 (18.6)	77 (18.8)
Treatment-related TEAE leading to discontinuation	8 (5.6)	31 (8.2)	33 (8.1)	8 (5.6)	32 (8.5)	34 (8.3)
TEAE leading to treatment interruption	87 (60.8)	222 (58.9)	238 (58.2)	89 (62.2)	225 (59.7)	241 (58.9)
Treatment-related TEAE leading to treatment interruption	69 (48.3)	188 (49.9)	199 (48.7)	71 (49.7)	191 (50.7)	202 (49.4)
TEAE leading to dose reduction	72 (50.3)	173 (45.9)	181 (44.3)	75 (52.4)	177 (46.9)	185 (45.2)
Treatment-related TEAE leading to dose reduction	69 (48.3)	167 (44.3)	175 (42.8)	72 (50.3)	171 (45.4)	179 (43.8)

Source: Table 3.15.1 (Day 120 Update, Analysis of Safety, Section 5.3.5.3)
Abbreviations: BID = twice daily; BRCA = breast cancer gene; MAA = Marketing Authorisation Application; N or n = number of patients; TEAE = treatment-emergent adverse event.
Notes: Initial MAA data are from combined studies with a cut-off as of 29 April 2016 for the ongoing Studies CO-338-010 and CO-338-017 and final data for Study CO-338-023. Updated MAA data are from combined studies with a cut-off as of 10 April 2017 for the ongoing Studies CO-338-010 and CO-338-017 and final data for Study CO-338-023.
[a] TEAE is defined as any AE occurring or worsening on or after the first dose of study drug and within 28 days after the last dose.

Overall, the rates of TEAEs, serious AEs (SAEs), Grade 3 and higher TEAEs, and TEAEs with an outcome of death were comparable between patients in the primary efficacy population, patients with BRCAmut OC in the safety population, all OC patients, and patients in the overall safety population. The TEAEs that led to treatment discontinuation, dose reduction, and/or treatment interruption occurred comparably between patients with BRCAmut OC in the primary efficacy and safety populations, but more often for these populations compared to all patients with OC and the overall safety population. These higher rates are likely due to the longer duration of treatment of patients with BRCAmut OC (medians of 236.5 days in the efficacy population, 238.0 days in the BRCAmut OC safety population, 168.0 days in all OC patients, and 168.0 days in overall safety population.

Common Adverse Events

A summary of TEAEs that occurred in ≥ 20% of patients in any subgroup based on the incidence in SOCs and PTs is provided in Table 24.

Treatment-emergent adverse events (TEAEs) were defined as AEs with onset dates on or after the date of first dose of rucaparib through the date of the last rucaparib dose plus 28 days. If all or part of the date of onset of the AE was missing and it could not be determined if the AE met the definition for treatment-emergent, the AE was considered to be treatment-emergent.

The most common TEAEs reported in the ovarian cancer patients with a BRCA mutation were generally consistent with those observed within the total ovarian cancer and the overall population. The most frequently reported TEAEs occurred in the MedDRA SOCs of Gastrointestinal Disorders (96.5%), General Disorders and Administration Site Conditions (87.4%), Investigations (71.3%), and Nervous System Disorders (70.6%). The most common TEAEs, irrespective of relationship to rucaparib, were combined fatigue/asthaenia (79.7%), nausea (76.9%), combined anaemia/decreased haemoglobin (54.5%), vomiting (50.3%), combined ALT/AST increased (47.6%), constipation (41.3%), and dysgeusia (39.2%).

Table 24. TEAEs Reported in ≥ 20% of Patients: Safety Population (Combined Studies CO-338-010, CO-338-017, and CO 338-023)

SOC PT	600 mg BID				
	Ovarian Cancer BRCA N = 143	Ovarian Cancer Non-BRCA N = 234	All Ovarian Cancer N = 377	Other Tumors N = 32	Overall N = 409
	n (%)				
Combined Asthenia/Fatigue	**114 (79.7)**	**176 (75.2)**	**290 (76.9)**	**14 (43.8)**	**304 (74.3)**
Fatigue	91 (63.6)	145 (62.0)	236 (62.6)	13 (40.6)	249 (60.9)
Asthenia	33 (23.1)	38 (16.2)	71 (18.8)	2 (6.3)	73 (17.8)
Combined Anemia and/or Low/Decreased Hemoglobin	**78 (54.5)**	**87 (37.2)**	**165 (43.8)**	**11 (34.4)**	**176 (43.0)**
Anaemia	77 (53.8)	84 (35.9)	161 (42.7)	11 (34.4)	172 (42.1)
Combined ALT/AST Increased	**68 (47.6)**	**88 (37.6)**	**156 (41.4)**	**9 (28.1)**	**165 (40.3)**
Alanine aminotransferase increased	64 (44.8)	81 (34.6)	145 (38.5)	9 (28.1)	154 (37.7)
Aspartate aminotransferase increased	61 (42.7)	74 (31.6)	135 (35.8)	9 (28.1)	144 (35.2)
Combined Thrombocytopenia and/or Low/Decreased Platelets	**38 (26.6)**	**42 (17.9)**	**80 (21.2)**	**7 (21.9)**	**87 (21.3)**
Combined Neutropenia and/or Low/Decreased ANC	**32 (22.4)**	**29 (12.4)**	**61 (16.2)**	**5 (15.6)**	**66 (16.1)**
Gastrointestinal Disorders	**138 (96.5)**	**220 (94.0)**	**358 (95.0)**	**27 (84.4)**	**385 (94.1)**
Nausea	110 (76.9)	180 (76.9)	290 (76.9)	16 (50.0)	306 (74.8)
Vomiting	72 (50.3)	102 (43.6)	174 (46.2)	11 (34.4)	185 (45.2)
Constipation	59 (41.3)	91 (38.9)	150 (39.8)	8 (25.0)	158 (38.6)
Diarrhoea	51 (35.7)	79 (33.8)	130 (34.5)	8 (25.0)	138 (33.7)
Abdominal pain	52 (36.4)	68 (29.1)	120 (31.8)	10 (31.3)	130 (31.8)
Abdominal distension	30 (21.0)	40 (17.1)	70 (18.6)	4 (12.5)	74 (18.1)
General Disorders and Administration Site Conditions	**125 (87.4)**	**192 (82.1)**	**317 (84.1)**	**19 (59.4)**	**336 (82.2)**
Nervous System Disorders	**101 (70.6)**	**146 (62.4)**	**247 (65.5)**	**18 (56.3)**	**265 (64.8)**
Dysgeusia	56 (39.2)	92 (39.3)	148 (39.3)	6 (18.8)	154 (37.7)
Headache	36 (25.2)	33 (14.1)	69 (18.3)	3 (9.4)	72 (17.6)
Dizziness	28 (19.6)	36 (15.4)	64 (17.0)	8 (25.0)	72 (17.6)
Investigations	**102 (71.3)**	**138 (59.0)**	**240 (63.7)**	**17 (53.1)**	**257 (62.8)**
Blood creatinine increased	37 (25.9)	42 (17.9)	79 (21.0)	4 (12.5)	83 (20.3)
Metabolism and Nutrition Disorders	**84 (58.7)**	**122 (52.1)**	**206 (54.6)**	**16 (50.0)**	**222 (54.3)**
Decreased appetite	53 (37.1)	96 (41.0)	149 (39.5)	8 (25.0)	157 (38.4)
Blood and Lymphatic System Disorders	**82 (57.3)**	**99 (42.3)**	**181 (48.0)**	**12 (37.5)**	**193 (47.2)**
Infections and Infestations	**77 (53.8)**	**85 (36.3)**	**162 (43.0)**	**11 (34.4)**	**173 (42.3)**
Urinary tract infection	30 (21.0)	28 (12.0)	58 (15.4)	5 (15.6)	63 (15.4)
Respiratory, Thoracic and Mediastinal Disorders	**69 (48.3)**	**85 (36.3)**	**154 (40.8)**	**14 (43.8)**	**168 (41.1)**
Dyspnoea	28 (19.6)	52 (22.2)	80 (21.2)	4 (12.5)	84 (20.5)
Musculoskeletal and Connective Tissue Disorders	**60 (42.0)**	**83 (35.5)**	**143 (37.9)**	**16 (50.0)**	**159 (38.9)**
Skin and Subcutaneous Tissue Disorders	**65 (45.5)**	**86 (36.8)**	**151 (40.1)**	**7 (21.9)**	**158 (38.6)**
Psychiatric Disorders	**33 (23.1)**	**50 (21.4)**	**83 (22.0)**	**10 (31.3)**	**93 (22.7)**
Renal and Urinary Disorders	**29 (20.3)**	**46 (19.7)**	**75 (19.9)**	**4 (12.5)**	**79 (19.3)**
Vascular Disorders	**24 (16.8)**	**46 (19.7)**	**70 (18.6)**	**9 (28.1)**	**79 (19.3)**

Source: Table 3.1.2.1 (Section 5.3.5.3)

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BID = twice daily; BRCA = breast cancer gene; N or N = number of patients; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.

Note: Combined terms, then SOCs and PTs are presented in order of descending incidence. If a PT is included under a combined term heading, it is not presented under the respective SOC.

Frequency differences in a few specific PTs were recorded when comparing ovarian cancer patients with a BRCA mutation to the overall, all ovarian cancer and non- BRCA populations. These included: anaemia/ low haemoglobin, increased ALT/AST, thrombocytopenia/ decreased platelets, neutropenia/ decreased ANC and increased creatinine. This is likely a reflection of the fact that the patients with BRCA mutant ovarian cancer remained on treatment longer. An analysis of TEAE data normalized for time on treatment between patients with BRCA mutant ovarian cancer and other patient groups showed that the differences were less marked when adjusting for time on treatment. The increased frequency of anaemia and neutropenia persisted even after adjusting for time on treatment. Also, the laboratory data indicate that the effect of rucaparib treatment on haemoglobin, neutrophils and ALT/AST elevation, as measured by a shift from baseline to a worsening CTCAE Grade, is similar across the groups (see section on laboratory results).

The effect of rucaparib treatment on haemoglobin, as measured by a shift from baseline to a worsening CTCAE Grade, is similar across the groups: 69.9% to Grade 1 to 4 (29.4% to Grade 3) in BRCA mutant ovarian cancer; 66.6% to Grade 1 to 4 (23.3% to Grade 3) in the ovarian cancer population; 65.6% to Grade 1 to 4 (15.6% to Grade 3) in other tumours; and 66.5% to Grade 1 to 4 (22.7% to Grade 3) in the overall patient population.

For most TEAEs, including haematological, the incidence within 30 days of the first dose was relatively low compared to the overall incidence throughout the study. However, for increased transaminases the incidence at 30 days was relatively high in relation to the final reported incidence (e.g. BRCA mutant 37.1% at 30 days vs. 47.6% in total; all OC 33.7% at 30 days vs. 41.4% in total).

Consistent with the high frequency of anaemia, 74.3% of patients experienced TEAEs of asthenia or fatigue. These events were more common in patients with ovarian cancer (76.9%) than in patients with other tumours (43.8%), likely due to difference in time on rucaparib treatment between these two groups.

An apparent difference in TEAEs of ALT/AST elevation was observed between the BRCA mutant ovarian cancer patients and the overall patient population; however, more objective assessment of laboratory data indicate that the effect of rucaparib treatment on ALT/AST, as measured by a shift from baseline to a worsening CTCAE grade, is similar between BRCA mutant ovarian cancer patients (74.8% ALT, 70.6% AST), ovarian cancer patients (74.3% ALT, 73.5% AST), and the overall patient population (71.6% ALT, 71.1% AST). Patients with other solid tumours had a lower overall frequency of ALT/AST elevations reported as a TEAE (28.1%) and also had a lower frequency of shift in CTCAE grade from baseline (40.6% ALT, 43.8% AST).

Updated data

TEAEs in the SOCs of Gastrointestinal Disorders and General Disorders and Administrative Site Conditions were reported most frequently in all patient populations (96.2% and 90.6%, respectively, in the efficacy population; 96.5% and 88.8%, respectively, in patients with BRCAmut OC in the safety population; 94.4% and 84.4%, respectively, in the OC patient population; and 93.6% and 82.4%, respectively, in the overall safety population). Nausea (84%), fatigue (63.2%), and anaemia (57.5%) were the most common TEAEs reported in the efficacy population. In patients with BRCAmut OC in the safety population the rates of nausea (79.7%), fatigue (65.0%), and anaemia (53.1%) were similar to the rates in patients in the efficacy population. Nausea and fatigue also occurred at generally similar rates in the OC population (78.0% and 62.9%, respectively) and overall safety population (75.8% and 61.1%, respectively) compared to patients with BRCAmut OC; however, anaemia occurred at a lower rate in the OC population (42.4%) and overall safety population (41.8%) compare to the patient populations with BRCAmut OC. While most TEAEs occurred at similar rates across all patient populations, several TEAEs had similar rates between patients with BRCAmut OC in the efficacy and safety populations, but lower rates in the OC and overall safety populations. This is likely due to patients with BRCAmut OC having a

longer median duration of treatment (236.5 days and 238.0 days, respectively) compared to the median duration of treatment of 168.0 days in both the OC and overall safety populations

Treatment-related Adverse Events

Treatment-related TEAEs that occurred in ≥ 20% of patients based on the incidence in SOCs and PTs in any subgroup are summarized in Table 25.

The most frequently reported treatment-related TEAEs in the ovarian cancer population occurred in the MedDRA SOCs of Gastrointestinal Disorders (82.0%), General Disorders and Administration Site Conditions (71.9%), Investigations (58.1%), and Nervous System Disorders (52.0%). The most common treatment-related TEAEs (by PT) were nausea (68.7%), combined terms of asthenia/fatigue (68.7%), combined terms of anaemia and/or low/decreased haemoglobin (40.6%), combined terms of ALT/AST increased (40.1%), and dysgeusia (36.6%).

The most frequently reported treatment-related TEAEs in ovarian cancer patients with a BRCA mutation occurred in the MedDRA SOCs of Gastrointestinal Disorders (80.4%), General Disorders and Administration Site Conditions (73.4%), Investigations (65.7%), and Nervous System Disorders (53.1%). The most common treatment-related TEAEs (by PT) were combined terms of asthenia/fatigue (71.3%), nausea (65.7%), combined terms of anaemia and/or low/decreased haemoglobin (51.7%), combined terms of ALT/AST increased (45.5%), and dysgeusia (37.1%).

Table 25. Treatment-related TEAEs Reported in ≥ 20% of Patients: Safety Population (Combined Studies CO-338-010, CO-338-017, and CO-338-023)

SOC PT	600 mg BID				
	Ovarian Cancer BRCA N = 143	Ovarian Cancer Non-BRCA N = 234	All Ovarian Cancer N = 377	Other Tumors N = 32	Overall N = 409
	n (%)				
Any Treatment-related TEAE	**140 (97.9)**	**220 (94.0)**	**360 (95.5)**	**28 (87.5)**	**388 (94.9)**
Combined Asthenia/Fatigue	**102 (71.3)**	**157 (67.1)**	**259 (68.7)**	**11 (34.4)**	**270 (66.0)**
Fatigue	79 (55.2)	128 (54.7)	207 (54.9)	11 (34.4)	218 (53.3)
Asthenia	31 (21.7)	34 (14.5)	65 (17.2)	1 (3.1)	66 (16.1)
Combined Anemia and/or Low/Decreased Hemoglobin	**74 (51.7)**	**79 (33.8)**	**153 (40.6)**	**9 (28.1)**	**162 (39.6)**
Anaemia	73 (51.0)	76 (32.5)	149 (39.5)	9 (28.1)	158 (38.6)
Combined ALT/AST Increased	**65 (45.5)**	**86 (36.8)**	**151 (40.1)**	**8 (25.0)**	**159 (38.9)**
Alanine aminotransferase increased	61 (42.7)	78 (33.3)	139 (36.9)	7 (21.9)	146 (35.7)
Aspartate aminotransferase increased	58 (40.6)	70 (29.9)	128 (34.0)	8 (25.0)	136 (33.3)
Combined Thrombocytopenia and/or Low/Decreased Platelets	**38 (26.6)**	**41 (17.5)**	**79 (21.0)**	**7 (21.9)**	**86 (21.0)**
Overall Neutropenia and/or Low/Decreased ANC	**32 (22.4)**	**27 (11.5)**	**59 (15.6)**	**5 (15.6)**	**64 (15.6)**
Gastrointestinal Disorders	**115 (80.4)**	**194 (82.9)**	**309 (82.0)**	**18 (56.3)**	**327 (80.0)**
Nausea	94 (65.7)	165 (70.5)	259 (68.7)	10 (31.3)	269 (65.8)
Vomiting	47 (32.9)	71 (30.3)	118 (31.3)	6 (18.8)	124 (30.3)
Constipation	31 (21.7)	54 (23.1)	85 (22.5)	2 (6.3)	87 (21.3)
Diarrhoea	28 (19.6)	46 (19.7)	74 (19.6)	7 (21.9)	81 (19.8)
General Disorders and Administration Site Conditions	**105 (73.4)**	**166 (70.9)**	**271 (71.9)**	**14 (43.8)**	**285 (69.7)**
Investigations	**94 (65.7)**	**125 (53.4)**	**219 (58.1)**	**14 (43.8)**	**233 (57.0)**
Nervous System Disorders	**76 (53.1)**	**120 (51.3)**	**196 (52.0)**	**7 (21.9)**	**203 (49.6)**
Dysgeusia	53 (37.1)	85 (36.3)	138 (36.6)	4 (12.5)	142 (34.7)
Metabolism and Nutrition Disorders	**58 (40.6)**	**95 (40.6)**	**153 (40.6)**	**9 (28.1)**	**162 (39.6)**
Decreased appetite	42 (29.4)	77 (32.9)	119 (31.6)	6 (18.8)	125 (30.6)
Blood and Lymphatic System Disorders	**76 (53.1)**	**89 (38.0)**	**165 (43.8)**	**10 (31.3)**	**175 (42.8)**
Skin and Subcutaneous Tissue Disorders	**47 (32.9)**	**61 (26.1)**	**108 (28.6)**	**2 (6.3)**	**110 (26.9)**

Source: Table 3.1.3.1 (Section 5.3.5.3)

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BID = twice daily; BRCA = breast cancer gene; N or n = number of patients; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.

Note: Combined terms, then SOCs and PTs are presented in order of descending incidence. If a PT is included under a combined term heading, it is not repeated under the respective SOC.

Updated data

Treatment-related TEAEs also appeared to have a similar trend of consistent frequencies in patients with BRCA ovarian cancer in the efficacy and safety populations, but lower frequencies in the OC and overall safety populations, likely due to longer treatment exposure in OC patients. Overall, the most common related TEAEs for patients in the efficacy population were in the SOCs of Gastrointestinal Disorders (84.9%), General and

Administration Site Conditions (78.3%), and Investigations (68.9%). The most common treatment-related TEAEs in the efficacy population were nausea (70.8%), fatigue and anaemia (each 54.7%), ALT increase (45.3%), and AST increase (43.4%)

TEAEs Grade ≥ 3

Grade 3 or higher TEAEs occurring in ≥ 5% of patients in any subgroup are summarized in Table 26.

In OC patients with a BRCA mutation, the overall incidence of Grade ≥3 TEAEs, regardless of causality, was 65.7%. In OC patients with a BRCA mutation the most common Grade ≥3 TEAE by PT were combined terms of anaemia and/or low/decreased haemoglobin (29.4%), asthenia/fatigue (14.0%), increased ALT/AST (12.6%), neutropenia and/or low/decreased ANC (10.5%), malignant neoplasm progression (9.1%), and vomiting (5.6%).

There were no notable differences in the total frequency of Grade ≥3 TEAEs between the overall patient population (62.6%) and ovarian cancer population (61.5%) as compared to patients with BRCA mutant ovarian cancer (65.7%), nor in the frequency for the most commonly-reported PTs.

The greater frequency of Grade ≥3 TEAEs in non-OC patients can be attributed to the enrolment of pancreatic cancer patients, where the overall incidence of Grade ≥3 TEAEs was 78.9% (Study CO-338-023 CSR).

Table 26. Grade 3 or Higher TEAEs Reported in ≥ 5% of Patients: Safety Population (Combined Studies CO-338-010, CO-338-017, and CO-338-023)

SOC PT	600 mg BID				
	Ovarian Cancer BRCA N = 143	Ovarian Cancer Non-BRCA N = 234	All Ovarian Cancer N = 377	Other Tumors N = 32	Overall N = 409
	n (%)				
Any ≥ Grade 3 TEAE	**94 (65.7)**	**138 (59.0)**	**232 (61.5)**	**24 (75.0)**	**256 (62.6)**
Combined Anemia and/or Low/Decreased Hemoglobin	**42 (29.4)**	**52 (22.2)**	**94 (24.9)**	**8 (25.0)**	**102 (24.9)**
Anaemia	41 (28.7)	50 (21.4)	91 (24.1)	8 (25.0)	99 (24.2)
Combined Asthenia/Fatigue	**20 (14.0)**	**22 (9.4)**	**42 (11.1)**	**4 (12.5)**	**46 (11.2)**
Fatigue	12 (8.4)	15 (6.4)	27 (7.2)	4 (12.5)	31 (7.6)
Asthenia	8 (5.6)	8 (3.4)	16 (4.2)	1 (3.1)	17 (4.2)
Combined ALT/AST Increased	**18 (12.6)**	**23 (9.8)**	**41 (10.9)**	**4 (12.5)**	**45 (11.0)**
Alanine aminotransferase increased	17 (11.9)	21 (9.0)	38 (10.1)	4 (12.5)	42 (10.3)
Combined Neutropenia and/or Low/Decreased ANC	**15 (10.5)**	**18 (7.7)**	**33 (8.8)**	**5 (15.6)**	**38 (9.3)**
Neutropenia	10 (7.0)	10 (4.3)	20 (5.3)	2 (6.3)	22 (5.4)
Neutrophil count decreased	5 (3.5)	8 (3.4)	13 (3.4)	4 (12.5)	17 (4.2)
Combined Thrombocytopenia and/or Low/Decreased Platelets	**5 (3.5)**	**13 (5.6)**	**18 (4.8)**	**4 (12.5)**	**22 (5.4)**
Thrombocytopenia	3 (2.1)	8 (3.4)	11 (2.9)	2 (6.3)	13 (3.2)
Platelet count decreased	2 (1.4)	5 (2.1)	7 (1.9)	2 (6.3)	9 (2.2)
Blood and Lymphatic System Disorders	**45 (31.5)**	**61 (26.1)**	**106 (28.1)**	**9 (28.1)**	**115 (28.1)**
Investigations	**32 (22.4)**	**49 (20.9)**	**81 (21.5)**	**9 (28.1)**	**90 (22.0)**
Gastrointestinal Disorders	**25 (17.5)**	**44 (18.8)**	**68 (18.3)**	**6 (18.8)**	**75 (18.3)**
Nausea	7 (4.9)	12 (5.1)	19 (5.0)	2 (6.3)	21 (5.1)
Vomiting	8 (5.6)	7 (3.0)	15 (4.0)	2 (6.3)	17 (4.2)
Abdominal pain	4 (2.8)	9 (3.8)	13 (3.4)	4 (12.5)	17 (4.2)
Ascites	3 (2.1)	7 (3.0)	10 (2.7)	3 (9.4)	13 (3.2)
General Disorders and Administration Site Conditions	**21 (14.7)**	**23 (9.8)**	**44 (11.7)**	**5 (15.6)**	**49 (12.0)**
Metabolism and Nutrition Disorders	**15 (10.5)**	**26 (11.1)**	**41 (10.9)**	**1 (3.1)**	**42 (10.3)**
Infections and Infestations	**9 (6.3)**	**13 (5.6)**	**22 (5.8)**	**6 (18.8)**	**28 (6.8)**
Sepsis	1 (0.7)	4 (1.7)	5 (1.3)	3 (9.4)	8 (2.0)
Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps)	**13 (9.1)**	**11 (4.7)**	**24 (6.4)**	**3 (9.4)**	**27 (6.6)**
Malignant neoplasm progression	13 (9.1)	9 (3.8)	22 (5.8)	2 (6.3)	24 (5.9)
Nervous System Disorders	**8 (5.6)**	**5 (2.1)**	**13 (3.4)**	**1 (3.1)**	**14 (3.4)**
Respiratory, Thoracic and Mediastinal Disorders	**4 (2.8)**	**3 (1.3)**	**7 (1.9)**	**2 (6.3)**	**9 (2.2)**
Hepatobiliary Disorders	**1 (0.7)**	**2 (0.9)**	**3 (0.8)**	**3 (9.4)**	**6 (1.5)**
Jaundice cholestatic	0	0	0	2 (6.3)	2 (0.5)

Source: Table 3.1.6 (Section 5.3.5.3)

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BID = twice daily; BRCA = breast cancer gene; N or n = number of patients; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.

Note: combined terms, then SOCs and PTs are presented in order of descending incidence. If a PT is included under a combined term heading, it is not presented under the respective SOC.

Updated data

Grade 3 and higher TEAEs appeared consistent between patients with BRCAmut OC in the efficacy and safety populations and, for most TEAEs, also consistent with the OC and overall safety populations; however, several TEAEs also appeared to follow the trend of being slightly more frequent in patients with BRCAmut OC in the efficacy and safety populations than in the OC and overall safety populations. Overall, the most common Grade 3 or higher TEAEs for patients with BRCAmut OC in the efficacy population were in the SOCs of Blood and

Lymphatic System Disorders (33.0%) and Investigations (26.4%). The most common Grade 3 or higher TEAE was anaemia (24.7% to 31.1% of patients across all populations); almost all incidences of Grade 3 and higher anaemia were treatment-related. Overall, the majority of TEAEs were Grade 1 or 2 in all population groups

Treatment-related TEAEs Grade ≥ 3

Treatment-related Grade ≥3 TEAEs occurring in ≥ 5% of patients in any subgroup are summarized in Table 27.

In the ovarian cancer patients with a BRCA mutation, treatment-related Grade ≥3 TEAEs were experienced by 49.7% of patients. The most commonly reported treatment-related Grade ≥3 TEAEs (by PT) that were combined terms of anaemia and/or low/decreased haemoglobin (28.7%), increased ALT/AST (11.9%), asthenia/fatigue (10.5%), and neutropenia and/or low/decreased ANC (10.5%).

There were no notable differences in frequency for treatment-related Grade ≥3 TEAEs between the overall population (46.7%) and ovarian cancer population (47.2%) as compared to patients with BRCA mutant ovarian cancer (49.7%). The frequency of treatment-related Grade ≥3 TEAEs was 40.6% for patients with other tumours and 45.7% for those with non-BRCA ovarian cancer.

Table 27. Treatment-related Grade 3 or Higher TEAEs Reported in ≥ 5% of Patients: Safety Population (Combined Studies CO-338-010, CO-338-017, and CO 338-023)

SOC PT	600 mg BID				
	Ovarian Cancer BRCA N = 143	Ovarian Cancer Non-BRCA N = 234	All Ovarian Cancer N = 377	Other Tumors N = 32	Overall N = 409
	n (%)				
Any Treatment-related ≥ Grade 3 TEAE	**71 (49.7)**	**107 (45.7)**	**178 (47.2)**	**13 (40.6)**	**191 (46.7)**
Combined Anemia and/or Low/Decreased Hemoglobin	**41 (28.7)**	**46 (19.7)**	**87 (23.1)**	**6 (18.8)**	**93 (22.7)**
Anaemia	40 (28.0)	44 (18.8)	84 (22.3)	6 (18.8)	90 (22.0)
Combined ALT/AST Increased	**17 (11.9)**	**20 (8.5)**	**37 (9.8)**	**3 (9.4)**	**40 (9.8)**
Alanine aminotransferase increased	16 (11.2)	20 (8.5)	36 (9.5)	3 (9.4)	39 (9.5)
Combined Asthenia/Fatigue	**15 (10.5)**	**17 (7.3)**	**32 (8.5)**	**2 (6.3)**	**34 (8.3)**
Fatigue	9 (6.3)	14 (6.0)	23 (6.1)	2 (6.3)	25 (6.1)
Combined Neutropenia and/or Low/Decreased ANC	**15 (10.5)**	**16 (6.8)**	**31 (8.2)**	**5 (15.6)**	**36 (8.8)**
Neutropenia	10 (7.0)	8 (3.4)	18 (4.8)	2 (6.3)	20 (4.9)
Neutrophil count decreased	5 (3.5)	8 (3.4)	13 (3.4)	4 (12.5)	17 (4.2)
Combined Thrombocytopenia and/or Low/Decreased Platelets	**5 (3.5)**	**12 (5.1)**	**17 (4.5)**	**4 (12.5)**	**21 (5.1)**
Thrombocytopenia	3 (2.1)	7 (3.0)	10 (2.7)	2 (6.3)	12 (2.9)
Platelet count decreased	2 (1.4)	5 (2.1)	7 (1.9)	2 (6.3)	9 (2.2)
Blood and Lymphatic System Disorders	**44 (30.8)**	**54 (23.1)**	**98 (26.0)**	**7 (21.9)**	**105 (25.7)**
Investigations	**29 (20.3)**	**42 (17.9)**	**71 (18.8)**	**7 (21.9)**	**78 (19.1)**
General Disorders and Administration Site Conditions	**15 (10.5)**	**18 (7.7)**	**33 (8.8)**	**2 (6.3)**	**35 (8.6)**
Gastrointestinal Disorders	**7 (4.9)**	**23 (9.8)**	**30 (8.0)**	**0**	**30 (7.3)**
Metabolism and Nutrition Disorders	**3 (2.1)**	**15 (6.4)**	**18 (4.8)**	**0**	**18 (4.4)**

Source: Table 3.1.7 (Section 5.3.5.3)

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BID = twice daily; BRCA = breast cancer gene; N or n = number of patients; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.

Note: Combined terms, then SOCs and PTs are presented in order of descending incidence. If a PT is included under a combined term heading, it is not presented under the respective SOC.

Adverse Events of Special Interest (AESI)

Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukaemia (AML)

Myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) are considered adverse events of special interest (AESIs), that were presented over the full clinical development program to 12 September 2016. During this time about 1077 patients have received rucaparib and 10 cases have been reported; 7 MDS and 3 AML.

These events include AESIs reported for CO-338-010 (2 MDS), CO-338-017 (2 MDS, 1 AML), 5 patients (2 MDS, 2 AML, 1 MDS transformed to AML) enrolled in the blinded, randomized, ongoing Study CO-338-014 and treated with rucaparib, and 1 patient (AML) who received placebo in Study CO-338-014. All of the patients diagnosed with MDS or AML had been heavily pre-treated with chemotherapy, including platinum- and/or taxane-containing regimens. One patient had also received prior treatment with an alkylating agent

(cyclophosphamide) and one patient had received radiation for breast cancer. In patients diagnosed with MDS, duration from start of treatment to diagnosis was between 35 days and approximately 693 days; in patients diagnosed with AML, duration from start of treatment to diagnosis was between 106 and 850 days. All of the patients experienced cytopenias requiring modifications to study drug dosing or discontinuation of study drug prior to the diagnosis of MDS/AML. The cytogenetic abnormalities observed in the 3 patients diagnosed with AML were consistent with aberrations (primarily abnormalities in chromosome 5) typically observed in patients with secondary MDS/AML due to prior chemotherapy.

Serious adverse event / deaths / other significant events

Serious adverse events

Summaries of SAEs that occurred in ⩾ 5% of patients and all treatment-related SAEs are provided in Table 28 and Table 29, respectively.

Overall, SAEs, regardless of causality, were experienced by 29.6% of all patients, with malignant neoplasm progression (5.4%) and anaemia (4.9%) reported most frequently. SAEs were experienced by 27.9% of all ovarian cancer patients, with malignant neoplasm progression (5.3%) and anaemia (4.8%) reported most frequently. In ovarian cancer patients with a BRCA mutation, malignant neoplasm progression (8.4%) and anaemia (5.6%) were also the most frequently reported SAEs.

There were no notable differences in the frequency of SAEs between the overall patient population (29.6%) and patients with BRCA mutant ovarian cancer (31.5%). In ovarian cancer patients with a BRCA mutation, malignant neoplasm progression (8.4%) and anaemia (5.6%) were the most frequently reported SAEs. Patients with other tumours had a higher incidence of SAEs (50.0%) compared to those with ovarian cancer (27.9%).

The greater frequency of SAEs in non-ovarian tumours can be attributed to some extent to the pancreatic cancer patients enrolled in Study CO-338-023, where the overall incidence of SAEs, regardless of causality, was 63.2%.

Table 28. SAEs Reported in ≥ 5% of Patients: Safety Population (Combined Studies CO-338-010, CO-338-017, and CO-338-023)

SOC PT	600 mg BID				
	Ovarian Cancer BRCA N = 143	Ovarian Cancer Non-BRCA N = 234	All Ovarian Cancer N = 377	Other Tumors N = 32	Overall N = 409
	n (%)				
Any Serious TEAE	**45 (31.5)**	**60 (25.6)**	**105 (27.9)**	**16 (50.0)**	**121 (29.6)**
Combined Anemia and/or Low/Decreased Hemoglobin	**8 (5.6)**	**10 (4.3)**	**18 (4.8)**	**2 (6.3)**	**20 (4.9)**
Anaemia	8 (5.6)	10 (4.3)	18 (4.8)	2 (6.3)	20 (4.9)
Combined Thrombocytopenia and/or Low/Decreased Platelets	**1 (0.7)**	**0**	**1 (0.3)**	**2 (6.5)**	**3 (0.7)**
Blood and Lymphatic System Disorders	**9 (6.3)**	**14 (6.0)**	**23 (6.1)**	**3 (9.4)**	**26 (6.4)**
Gastrointestinal Disorders	**18 (12.6)**	**23 (9.8)**	**41 (10.9)**	**7 (21.9)**	**48 (11.7)**
Abdominal pain	1 (0.7)	2 (0.9)	3 (0.8)	2 (6.3)	5 (1.2)
Infections and Infestations	**9 (6.3)**	**13 (5.6)**	**22 (5.8)**	**5 (15.6)**	**27 (6.6)**
Sepsis	1 (0.7)	4 (1.7)	5 (1.3)	3 (9.4)	8 (2.0)
Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps)	**12 (8.4)**	**10 (4.3)**	**22 (5.8)**	**3 (9.4)**	**25 (6.1)**
Malignant neoplasm progression	12 (8.4)	8 (3.4)	20 (5.3)	2 (6.3)	22 (5.4)
Respiratory, Thoracic and Mediastinal Disorders	**1 (0.7)**	**5 (2.1)**	**6 (1.6)**	**2 (6.3)**	**8 (2.0)**
Hepatobiliary Disorders	**0**	**1 (0.4)**	**1 (0.3)**	**3 (9.4)**	**4 (1.0)**
Jaundice cholestatic	0	0	0	2 (6.3)	2 (0.5)
Vascular Disorders	**0**	**1 (0.4)**	**1 (0.3)**	**2 (6.3)**	**3 (0.7)**

Source: Table 3.1.4 (Section 5.3.5.3)

Abbreviations: BID = twice daily; BRCA = breast cancer gene; N or n = number of patients; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.

Treatment-related SAEs were experienced by 9.5% of patients overall, 9.5% of OC patients and 8.4% of OC patients with a BRCA mutation; the most common treatment-related SAE was anaemia (4.6%, 4.5% and 5.6% patients respectively). No other treatment-related SAEs were experienced by more than 1% of patients overall.

All other treatment related SAEs were reported by single patients with BRCA mutant OC, including thrombocytopenia, neutropenia, febrile neutropenia, nausea, vomiting, increased blood creatinine, increased blood cholesterol and dehydration.

Table 29. Treatment-related SAEs Reported in Any Patient: Safety Population (Combined Studies CO-338-010, CO-338-017, and CO-338-023)

SOC PT	600 mg BID				
	Ovarian Cancer BRCA N = 143	Ovarian Cancer Non-BRCA N = 234	All Ovarian Cancer N = 377	Other Tumors N = 32	Overall N = 409
	n (%)				
Any Treatment-related Serious TEAE	**12 (8.4)**	**24 (10.3)**	**36 (9.5)**	**3 (9.4)**	**39 (9.5)**
Combined Anemia and/or Low/Decreased Hemoglobin	**8 (5.6)**	**9 (3.8)**	**17 (4.5)**	**2 (6.3)**	**19 (4.6)**
Anaemia	8 (5.6)	9 (3.8)	17 (4.5)	2 (6.3)	19 (4.6)
Combined Thrombocytopenia and/or Low/Decreased Platelets	**1 (0.7)**	**0**	**1 (0.3)**	**1 (3.1)**	**2 (0.5)**
Thrombocytopenia	1 (0.7)	0	1 (0.3)	1 (3.1)	2 (0.5)
Combined Neutropenia and/or Low/Decreased ANC	**1 (0.7)**	**2 (0.9)**	**3 (0.8)**	**0**	**3 (0.7)**
Neutropenia	1 (0.7)	1 (0.4)	2 (0.5)	0	2 (0.5)
Neutrophil count decreased	0	1 (0.4)	1 (0.3)	0	1 (0.2)
Combined Asthenia/Fatigue	**0**	**1 (0.4)**	**1 (0.3)**	**0**	**1 (0.2)**
Asthenia	0	1 (0.4)	1 (0.3)	0	1 (0.2)
Combined ALT/AST Increased	**0**	**1 (0.4)**	**1 (0.3)**	**0**	**1 (0.2)**
Alanine aminotransferase increased	0	1 (0.4)	1 (0.3)	0	1 (0.2)
Blood and Lymphatic System Disorders	**9 (6.3)**	**12 (5.1)**	**21 (5.6)**	**3 (9.4)**	**24 (5.9)**
Febrile neutropenia	1 (0.7)	2 (0.9)	3 (0.8)	0	3 (0.7)
Pancytopenia	0	0	0	1 (3.1)	1 (0.2)
Gastrointestinal Disorders	**1 (0.7)**	**7 (3.0)**	**8 (2.1)**	**1 (3.1)**	**9 (2.2)**
Vomiting	1 (0.7)	3 (1.3)	4 (1.1)	0	4 (1.0)
Nausea	1 (0.7)	2 (0.9)	3 (0.8)	0	3 (0.7)
Constipation	0	2 (0.9)	2 (0.5)	0	2 (0.5)
Diarrhoea	0	1 (0.4)	1 (0.3)	1 (3.1)	2 (0.5)
Colitis	0	1 (0.4)	1 (0.3)	0	1 (0.2)
Investigations	**2 (1.4)**	**6 (2.6)**	**8 (2.1)**	**0**	**8 (2.0)**
Blood creatinine increased	1 (0.7)	1 (0.4)	2 (0.5)	0	2 (0.5)
Blood cholesterol increased	1 (0.7)	0	1 (0.3)	0	1 (0.2)
Lymphocyte count decreased	0	1 (0.4)	1 (0.3)	0	1 (0.2)
Transaminases increased	0	1 (0.4)	1 (0.3)	0	1 (0.2)
Weight decreased	0	1 (0.4)	1 (0.3)	0	1 (0.2)
Renal and Urinary Disorders	**0**	**3 (1.3)**	**3 (0.8)**	**0**	**3 (0.7)**
Acute kidney injury	0	3 (1.3)	3 (0.8)	0	3 (0.7)

General Disorders and Administration Site Conditions	**0**	**1 (0.4)**	**1 (0.3)**	**1 (3.1)**	**2 (0.5)**
Pyrexia	0	0	0	1 (3.1)	1 (0.2)
Metabolism and Nutrition Disorders	**1 (0.7)**	**1 (0.4)**	**2 (0.5)**	**0**	**2 (0.5)**
Dehydration	1 (0.7)	0	1 (0.3)	0	1 (0.2)
Hypercholesterolaemia	0	1 (0.4)	1 (0.3)	0	1 (0.2)
Respiratory, Thoracic and Mediastinal Disorders	**0**	**1 (0.4)**	**1 (0.3)**	**0**	**1 (0.2)**
Dyspnoea	0	1 (0.4)	1 (0.3)	0	1 (0.2)
Congenital, Familial and Genetic Disorders	**0**	**1 (0.4)**	**1 (0.3)**	**0**	**1 (0.2)**
Long QT syndrome congenital	0	1 (0.4)	1 (0.3)	0	1 (0.2)
Infections and Infestations	**0**	**1 (0.4)**	**1 (0.3)**	**0**	**1 (0.2)**
Sepsis	0	1 (0.4)	1 (0.3)	0	1 (0.2)

Source: Table 3.1.5 (Section 5.3.5.3)

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BID = twice daily; BRCA = breast cancer gene; N or n = number of patients; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.

Updated data

Malignant neoplasm progression (7.5%) and anaemia (6.6%) were the most common SAEs in patients in the efficacy population; these SAEs occurred at similar rates in the other patient populations. Most SAEs of anaemia were related to rucaparib in all patient populations. No SAEs of malignant neoplasm progression were related to rucaparib.

Table 3. SAEs Reported in ≥ 5% of Patients: Subgroups of BRCA-mutant Ovarian Cancer Patients in the Efficacy and Safety Populations Relative to All Ovarian Cancer Patients and the Overall Safety Population

	600 mg BID			
System Organ Class Preferred Term	Ovarian Cancer BRCA in Efficacy Population* (N=106)	Ovarian Cancer BRCA in Safety Population (N=143)	All Ovarian Cancer (N=377)	Overall Safety Population (N=409)
	n (%)			
Number of Patients with at Least 1 SAE	**38 (35.8)**	**46 (32.2)**	**108 (28.6)**	**124 (30.3)**
Combined Anemia and/or Low/Decreased Hemoglobin	**7 (6.6)**	**8 (5.6)**	**19 (5.0)**	**21 (5.1)**
Gastrointestinal Disorders	**16 (15.1)**	**19 (13.3)**	**43 (11.4)**	**50 (12.2)**
Infections and Infestations	**7 (6.6)**	**9 (6.3)**	**23 (6.1)**	**28 (6.8)**
Blood and Lymphatic System Disorders	**8 (7.5)**	**9 (6.3)**	**24 (6.4)**	**27 (6.6)**
Anaemia	7 (6.6)	8 (5.6)	19 (5.0)	21 (5.1)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**9 (8.5)**	**12 (8.4)**	**22 (5.8)**	**26 (6.4)**
Malignant neoplasm progression	8 (7.5)	11 (7.7)	19 (5.0)	22 (5.4)

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BID = twice daily; BRCA = breast cancer gene; N or N = number of patients; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.

Notes: Combined terms are presented, then SOCs and PTs are presented in order of descending incidence in the Overall Safety Population.

Data are from combined studies with a cut-off as of 10 April 2017 for the ongoing Studies CO-338-010 and CO-338-017 and final data for Study CO-338-023.

Sources: Table 3.28.4 and Table 3.15.4 (Day 120 Update, Analysis of Safety, Section 5.3.5.3)

Deaths

TEAEs with an outcome of death are presented in Table 30. TEAEs with an outcome of death were reported in 14/409 (3.4%) patients, including 5 patients (3.5%) with BRCA mutant ovarian cancer.

The frequency of TEAEs with an outcome of death was higher in patients with other tumours (N = 5, 15.6%) compared to those with ovarian cancer (N = 9, 2.4%). Three of the 5 patients with other tumours who died were pancreatic cancer patients in Study CO-338-023. The most frequently reported TEAE with an outcome of death was malignant neoplasm progression (10 patients, 2.4%). All other TEAEs with an outcome of death were reported for single patients.

Among BRCA positive ovarian cancer patients, all 5 (3.5%) patients who died were assessed as having died due to disease progression, with 1 (0.7%) of these deaths also involving hyponatremia. None of these deaths was related to rucaparib.

Nine deaths occurred in the all ovarian cancer population, 8 due to disease progression and 1 due to sepsis in a patient with bilateral ureteric obstruction due to disease progression. The age of patients ranged from 35 to 75 (mean 60.3 years). Disease progression occurred between 4 and 161 days (mean 41.1 days) of starting rucaparib. Four of the 9 patients presented with symptoms of progression within 13 days of starting rucaparib.

Table 30. TEAEs with an Outcome of Death: Safety Population (Combined Studies CO-338-010, CO-338-017, and CO-338-023)

SOC PT	600 mg BID				
	Ovarian Cancer BRCA N = 143	Ovarian Cancer Non-BRCA N = 234	All Ovarian Cancer N = 377	Other Tumours N = 32	Overall N = 409
	n (%)				
Any TEAE with an Outcome of Death	**5 (3.5)**	**4 (1.7)**	**9 (2.4)**	**5 (15.6)**	**14 (3.4)**
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	**5 (3.5)**	**3 (1.3)**	**8 (2.1)**	**2 (6.3)**	**10 (2.4)**
Malignant neoplasm progression	5 (3.5)	3 (1.3)	8 (2.1)	2 (6.3)	10 (2.4)
Gastrointestinal Disorders	**0**	**0**	**0**	**1 (3.1)**	**1 (0.2)**
Upper gastrointestinal haemorrhage	0	0	0	1 (3.1)	1 (0.2)
Respiratory, Thoracic and Mediastinal Disorders	**0**	**0**	**0**	**2 (6.3)**	**2 (0.5)**
Acute respiratory failure/Respiratory failure	0	0	0	2 (6.3)[a]	2 (0.5)
Infections and Infestations	**0**	**1 (0.4)**	**1 (0.3)**	**0**	**1 (0.2)**
Sepsis	0	1 (0.4)	1 (0.3)	0	1 (0.2)
Metabolism and Nutrition Disorders	**1 (0.7)**	**0**	**1 (0.3)**	**0**	**1 (0.2)**
Hyponatremia	1 (0.7)	0	1 (0.3)	0	1 (0.2)
Renal and Urinary Disorders	**0**	**0**	**0**	**1 (3.1)**	**1 (0.2)**
Acute kidney injury	0	0	0	1 (3.1)	1 (0.2)

Source: Table 3.1.10 (Section 5.3.5.3)

Abbreviations: BID = twice daily; BRCA = breast cancer gene; N or n = number of patients; PT = preferred term; SAE = serious adverse event; SOC = system organ class; TEAE = treatment-emergent adverse event.

[a] One patient was initially reported as experiencing an SAE of pulmonary embolism that led to discontinuation of rucaparib and death. The events experienced by this patient were updated to SAEs of both pulmonary embolism (not related) and atrial fibrillation (not related), and death due to acute respiratory failure (not related) secondary to disease progression, upon a follow-up SAE report after the data cut-off date for this ongoing study.

Updated data

The frequencies of TEAEs having an outcome of death ranged from 2.7% to 4.2% patients across the different patient populations. Malignant neoplasm progression was the most common TEAE with an outcome of death across all patient populations. An event of B-cell type acute leukaemia was the only TEAE with an outcome of death that was considered related to rucaparib.

Overall, there were 31 patients who died due to TEAE(s) in Studies CO-338-010, CO-338-014, CO-338-017, CO-338-023, and CO-338-044. There were 10 patients (1 patient in Study CO-338-010; 6 patients in Study CO-338-014; and 3 patients in Study CO-338-017) with a TEAE leading to death and assessed as related to rucaparib by the investigator. Five of the related TEAEs leading to death were cases of MDS/ AML where relationship to study drug could not be ruled out; however, there are many confounding risk factors in assessing drug relationship in the cases of MDS/AML. Reports of general health deterioration were frequently in relation to progression of the patient's underlying cancer

Table 5. TEAEs with an Outcome of Death: Subgroup of BRCA-mutant Ovarian Cancer Patients in the Efficacy Population Relative to All Ovarian Cancer Patients and the Overall Safety Population

System Organ Class Preferred Term	600 mg BID Ovarian Cancer BRCA in Efficacy Population[a] (N=106) n (%)	600 mg BID Ovarian Cancer BRCA in Safety Population (N=143) n (%)	600 mg BID All Ovarian Cancer (N=377) n (%)	600 mg BID Overall Safety Population (N=409) n (%)
Number of Patients with a TEAE Outcome of Death	**4 (3.8)**	**6 (4.2)**	**10 (2.7)**	**15 (3.7)**
Gastrointestinal Disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.2)**
Upper gastrointestinal haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Infections and Infestations	**0 (0.0)**	**0 (0.0)**	**1 (0.3)**	**1 (0.2)**
Sepsis	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	4 (3.8)	**6 (4.2)**	**9 (2.4)**	**12 (2.9)**
B-cell type acute leukemia	1 (0.9)	1 (0.7)	1 (0.3)	1 (0.2)
Malignant neoplasm progression	3 (2.8)	5 (3.5)	8 (2.1)	11 (2.7)
Renal and Urinary Disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.2)**
Acute kidney injury	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Respiratory, Thoracic and Mediastinal Disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.2)**
Respiratory failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BID = twice daily; BRCA = breast cancer gene; N or N = number of patients; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.

Note: Combined terms are presented, then SOCs and PTs are presented in order of descending incidence in the Overall Safety Population.

Data are from combined studies with a cut-off as of 10 April 2017 for the ongoing Studies CO-338-010 and CO-338-017 and final data for Study CO-338-023.

Sources: Table 3.28.10 and Table 3.15.10 (Day 120 Update, Analysis of Safety, Section 5.3.5.3)

Laboratory findings

National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grade shifts from baseline in key laboratory parameters are summarized in Table 31. In addition, Table 32 summarizes all Grade 1 to 4 laboratory abnormalities that occurred during rucaparib treatment, regardless of whether there was a shift in CTCAE grade from baseline. The most notable laboratory abnormalities were decreased haemoglobin (and associated increase in mean corpuscular volume [MCV] and mean corpuscular haemoglobin [MCH]),

increased ALT, increased AST, and increased serum creatinine, similar to the TEAEs reported. Decreased platelets, neutrophils, leukocytes, lymphocytes and increased cholesterol were observed to a lesser extent.

Table 31 Shifts in Key Laboratory Parameters in Patients Treated with 600 mg Rucaparib: Safety Population (Combined Studies CO-338-010, CO-338-017, and CO-338-023)

Key Laboratory Parameter	Shift from Baseline in CTCAE Grade									
	600 mg BID									
	Ovarian Cancer BRCA N = 143		Ovarian Cancer Non-BRCA N = 234		All Ovarian Cancer N = 377		Other Tumors N = 32		Overall N = 409	
	n (%)									
	Grade 1-4[a]	Grade 3/4[b]	Grade 1-4[a]	Grade 3/4[b]	Grade 1-4[a]	Grade 3/4[b]	Grade 1-4[a]	Grade 3/4[b]	Grade 1-4[a]	Grade 3/4[b]
Increase in creatinine	126 (88.1)	1 (0.7)	221 (94.4)	4 (1.7)	347 (92.0)	5 (1.3)	27 (84.4)	0	374 (91.4)	5 (1.2)
Increase in AST	101 (70.6)	4 (2.8)	176 (75.2)	13 (5.6)	277 (73.5)	17 (4.5)	14 (43.8)	1 (3.1)	291 (71.1)	18 (4.4)
Increase in ALT	107 (74.8)	19 (13.3)	173 (73.9)	28 (12.0)	280 (74.3)	47 (12.5)	13 (40.6)	2 (6.3)	293 (71.6)	49 (12.0)
Increase in cholesterol	62 (43.4)	6 (4.2)	88 (37.6)	3 (1.3)	150 (39.8)	9 (2.4)	4 (12.5)	0	154 (37.7)	9 (2.2)
Decrease in hemoglobin	100 (69.9)	42 (29.4)	151 (64.5)	46 (19.7)	251 (66.6)	88 (23.3)	21 (65.6)	5 (15.6)	272 (66.5)	93 (22.7)
Decrease in platelets	65 (45.5)	8 (5.6)	82 (35.0)	16 (6.8)	147 (39.0)	24 (6.4)	10 (31.3)	3 (9.4)	157 (38.4)	27 (6.6)
Decrease in neutrophils	53 (37.1)	14 (9.8)	80 (34.2)	23 (9.8)	133 (35.3)	37 (9.8)	9 (28.1)	5 (15.6)	142 (34.7)	42 (10.3)
Decrease in lymphocytes	60 (42.0)	9 (6.3)	109 (46.6)	17 (7.3)	169 (44.8)	26 (6.9)	12 (37.5)	2 (6.3)	181 (44.3)	23 (5.6)

Source: Tables 4.1.1 and 4.1.2 (Section 5.3.5.3)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BID = twice daily; BRCA = breast cancer gene; N or n = number of patients.

[a] Any worsening shift in CTCAE grade from baseline

[b] Any shift to CTCAE Grade 3/4 from baseline

Percentages are based on subgroup denominators (N).

Table 32 Key Laboratory Parameters in Patients Treated with 600 mg Rucaparib: Safety Population (Combined Studies CO-338-010, CO-338-017, and CO-338-023)

Key Laboratory Parameter	CTCAE Grade									
	600 mg BID									
	Ovarian Cancer BRCA N = 143		Ovarian Cancer Non-BRCA N = 234		All Ovarian Cancer N = 377		Other Tumors N = 32		Overall N = 409	
	n (%)									
	Grade 1-4[a]	Grade 3/4[b]	Grade 1-4[a]	Grade 3/4[b]	Grade 1-4[a]	Grade 3/4[b]	Grade 1-4[a]	Grade 3/4[b]	Grade 1-4[a]	Grade 3/4[b]
Increase in creatinine	137 (95.8)	1 (0.7)	229 (97.9)	4 (1.7)	366 (97.1)	5 (1.3)	30 (93.8)	0	396 (96.8)	5 (1.2)
Increase in AST	111 (77.6)	4 (2.8)	184 (78.6)	13 (5.6)	295 (78.2)	17 (4.5)	28 (87.5)	1 (3.1)	323 (79.0)	18 (4.4)
Increase in ALT	110 (76.9)	19 (13.3)	180 (76.9)	28 (12.0)	290 (76.9)	47 (12.5)	18 (56.3)	2 (6.3)	308 (75.3)	49 (12.0)
Increase in cholesterol	104 (72.7)	6 (4.2)	142 (60.7)	3 (1.3)	246 (65.3)	9 (2.4)	6 (18.8)	0	252 (61.6)	9 (2.2)
Decrease in hemoglobin	115 (80.4)	42 (29.4)	178 (76.1)	46 (19.7)	293 (77.7)	88 (23.3)	27 (84.4)	5 (15.6)	320 (78.2)	93 (22.7)
Decrease in lymphocytes	81 (56.6)	9 (6.3)	132 (56.4)	17 (7.3)	213 (56.5)	26 (6.9)	18 (56.3)	2 (6.3)	231 (56.4)	28 (6.8)
Decrease in platelets	70 (49.0)	8 (5.6)	88 (37.6)	16 (6.8)	158 (41.9)	24 (6.4)	11 (34.4)	3 (9.4)	169 (41.3)	27 (6.6)
Decrease in neutrophils	54 (37.8)	14 (9.8)	82 (35.0)	23 (9.8)	136 (36.1)	37 (9.8)	9 (28.1)	5 (15.6)	145 (35.5)	42 (10.3)

Source: Tables 4.1.1 and 4.1.2 (Section 5.3.5.3)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BID = twice daily; BRCA = breast cancer gene; N or n = number of patients.

[a] Patients were allowed on study with Grade 1 or Grade 2 lab abnormalities at baseline

[b] CTCAE Grade 3/4 post baseline

Percentages are based on subgroup denominators (N).

The laboratory parameter abnormalities discussed below are based on data for the overall safety population, with tumour subgroup data discussed if notable differences were observed.

Haematology

Based on laboratory data, myelosuppression was observed during rucaparib therapy, with notable shifts from baseline for haemoglobin concentrations and lymphocyte, platelet and neutrophil counts (Table 2.7.4-24). In most patients, myelosuppression was a delayed effect that manifested beyond the first cycle of treatment. There were no notable differences in haematological laboratory abnormalities among the tumour subgroups.

The most frequently observed haematology laboratory finding was a decrease in haemoglobin, consistent with anaemia being reported as one of the most common TEAEs. A decrease in haemoglobin (CTCAE Grade 1-4) from baseline was observed in 66.5% of patients (Grade 3, 22.7%) in the overall patient population, 66.6% (Grade 3, 23.3%) of all ovarian cancer patients and in 69.9% (Grade 3, 29.4%) of the BRCA mutant ovarian cancer patients. The Grade 3 haemoglobin laboratory observations generally occurred later in treatment (Cycle 3 Day 1 and beyond). Anaemia was macrocytic, with increases in MCV and MCH but no apparent increase in reticulocytes. In ovarian cancer patients with a BRCA mutation, 49 (34.3%) received a blood transfusion (range = 1-10) during treatment with rucaparib; most (N=34) required one transfusion; the median time to transfusion was approximately 2 months.

Anaemia was managed with supportive care as well as with dose interruption and/or dose reduction(s) (Study CO-338-010; Study CO-338-017). A total of 35 patients (8.6%) received an anti-anaemia concomitant medication (eg, iron preparation, erythropoietin) either as a supplement prior to initiating rucaparib (n = 17; 4.2%) or as treatment for anaemia while receiving rucaparib (n = 20; 4.9%), with 1 patient (0.2%) taking iron supplements prior to initiating rucaparib and requiring epoetin beta during treatment with rucaparib.

In the BRCA mutant ovarian cancer group, a decrease in lymphocytes, platelets, or neutrophils from baseline to a worsening CTCAE Grade occurred in 42.0%, 45.5%, and 37.1% of patients, respectively. A shift to CTCAE Grade ≥3 lymphocytes, platelets, or neutrophils was observed in 6.3%, 5.6%, and 9.8% of patients with BRCA mutant ovarian cancer, respectively.

Similar to haemoglobin, the time of onset for CTCAE Grade ≥3 lymphocytes, platelets, or neutrophils was generally later in treatment (Cycle 3 Day 1 and beyond). Seven patients (1.7%) required a platelet transfusion. Five patients received a single transfusion of platelets; 1 patient received 5 separate platelet transfusions over a course of 6 days, and 1 patient received 3 separate platelet transfusions over a course of 8 days.

Clinical Chemistry

The majority of patients with normal clinical chemistry parameters at baseline maintained normal levels during treatment, with shifts to Grade 1 reported for most of the remaining patients; however, notable shifts from baseline were observed for creatinine, ALT, AST, and cholesterol concentrations in the majority of patients. There were no notable differences in clinical chemistry laboratory abnormalities among the tumour subgroups, apart from 'other tumours' for AST, ALT and cholesterol.

ALT/AST Elevations

In all BRCA mutant ovarian cancer patients, an increase in ALT or AST from baseline to a worsening CTCAE grade occurred in 74.8% and 70.6% of patients, respectively. A shift to CTCAE Grade ≥3 ALT or AST was observed in 13.3% and 2.8% of BRCA mutant ovarian cancer patients, respectively. The ALT/AST elevations occurred early in treatment (ie, in Cycle 1 or by Day 1 of Cycle 2) and then resolved or stabilized over time. Treatment with rucaparib was continued at either the initial 600 mg BID dose or a lower dose. Elevations in ALT/AST were generally not accompanied by a concomitant elevation in bilirubin.

One patient with relapsed ovarian cancer developed ALT/AST > 3 x ULN and bilirubin > 2 xULN without evidence of cholestasis (i.e. elevated ALP) after 2 weeks of rucaparib treatment. ALT, AST and bilirubin levels decreased when rucaparib was held and increased when dosing was resumed, suggesting a temporal relationship. The patient had metastatic liver disease at baseline, which confounded the assessment. The results on Cycle 1 Day 15 were not observed at any subsequent laboratory assessment, although treatment with rucaparib continued for a total of 159 days. On this basis, the event was not considered to have demonstrated evidence of drug-induced liver injury.

Creatinine Elevations

In BRCA mutant ovarian cancer patients, an increase in serum creatinine from baseline to a worsening CTCAE grade occurred in 88.1% of patients (64.3% to Grade 1, 23.1% to Grade 2, and 0.7% to Grade 4; no patient had a shift to Grade 3). The elevations were observed early in treatment (Day 15 of Cycle 1) and then stabilized with continued rucaparib treatment. Serum creatinine levels decreased with interruption or discontinuation of rucaparib, and increase again with resumption of treatment. Rucaparib is an inhibitor of multidrug and toxin extrusion 1 (MATE1) and multidrug and toxin extrusion 2-K (MATE2-K) transporters and a moderate inhibitor of organic cation transporter 2 (OCT2), which mediate renal excretion of creatinine. Therefore, the elevations in creatinine observed in patients are thought to be due to inhibition of the renal transporters MATE1 and MATE2-K by rucaparib.

Cholesterol Elevations

An increase in total cholesterol from baseline to a worsening CTCAE grade occurred in 37.7%, 39.8%, and 43.4% of all patients, all ovarian cancer patients, and BRCA mutant ovarian cancer patients, respectively. Increase to CTCAE Grade 3 or greater total cholesterol occurred in 2.2%, 2.4%, and 4.2% of all patients, all ovarian cancer patients, and BRCA mutant ovarian cancer patients, respectively. The few Grade 3 events observed were successfully managed by treatment modification (interrupting treatment and/or reducing the rucaparib dose) and/or concomitant treatment with a 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitor (statin).

Vital Signs, Physical Findings, and Other Observations Related to Safety

Vital Signs

There were no notable changes from baseline in diastolic or systolic blood pressure, heart rate, body temperature or weight.

Prolongation of QT and cardiac toxicity

The Phase 1 (Part 1) dose-escalation portion of Study CO-338-010 included serial ECGs (as triplicate reads) and independent central review in order to assess the effect of oral rucaparib on QT interval corrected (QTc). A total of 56 patients were enrolled and 55 patients were evaluable and ECG data were available for up to 22 cycles in the patient with the longest duration on treatment. Rucaparib was administered continuously at doses of 40 mg QD to 840 mg BID in 3-week treatment cycles.

One patient with a history of previous episodes of prolonged QTc and a provisional diagnosis of a congenital prolonged QT syndrome made before study entry experienced Grade 4 ventricular tachyarrhythmia approximately 3 weeks after initiating rucaparib. The event was judged related to rucaparib owing to the short latency between starting rucaparib and the onset of the event.

Risk of QT prolongation cannot be ruled out since the at 600 mg BID, the recommended dose, the mean values for change of QTcF in Cycle 1 ranged from 5.0 to 14.0 msec, which is higher than 5 ms established in the

Guidance E14 for evaluation of QT/QTc. 95% CI for the mean values for the change of QTc has not been provided.

Safety in special populations

Intrinsic Factors

Age

A summary of TEAEs for patients aged < 65 years, 65 to 74 years, and 75 to 86 years is presented in Table 33.

There were no notable differences in the proportions of patients aged < 65 years (N = 240), 65 to 74 years (N = 125), and 75 to 86 years (N = 44) who experienced TEAEs, treatment-related TEAEs, SAEs, or TEAEs of Grade 3 or higher (Table 33). Treatment-related TEAEs of Grade ≥3 were more frequently reported in patients aged 65 to 74 years (55.2%) than in patients aged < 65 years (42.5%) or 75 to 86 years (45.5%). The incidence of TEAEs with an outcome of death was comparable in all subgroups (2.9%, 4.0%, and 4.5% for patients aged < 65 years, 65-74 years, and 75-86 years, respectively).

A greater proportion of patients aged 75 to 86 years experienced TEAEs that led to rucaparib discontinuation (31.8% versus 14.6% for patients aged < 65 years and 22.4% for patients aged 65-74 years). Similarly, patients aged 75 to 86 years experienced a higher incidence of treatment-related TEAEs leading to rucaparib discontinuation (18.2% versus 5.8% for patients aged < 65 years and 8.8% for patients aged 65-74 years). The oldest age group also experienced more TEAEs that led to treatment interruption or dose reduction. The incidence of TEAEs leading to dose reduction or treatment interruption was 60.4%, 68.0%, and 72.7% for patients aged < 65 years, 65 to 74 years, and 75 to 86 years, respectively. Treatment-related TEAEs leading to dose reduction or treatment interruption were reported in 52.1%, 59.2% and 68.2% of patients aged < 65 years, 65 to 74 years, and 75 to 86 years, respectively.

Table 33. Overall Summary of TEAEs by Age: Safety Population (Combined Studies CO-338-010, CO-338-017, and CO-338-023)

	600 mg BID		
	Age < 65 Years N = 240	Age 65-74 years N = 125	Age 75-86 Years N = 44
TEAE[a]	240 (100)	125 (100)	44 (100)
Treatment-related TEAE	225 (93.8)	120 (96.0)	43 (97.7)
Serious TEAE[a]	69 (28.8)	41 (32.8)	11 (25.0)
Treatment-related serious TEAE	20 (8.3)	14 (11.2)	5 (11.4)
≥ Grade 3 TEAE[a]	143 (59.6)	85 (68.0)	28 (63.6)
Treatment-related ≥ Grade 3 TEAE	102 (42.5)	69 (55.2)	20 (45.5)
TEAE with an outcome of death[a]	7 (2.9)	5 (4.0)	2 (4.5)
Treatment-related TEAE with an outcome of death	0	0	0
TEAE leading to discontinuation[a]	35 (14.6)	28 (22.4)	14 (31.8)
Treatment-related TEAE leading to discontinuation	14 (5.8)	11 (8.8)	8 (18.2)
TEAE leading to treatment interruption or dose reduction	145 (60.4)	85 (68.0)	32 (72.7)
Treatment-related TEAE leading to treatment interruption or dose reduction	125 (52.1)	74 (59.2)	30 (68.2)

Source: Tables 3.2.1, 3.3.1, and 3.14.1 (Section 5.3.5.3)

Abbreviations: BID = twice daily; N = number of patients; TEAE = treatment-emergent adverse event.

[a] Included events of disease progression.

Table 34: Selected TEAEs by SOC and PT; safety population by age

MedDRA Terms	Age <65 N=240	Age 65-74 N=125	Age 75-86 N=44
Increased AST/ALT	42.1%	36.8%	40.9%
Anaemia	41.7%	44.8%	45.5%
Asthenia	72.1%	78.4%	75%
Decreased neutrophils	18.8%	12.0%	13.6%
Decreased platelets	23.3%	16.8%	22.7%
GI disorders	94.2%	94.4%	93.2%
Psychiatric disorders (related)	25.4% (7.1%)	20.8% (4.0%)	13.6% (11.4%)
Nervous system disorders	66.7%	59.2%	70.5%
Hepatobiliary	3.3%	1.6%	2.3%
Cardiac disorders	4.2%	5.6%	9.1%
Increased cholesterol	4.2%	8.0%	4.5%
Increased creatinine	20.0%	17.6%	29.5%
Infections and infestations	40.0%	49.6%	34.1%
Renal disorders (related)	19.2% (2.5%)	21.6% (1.6%)	13.6% (2.3)

Gender

There were no notable differences in the proportions of female (N = 393) and male (N = 16) patients who experienced TEAEs, treatment-related TEAEs, TEAEs of Grade 3 or above, or TEAEs leading to rucaparib discontinuation, or treatment interruption. The low number of male patients precludes meaningful comparison between these subgroups.

Race

There were no notable differences in the proportions of White (N = 329) and non-White (N = 40) patients who experienced TEAEs, treatment-related TEAEs, SAEs, TEAEs of Grade 3 or above, or TEAEs leading to rucaparib discontinuation. More treatment interruptions were reported for non-Whites (75.0%) than Whites (55.6%), and the frequency of dose reductions was 52.5% for non-Whites versus 41.6% for Whites.

BRCA Mutation (gBRCA, sBRCA, Unknown BRCA) versus No BRCA Mutation (Non-BRCA)

Overall, there were no notable differences in the proportions of patients with a gBRCA mutation (N = 108), sBRCA mutation (N = 23), unknown germline/somatic BRCA status (N = 12), or those without a BRCA mutation (non-BRCA; N = 234) who experienced TEAEs, treatment-related TEAEs, or SAEs; however, due to the low number of patients with a sBRCA mutation (N = 23) or unknown germline/somatic BRCA status (n = 12), comparisons involving these groups should be interpreted cautiously. A greater proportion of patients with a gBRCA mutation experienced TEAEs and discontinuation rucaparib as compared to gBRCA, non-BRCA or all patients with ovarian cancer. A greater proportion of patients with a gBRCA mutation experienced TEAEs (regardless of causality) of Grade ≥ 3 as compared to non-BRCA patients (gBRCA mutation = 68.5%; non-BRCA = 59.0%) or a TEAE (regardless of causality) that led to rucaparib discontinuation, dose reduction, or treatment interruption (gBRCA mutation = 79.6%; non-BRCA = 65.0%); however, the frequencies of treatment-related TEAEs of Grade 3 or higher were comparable between gBRCA (50.9%) and non-BRCA patients (45.7%), as were

those of treatment-related TEAEs leading to rucaparib discontinuation, dose reduction, or treatment interruption (gBRCA = 65.7%; non-BRCA = 57.3%). Any differences observed between the gBRCA and non-BRCA groups may be related to the longer duration on treatment for patients with a BRCA mutation median duration of treatment = 224 days) versus those without (median duration of treatment = 112.5 days). This should be confirmed with update safety profile.

While there was a difference in the frequency of ALT/AST elevation and anaemia AEs reported in ovarian cancer patients with a BRCA mutation versus in ovarian cancer patients without a BRCA mutation, there were no significant differences in the observed laboratory shifts for ALT/AST or haemoglobin in the subgroups. Specifically, 51.9% of patients with a gBRCA mutation experienced TEAEs of ALT/AST elevation compared with 21.7% of patients with a sBRCA mutation, 58.3% of unknown germline/somatic BRCA status, and 37.6% of patients with no BRCA mutation. The combined terms of anaemia and/or low/decreased haemoglobin were reported for 57.4% of patients with a gBRCA mutation, 34.8% of patients with a sBRCA mutation, 66.7% of patients with unknown germline/somatic BRCA status, and 37.2% of patients with no BRCA mutation.

Renal Impairment

Study enrolment required serum creatinine ≤ 1.5 × ULN; 84 patients with mild renal impairment (by NCI Organ Dysfunction Working Group criteria as an estimated CrCL of 40-59 mL/min) were enrolled.

The safety and effectiveness of rucaparib has not been evaluated in patients with moderate (defined as estimated CrCL of 20-39 mL/min) or severe renal impairment (defined as CrCL < 20 mL/min) and a PK study specifically in patients with renal impairment has not been conducted. No dose modification for renal impairment is proposed based on the population PK data.

There were no notable differences in the frequencies of TEAEs between patients with or without renal impairment, or among the subgroups in each category (ie, BRCA mutant ovarian cancer, all ovarian cancer, and overall populations). All patients experienced at least 1 TEAE, with treatment-related TEAEs reported for 97.6% of patients with renal impairment and for 94.2% of patients without renal impairment. SAEs were reported for 32.1% of patients with renal impairment and 28.9% of patients without renal impairment, with treatment-related SAEs occurring in 13.1% of patients with renal impairment and 8.6% of patients without renal impairment. A total of 69.0% of patients with renal impairment experienced a TEAE of Grade 3 or higher, compared to 60.9% of patients without renal impairment. Slightly more patients with renal impairment had a TEAE that led to treatment interruption and/or dose reduction as compared to patients without renal impairment (70.2% versus 62.5%, respectively). A TEAE (any causality) led to discontinuation of rucaparib in 29.8% of patients with renal impairment and 16.0% of patients without renal impairment. A treatment-related TEAE leading to discontinuation occurred in 15.5% of patients with renal impairment and in 6.2% of patients without renal impairment. A TEAE with an outcome of death was reported in 5 patients (6.0%) with renal impairment and in 9 patients (2.8%) without renal impairment; no TEAE that led to death was considered related to rucaparib.

In the all ovarian cancer population, there were generally more TEAEs in each category for those with mild renal impairment compared to normal renal function. More patients with mild renal impairment compared to those with no renal impairment experienced Grade ≥3 TEAEs (68.8% vs. 59.6%) and TEAEs leading to discontinuation (28.8% vs. 15.8%), treatment interruption (70% vs. 55.9%) or dose reduction (53.8% vs. 43.8%). There were more TEAEs leading to death in the former group (5.0% vs. 1.7%), although none were considered treatment related. Taken together, these data suggest that no dosage adjustment is required in patients with mild or moderate renal impairment. Rucaparib should be used with caution in patients with severe renal impairment (SmPC Section 4.2).

Hepatic Impairment

Study enrolment required ALT and AST ≤3 x ULN; 46 patients with mild hepatic impairment (NCI Organ Dysfunction Working Group criteria AST > ULN with total bilirubin ≤ ULN or any AST level with total bilirubin > 1.0-1.5 × ULN).

No formal studies have been performed with rucaparib in patients with hepatic impairment. Entry criteria for rucaparib clinical studies excluded patients with significant hepatic impairment.

Rucaparib has not been evaluated in patients with moderate (defined as any ALT/AST level and total bilirubin > 1.5-3 × ULN) or severe hepatic impairment (defined as any ALT/AST level and total bilirubin > 3 × ULN).

There were no notable differences between patients with or without hepatic impairment, or among the subgroups in each category (ie, BRCA mutant ovarian cancer, all ovarian cancer, and overall populations). A treatment-related TEAE was reported in 91.3% of patients with hepatic impairment and in 95.3% of patients without hepatic impairment. An SAE was reported in 39.1% of patients with hepatic impairment and in 28.4% of patients without hepatic impairment, with a treatment-related SAE reported in 8.7% of patients with hepatic impairment and in 9.6% of patients without hepatic impairment. There was no discernible difference in occurrence of TEAEs of Grade ≥ 3 (63.0% of patients with hepatic impairment; 62.5% of patients without hepatic impairment).

TEAEs that led to treatment interruption and/or dose reduction occurred at a lower rate in patients with hepatic impairment than in patients without hepatic impairment (54.3% versus 65.3%, respectively). TEAEs led to discontinuation of rucaparib in 23.9% of patients with hepatic impairment and in 18.2% of patients without hepatic impairment, with a treatment-related TEAE leading to discontinuation of rucaparib in 6.5% of patients with hepatic impairment as compared to 8.3% of patients without hepatic impairment. A TEAE with an outcome of death was reported in 4 patients (8.7%) with hepatic impairment and in 10 patients (2.8%) without hepatic impairment; no TEAE that led to death was considered related to rucaparib.

More patients with normal hepatic function at baseline than patients with hepatic impairment at baseline had a shift from normal or Grade 1 ALT at baseline to Grade 3/4 increased ALT (12.7% versus 6.5%), and fewer patients with normal hepatic function at baseline than patients with hepatic impairment at baseline had a shift from normal or Grade 1 bilirubin at baseline to Grade 3/4 increased bilirubin (1.7% versus 6.5%). There were no similar differences noted for other clinical chemistry parameters, including increased AST.

In addition, no difference in the safety profile of rucaparib has been observed in patients with mild hepatic impairment. Taken together, these data suggest that no dosage adjustment is required in patients with mild hepatic impairment. Rucaparib should be used with caution in patients with moderate or severe hepatic impairment (SmPC Section 4.2).

Looking at the ‘all ovarian cancer’ population, there were no discernible differences between those with mild hepatic impairment and normal hepatic function with regards to the summary of TEAEs, except more TEAEs leading to discontinuation (28.1% vs. 17.7%). There were no notable differences in the shifts in CTCAE grade that would indicate that patients with hepatic impairment at baseline had more laboratory abnormalities while receiving treatment with rucaparib. More patients with normal baseline hepatic function than patients with baseline hepatic impairment had a shift from normal or Grade 1 ALT at baseline to Grade 3/4 increased ALT (12.7% versus 6.5%). Fewer patients with normal baseline hepatic function than patients with baseline hepatic impairment had a shift from normal or Grade 1 bilirubin at baseline to Grade 3/4 increased bilirubin (1.7% versus 6.5%).

Paediatric Population

Paediatric patients were not included in clinical studies with rucaparib. All studies to date have required that patients are ≥ 18 years of age. Therefore, the safety of rucaparib in paediatric patients has not been established. In addition, there have been no nonclinical studies specifically performed in juvenile animals.

Extrinsic Factors

Region

There were no notable differences in the safety profile (including TEAEs, treatment-related TEAEs, SAEs, TEAEs of Grade ≥ 3, and TEAEs leading to rucaparib discontinuation, dose reduction or treatment interruption) of patients (N = 123) treated at investigational sites in the European Union (EU) as compared to patients (N = 286) treated at investigational sites in other regions.

Drug Interactions

Drug interaction data are discussed in Section 2.4.3. Pharmacology.

Use in Pregnancy and Lactation

Patients who were lactating or pregnant were excluded from the clinical studies with rucaparib.

Based on the mechanism of action and nonclinical studies, rucaparib has the potential to cause foetal harm when administered to pregnant women.

There are no animal studies on the excretion of rucaparib in breast milk. It is unknown whether rucaparib or its metabolites are excreted in human milk. A risk to newborns/infants cannot be excluded. Rucaparib must not be used during breast-feeding.

Patients should be advised to use effective contraception during treatment with rucaparib and for 6 months after the final dose.

Photosensitivity

Photosensitivity was initially reported in the Phase 1 dose-escalation portion of Study CO-338-010 (Part 1, 10.7%). Based on the reports of photosensitivity in the early portion of this study, guidance for sun protection was included in subsequent portions of Study CO-338-010 as well as in all other Phase 2 and Phase 3 protocols evaluating rucaparib.

A total of 43 patients (10.5%) in the overall safety population and 15 patients (10.5%) with BRCA mutant ovarian cancer experienced photosensitivity. None of the events of photosensitivity were of Grade ≥ 3 severity.

Incidence of Treatment Emergent Adverse Events by Decreasing Frequency of Combined Preferred Term with 95% Confidence Intervals
Safety Population

Preferred Term	Ovarian cancer BRCA (N=143)	Ovarian cancer Non-BRCA (N=234)	All Ovarian cancer (N=377)	Other tumors (N=32)	Overall (N=409)
Combined Photosensitivity	15 (10.5%) [6.0 - 16.7%]	28 (12.0%) [8.1 - 16.8%]	43 (11.4%) [8.4 - 15.1%]	0	43 (10.5%) [7.7 - 13.9%]

Overdose

One patient in Part 2 of Study CO-338-017 received 900 mg BID rucaparib for 9 consecutive days (planned dose was 600 mg BID) as of the visit cut-off date. Adverse events (AEs) observed in this patient were consistent with those observed to date with rucaparib.

There is no known antidote for overdoses of rucaparib. In the event of suspected overdose, the patient should be monitored with appropriate haematology and clinical chemistry and should receive supportive therapy, as necessary.

Drug Abuse

Given the pharmacological class of rucaparib and the absence of psychotropic effects, there is no expected potential for drug abuse.

Based on in vitro transporter studies, rucaparib is a substrate of P-gp and BCRP, and there was minimal penetration of rucaparib-derived radioactivity through the blood-brain barrier in a [14C]rucaparib tissue distribution study in the rat.

Thus, it is unlikely that rucaparib exposures in the CNS would be sufficient to translate to any effects in patients.

Withdrawal and Rebound

There have been no reports of withdrawal or rebound with short-term or long-term use of rucaparib.

Effects on Ability to Drive or Operate Machinery or Impairment of Mental

No studies on the effects on the ability to drive and use machines have been performed with rucaparib. However, caution is advised in patients who report fatigue, nausea, or dizziness during treatment with rucaparib. Neurobehavioral assessments were incorporated in the GLP 28-day repeat-dose toxicity studies for rucaparib in rats. There were no neurobehavioral findings except slightly lower hind limb grip strength at the highest dose evaluated.

Safety related to drug-drug interactions and other interactions

For Drug interaction analyses referred to Clinical Pharmacology Studies. (See the PK)

Discontinuation due to adverse events

Adverse events leading to discontinuation of treatment

TEAEs that led to discontinuation of rucaparib reported in ≥ 2 patients in any subgroup are summarized in Table 35.

Overall, 77 (18.8%) patients discontinued rucaparib due to TEAEs, most frequently due to malignant neoplasm progression (22 patients, 5.4%) and combined terms of asthenia/fatigue (10 patients, 2.4%). There were no notable differences among the different subgroups. Median times to discontinuation due to a TEAE were 105 days for patients with BRCA mutant ovarian cancer and 64 days for patients with non-BRCA ovarian cancer. Median time to discontinuation was shorter for patients with other tumours (34 days), although this number was derived from only 7 patients.

Table 35. TEAEs that Led to Discontinuation of Rucaparib in ≥ 2 Patients: Safety Population (Combined Studies CO-338-010, CO-338-017, and CO-338-023)

SOC PT	600 mg BID				
	Ovarian Cancer BRCA N = 143	Ovarian Cancer Non-BRCA N = 234	All Ovarian Cancer N = 377	Other Tumors N = 32	Overall N = 409
	n (%)				
Any TEAE Leading to Discontinuation	**27 (18.9)**	**43 (18.4)**	**70 (18.6)**	**7 (21.9)**	**77 (18.8)**
Combined Asthenia/Fatigue	**1 (0.7)**	**8 (3.4)**	**9 (2.4)**	**1 (3.1)**	**10 (2.4)**
Asthenia	0	2 (0.9)	2 (0.5)	0	2 (0.5)
Fatigue	1 (0.7)	7 (3.0)	8 (2.1)	1 (3.1)	9 (2.2)
Combined Thrombocytopenia and/or Low/Decreased Platelets	**0**	**5 (2.1)**	**5 (1.3)**	**1 (3.1)**	**6 (1.5)**
Thrombocytopenia	0	4 (1.7)	4 (1.1)	1 (3.1)	5 (1.2)
Combined Anemia and/or Low/Decreased Hemoglobin	**1 (0.7)**	**3 (1.3)**	**4 (1.1)**	**0**	**4 (1.0)**
Anaemia	1 (0.7)	3 (1.3)	4 (1.1)	0	4 (1.0)
Gastrointestinal Disorders	**10 (7.0)**	**16 (6.8)**	**26 (6.9)**	**1 (3.1)**	**27 (6.6)**
Small intestinal obstruction	1 (0.7)	5 (2.1)	6 (1.6)	0	6 (1.5)
Nausea	3 (2.1)	2 (0.9)	5 (1.3)	0	5 (1.2)
Ascites	2 (1.4)	2 (0.9)	4 (1.1)	0	4 (1.0)
Abdominal pain	0	3 (1.3)	3 (0.8)	0	3 (0.7)
Diarrhoea	0	2 (0.9)	2 (0.5)	0	2 (0.5)
Intestinal obstruction	2 (1.4)	0	2 (0.5)	0	2 (0.5)
Vomiting	2 (1.4)	1 (0.4)	3 (0.8)	0	3 (0.7)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	**12 (8.4)**	**9 (3.8)**	**21 (5.6)**	**1 (3.1)**	**22 (5.4)**
Malignant neoplasm progression	12 (8.4)	8 (3.4)	20 (5.3)	1 (3.1)	21 (5.1)
General Disorders and Administration Site Conditions	**1 (0.7)**	**8 (3.4)**	**9 (2.4)**	**1 (3.1)**	**10 (2.4)**
Investigations	**2 (1.4)**	**4 (1.7)**	**6 (1.6)**	**0**	**6 (1.5)**
Blood and Lymphatic System Disorders	**1 (0.7)**	**7 (3.0)**	**8 (2.1)**	**1 (3.1)**	**9 (2.2)**
Respiratory, Thoracic and Mediastinal Disorders	**2 (1.4)**	**1 (0.4)**	**3 (0.8)**	**3 (9.4)**	**6 (1.5)**
Dyspnoea	1 (0.7)	1 (0.4)	2 (0.5)	1 (3.1)	3 (0.7)
Infections and Infestations	**1 (0.7)**	**2 (0.9)**	**3 (0.8)**	**1 (3.1)**	**4 (1.0)**
Sepsis	0	2 (0.9)	2 (0.5)	0	2 (0.5)
Metabolism and Nutrition Disorders	**0**	**3 (1.3)**	**3 (0.8)**	**0**	**3 (0.7)**
Decreased appetite	0	2 (0.9)	2 (0.5)	0	2 (0.5)
Musculoskeletal and Connective Tissue Disorders	**0**	**2 (0.9)**	**2 (0.5)**	**0**	**2 (0.5)**
Nervous System Disorders	**2 (1.4)**	**2 (0.9)**	**4 (1.1)**	**0**	**4 (1.0)**
Renal and Urinary Disorders	**0**	**1 (0.4)**	**1 (0.3)**	**1 (3.1)**	**2 (0.5)**

Source: Table 3.1.12.1.1 (Section 5.3.5.3)

Abbreviations: BID = twice daily; BRCA = breast cancer gene; N or n = number of patients; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.

Treatment-related TEAEs that led to discontinuation of rucaparib reported in ≥ 2 patients in any subgroup are presented in Table 36. The incidence of treatment-related TEAEs that led to discontinuation of rucaparib was low (33 patients, 8.1% overall) and included combined asthenia/fatigue (10 patients, 2.4%), nausea (5 patients, 1.2%), combined thrombocytopenia and/or low/ decreased platelets (5 patients, 1.2%), anaemia (4 patients, 1.0%), dyspnoea (2 patients, 0.5%), diarrhoea (2 patients, 0.5%) and vomiting (2 patients, 0.5%). All other treatment-related TEAEs that led to discontinuation were experienced by 1 patient (0.2%).

Table 36. Treatment-related TEAEs that Led to Discontinuation of Rucaparib in ≥ 2 Patients in Any Subgroup: Safety Population (Combined Studies CO-338-010, CO-338-017, and CO 338-023)

SOC PT	600 mg BID				
	Ovarian Cancer BRCA N = 143	Ovarian Cancer Non-BRCA N = 234	All Ovarian Cancer N = 377	Other Tumors N = 32	Overall N = 409
	n (%)				
Any Treatment-related TEAE Leading to Discontinuation	**8 (5.6)**	**23 (9.8)**	**31 (8.2)**	**2 (6.3)**	**33 (8.1)**
Combined Asthenia/Fatigue	**1 (0.7)**	**8 (3.4)**	**9 (2.4)**	**1 (3.1)**	**10 (2.4)**
Fatigue	1 (0.7)	7 (3.0)	8 (2.1)	1 (3.1)	9 (2.2)
Asthenia	0	2 (0.9)	2 (0.5)	0	2 (0.5)
Combined Anemia and/or Low/Decreased Hemoglobin	**1 (0.7)**	**3 (1.3)**	**4 (1.1)**	**0**	**4 (1.0)**
Anaemia	1 (0.7)	3 (1.3)	4 (1.1)	0	4 (1.0)
Combined Thrombocytopenia and/or Low/Decreased Platelets	**0**	**4 (1.7)**	**4 (1.1)**	**1 (3.1)**	**5 (1.2)**
Thrombocytopenia	0	3 (1.3)	3 (0.8)	1 (3.1)	4 (1.0)
General Disorders and Administration Site Conditions	**1 (0.7)**	**8 (3.4)**	**9 (2.4)**	**1 (3.1)**	**10 (2.4)**
Blood and Lymphatic System Disorders	**1 (0.7)**	**6 (2.6)**	**7 (1.9)**	**1 (3.1)**	**8 (2.0)**
Gastrointestinal Disorders	**3 (2.1)**	**3 (1.3)**	**6 (1.6)**	**0**	**6 (1.5)**
Diarrhoea	0	2 (0.9)	2 (0.5)	0	2 (0.5)
Nausea	3 (2.1)	2 (0.9)	5 (1.3)	0	5 (1.2)
Vomiting	1 (0.7)	1 (0.4)	2 (0.5)	0	2 (0.5)
Investigations	**1 (0.7)**	**4 (1.7)**	**5 (1.3)**	**0**	**5 (1.2)**
Metabolism and Nutrition Disorders	**0**	**2 (0.9)**	**2 (0.5)**	**0**	**2 (0.5)**
Nervous System Disorders	**0**	**2 (0.9)**	**2 (0.5)**	**0**	**2 (0.5)**
Respiratory, Thoracic and Mediastinal Disorders	**1 (0.7)**	**1 (0.4)**	**2 (0.5)**	**1 (3.1)**	**3 (0.7)**
Dyspnoea	0	1 (0.4)	1 (0.3)	1 (3.1)	2 (0.5)

Source: Table 3.1.12.2.1 (Section 5.3.5.3)

Abbreviations: BID = twice daily; BRCA = breast cancer gene; N or n = number of patients; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.

Updated data

Gastrointestinal disorders were the most frequent TEAEs leading to rucaparib discontinuation (7.1% to 9.4 %) across all populations. Malignant neoplasm progression was the most common TEAE leading to rucaparib discontinuation in 6.6% of patients in the efficacy population, 6.3% of patients with BRCAmut OC in the safety population, 4.0% of OC patients, and 4.4% in the overall safety population. No TEAEs of malignant neoplasm progression leading to rucaparib discontinuation were treatment-related.

Adverse Events leading to dose reduction or interruption

Events leading to dose modifications that occurred in ≥ 5% of patients in any subgroup are summarized in Table 37. The low rate of treatment discontinuation due to treatment-related TEAEs (less than 10% in any subgroup, Table 36), indicates that the dose modification recommendations were effective in allowing patients to continue rucaparib treatment.

In ovarian cancer patients with a BRCA mutation, 71.3% experienced a TEAE leading to dose reduction or interruption; 50.3% of patients experienced a TEAE leading to dose reduction and 60.8% of patients experienced a TEAE leading to treatment interruption. The most frequent TEAEs (≥ 5% of patients) that led to dose reduction or treatment interruption in ovarian cancer patients with a BRCA mutation were combined terms

of anaemia and/or low/decreased haemoglobin (29.4%), asthenia/fatigue (24.5%), nausea (18.9%), thrombocytopenia and/or low/decreased platelets (12.6%), vomiting (12.6%), combined terms of ALT/AST increased (10.5%), and combined terms of neutropenia/ANC decreased (10.5%).

Asthenia/fatigue and vomiting and nausea led to treatment interruption or dose reduction in patients with other tumours less frequently (3.1%) compared to ovarian cancer patients (20.7%), likely due to the longer treatment duration for the latter group. The frequencies for other PTs were comparable.

The median time to a TEAE that led to dose reduction or treatment interruption of rucaparib was comparable between patients with BRCA mutant ovarian cancer and all ovarian cancer patients (25.5 and 23.0 days, respectively).

Table 37. TEAEs that Led to Dose Reduction or Interruption of Rucaparib in ≥ 5% of Patients: Safety Population (Combined Studies CO-338-010, CO-338-017, and CO-338-023)

SOC PT	600 mg BID				
	Ovarian Cancer BRCA N = 143	Ovarian Cancer Non-BRCA N = 234	All Ovarian Cancer N = 377	Other Tumors N = 32	Overall N = 409
	n (%)				
Any TEAE Leading Dose Reduction or Interruption	**102 (71.3)**	**143 (61.1)**	**245 (65.0)**	**17 (53.1)**	**262 (64.1)**
Combined Anemia and/or Low/Decreased Hemoglobin	**42 (29.4)**	**41 (17.5)**	**83 (22.0)**	**5 (15.6)**	**88 (21.5)**
Anaemia	41 (28.7)	39 (16.7)	80 (21.2)	5 (15.6)	85 (20.8)
Combined Asthenia/Fatigue	**35 (24.5)**	**43 (18.4)**	**78 (20.7)**	**1 (3.1)**	**79 (19.3)**
Fatigue	26 (18.2)	35 (15.0)	61 (16.2)	1 (3.1)	62 (15.2)
Asthenia	10 (7.0)	9 (3.8)	19 (5.0)	0	19 (4.6)
Combined ALT/AST Increased	**15 (10.5)**	**24 (10.3)**	**39 (10.3)**	**4 (12.5)**	**43 (10.5)**
Alanine aminotransferase increased	15 (10.5)	22 (9.4)	37 (9.8)	4 (12.5)	41 (10.0)
Aspartate aminotransferase increased	11 (7.7)	14 (6.0)	25 (6.6)	2 (6.3)	27 (6.6)
Combined Thrombocytopenia and/or Low/Decreased Platelets	**18 (12.6)**	**20 (8.5)**	**38 (10.1)**	**5 (15.6)**	**43 (10.5)**
Thrombocytopenia	14 (9.8)	16 (6.8)	30 (8.0)	3 (9.4)	33 (8.1)
Platelet count decreased	6 (4.2)	5 (2.1)	11 (2.9)	3 (9.4)	14 (3.4)
Combined Neutropenia and/or Low/Decreased ANC	**15 (10.5)**	**12 (5.1)**	**27 (7.2)**	**3 (9.4)**	**30 (7.3)**
Neutropenia	10 (7.0)	7 (3.0)	17 (4.5)	0	17 (4.2)
Neutrophil count decreased	5 (3.5)	5 (2.1)	10 (2.7)	3 (9.4)	13 (3.2)
Gastrointestinal Disorders	**42 (29.4)**	**62 (26.5)**	**104 (27.6)**	**6 (18.8)**	**110 (26.9)**
Nausea	27 (18.9)	42 (17.9)	69 (18.3)	2 (6.3)	71 (17.4)
Vomiting	18 (12.6)	29 (12.4)	47 (12.5)	1 (3.1)	48 (11.7)
Abdominal pain	8 (5.6)	11 (4.7)	19 (5.0)	1 (3.1)	20 (4.9)
Blood and Lymphatic System Disorders	**48 (33.6)**	**50 (21.4)**	**98 (26.0)**	**6 (18.8)**	**104 (25.4)**
Investigations	**34 (23.8)**	**50 (21.4)**	**84 (22.3)**	**9 (28.1)**	**93 (22.7)**
General Disorders and Administration Site Conditions	**39 (27.3)**	**49 (20.9)**	**88 (23.3)**	**2 (6.3)**	**90 (22.0)**
Infections and Infestations	**9 (6.3)**	**4 (1.7)**	**13 (3.4)**	**2 (6.3)**	**15 (3.7)**
Metabolism and Nutrition Disorders	**8 (5.6)**	**22 (9.4)**	**30 (8.0)**	**1 (3.1)**	**31 (7.6)**
Nervous System Disorders	**9 (6.3)**	**18 (7.7)**	**27 (7.2)**	**1 (3.1)**	**28 (6.8)**
Hepatobiliary Disorders	**1 (0.7)**	**2 (0.9)**	**3 (0.8)**	**2 (6.3)**	**5 (1.2)**
Jaundice cholestatic	0	0	0	2 (6.3)	2 (0.5)

Source: Table 3.1.15.1.1 (Section 5.3.5.3)

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BID = twice daily; BRCA = breast cancer gene; N or n = number of patients; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.

Treatment-related TEAEs that led to rucaparib dose reduction or treatment interruption are presented in Table 38.

Table 38. Incidence of Related Treatment Emergent Adverse Events That Led to Dose Reduction or Interruption of Study Drug by System Organ Class and Preferred Term Safety Population

System Organ Class Preferred Term	Ovarian cancer BRCA (N=143)	Ovarian cancer Non-BRCA (N=234)	All Ovarian cancer (N=377)	Other tumours (N=32)	Overall (N=409)
Number of Patients With at Least One Treatment-related TEAE Leading to Study Drug Interruption or Reduction	88 (61.5%)	129 (55.1%)	217 (57.6%)	12 (37.5%)	229 (56.0%)
Combined ALT/AST Increased	14 (9.8%)	23 (9.8%)	37 (9.8%)	4 (12.5%)	41 (10.0%)
Anaemia	41 (28.7%)	37 (15.8%)	78 (20.7%)	5 (15.6%)	83 (20.3%)
Combined Asthenia/Fatigue	33 (23.1%)	41 (17.5%)	74 (19.6%)	1 (3.1%)	75 (18.3%)
Combined Neutropenia and/or low/decreased ANC	15 (10.5%)	12 (5.1%)	27 (7.2%)	3 (9.4%)	30 (7.3%)
Combined Thrombocytopenia and/or low/decreased platelet	18 (12.6%)	19 (8.1%)	37 (9.8%)	5 (15.6%)	42 (10.3%)
Cardiac disorders	0	1 (0.4%)	1 (0.3%)	0	1 (0.2%)
Nausea	24 (16.8%)	36 (15.4%)	60 (15.9%)	0	60 (14.7%)
Vomiting	12 (8.4%)	22 (9.4%)	34 (9.0%)	0	34 (8.3%)
Blood creatinine increased	7 (4.9%)	9 (3.8%)	16 (4.2%)	1 (3.1%)	17 (4.2%)
Metabolism and nutrition disorders	7 (4.9%)	17 (7.3%)	24 (6.4%)	1 (3.1%)	25 (6.1%)
Decreased appetite	4 (2.8%)	7 (3.0%)	11 (2.9%)	1 (3.1%)	12 (2.9%)
Nervous system disorders	8 (5.6%)	14 (6.0%)	22 (5.8%)	0	22 (5.4%)

In ovarian cancer patients with a BRCA mutation, 61.5% experienced treatment-related TEAEs that led to rucaparib dose reduction or treatment interruption; 48.3% of patients experienced treatment-related TEAEs that led to dose reduction and 48.3% of patients experienced treatment-related TEAEs that led to treatment interruption. The most frequently reported treatment-related TEAEs that led to rucaparib dose reduction or treatment interruption were combined terms of anaemia and/or low/decreased haemoglobin (29.4%), combined terms of asthenia/fatigue (23.1%), nausea (16.8%), combined terms of thrombocytopenia/decreased platelets (12.6%), combined terms of neutropenia/decreased ANC (10.5%), combined terms of ALT/AST increased (9.8%), and vomiting (8.4%).

Study CO-338-014 (ARIEL3)

Results from the ARIEL3 trial were presented within the D180 response package. The results of Study CO-338-014 confirmed that the safety profile of rucaparib is similar in ovarian cancer patients treated with rucaparib in either the treatment or maintenance setting.

In the treatment setting, the most common TEAEs were combined asthenia/fatigue, nausea, combined anaemia and/or low/decreased haemoglobin, combined ALT/AST increased, diarrhoea, vomiting, and decreased appetite. Commonly experienced Grade 3 or higher TEAEs included combined anaemia and/or low/decreased haemoglobin, combined ALT/AST increased, and combined asthenia/fatigue. The most common SAEs and TEAEs leading to death or study drug discontinuation were from malignant neoplasm progression.

In the maintenance setting, rucaparib demonstrated a manageable side-effect profile. In the safety population of 561 patients who initiated treatment with either 600 mg twice daily (BID) of rucaparib or matched placebo (rucaparib, n = 372; placebo, n = 189). Comparable to the treatment setting, the most common TEAEs occurring in the rucaparib group were nausea, combined asthenia/fatigue, dysgeusia, combined anaemia/low or decreased haemoglobin, constipation and vomiting, combined ALT/AST increased and diarrhoea. The most common Grade 3 or higher TEAEs in patients treated with rucaparib relative to placebo were combined anaemia and/or low/decreased haemoglobin and combined ALT/AST increased. Of note, the latter were not associated with drug-induced hepatotoxicity.

In CO-338-014 (ARIEL3), currently ongoing, TEAEs with an outcome of death occurred in 6 patients treated with rucaparib; of these, 2 events (1 of AML, 1 of MDS) were assessed as related to rucaparib. For placebo, 2 patients experienced a TEAE with an outcome of death; neither of these events were related to treatment. Other serious TEAEs occurred in 21.0% of rucaparib-treated patients and 10.6% of placebo-treated patients; 4.3% of patients in the rucaparib group had a serious event of combined anaemia and/or low/decreased haemoglobin compared to 1 patient (0.5%) in the placebo group.

A total of 54.6% patients in the rucaparib group had a TEAE that led to a dose reduction compared with 4.2% in the placebo group. Similarly, a greater incidence of patients in the rucaparib treatment arm had a TEAE that led to a treatment interruption (63.7% rucaparib; 10.1% placebo). The treatment discontinuation rate for TEAEs was 14.2% for rucaparib treated patients and 2.6% for the placebo group. Discontinuation of rucaparib was primarily due to events of combined anaemia and/or low/decreased haemoglobin (3.0%), combined thrombocytopenia and/or low/decreased platelets (2.7%), and nausea (2.4%).

Across the clinical development program for oral rucaparib, the rate of treatment-emergent (ie, occurring while on treatment or within 28 days after the last dose) MDS/AML was 0.5% (5 cases/~1.077). The rate of all MDS/AML events including those occurring more than 28 days after the last dose was 0.9% (10/~1.077).

Post marketing experience

Starting in January 2017, following the approval of rucaparib (Rubraca®) in the United States, the Clovis Safety Committee holds monthly meetings to review and evaluate the rucaparib postmarketing (PM) data, as a routine safety surveillance practice. The committee reviews AE line listings, which are quality controlled and medically reviewed, to determine if potential signals or safety concerns exist.

For the period of January 2017 to April 2017, there were no safety signals detected from the PM setting. There was a noted increase in the number of reports of headache, dyspepsia, and stomatitis with a temporal association to rucaparib; however, all of these events had plausible alternative causes. The committee considered and evaluated these events, concluding that they do not represent new safety risks, at present, due to significant confounding factors and limited clinical information. Monitoring and reviews of these events will continue.

As of 10 April 2017, there were 1,066 AEs, in total, reported from PM sources. Of these, there were 152 SAEs, of which 97 SAEs were unexpected per the United States Prescribing Information for Rubraca®. There were 520 unexpected events reported overall, of which 423 events were not serious.

The SOC with the highest number of events (319) was Gastrointestinal disorders; 15 events in this SOC were unexpected SAEs. The SOCs with the next most frequently reported unexpected SAEs were General disorders and Administration site conditions (14), Neoplasms benign, malignant and unspecified (incl cysts and polyps) (11), Metabolism and nutrition disorders (9), Respiratory, thoracic, and mediastinal disorders (6), Surgical and medical procedures (6), Investigations (5), Infections and infestations (5), Hepatobiliary disorders (4), Psychiatric disorders (4), Musculoskeletal and connective tissue disorders (3), Nervous system disorders (3), Vascular disorders (3), Blood and lymphatic system disorders (2),and Injury, poisoning, and procedural complications (2). The following SOCs each had one unexpected SAE: Cardiac disorders, Endocrine disorders, Renal and urinary disorders, and Social circumstances.

The most frequently reported unexpected SAEs in the SOC of Gastrointestinal disorders were gastrointestinal obstruction events, which included intestinal obstruction (4), small intestinal obstruction (4), and large

intestinal obstruction (1). Other unexpected SAEs reported in this SOC included ascites (2), abdominal discomfort (1), abdominal distension (1), flatulence (1), and gastroesophageal reflux disease (1).

The most frequently reported unexpected SAEs in the SOC of General disorders and administration site conditions were deaths (5). Information regarding the circumstances of these cases of death were minimal or not reported. Also reported under the SOC of General disorders and administration site conditions were 2 events of Terminal state (1 event led to death, but the patient was reported as “on the brink of death” prior to starting Rubraca® as a last effort to save her life) and 2 events of Disease progression (1 event led to death).

The most frequently reported unexpected SAEs in the SOC Neoplasms benign, malignant, and unspecified (incl cysts and polyps) were malignant neoplasm progression (8 events, one of which was fatal). Single SAEs of colon cancer, malignant pleural effusion, and metastases to the peritoneum were also reported in this SOC. As of the 10 April 2017 data cut-off, there were no spontaneous reports of MDS or AML.

As of 10 April 2017, there were 26 non-serious reports of off-label use received into the safety database. Of the 13 medically confirmed cases, the indications included peritoneal cancer (with and without/ unknown BRCA mutation) (6), BRCA negative ovarian cancer (1), cancer of the parametrium (1), BRCA somatic mutation of vulvar cancer (1), and FTC (2). Twelve of these cases were associated with SAEs, however, none were fatal or life-threatening, and they were all consistent with rucaparib safety profile. Hence, these off-label use cases have not raised safety concern at present.

2.6.1. Discussion on clinical safety

The safety data set is based on patients from 3 open label studies (Study CO-338-010, Study CO-338-017 [ARIEL2], and Study CO-338-023 [RUCAPANC]) treated with rucaparib 600 mg BID until disease progression or other reason for discontinuation and is currently small (409 patients overall, 377 with ovarian cancer and 143 with claimed indication of BRCA mutation ovarian cancer) and the possibility of detecting uncommon and rare AEs is limited. An update of safety data was presented and results for 106 subjects that comprise the primary efficacy population together with a summary of post-marketing AE reports. Although the number of patients in current studies are too low to allow precision in the assessment of differences between the “BRCAm” and the “not BRCAm” patients and differences between the “sBRCAm” and the “gBRCAm” patients, safety analyses were carried out in these subpopulations.

According to the initial submission of safety data, the median duration of treatment in patients with BRCA mutant ovarian cancer was 7.5 months. Approximately 25% of patients with BRCA mutant ovarian cancer received > 12 months of treatment, and 69.2% of patients received > 6 months of treatment. About 10.6% of patients in the BRCA mutant ovarian cancer discontinued treatment due to AEs and 79.8% of patients due to progressive disease.

All patients reported TEAEs, the majority (~95%) considered treatment related. Nearly one-third of patients reported a serious TEAE, just fewer than 10% were deemed treatment related. The summary TEAE profile in patients with BRCA mutant ovarian cancer was similar to the total safety population, as well as the ovarian cancer population.

Nausea, vomiting, fatigue (including asthenia), anaemia, decreased neutrophils (neutropenia), decreased lymphocytes (lymphopenia), decreased platelets (thrombocytopenia), diarrhoea, abdominal pain, abdominal distension, decreased appetite, headache, dizziness, dysgeusia, increased blood creatinine, dyspnoea, urinary tract infection and increased ALT/AST are adverse drug reactions observed with rucaparib treatment. The events are generally low grade and manageable without requiring discontinuation of rucaparib treatment.

BRCA mutant ovarian cancer:

The TEAE profile was similar to that of the total safety population as well as the ovarian cancer population: all patients experienced TEAEs, 97.9% of whom experienced TEAEs that were considered treatment-related. SAEs were reported for 31.5% of patients with BRCA mutant ovarian cancer, with the incidence of treatment-related SAEs at 8.4%. In total, 65.7% of patients with BRCA mutant ovarian cancer experienced TEAEs of Grade 3 or higher. TEAEs led to treatment interruption and/or reduction in 71.3% of patients (treatment interruption = 60.8%, dose reduction = 50.3%). TEAEs led to discontinuation of rucaparib in 18.9% of patients with BRCA mutant ovarian cancer; treatment-related TEAEs led to discontinuation in 5.6% of patients. TEAEs with an outcome of death were reported in 3.5% of patients with BRCA mutant ovarian cancer; none of these was considered related to treatment.

There were no notable differences in the proportions of patients with a gBRCA mutation (N = 108), sBRCA mutation (N = 23), unknown germline/somatic BRCA status (N = 12), or those without a BRCA mutation (non-BRCA; N = 234) who experienced TEAEs, treatment-related TEAEs, or SAEs; however, due to the low number of patients with a sBRCA mutation or unknown germline/somatic BRCA status, comparisons involving these groups should be interpreted cautiously. A greater proportion of patients with a gBRCA mutation experienced TEAEs (regardless of causality) of Grade ≥3 as compared to non-BRCA patients (gBRCA mutation = 68.5%; non-BRCA = 59.0%) or a TEAE (regardless of causality) that led to rucaparib discontinuation, dose reduction, or treatment interruption (gBRCA mutation = 79.6%; non-BRCA = 65.0%); however, the frequencies of treatment-related TEAEs of Grade ≥3 were comparable between gBRCA (50.9%) and non-BRCA patients (45.7%), as were those of treatment-related TEAEs leading to rucaparib discontinuation, dose reduction, or treatment interruption (gBRCA = 65.7%; non-BRCA = 57.3%). While there was a difference in the frequency of ALT/AST elevation and anaemia AEs reported in ovarian cancer patients with a BRCA mutation versus in ovarian cancer patients without a BRCA mutation, there were no significant differences in the observed laboratory shifts for ALT/AST or haemoglobin in the subgroups.

The most common TEAEs, reported were consistent with those observed within the total ovarian cancer population and the overall population, and irrespective of relationship to rucaparib, were combined fatigue/asthenia (79.7%), nausea (76.9%), combined anaemia/decreased haemoglobin (54.5%), vomiting (50.3%), combined ALT/AST increased (47.6%), constipation (41.3%), and dysgeusia (39.2%). The most frequently reported treatment-related TEAEs were combined terms of asthenia/fatigue (71.3%), nausea (65.7%), combined terms of anaemia and/or low/decreased haemoglobin (51.7%), combined terms of ALT/AST increased (45.5%), and dysgeusia (37.1%).

The overall incidence of Grade ≥ 3 TEAEs, regardless of causality, was 65.7% and were combined terms of anaemia and/or low/decreased haemoglobin (29.4%), combined terms of asthenia/fatigue (14.0%), combined terms of ALT/AST increased (12.6%), combined terms of neutropenia and/or low/decreased ANC (10.5%), malignant neoplasm progression (9.1%), and vomiting (5.6%).

Treatment-related Grade ≥ 3 TEAEs were experienced by 49.7% of patients. The most commonly reported were combined terms of anaemia and/or low/decreased haemoglobin (28.7%), combined terms of ALT/AST increased (11.9%), combined terms of asthenia/fatigue (10.5%), and combined terms of neutropenia and/or low/decreased ANC (10.5%).

SAEs: malignant neoplasm progression (8.4%) and anaemia (5.6%) were also the most frequently reported SAEs. There were no notable differences in the frequency of SAEs between the overall patient population (29.6%) and patients with BRCA mutant ovarian cancer (31.5%).

Treatment-related SAEs were experienced by 9.5% of ovarian cancer patients and 8.4% of ovarian cancer patients with a BRCA mutation, with the most common treatment-related SAE being anaemia (in 4.5% and 5.6% of patients, respectively).

The incidence of treatment-related TEAEs leading to discontinuation of rucaparib was 5.6% in patients with BRCA mutant ovarian cancer and included nausea (2.1%), fatigue, anaemia and vomiting (0.7% each).

Relatively few patients discontinued treatment due to a TEAE; the most common reason was gastrointestinal (GI) disorders (6.1%). Treatment-related TEAE discontinuations were lower (8.1%). Discontinuations tended to occur later, at a median of 85 days in the all ovarian cancer population and 105 days in the ovarian BRCA group.

Treatment-related TEAEs that led to rucaparib dose reduction or treatment interruption were 61.5% in ovarian cancer patients with a BRCA mutation; 48.3% led to dose reduction and 48.3% led to treatment interruption. The most frequently reported treatment-related TEAEs that led to rucaparib dose reduction or treatment interruption were combined terms of anaemia and/or low/decreased haemoglobin (29.4%), combined terms of asthenia/fatigue (23.1%), nausea (16.8%), combined terms of thrombocytopenia/decreased platelets (12.6%), combined terms of neutropenia/decreased ANC (10.5%), combined terms of ALT/AST increased (9.8%), and vomiting (8.4%).

Updated safety analyses with a longer follow-up (data cut-off of 10 April 2017) were submitted as part of the D120 responses. Overall, the rates of TEAEs, SAEs, Grade 3 and higher TEAEs, and TEAEs with an outcome of death were comparable between the patients with BRCAmut OC in the primary efficacy and safety populations, all OC patients, and patients in the overall safety population.

Some TEAEs were reported more frequently in patients with BRCAmut OC, but the duration of rucaparib treatment was generally longer in these patients than in the OC and overall safety populations and is the likely cause of some higher TEAE rates in this population.

AESIs: 10 cases of MDS/ AML, as of *10 April 2017*, and including all studies in the rucaparib clinical development program (1077 patients exposed to rucaparib). In the group of patients receiving rucaparib, five cases of MDS/AML occurred while patient was on treatment with rucaparib or within the 28-day safety follow-up period after treatment discontinuation and five cases occurred more than 28 days after rucaparib treatment discontinuation. Although no firm conclusion on causal relationship can be established between rucaparib treatment and the development of AML/MDS because of the presence of potential confounding factors such as prior chemotherapy in some patients, a deleterious BRCA mutation that may predispose patients to develop further malignancies and in addition the confounding effect of time course between end of rucaparib treatment and development of MDS/AML. MDS/ AML is listed as an important potential risk of Rubraca treatment, to be followed up in the RMP.

Clinical Chemistry: Notable shifts from baseline were observed for creatinine, ALT, AST, and cholesterol concentrations in the majority of patients. There were no notable differences in clinical chemistry laboratory abnormalities among the tumour subgroups, apart from 'other tumours' for AST, ALT and cholesterol.

In all BRCA mutant ovarian cancer patients, an increase in ALT or AST from baseline to a worsening CTCAE grade occurred in 74.8% and 70.6% of patients, respectively. A shift to CTCAE Grade 3 or greater ALT or AST was observed in 13.3% and 2.8% of BRCA mutant ovarian cancer patients, respectively. The ALT/AST elevations occurred early in treatment.

One patient with relapsed ovarian cancer of the 409 patients was observed to have ALT/AST > 3 × ULN and bilirubin levels > 2 × ULN without evidence of cholestasis after 2 weeks of treatment with rucaparib. The role of rucaparib in the hepatic toxicity cannot be excluded. No Hy's Law cases have been recorded.

In BRCA mutant ovarian cancer patients, an increase in serum creatinine from baseline to a worsening CTCAE grade occurred in 88.1% of patients (64.3% to Grade 1, 23.1% to Grade 2, and 0.7% to Grade 4; no patient had a shift to Grade 3). The elevations were thus frequent and observed early in treatment. Serum creatinine levels decreased with interruption or discontinuation of rucaparib, and increase again with resumption of treatment. The clinical significance of creatinine increases is unknown for the applicant as for the time being no clinical sequalae have been observed.

Increase to CTCAE Grade ≥ 3 total cholesterol occurred in 2.2%, 2.4%, and 4.2% of all patients, all ovarian cancer patients, and BRCA mutant ovarian cancer patients, respectively. The Grade 3 events observed were successfully managed by treatment modification and/or concomitant treatment. The clinical significance of cholesterol increases is unknown.

There was a higher frequency of anaemia, neutropenia and elevated ALT/AST in the BRCA mutant population; the haematology abnormalities were apparent after adjusting for time on treatment. However, this increase in the BRCA mutant OC population was not evident when the laboratory results rather than TEAEs were compared.

Safety population which included 175 patients with a BRCA mutation and 234 patients without BRCA mutation:

Slight increases were observed in the incidence of some TEAEs in the gBRCA patient subpopulation. Although these differences are likely due to the longer duration of treatment, the median duration of exposure in both sBRCA and gBRCA were 222.5 days and 237.5 days respectively, which is considered similar. The time-adjusted event frequencies are generally higher in gBRCA patients compared with the s-BRCA group, nevertheless, it is agreed that the very limited number of patients with sBRCA mutations (n = 28) prevents from drawing firm conclusions.

An apparent increase was observed in some laboratory measurements. ALT/AST, thrombocytopenia, and anaemia were greater in the gBRCA versus the sBRCA and non-BRCA subgroups. The applicant argues that these differences were minimal when using the more objective measurement of relevant supporting laboratory parameters which is supported.

Elevated transaminases were an early event, occurring within Cycle 1. Haematological abnormalities tended to manifest later (Cycle 3 and beyond). Other common laboratory abnormalities included increased creatinine and increased cholesterol, the former attributed to transporter inhibition, the latter of uncertain aetiology.

Prolongation of QT and cardiac toxicity: One patient with a history of previous episodes of prolonged QTc and a provisional diagnosis of a congenital prolonged QT syndrome made before study entry experienced Grade 4 ventricular tachyarrhythmia approximately 3 weeks after initiating rucaparib.

Risk of QT prolongation cannot be ruled out since at 600 mg BID, the recommended dose, the mean values for change of QTcF in Cycle 1 ranged from 5.0 to 14.0 msec, which is higher than 5 ms established in the Guidance E14 for evaluation of QT/QTc. 5 cases of cardiac or related events potentially associated with QT prolongation (1 patient with SAE of grade 4 arrhythmia, 2 patients with SAE of cardiac arrest, and 2 patients with SAE of syncope) were identified in patients (n = 1077) that have been exposed to oral rucaparib in Clovis-sponsored studies as of 10 April 2017. No ECG information was available for the 4 patients with cardiac arrest or syncope. Information about QT prolongation is included in section 5.1. of the SmPC and additionally QTc prolongation is listed as an important potential risk in the RMP.

Skin toxicity associated with rucaparib (i.e. photosensitivity) is a concern. A total of 43 patients (10.5%) in the overall safety population and 15 patients (10.5%) with BRCA mutant ovarian cancer experienced photosensitivity. None of the events of photosensitivity was of Grade 3 or higher severity.

Information on photosensitivity has been included in section 4.4 of SmPC. *The effect of rucaparib on* Photosensitivity *is considered as* an important potential risk *in the RMP.*

No direct causal relationship can be established between rucaparib treatment and the risk of secondary cancer as a result of long-term DNA-repair inhibition. Given this risk, however, the effect of rucaparib on New Primary Malignancy is considered as an important potential risk in the RMP.

Hepatic and renal impairment: The safety and effectiveness of rucaparib has not been evaluated in patients with moderate or severe hepatic and severe renal impairment and a PK study specifically in patients with hepatic and renal impairment has not been conducted. This has been reflected in the SmPC and RMP. No dose adjustment to the recommended starting dose is required for patients with mild hepatic impairment and mild or moderate renal impairment.

CTCAE ≥grade 3 events, SAEs and adverse events leading to dose interruptions and/or reductions were reported more frequently in patients with mild or moderate renal compared with normal renal function. Rucaparib should not be used in patients with moderate or severe renal impairment because the safety profile of rucaparib has not been evaluated in those patients.

Paediatric patients (< 18 years old) were not included in clinical studies with rucaparib. Therefore, the safety of rucaparib in paediatric patients has not been established, nor has it been considered appropriate to conduct nonclinical studies specifically in juvenile animals.

Age: No dose adjustment to the recommended starting dose is required for elderly patients (≥ 65 years of age) in the SmPC.

Although there is limited clinical data in patients over 75 years, it is considered that there is an indication of higher frequency of several TEAE patients who are ≥65 years of age (Sections 4.2).

2.6.2. Conclusions on the clinical safety

Relevant information is currently presented in the SmPC. Warnings and precautions sections cover the most relevant information regarding haematological toxicity, AML/MDS, photosensitivity and GI toxicity.

Additional studies are expected to provide further information regarding effects of rucaparib on QT interval, as for the time being the risk of QT prolongation cannot be ruled out, and in patients with hepatic impairment (see RMP).

The safety has been considered sufficiently characterised in the context of a conditional MA. Additional data from confirmatory studies will be provided in support of the overall safety profile of rucaparib.

2.7. Risk Management Plan

Safety concerns

Summary of the safety concerns

Safety Concerns
Important Identified Risks
1. Myelosuppression
2. Nausea and vomiting
Important Potential Risks
3. MDS/AML
4. New primary malignancy
5. QTc interval prolongation
6. Photosensitivity
7. Embryotoxicity and teratogenicity
8. Drug-drug interactions with substrates of CYP1A2, CYP2C9, CYP3A, MATE1, MATE2-K, OCT1, OCT2, and BCRP
Missing Information
9. Use in patients for longer than 18 months
10. Effects of rucaparib on fertility
11. The effect on an infant of a nursing mother receiving rucaparib
12. Safety in patients with severe renal impairment
13. Safety in patients with moderate or severe hepatic impairment
14. Characterisation of metabolites of rucaparib
15. Drug-drug interaction with oral contraceptives
16. Efficacy and safety of rucaparib in patients previously treated with olaparib or another PARP inhibitor

Pharmacovigilance plan

Table 39. Ongoing and Planned Additional Pharmacovigilance Studies/Activities in the Pharmacovigilance Plan

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
CO-338-043 (ARIEL4): A Phase 3	Primary: To compare the anti-tumour	Myelosuppression Nausea and	Enrolment ongoing	Final report: 2Q 2023

Multicentre, Randomised Study of Rucaparib versus Chemotherapy in Patients with Relapsed, BRCA-mutant, High-Grade Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer Category 2	efficacy, as measured by investigator assessment of the PFS, of oral single-agent rucaparib, versus chemotherapy in patients with BRCA-mutant relapsed, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer. Secondary: To evaluate the safety and tolerability of rucaparib versus cytotoxic chemotherapy in patients with relapsed high-grade serous or endometrioid tBRCA-mutant epithelial ovarian, fallopian tube, or primary peritoneal cancer.	vomiting MDS/AML New primary malignancy QTc interval prolongation Photosensitivity Use in patients for longer than 18 months		
Study CO-338-078 Category 3	A Phase 1, Open-Label, Parallel Group Study to Determine the Pharmacokinetics, Safety and Tolerability of Rucaparib in Patients with an Advanced Solid Tumour and Either Moderate Hepatic Impairment or Normal Hepatic Function	Effect of moderate hepatic impairment on rucaparib PK	Planned	Final report (Part I): 3Q 2019
In vivo DDI study with	A phase 1, open label, DDI study to	Drug-drug interactions with	Planned	Final protocol:

contraceptives Category 3	determine the effect of rucaparib on the pharmacokinetics of oral contraceptives in female patients with advanced solid tumours	oral contraceptives		3Q 2108
In vivo DDI study with BCRP substrate Category 3	A phase 1, open label, DDI study to determine the effect of rucaparib on the PK of rosuvastatin in patients with advanced solid tumours	Drug-drug interactions with substrates of CYP1A2, CYP2C9, CYP3A, MATE1, MATE2-K, OCT1, OCT2, and BCRP	Planned	Final protocol: 3Q 2018

Risk minimisation measures

Summary of the risk minimisation measures

Safety Concern	Proposed Routine Risk Minimisation Measures	Proposed Additional Risk Minimisation Measures
Important Identified Risks		
Myelosuppression	SmPC and PIL	None
Nausea and vomiting	SmPC and PIL	None
Important Potential Risks		
MDS/AML	SmPC and PIL	None
New primary malignancy	None	None
QTc interval prolongation	None	None
Photosensitivity	SmPC and PIL	None
Embryotoxicity and teratogenicity	SmPC and PIL	None
Drug Drug Interaction with substrates of CYP1A2, CYP2C9, CYP3A, MATE1, MATE2-K, OCT1, OCT2, and BCRP	SmPC and PIL	None
Missing Information		
Use in patients longer than 18 months	SmPC	None
Effect of rucaparib on fertility	SmPC	None
The effect on an infant of nursing mother receiving rucaparib	SmPC and PIL	None
Safety in patients with severe renal impairment	SmPC	None
Safety in patients with moderate or severe hepatic impairment	SmPC	None

Safety Concern	Proposed Routine Risk Minimisation Measures	Proposed Additional Risk Minimisation Measures
Important Identified Risks		
Characterisation of metabolites of rucaparib	None	None
Drug Drug Interaction with oral contraceptives	SmPC	None
Efficacy and safety of rucaparib in patients previously treated with olaparib or another PARP inhibitor	SmPC	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.4, dated 20 March 2018, is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

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

Periodic Safety Update Reports submission requirements

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

2.9. New Active Substance

The applicant compared the structure of rucaparib with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers rucaparib to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

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

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Rubraca (rucaparib) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, that was not contained in any medicinal product authorised in the EU and it is also approved as a conditional marketing authorisation [REG Art 14(7)].

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

The revised applied indication for Rubraca is as monotherapy treatment of adult patients with platinum sensitive, relapsed or progressive, BRCA mutated (germline and/or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with two or more prior lines of platinum based chemotherapy, and who are unable to tolerate further platinum based chemotherapy.

3.1.1. Disease or condition

Ovarian cancer is the second most common gynecologic malignancy worldwide and the leading cause of death attributed to gynecological cancer. After initial therapy, most women will have a PFI following their frontline platinum regimen of approximately 1.5 to 2 years, depending on the extent of post-operative residual disease and response to chemotherapy. Relapse still occurs, however, in the majority of cases, and only 10% to 30% of women experience long-term survival. Advanced stage disease is associated with a 5-year survival rate of only 30% to 40%.

3.1.2. Available therapies and unmet medical need

Patients with platinum-sensitive disease are typically retreated with platinum-based therapy until they no longer respond to or can no longer tolerate such treatment. If they cannot tolerate platinum due to toxicity or hypersensitivity then trabectedin with liposomal doxorubicin is an approved available option associated with high activity.

Clinical efficacy data come from a pooled analysis of patients enrolled in two uncontrolled Phase 2 open-label studies. The primary efficacy population comprises 106 ovarian cancer patients harboring a deleterious BRCA mutation who received 2 or more prior regimens of chemotherapy. The platinum-sensitive population was 79 patients.

3.2. Favourable effects

The investigator-assessed RECIST ORR in platinum-sensitive patients was 64.6% (n=51) [95% CI, 53.0%-75.0%, N = 79], 35.0% [95% CI, 15.4%-59.2%, N = 20]. The proportion of patients with complete

response was 10.1%. Median DOR was 294 days (224-393 days) (9.7 months) and median PFS was of 332 days (10.9 months). Median overall survival was not reached. The ORR was 65.2% and 61.5% for gBRCA and sBRCA respectively.

The activity shown in terms of ORR and DOR is considered high and convincing enough to rule out a significant detriment compared to trabectedin+pegylated liposomal doxorubicin (PLD) (this is expected to be confirmed post-approval from ARIEL4). The high ORR associated with rucaparib in a more extensively pre-treated population compared to T+PLD historical control indicates a potential advantage for some patients (see further discussion in 3.7.3).

3.3. Uncertainties and limitations about favourable effects

There is no clinical evidence of the potential benefit of retreating patients with PARPi. No patient in rucaparib clinical trials had received previous treatment with a PARPi that had demonstrated clinical activity up to date. This is reflected in the SmPC.

Although the durable response in a high proportion of patients is considered a benefit, and the data observed for time-related endpoints are reassuring that the efficacy is adequate compared to available treatment options, there is a need to further quantify the efficacy of Rubraca in the therapeutic context of the approved indication in terms of time-related outcomes in a comparative trial (Annex II).

3.4. Unfavourable effects

The most common AEs with rucaparib (occurring in >20%) were: nausea, fatigue/asthenia, vomiting, anaemia and/or low/decreased haemoglobin, ALT/AST increased, constipation, decreased appetite and dysgeusia. The most frequent AEs with rucaparib are in accordance with the AEs observed for other PARP inhibitors. The AEs have been frequently reported with higher rates in patients with BRCA mutant ovarian cancer compared to patients with other tumours.

In general, the safety profile of rucaparib in the ovarian cancer patients with a BRCA mutation includes adverse events in the MedDRA SOCs Gastrointestinal Disorders, haematotoxicity, General Disorders and Administration Site Conditions, Investigations and Nervous System Disorders. The most common TEAEs, irrespective of relationship to rucaparib, were combined fatigue/asthenia, nausea, combined anaemia/decreased haemoglobin, vomiting, combined ALT/AST increased, constipation, and dysgeusia, and were generally consistent with those observed within the total ovarian cancer population and the overall safety population.

The most common Grade ≥ 3 TEAE by PT were combined terms of anaemia and/or low/decreased haemoglobin, combined terms of asthenia/fatigue, combined terms of ALT/AST increased, combined terms of neutropenia and/or low/decreased, malignant neoplasm progression, and vomiting.

In ovarian cancer patients with a BRCA mutation, the most frequently reported treatment-related TEAEs that led to rucaparib dose reduction or treatment interruption were combined terms of anaemia and/or low/decreased haemoglobin, combined terms of asthenia/fatigue, nausea, combined terms of thrombocytopenia/decreased platelets, combined terms of neutropenia/decreased ANC, combined terms of ALT/AST increased, and vomiting.

3.5. Uncertainties and limitations about unfavourable effects

Risk of QT prolongation cannot be ruled out (see SmPC). Future studies are expected to provide additional information (see RMP).

The safety of rucaparib has not been evaluated in patients with moderate or severe hepatic impairment and severe renal impairment (see SmPC). Studies are expected to provide additional information regarding effects of rucaparib on hepatic impairment. Additional data from future studies will be provided in support of this (see RMP).

3.6. Effects Table

Table 40. Effects Table for Rubraca in OC after at least two previous treatments (data cut-off: 10 April 2017).

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence
ORR	Proportion of patients with a confirmed CR or PR on subsequent tumour assessment	%	64.6	N/A	Pooled data from two studies including BRCA positive patients with at least two prior chemo regimens - population heterogeneity Lack of comparator Low sample size of some subgroups analysed.
DoR	Duration of response in patients with a RECIST Version 1.1 CR or PR as determined by investigator assessment	Days	294		
PFS	Progression free survival	Median (days)	332		
Treatment-related TEAE	Treatment-related TEAE	%	97.9	N/A	
Treatment-related serious TEAE		%	9.1	N/A	
Treatment-related Grade ≥ 3 TEAE		%	50.3	N/A	
Treatment-related TEAE with an outcome of death		%	0.7	N/A	
Nausea		%	79.7	N/A	
Fatigue		%	65.0	N/A	
Vomiting		%	55.7	N/A	
Malignant neoplasm progression	Grade ≥3	%	9.1	N/A	

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence
Anaemia	Treatment-related TEAE Grade ≥3	%	28.7	N/A	
ALT increased		%	11.2	N/A	
Neutropenia		%	7.0	N/A	

Abbreviations: ALT (alanine aminotransferase), AST (aspartate aminotransferase), DoR (duration of response), PFS (progression free survival), ORR (overall response rate) OS (overall survival) TEAE (treatment-emergent adverse event).

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The most up-to-date results confirm that the overall outcomes are mainly dominated by the platinum-sensitive subgroup.

In a population with platinum-sensitive ovarian cancer previously treated with at least two therapies, a durable response rate of almost 65% is considered clinically meaningful. Considering that barely 30% of women in this population experience long term survival, the available efficacy results seem promising.

Efficacy has been established on the basis of durable ORR. The magnitude of this effect is such that it can be assumed that this will result in a favourable effect on long-term outcomes such as PFS and OS. Although the durable response in a high proportion of patients is considered a benefit, and the data observed for time-related endpoints are reassuring that the efficacy is adequate compared to available treatment options, there is a need to further quantify the efficacy of Rubraca in the therapeutic context of the approved indication in terms of time-related outcomes in a comparative trial.

Although more frequent, other AEs, like anaemia, vomiting, nausea are generally of low grade and could be manageable with specific therapy.

The safety profile of rucaparib monotherapy appears sufficiently characterised. Additional data from future studies are expected to be provided in support of the overall safety.

3.7.2. Balance of benefits and risks

A durable ORR of 53%-65% along with PFS results in the **platinum-sensitive** setting could be considered of compelling clinical relevance in light of current alternatives and this could serve as basis for a CMA taking into account the recognised unmet medical need in a population unable to tolerate further platinum. The efficacy results in this population as compared to the sufficiently characterised safety profile support a positive benefit-risk balance.

3.7.3. Additional considerations on the benefit-risk balance

As comprehensive data on the product are not available, a conditional marketing authorisation was requested by the applicant in the initial submission.

Rubraca is intended to treat patients with advanced ovarian cancer who have been treated with two or more prior lines of platinum-based chemotherapy. Advanced stage disease is associated with a 5-year survival rate of only 30% to 40%, which along with the fact that these patients have received at least two or more prior lines of platinum-based chemotherapy, pose a dismal prognosis to these patients. Therefore, the product is considered to belong within the category of "aimed at treating, preventing or diagnosing seriously debilitating or life-threatening diseases".

The initial applied indication was restricted to the platinum-sensitive population where there are limited efficacious and tolerable treatment options.

Conditional marketing authorisations may be granted if the CHMP finds that all the following requirements are met:

1. the benefit-risk balance of the product is positive;

The results in the platinum-sensitive population and comparative literature review support a positive benefit-risk balance.

2. It is likely that the applicant will be able to provide comprehensive data;

Efficacy has been established on the basis of durable ORR. The magnitude of this effect is such that it can be assumed that this will result in a favourable effect on long-term outcomes such as PFS and OS. Although the durable response in a high proportion of patients is considered a benefit, and the data observed for time-related endpoints are reassuring that the efficacy is adequate compared to available treatment options, there is a need to further quantify the efficacy of Rubraca in the therapeutic context of the approved indication in terms of time-related outcomes in a comparative trial. The ARIEL4 study (confirmatory trial, study CO-338-043), is a Phase 3 multicenter, open-label, randomized study evaluating rucaparib versus chemotherapy for treatment of relapsed BRCA-mutant ovarian cancer. The study is being conducted in the US, Europe, and other regions and planned to enrol approximately 345 patients. Patient randomisation is 2:1 to receive rucaparib or chemotherapy, therefore approximately 230 patients were expected to be treated with rucaparib.

The CO-338-043 study design was revised based on CHMP feedback; specifically, to expand the treatment options for platinum-sensitive patients. Patients with platinum-resistant (patients who progressed ≥ 1 to < 6 months after the last dose of platinum-based chemotherapy) or partially platinum-sensitive (patients who progressed ≥ 6 to < 12 months after last dose of platinum-based chemotherapy) disease will be randomized 2:1 to receive rucaparib or weekly Paclitaxel. Patients with platinum-sensitive disease (patients who progressed ≥ 12 months after last dose of platinum-based chemotherapy) will be randomized 2:1 to receive rucaparib or platinum-based chemotherapy.

Full operational evaluation of the conduct of Study CO-338-043 has been assessed and the study was deemed to be feasible and fully enrolled by 2020.

The Applicant was recommended to amend the Study CO-338-043 protocol to ensure that at least 270 partially platinum-sensitive patients are enrolled for confirmation of the EU proposed indication. As a result, study completion date is revised to be expected in Q2 2023.

Based on the above, the CHMP considered that ARIEL4 is likely to provide comprehensive data suitable to confirm the positive benefit-risk balance of Rubraca.

3. Unmet medical needs will be fulfilled;

The proposed restricted population unable to tolerate further platinum therapy has limited efficacious treatment options, with more toxicity than PARPi. The only approved regimen considered to be associated with high activity is the combination of trabectedin+liposomal doxorubicin (PLD). However, this regimen is also associated with considerable toxicity and with certain complexities to its administration (use of central catheter, specific criteria required for treatment initiation, weekly monitoring of haematological parameters).

If taking into account that rucaparib was studied in a later line setting it seems likely that even in a worst-case scenario, rucaparib efficacy findings could be comparable to those of trabectedin+PLD.

From a safety point of view, rucaparib seems to offer a different safety profile than trabectedin+PLD, with important reductions in haematologic AEs and other relevant side effects. More specifically, the adverse reactions CTCAE Grade 3 or higher for anaemia, neutropenia and thrombocytopenia were 23%, 9% and 5% for rucaparib, as compared to 19%, 72% and 23% for the T+PLD respectively (see SmPCs).

Rucaparib, as an orally administered drug, may also improve patient´s convenience compared to intravenous administered alternatives, with no risk of infusion reactions.

It is acknowledged that there is an unmet need for more active and tolerable treatments capable of prolonging the life expectancy of patients with platinum-sensitive ovarian cancer, previously treated with at least two lines of platinum chemotherapy, who are unable to tolerate further platinum. This population has limited treatment options. Despite the availability of treatment options with possibly comparable efficacy, there remains an unmet medical need for these patients and the safety profile with lower frequencies of some important AEs, together with improvements such as ambulatory treatment, constitute a major therapeutic advantage.

In conclusion, it is considered that that Rubraca introduces a major therapeutic advantage over authorised products.

4. The benefit to public health of the medicinal product's immediate availability on the market outweighs the risks due to need for further data.

Finally, regarding the possibility that the benefit of the medicinal product's immediate availability on the market outweighs the risks due to need for further data, it can be concluded that the available data support a positive B/R for this population, and there are no PARPi currently authorised in BRCA mutant patients for the proposed indication. Thus, the benefit to public health of the medicinal product's immediate availability on the market outweighs the risks, which are considered low, due to need for further data.

3.8. Conclusions

The overall B/R of Rubraca is positive.

Divergent positions are appended to this report.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Rubraca is not similar to Yondelis and Zejula within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the risk-benefit balance of Rubraca is favourable in the following indication:

Rubraca is indicated as monotherapy treatment of adult patients with platinum sensitive, relapsed or progressive, BRCA mutated (germline and/or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with two or more prior lines of platinum based chemotherapy, and who are unable to tolerate further platinum based chemotherapy.

The CHMP therefore recommends the granting of a conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription. (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to further confirm the safety and efficacy of rucaparib in the treatment of platinum sensitive, relapsed or progressive, BRCA mutated (germline and/ or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, the MAH should submit the results of study CO-338-043 (ARIEL4), a phase 3, multicentre, open-label, randomised study evaluating the efficacy and safety of rucaparib versus chemotherapy for treatment of relapsed ovarian cancer.	Due date: Q2 2023

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

These conditions fully reflect the advice received from the PRAC.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that rucaparib is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

APPENDIX

DIVERGENT POSITION DATED 22.03.2018

DIVERGENT POSITION DATED 22.03.2018

Rubraca EMEA/H/C/004272

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation of Rubraca indicated as monotherapy treatment of adult patients with platinum sensitive, relapsed or progressive, BRCA mutated (germline and/or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with two or more prior lines of platinum based chemotherapy, and who are unable to tolerate further platinum based chemotherapy.

The reason for divergent opinion was the following:

Divergent opinion Rubraca:

It is the opinion of the undersigned members:

Based on the currently available data we consider the benefit-risk balance for rucaparib in the proposed restricted indication to remain undetermined. Major uncertainties exist regarding the quality of the data, as the current pivotal results for the rucaparib application are derived from a post-hoc analysis from pooled data from two single arm trials involving only 106 patients.

Also replication of the results was not provided. In the absence of a head-to-head comparison to standard of care, there are large uncertainties on the robustness and validity of the results.

As a consequence, the current results cannot be contextualised and any reliable estimation of effect size is prevented.

Although the activity of the drug in terms of response rate is noted, the assumed better toxicity profile as compared to standard of care does not outweigh the major uncertainties regarding efficacy.

In conclusion, we cannot conclude on a positive relative B/R and until more is known, the application is considered not approvable.

Alar Irs _____

Bruno Sepodes _____

Johann Lodewijk Hillege_____