13 December 2018
EMA/902679/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Rubraca

International non-proprietary name: rucaparib

Procedure No. EMEA/H/C/004272/II/0001

Note

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

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List of abbreviations

ADP	adenosine diphosphate
ADR(s)	adverse drug reaction(s)
AE(s)	adverse event(s)
AESI(s)	adverse event(s) of special interest
ALT	alanine aminotransferase
AME	absorption, metabolism, and excretion
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC_{ss}	area under the concentration-time curve at steady-state
AUCavg,ss*	averaged steady-state area under the concentration-time curve
BCRP	breast cancer resistance protein
BID	twice a day
BRCA	breast cancer gene
BRCA1	breast cancer gene 1
BRCA2	breast cancer gene 2
CA-125	cancer antigen-125
Caco	human colon carcinoma cell line
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL	clearance
CLcr	creatinine clearance
CMA	Conditional Marketing Authorization
C_{max}	maximum plasma drug concentration
C_{min}	minimum plasma drug concentration
CNS	central nervous system
CR	complete response
CSR	clinical study report
CTA	clinical trial assay
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DAT	dopamine transporter
DDI	drug-drug interaction
DNA	deoxyribonucleic acid
DSB(s)	double-strand break(s)
EC	European Commission
ECG	electrocardiogram

ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EOC	epithelial ovarian cancer
ER	exposure-response
ESMO	European Society for Medical Oncology
EU	European Union
F1	bioavailability
FDA	Food and Drug Administration
FIGO	International Federation of Gynecology and Obstetrics
FMI	Foundation Medicine, Incorporated
FTC	fallopian tube cancer
gBRCA	germline mutation in BRCA (BRCA1 and BRCA2)
GCP	Good Clinical Practice
HPLC	high-performance liquid chromatography
hr	hour
HR	hazard ratio
HRD	homologous recombination deficiency
HRR	homologous recombination repair
ICH	International Conference on Harmonisation
IC50	half maximal inhibitory concentration
INN	International Nonproprietary Name
invPFS	investigator-assessed progression-free survival
IRR	independent radiological review
irrPFS	independent radiology review of progression-free survival
ITT	intent-to-treat
IPSS-R	Revised International Prognostic Scoring System
ISS	Integrated Summary of Safety
LOH	loss of heterozygosity
MAA	Marketing Authorization Application
MDCK	Madin-Darby canine kidney
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MRP	multidrug resistance associated protein
NA	not assessable
NCI	National Cancer Institute
NCI-ODWG	National Cancer Institute-Organ Dysfunction Working Group
NDA	New Drug Application
NE	not evaluable
NET	norepinephrine transporter

NGS	next-generation sequencing
ORR	overall response rate
OS	overall survival
P-gp	P-glycoprotein
PA	protocol assistance
PARP	poly (ADP-ribose) polymerase
PD	progressive disease
PFI	progression-free interval
PFS	progression-free survival
PK	pharmacokinetic(s)
PPC	primary peritoneal cancer
PPK	population pharmacokinetics
PR	partial response
PT	Preferred Term
QTc	heart rate corrected QT interval
QTcF QT	interval corrected using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
SA	scientific advice
SAE(s)	serious adverse event(s)
sBRCA	somatic mutation in BRCA (BRCA1 or BRCA2)
SD	stable disease
SERT	serotonin transporter
SmPC	Summary of Product Characteristics
sNDA	supplemental New Drug Application
SOC	System Organ Class
SSB(s)	single-strand break(s)
T2V	Type II Variation
tBRCA	tumor tissue mutation in BRCA1 or BRCA2, includes gBRCA and sBRCA
t-MN	therapy-related myeloid neoplasms
TEAE(s)	treatment-emergent adverse event(s)
ULN	upper limit of normal
VEGF	vascular endothelial growth factor

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Clovis Oncology UK Limited submitted to the European Medicines Agency on 1 June 2018 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include new indication for Rubraca "Rubraca is indicated as monotherapy for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy". As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated with the expanded clinical efficacy and safety data. The Package Leaflet is also updated in accordance.
The updated RMP version 2.0 has also been submitted.
In addition, the applicant took the opportunity to propose the move of one paragraph from section 4.4 to 5.1 in the SmPC for consistency with other SmPC agents in this class with this indication.

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

Rubraca was designated as an orphan medicinal product EU/3/12/1049 on 10 October 2012 for the treatment of ovarian cancer.

Following the CHMP positive opinion on the change to the terms of this marketing authorisation and at the time of the review of the orphan designation by the Committee for Orphan Medicinal Products (COMP), this product was withdrawn from the Community Register of designated orphan medicinal products on 27 November 2018 on request of the sponsor. The relevant Withdrawal assessment report – Orphan maintenance can be found under the 'Assessment history' tab on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/rubraca

Information on paediatric requirements

Pursuant to Article 8 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 application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Protocol assistance

The applicant sought Scientific Advice (SA) from CHMP in 2012 (EMEA/H/SA/2392/1/2012/SME/III); follow-up Protocol Assistance (PA) (following the orphan designation) was sought in 2015 (EMEA/H/SA/2392/2/2015/PA/SME/I and EMEA/H/SA/2392/2/2015/PA/SME/I). The initial rounds of advice focused upon the nonclinical development program, and on the design of Study CO-338-014, the subject of this application. The final round of follow-up advice, received in February 2016, focused on the overall regulatory submission strategy for the recently approved treatment indication.

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

Timetable	Actual dates
Submission date	1 June 2018
Start of procedure:	23 June 2018
CHMP Rapporteur Assessment Report	30 August 2018
CHMP Co-Rapporteur Assessment Report	17 August 2018
PRAC Rapporteur Assessment Report	23 August 2018
PRAC Outcome	6 September 2018
CHMP members comments	10 September 2018
Updated CHMP Rapporteur(s) (Joint) Assessment Report	14 September 2018
Request for supplementary information (RSI)	20 September 2018
CHMP Rapporteur Assessment Report	21 November 2018
PRAC Rapporteur Assessment Report	21 November 2018
PRAC members comments	21 November 2018
Updated PRAC Rapporteur Assessment Report	22 November 2018
PRAC Outcome	29 November 2018
CHMP members comments	03 December 2018
Updated CHMP Rapporteur Assessment Report	05 December 2018
Opinion	13 December 2018

2. Scientific discussion

2.1. Introduction

Disease or condition

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

Epidemiology

Ovarian cancer (EOC, FTC, and PPC) is the second most common gynaecologic malignancy worldwide and the leading cause of death attributed to gynaecological cancer. It was estimated that there will be 184,799 ovarian cancer deaths and 295,414 newly diagnosed ovarian cancer worldwide in 2018[1]. A total of 75% of patients present with advanced disease (Stage III or IV)[2].

Biologic features

Most (~90%) ovarian tumours are surface epithelial in origin and of the papillary serous histology subtype (~75%), of which 70% are high grade[3]. The site of origin of EOC remains unclear; serous EOC and PPC may arise from the fallopian tube epithelium[4,5]; or within stem cells of the ovarian surface epithelium[3,6]. FTC is a rare gynaecological tumour accounting for 0.14% to 1.8%[7] of all female genital tract cancers. FTC originates in 1 or both fallopian tubes; most (>90%) tumours are serous adenocarcinomas, histologically indistinguishable from papillary serous ovarian carcinoma. FTC is thus defined morphologically by the invasion of the peritoneal surfaces with minimal or no involvement of the ovaries[8]. PPC is a rare neoplasm, thought to account for 10% of ovarian malignancies[9]. PPC originates from the cells of the peritoneal cavity, with a diagnosis based on minimal or non-involvement of the ovaries.

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.

The median age at presentation for the 3 types of cancer (EOC, PPC, and FTC) is 55 to 60 years[10,11]. Many women with EOC and PPC present with advanced disease and therefore have a poor prognosis. Although FTC may be diagnosed at earlier stages, the prognosis for patients with FTC is also poor.

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. Relapse still occurs, however, in the majority of cases, and only 10% to 30% of women experience long-term survival[3]. The 5-year survival rate for ovarian cancer is 46%[12]; however, rates are lower in advanced stage disease or disease with poor prognosis and ranges from 0% to 40% for the different subtypes of ovarian cancer[10,13].

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Management

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

Recurrent disease is classified as platinum resistant or platinum sensitive, depending on whether the disease recurred less than or greater than 6 months following previous platinum therapy, and this classification is highly prognostic and is important in determining optimal chemotherapeutic treatment options. Three subgroups of patients with relapsed ovarian cancer have been identified: patients with platinum-refractory disease who progress during platinum treatment; patients with platinum-resistant disease who develop recurrence <6 months from the completion of platinum chemotherapy; patients with platinum-sensitive disease: partially platinum-sensitive and platinum-sensitive recurrence are currently considered as separate sub-groups and are respectively defined by a relapse-free period of 6 to 12 months and >12 months following a response to the final dose of prior platinum treatment[14].

Maintenance therapy following a response to standard treatment provides an opportunity to extend the progression-free period. Options for maintenance following response to standard treatment include continuation of the initial combination chemotherapy regimen, continuation of only a single agent chemotherapy or introducing a new agent.

The vascular endothelial growth factor (VEGF) inhibitor, bevacizumab, is approved in the European Union in EOC, FTC, or PPC in the maintenance setting in combination with carboplatin and gemcitabine for treatment of first recurrence of platinum-sensitive EOC, FTC, or PPC.

More recently, two other PARP inhibitors, olaparib and niraparib, have been approved as monotherapy in the EU for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade EOC, FTC, or PPC who are in response (complete response [CR] or partial response [PR]) to platinum-based chemotherapy. An update to the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for diagnosis, treatment, and follow-up of newly diagnosed and relapsed EOC released in September 2016 included the recommendation that patients with recurrent high grade serous ovarian cancer and a germline or tumor BRCA mutation be offered maintenance olaparib after a response to platinum-based chemotherapy. The MAA for olaparib was approved on 18 December 2014 and the MAA for niraparib) was approved on 16 November 2017.

About the product

Rucaparib is an oral small molecule inhibitor of poly-adenosine diphosphate (ADP) ribose polymerase (PARP) enzymes, including PARP-1, PARP-2, and PARP-3. Rucaparib camsylate is the International Nonproprietary Name (INN) for the active moiety. Rucaparib is administered orally at a dose of 600 mg twice a day (BID) and is available in 200 mg, 250 mg, and 300 mg tablet strengths.

The European Commission granted a Conditional Marketing Authorization (CMA) for oral rucaparib as monotherapy treatment of adult patients with platinum sensitive, relapsed or progressive, breast cancer gene (BRCA) mutated (germline and/or somatic), high-grade epithelial ovarian (EOC), fallopian tube (FTC), or primary peritoneal cancer (PPC), who have been treated with two or more prior lines of platinum-based chemotherapy, and who are unable to tolerate further platinum based chemotherapy in May 2018.

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The scope of this variation is the extension of indication of Rucaparib as monotherapy for the maintenance treatment of adult patients with relapsed EOC, FTC, or PPC who are in a complete or partial response to platinum-based chemotherapy.

The MAH applied for the following indication:

"Rubraca is indicated as monotherapy for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy."

The recommended indication is the following:

Rubraca is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy (see SmPC section 4.1).

There is no requirement for BRCA testing prior to using Rubraca for the maintenance treatment of adult patients with relapsed high-grade epithelial ovarian cancer (EOC), fallopian tube cancer (FTC), or primary peritoneal cancer (PPC) who are in a complete or partial response to platinum-based chemotherapy.

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

For the maintenance treatment, patients should start treatment with Rubraca no later than 8 weeks after completion of their final dose of the platinum containing regimen (see SmPC section 4.2).

2.2. Non-clinical aspects

The Applicant submitted an updated ERA for Rucaparib.

No other new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity / environmental risk assessment

Table 1: 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 nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$ refined (e.g. prevalence, literature)	62.7	ng/L	> 0.01 ng/L threshold (Y)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**

Adsorption-Desorption	OECD 106				Pending
Ready Biodegradability Test	OECD 301B				Pending
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308				Pending
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC		µg/L	Pending
Daphnia sp. Reproduction Test	OECD 211	NOEC		µg/L	Pending
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC		µg/L	Pending
Activated Sludge, Respiration Inhibition Test	OECD 209	EC		µg/L	Pending
Sediment/Water Chironomid Toxicity	OECD 218				Pending

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 commits to perform the following studies as follow-up measures:

Study Type	Guideline	Status
Adsorption-Desorption (Koc)	OECD 106	• Preliminary study completed • Definitive study initiated May 2018
Ready Biodegradation (modified Sturm)	OECD 301B	• Completed: results pending
Aerobic Transformation in Aquatic Sediments	OECD 308	• Preliminary study completed • Definitive study initiated March 2018
Algal Toxicity	OECD 201	• Preliminary study completed • Definitive study initiated May 2018
Fish, Early Life Stage Test	OECD 210	Fathead Minnow (Pimephales promelas) • Preliminary study completed • Definitive study initiated April 2018
Daphnid Magna Reproduction Test	OECD 211	• Preliminary study completed • Definitive study initiated May 2018
Sludge Respiration Inhibition	OECD 209	• Preliminary study completed • Definitive study initiated May 2018
Sediment/Water Chironomid Toxicity	OECD 218	• Study initiated May 2018 based on preliminary results of OECD 308

2.2.2. Discussion on non-clinical aspects

The MAH provided an updated ERA considering the extended indication for rucaparib. The values for Fpen and PECsw parameters have been recalculated. The updated data related to ERA for rucaparib do not change the previous conclusions reached during the initial marketing authorisation application. In this sense the necessity to perform the Phase II Tier A ERA was confirmed, given that PECsw value was estimated above

the action limit. It should be noted that the new PECsw value should be considered for further estimations, i.e. outcome of Phase II Tier A by correspondent ratio PEC/PNEC.

The updated information does not modify the current SmPC.

2.2.3. Conclusion on the non-clinical aspects

Based on the updated data submitted in this application, the extended indication leads to a significant increase in environmental exposure further to the use of rucaparib. However, these new data do not modify the previous conclusion obtained in the initial assessment, considering that the action limit for PECsw was already exceeded. As a result of the above considerations, the available data do not allow concluding definitively on the potential risk of rucaparib to the environment and the applicant commits to perform the relevant phase II studies as follow-up measures and submit the results as soon as available (see list of studies under section 2.2.1). Pending phase II ERA studies will be completed in Q2 2019.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 2: Overview of the clinical studies contributing to the summary of clinical pharmacology

Study Number and Section	Study Title	Rucaparib Treatments (Route, Schedule, Doses)	Key Clinical Pharmacology Analyses
A4991014 Section 2.7.2.2.2.1	A Parallel Arms, Phase 1 Safety, Pharmacokinetic, and Pharmacodynamic Study of Poly(ADP-ribose)polymerase (PARP) Inhibitor Rucaparib in Combination with Several Chemotherapeutic Regimens in Adult Patients with Advanced Solid Tumors (Study A4991014 CSR [Section 5.3.4.2])	• IV, single, 12-40 mg • Oral, single, 12-360 mg • Oral, QD, 80-360 mg	• Single dose IV PK • Single dose oral PK • Steady state oral PK • PPK
CO-338-010 (Study 10) Section 2.7.2.2.2.2	A Phase 1/2, Open-label, Safety, Pharmacokinetic, and Preliminary Efficacy Study of Oral Rucaparib in Patients with gBRCA Mutation Ovarian Cancer, or Other Solid Tumor (Study CO-338-010 CSR [Section 5.3.4.2])	Phase 1 portion • Oral, single, 40-500 mg • Oral, QD, 40-600 mg • Oral, BID, 240-840 mg Phase 2 portion • Oral, BID, 600 mg	• Single dose oral PK • Steady state oral PK • Trough (C_{min}) PK • PK of different tablet strengths • Food effect • Metabolite profiling • QTc • PPK/ER
CO-338-017 (ARIEL2) Section 2.7.2.2.2.3	A Phase 2, Open-label Study of Rucaparib in Patients with Platinum-sensitive, Relapsed, High-grade Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer (Study CO-338-017 CSR, [Section 5.3.5.2])	• Oral, BID, 600 mg	• Trough (C_{min}) PK • PPK/ER
CO-338-014 (ARIEL3) Section 2.7.2.2.2.4	A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Rucaparib as Switch Maintenance Following Platinum-Based Chemotherapy in Patients with Platinum-Sensitive, High-Grade Serous or Endometrioid Epithelial Ovarian, Primary Peritoneal or Fallopian Tube Cancer (Study CO-338-014 CSR, [Section 5.3.5.1])	• Oral, BID, 600 mg	• Sparse PK[a] • PPK/ER

Study Number and Section	Study Title	Rucaparib Treatments (Route, Schedule, Doses)	Key Clinical Pharmacology Analyses
CO-338-044 Section 2.7.2.2.2.5	A Phase 1, Open-Label, Multiple-Probe Drug-Drug-Interaction Study to Determine the Effect of Rucaparib on Pharmacokinetics of Caffeine, S-Warfarin, Omeprazole, Midazolam, and Digoxin in Patients with Advanced Solid Tumors (Study CO-338-044 CSR [Section 5.3.3.4])	Part I • Oral, BID, 600 mg Part II • Oral, BID, 600 mg (optional)	• DDI
CO-338-045 Section 2.7.2.2.2.6	A Phase 1, Single-Dose Study of the Disposition of [^{14}C]-Radiolabeled Rucaparib in Patients with Advanced Solid Tumors (Study CO-338-045 Protocol [Section 5.3.3.2])	Part I • Oral, single, 600 mg Part II • Oral, BID, 600 mg (optional)	• Mass balance • Metabolite profiling
CO-338-078 Section 2.7.2.2.2.7	A Phase 1, Open-Label, Parallel Group Study to Determine the Pharmacokinetics, Safety and Tolerability of Rucaparib in Patients with an Advanced Solid Tumor and either Moderate Hepatic Impairment or Normal Hepatic Function (Study CO-338-078 Protocol [Section 5.3.3.3])	Part I • Oral, single, 600 mg Part II • Oral, BID, 600 mg (or lower in patients with hepatic impairment)	• Effect of hepatic function on PK of rucaparib and M324

Abbreviations: BID = twice a day;C_{min} = minimum plasma concentration; CSR = clinical study report; ER = exposure-response; gBRCA = germline mutation in brease cancer; IV = intravenous; PK = pharmacokinetic; PPK = population pharmacokinetic; QD = once a day

[a] Sparse PK included C_{min} and postdose concentrations

Note: Studies in the ovarian cancer treatment setting include Studies A4991014, CO-338-010, and CO-338-017. Study CO-338-014 supports ovarian cancer maintenance use. Dedicated clinical pharmacology studies include Studies CO-338-044, CO-338-045, and CO-338-078.

Table 3: Overview of the clinical studies contributing to the summary of clinical efficacy

Type of Study/ Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Patients/ Subjects	Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Reports of Efficacy and Safety Studies								
Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication								
CO-338-014 (ARIEL 3) Phase 3 Ovarian Cancer	Section 5.3.5.1 CO-338-014 CSR	**Primary:** To evaluate PFS by RECIST, as assessed by the investigator. **Secondary:** To evaluate PRO; To evaluate survival benefit; To evaluate PFS by RECIST, as assessed by IRR; To evaluate safety; To determine the population PK of rucaparib	Double-blind, randomized, placebo controlled	CO-338 (rucaparib); All patients received a starting dose of 600 mg oral rucaparib BID in continuous 28-day cycles	564 patients	Patients with relapsed, platinum-sensitive epithelian ovarian, fallopian tube, or primary peritoneal cancer	Patients continue on treatment until protocol-defined criteria for removal from study are met.	Enrollment completed with patients ongoing; Interim CSR with visit data cut-off 15 April 2017.

2.3.2. Pharmacokinetics

Pharmacokinetic interaction studies

In vivo DDI Study (Study CO-338-044)

Study CO-338-044 is a Phase 1, open-label, sequential, cocktail-based DDI study to assess the effect of rucaparib at steady state on the single-dose PK of substrates of CYP1A2, CYP2C9, CYP2C19, CYP3A4, and P-gp in patients with advanced solid tumors. The study consists of 2 parts: a DDI part (Part I) is complete and a rucaparib treatment part (Part II) is ongoing.

The DDI potential of rucaparib as a perpetrator was assessed following 7 consecutive days dosing at 600 mg BID. A total of 17 patients with an advanced solid tumor were enrolled in the study, with 16 patients evaluable for DDI.

Table 4: Effect of Rucaparib on Substrate Probes of CYP Enzymes and P-gp

Target/Probe	GMR (90% CI)			
	N	C_{max}	AUC_{0-last}[a]	AUC_{0-inf}
CYP1A2/Caffeine	16	0.99 (0.90 - 1.08)	2.26 (1.93 - 2.65)	2.55 (2.12 - 3.08)[b]
CYP2C9/S-Warfarin	14[c]	1.05 (0.99 - 1.12)	1.49 (1.40 - 1.58)	—[d]
CYP2C19/Omeprazole	16	1.09 (0.93 - 1.27)	1.55 (1.32 - 1.83)	1.55 (1.32 - 1.83)
CYP3A/Midazolam	16	1.13 (0.95 - 1.36)	1.39 (1.14 - 1.68)	1.38 (1.13 - 1.69)
P-gp/Digoxin	16	0.96 (0.84 - 1.10)	1.20 (1.12 - 1.29)	—[d]

Source: Table 19 in Study CO-338-044 Part I CSR

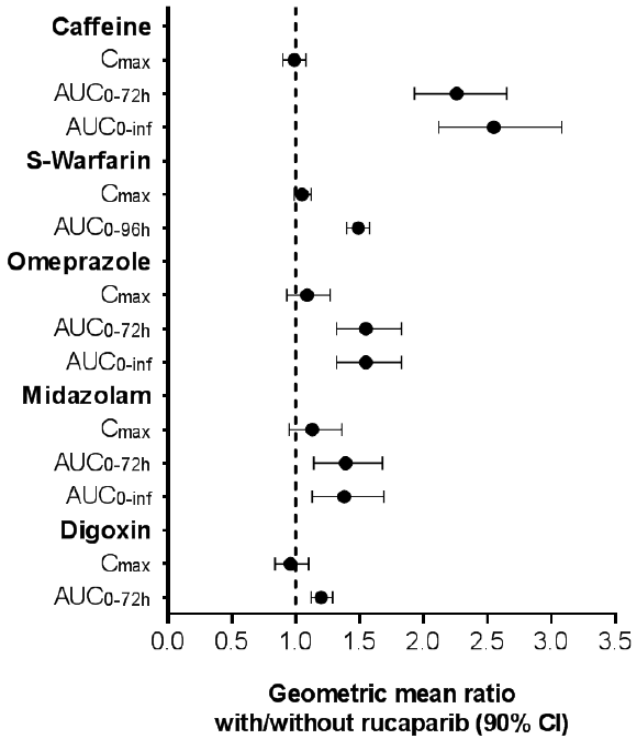
Abbreviations: AUC_{0-last}: area under the concentration-time curve from time 0 to the last quantifiable concentration; AUC_{0-inf} = AUC from time 0 to time infinity; C_{max}: maximum concentration, GMR: geometric mean ratio (with rucaparib/without rucaparib); 90% CI: 90% confidence interval; N: number of subjects

[a] AUC_{0-last} was calculated with concentrations up to 72 hours for caffeine, omeprazole, midazolam, and digoxin, but up to 96 hours for S-warfarin.

[b] N=11 as AUC_{0-inf} could not be precisely estimated for 5 patients.

[c] Two patients who were CYP2C9 poor metabolizers were excluded from the drug-drug interaction evaluation.

[d] AUC_{0-inf} could not be reliably estimated due to long half-lives.



Source: Table 19 in Study CO-338-044 Part 1 CSR

Abbreviations: AUC_{0-t}: area under the concentration-time curve from time 0 to the time t; AUC_{0-inf} = AUC from time 0 to time infinity; C_{max}: maximum concentration

Note: Weak inhibition and moderate inhibition are defined as geometric ratio of ≥ 1.25 to < 2-fold and ≥ 2 to < 5-fold increase in AUC, respectively.

Figure 1: Forest Plot of the Effect of Rucaparib on the C_{max} and AUC of the Substrate Probes

Using oral caffeine, S-warfarin, omeprazole, midazolam, and digoxin as specific probe substrates, rucaparib moderately inhibited CYP1A2, weakly inhibited CYP2C9, CYP2C19, and CYP3A, and marginally inhibited P-gp, respectively.

Pharmacokinetics in target population

A population pharmacokinetic model (PPK) model was developed with data from Studies A4991014, CO 338 010 and CO-338-017, and the effects of intrinsic and extrinsic factors on the PK of rucaparib were evaluated.

Rucaparib PPK analyses were based on a pooled dataset of observed concentrations from patients in Study CO-338-010 Part 1 (n = 56), Part 2A (n = 42), and Part 3 (n = 26), and CO-338-017 Part 1 and Part 2 (n = 300). A summary of the data included in the PPK analyses is provided below.

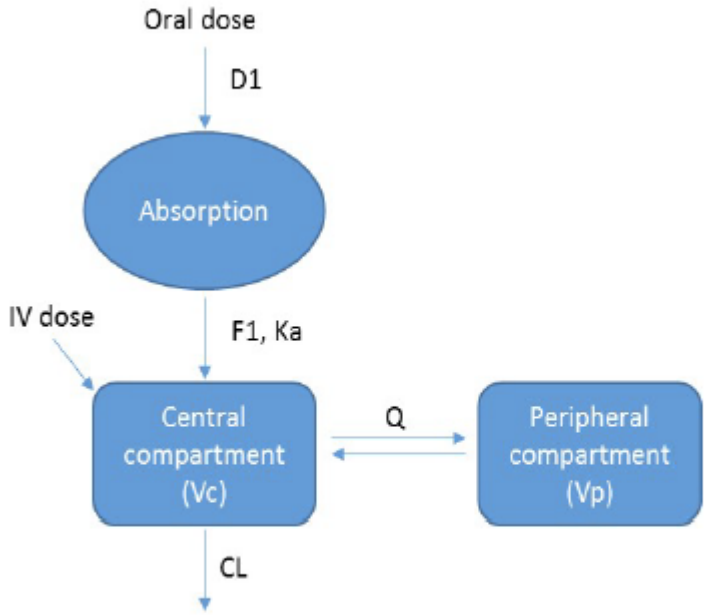
Table 5: Summary of PK Data Included in Population PK Analysis

Study Identifier	Description	Status/Cutoff Date	N	Sampling Design
A4991014 Phase 1	**Dose Escalation Portion** To assess safety and tolerability of escalating doses of rucaparib	Completed	IV and oral: 35[a]	IV rucaparib: 24, 27, or 40 mg as 30-minute IV infusion oral rucaparib: 72, 80, 120, 180, 240, 360 mg IV & oral: pre-dose, 0.25, 0.5, 1, 1.5, 2.5, 4, 6, 10, 24, and 48 hr after the start of the IV infusion or time of oral dosing
CO-338-010 (Study 10) Phase 1/2 Non-randomized open-label	**Part 1** (Phase 1 portion): Evaluate safety and MTD dose, single-dose and multi-dose PK, preliminary food effect on PK	Completed	Oral: 56	oral rucaparib, 40 to 300 mg QD, 240 to 840 mg BID cycle 1, day 1 and 15: pre-dose, 0.25, 0.5, 1, 1.5, 2.5, 4, 6, 8, 10, 24 hr post-dose cycle 1, day 8 and 22, and day 1 of cycles 3-9: pre-dose food effect study, cycle 1, day -7: pre-dose, 0.25, 0.5, 1, 1.5, 2.5, 4, 6, 8, 10, 24 hr post-dose
	Part 2A (Phase 2 portion): ORR per RECIST Version 1.1	Ongoing 30 Nov 2015	Oral: 42	oral rucaparib, 600 mg BID cycle 1, day 15 and cycle 2+, day 1: pre-dose
	Part 3 (Phase 2 PK portion): Further evaluation of PK of higher dose strength tablets at the RP2D; food effect on PK	Ongoing 10 Dec 2015	Oral: 26	oral rucaparib, 600 mg BID cycle 1, day -7, 1, 15: pre-dose, 0.25, 0.5, 1, 1.5, 2.5, 4, 6, 8, 10, 24 hr post-dose or pre-dose cycle 1, day 22, and cycle 2+, day 1: pre-dose
CO-338-017 (ARIEL2) Phase 2	**Part 1**: Progression-free survival by HRD subgroup.	Ongoing Feb 2016	Oral: 196	oral rucaparib, 600 mg BID cycle 1, day 15, and cycle 2+, day 1: 12 hr post-dose
	Part 2: ORR per RECIST Version 1.1 by HRD subgroup	Ongoing Feb 2016	Oral: 104	oral rucaparib, 600 mg BID cycle 1, day 15, and cycle 2+, day 1: 12 hr post-dose

Source: Table 1, Report QS-CLV-006, Section 5.3.3.5.
Abbreviations: HRD = homologous recombination DNA repair deficiency, MTD = maximum tolerated dose, mTNBC = metastatic triple-negative breast cancer, ORR = overall response rate, PFS = progression-free survival, PK = pharmacokinetics, RECIST = Response Evaluation Criteria in Solid Tumors, RP2D = recommended Phase 2 dose.[a] Initially, partial PK data (n = 30 for oral and n = 9 for IV) from Study A4991014 were used for model development. The final analysis dataset included 35 patients with both oral and IV PK data. Only single dose PK data without chemotherapy were included in the PPK analysis.

Initially, partial data (n = 30 for oral and n = 9 for IV) were used for model development. Late in the model development, additional Study A4991014 PK data became available, and a total of 35 patients from Study A4991014 with both intensive IV and oral PK data were included. The PPK dataset included data for tablets of different strengths (12, 40, 60, 120, 200, and 300 mg), IV doses of 12 to 40 mg, and oral dosages of 40 to 500 mg QD and 240 to 840 mg BID. After exclusion of samples below the limit of quantitation (BLQ), outliers, and data with errors, the full PPK dataset included 4064 observation records from 447 patients. The final PPK model was re-estimated with all data.

The model with 2-compartmental distribution with sequential zero-order release and first order absorption adequately described the PK data.



Source: Figure 2 of Report QS-CLV-006 (Section 5.3.3.5).

Abbreviations: CL = clearance, Cp = plasma concentration, D1 = duration of the zero-order absorption process, F1 = absolute bioavailability in the central compartment, Ka = absorption rate constant, Vc = volume of the central compartment, Vp = volume of the peripheral compartment.

Figure 2: Illustration of the Final Rucaparib PPK Model

Table 6: Rucaparib PPK Parameters

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} CrCL 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)	-	-

Source: Table 9 in Report QS-CLV-006 (Section 5.3.3.5)

CI = confidence interval, CL = clearance, CLcr = creatinine clearance, CV = coefficient of variation, D1 = duration of the zero-order absorption, F1 = absolute oral 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

While individual absorption kinetic parameters were modestly impacted by food status and dose level, the high variability in the preceding zero-order release kinetics suggested that food is not likely to significantly impact rucaparib PK. In addition, tablet strengths and formula composition did not impact rucaparib PK at 600 mg BID.

Following continuous 600 mg BID rucaparib dosing, the model-estimated steady-state AUC for patients with mild (CLcr 60 to 89 mL/min) and moderate (CLcr >30 to 60 mL/min) renal impairment was 15% and 33% higher than that of patients with normal renal function (CLcr ≥ 90 mL/min), respectively.

No apparent PK difference was observed between patients with normal or mildly impaired hepatic function. No dose modification is required for patients with mild or moderate renal impairment or mild hepatic impairment based on the PPK data.

Table 7: Effect of Intrinsic Factors on Rucaparib PK following 600 mg Rucaparib BID

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)
All patients	44373 (42%) N=372	2041.4 (39%) N=372	1619.1 (45%) N=372	1559.9 (86%) N=359
Age				
Age <65	43043 (42%) N=218	1984.7 (40%) N=218	1566.4 (45%) N=218	1498.7 (89%) N=218
Age ≥65 to <75	45193 (43%) N=114	2075.6 (40%) N=114	1652.3 (46%) N=114	1638.8 (72%) N=114
Age ≥75 to <85	49637 (35%) N=39	2267.1 (32%) N=39	1827.3 (38%) N=39	1677.9 (110%) N=39
Age ≥85	52611 N=1	2381.2 N=1	1958.0 N=1	1940.0 N=1
Renal function[a]				
Normal	39657 (43%) N=147	1839.5 (41%) N=147	1433.2 (45%) N=147	1428.2 (70%) N=142
Mild impairment	45488 (37%) N=149	2086.4 (34%) N=149	1665 (40%) N=149	1584.4 (100%) N=145
Moderate impairment	52524 (42%) N=76	2392.7 (39%) N=76	1940.7 (46%) N=76	1798.7 (84%) N=72
Hepatic function[b]				
Normal	44794 (41%) N=337	2060.9 (39%) N=337	1634.3 (45%) N=337	1605.6 (79%) N=327
Mild impairment	40646 (45%) N=34	1868.3 (43%) N=34	1484.9 (48%) N=34	1146.9 (150%) N=31
Moderate impairment	36367 (NA) N=1	1689.6 (NA) N=1	1308.6 (NA) N=1	1710 (NA) N=1
BRCA mutation				
tBRCA, germline	43856 (48%) N=111	2027.4 (46%) N=111	1593 (52%) N=111	1466.9 (110%) N=108
tBRCA, somatic	40800 (42%) N=23	1883.9 (39%) N=23	1480.7 (46%) N=23	1304.9 (140%) N=23
tBRCA, unknown germline/somatic status	42444 (58%) N=18	1962.1 (56%) N=18	1542.3 (61%) N=18	1512.7 (54%) N=17
non-tBRCA/ BRCAunknown	45193 (37%) N=220	2072.5 (34%) N=220	1654.3 (40%) N=220	1645.4 (71%) N=211

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)
BRCA status				
tBRCA1	44063 (42%) N=89	2029.8 (39%) N=89	1604.9 (46%) N=89	1400.8 (130%) N=88
tBRCA2	42038 (57%) N=63	1952.2 (55%) N=63	1520.7 (60%) N=63	1513.8 (72%) N=60
non-tBRCA/ BRCAunknown	45193 (37%) N=220	2072.5 (34%) N=220	1654.3 (40%) N=220	1645.4 (71%) N=211
Race				
White	44267 (42%) N=298	2036.4 (39%) N=298	1615.7 (45%) N=298	1619.7 (71%) N=287
Asian	44605 (39%) N=22	2047.9 (36%) N=22	1630.6 (42%) N=22	843.25 (350%) N=21
Black	61447 (28%) N=8	2774.3 (27%) N=8	2292.4 (29%) N=8	2437.4 (41%) N=8
American Indian/ Alaska Native	51471 (NA) N=1	2332.9 (NA) N=1	1911.9 (NA) N=1	2520 (NA) N=1
Other	42205 (43%) N=43	1952.2 (40%) N=43	1528.3 (47%) N=43	1489.7 (72%) N=42
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; Day 120 Q87.

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, ULN = upper limit of normal.

[a] Categories of renal function are according to EMA criteria[1,4] based on baseline CLcr, as estimated by Cockcroft-Gault method: normal (≥ 90 mL/min), mild (60 to 89 mL/min), moderate (30 to 59 mL/min), and severe (< 30 mL/min).

[b] Categories of hepatic function are accordingl to NCI-ODWG criteria[3] based on an assumed bilirubin upper limit of normal range (ULN) of 1.2 mg/dL and AST ULN of 40 U/L: normal (AST ≤ ULN and total bilirubin ≤ ULN), mild (AST > ULN with total bilirubin ≤ ULN or any AST level with total bilirubin > 1.0-1.5 × ULN), moderate (AST level with total bilirubin > 1.5-3.0 × ULN).

Drug interactions with rucaparib as a victim were assessed in a PPK analysis. CYP2D6 phenotypes (poor metabolizers, intermediate metabolizers, normal metabolizers, and ultrarapid metabolizers) and CYP1A2 phenotypes (normal metabolizers and hyperinducers) did not significantly impact the steady-state exposure of rucaparib at 600 mg BID. Concomitant administration of strong CYP1A2 or CYP2D6 inhibitors did not show significant impact on rucaparib PK. Current smokers had overlapping rucaparib exposures as compared to nonsmokers and former smokers. Collectively, the results suggest that CYP1A2 and CYP2D6 play limited role in rucaparib metabolism.

Table 8: Effect of Extrinsic Factors on Rucaparib PK following 600 mg Rucaparib BID

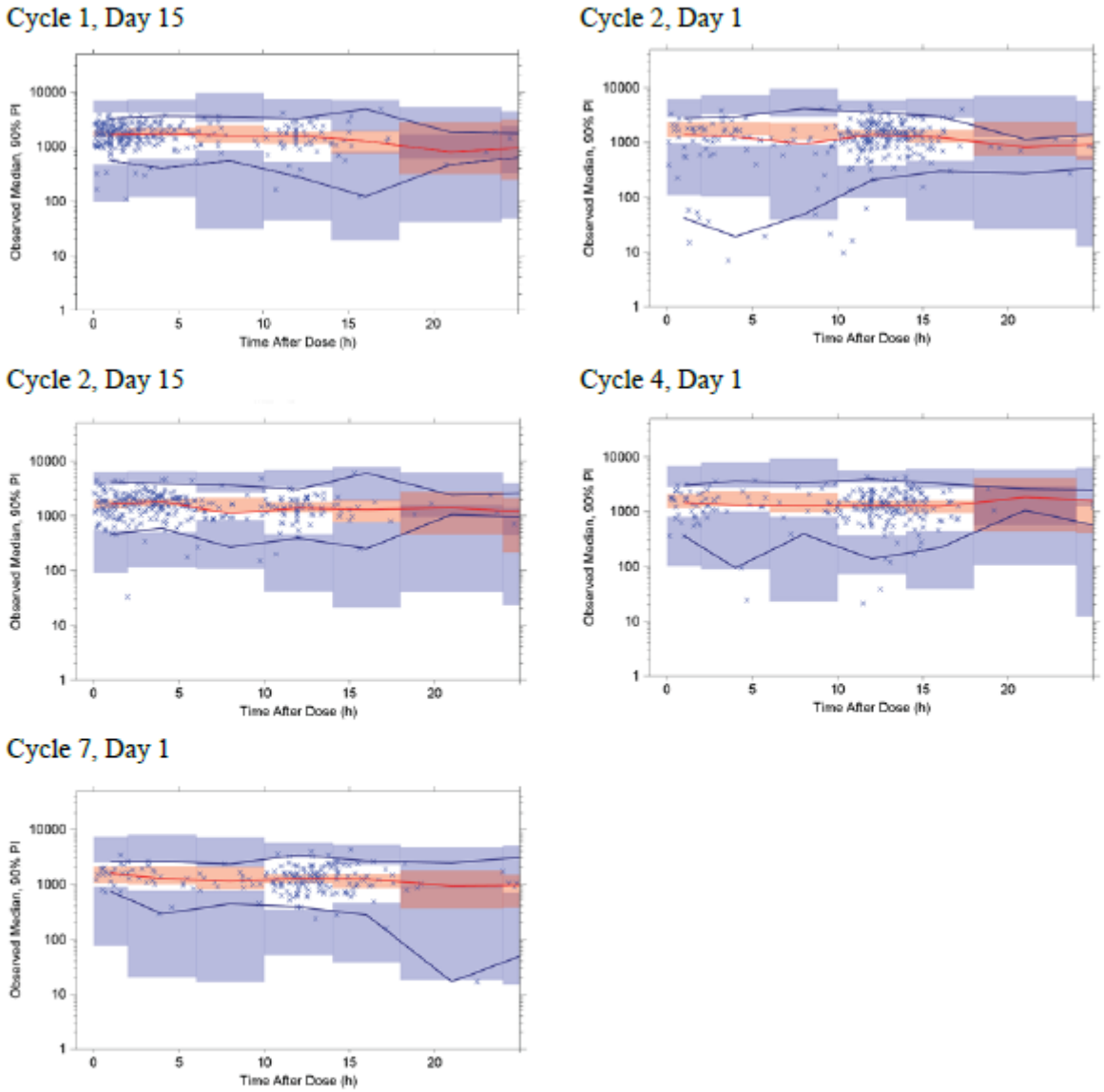
Population	Predicted AUC_{ss} (ng.hr/mL)	Predicted $C_{max,ss}$ (ng/mL)	Predicted $C_{min,ss}$ (ng/mL)	Observed $C_{min,ss}$ (ng/mL)
All patients	44373 (42%) N=372	2041.4 (39%) N=372	1619.1 (45%) N=372	1559.9 (86%) N=359
Concomitant PPI				
No concomitant PPI	43153 (41%) N=245	1986.9 (39%) N=245	1572.9 (45%) N=245	1502.8 (94%) N=235
With concomitant PPI	46824 (42%) N=127	2150.9 (39%) N=127	1712.2 (45%) N=127	1674 (70%) N=124
Concomitant CYP1A2 Inhibitor				
No concomitant CYP1A2 inhibitor	44036 (41%) N=353	2026.2 (38%) N=353	1606.4 (44%) N=353	1560.4 (84%) N=340
With concomitant CYP1A2 inhibitor	51120 (55%) N=19	2346.1 (52%) N=19	1874.9 (60%) N=19	1550.5 (130%) N=19
Concomitant CYP2D6 inhibitor				
No concomitant CYP2D6 inhibitor	44375 (41%) N=350	2040.8 (38%) N=350	1619.7 (44%) N=350	1568.2 (86%) N=337
With concomitant CYP2D6 inhibitor	44334 (52%) N=22	2050.9 (52%) N=22	1609.8 (54%) N=22	1437 (86%) N=22
Concomitant P-gp inhibitor				
No concomitant P-gp inhibitor	44419 (41%) N=345	2041.7 (38%) N=345	1622.3 (44%) N=345	1576 (86%) N=334
With concomitant P-gp inhibitor	43790 (51%) N=27	2037.1 (48%) N=27	1578.9 (56%) N=27	1359.7 (87%) N=25
Smoking				
Missing	41965 (37%) N=2	1931.1 (34%) N=2	1529.1 (41%) N=2	1647.2 (56%) N=2
Current smoker	34011 (57%) N=16	1599.5 (54%) N=16	1206.8 (61%) N=16	1109.3 (76%) N=16
Former smoker	44530 (41%) N=97	2048.7 (39%) N=97	1625.6 (44%) N=97	1587 (69%) N=95
Never smoker	45073 (40%) N=257	2070.8 (38%) N=257	1647.3 (44%) N=257	1583.5 (93%) N=246

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; PK = pharmacokinetics, P-gp = P-glycoprotein, PPI = proton pump inhibitor.
[a] Categories of hepatic function impairment are calculated from NCI ODWG criteria based on an assumed bilirubin ULN of 1.2 mg/dL and AST ULN of 40 U/L.

No clinically significant effect of concomitant use of PPIs on absolute oral bioavailability (F1) was observed. No clinically significant effect on rucaparib PK was observed for body weight, body mass index (BMI), race, age, and alpha-1 acid glycoprotein (AAG) concentrations.

In Study CO-338-014, patients randomized to the active treatment arm initiated dosing with rucaparib 600 mg BID. Sparse PK data, including 1440 evaluable concentrations from 359 patients, were collected on Cycle 1 Day 15 post-dose, Cycle 2 Day 1 predose, Cycle 2 Day 15 post-dose, Cycle 4 Day 1 predose, and Cycle 7 Day 1 predose. External validation of the existing PPK model via visual predictive check (VPC) was conducted with the CO-338-014 data.

When stratified by Treatment Cycle and Day, the median of the observed data mostly fell within the simulated median prediction interval. Where sufficient observed data are available to accurately compute percentiles, the 5th and 95th percentiles primarily fell within the simulated lower and upper prediction intervals.



Source: Figure 7, Report QS-CLV-008

Abbreviations: PI = prediction interval

Note: The VPC is stratified by Treatment Cycle and Day. The solid red line represents the median of the observed data. The solid blue lines represent the 5th and 95th percentiles of the observed data. The shaded regions encompass 90% of the simulated values (n=1000) of the predicted medians (orange), 5th (blue), and 95th (blue) percentiles. Data points (x's) represent the individual observed data.

Figure 3: Visual Prediction Check of PK Data from Study CO-338-014 Using the Existing Population PK model

The observed plasma exposure of rucaparib in Study CO-338-014 was approximately 20% lower as compared to previous studies, although the exposures were largely overlapping and only sparse PK data from Study CO-338-014 were available for comparison.

Additional models were tested to evaluate the study effect on PK parameters. The estimates of CL for Study CO-338-014 were 11.4 L/hr, compared to 10.3 L/hr for the existing PPK model. Consistently, when a study effect on F1 was estimated, F1 was lower (32.1%) compared to that of the existing PPK model (37.2%). Model covariates (baseline albumin and CrCL) only explained part of the difference in CL between Study CO-338-014 and previous analysis.

2.3.3. Pharmacodynamics

Mechanism of action

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. Increased rucaparib-induced cytotoxicity and anti-tumour activity was observed in tumour cell lines with deficiencies in BRCA1/2 and other DNA repair genes. Rucaparib has been shown to decrease tumour growth in mouse xenograft models of human cancer with or without deficiencies in BRCA (See SmPC section 5.1).

Primary and Secondary pharmacology

Alterations in the HRR pathway

From analysis of The Cancer Genome Atlas (TCGA) it is estimated that approximately 50% of patients with high – grade serous ovarian cancer (HGSOC) have alterations in the HRR pathway including:

1. Germline mutations in the BRCA1 and BRCA2 genes (gBRCA) in up to 15% of all EOC. Patients carry heterozygous deleterious mutations in their germline DNA and develop tumours when the remaining wild-type functional allele is inactivated.

2. Somatic BRCA1/2 mutations (sBRCA) in 6% to 8% of HGSOC patients

3. Mutation in a homologous recombination gene other than BRCA1/2 (approximately 16% of HGSOC patients). Nonclinical studies have identified RAD proteins (e.g. RAD51, RAD51C, RAD52, RAD54L), Fanconi Anaemia proteins (e.g. FANCA, FANCC, FANCD2) and many others (e.g. ATM, ATR, CHEK1, CHEK2) as being involved in homologous recombination.

4. Functional silencing of homologous recombination genes, through BRCA promoter methylation (~ 10% of HGSOC patients) or other mechanisms.

Mutations in BRCA and other known HRR genes in tumour can be detected through next-generation sequencing (NGS). Another approach for identifying non-BRCA patients with HRD tumours is to assess the level of genome-wide LOH within the tumour, which can identify HRD tumours regardless of the underlying mechanisms.

An NGS-based test using DNA extracted from patient tumour tissue samples and performed at central laboratory by Foundation Medicine, Incorporated (FMI) was developed. The test detects alterations in BRCA1 and BRCA2 genes, as well as other HRD genes. This test is also able to assess the percentage of genome-wide LOH i.e. phenotypic genomic instability to classify non-BRCA HRD (nbHRD).

Using platinum sensitivity as a surrogate for rucaparib response, the sponsor analysed the TCGA dataset to assess the correlation between the level of genomic scarring and clinical outcome following platinum-based therapy. A LOH cut-off of $\geq$ 14% was identified and tested in the treatment setting in Study CO-338-017 [ARIEL2] Part 1. The initial results indicated that patients with LOH $\geq$ 14%, had a significantly longer PFS (HR 0.62, 95% CI, 0.42-0.90; p = 0.011) compared to those with LOH < 14%.

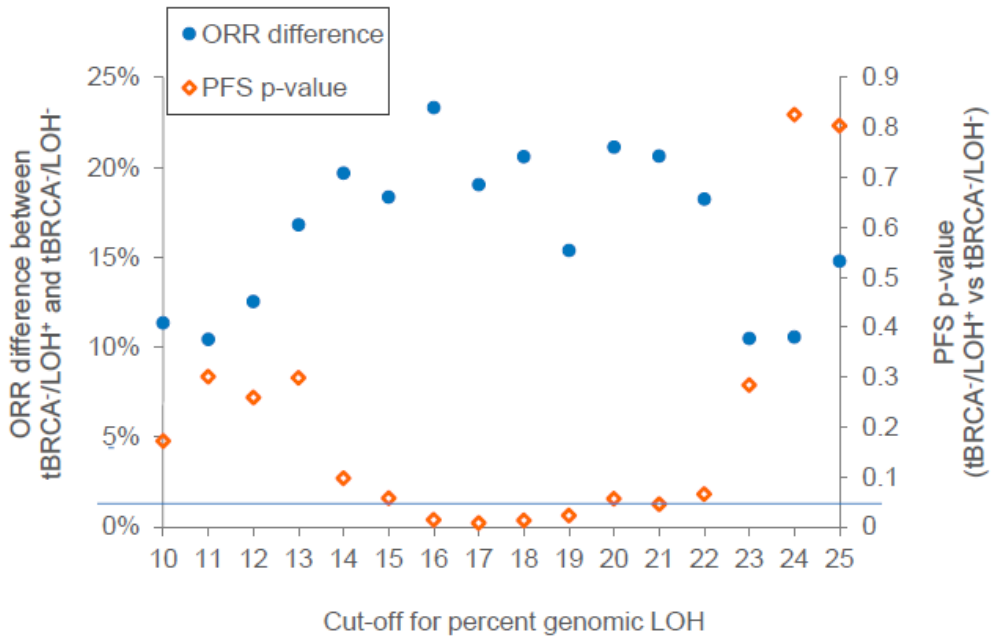


Figure 4: Plot of differential ORR and PFS Between tBRCA^{-}/LOH+ and tBRCA^{-}/LOH^{-} Subgroups at Different Percent Genomic LOH Cut Offs in ARIEL2 Part 1

PK/PD modelling

Exposure-Response Analysis for Study CO-338-014

In Study CO-338-014, 564 patients were randomized, 375 to the rucaparib arm and 189 to the placebo group. The ITT population consisted of all randomized patients. The starting dose for all rucaparib patients was 600 mg BID. The safety population (N = 561) included all patients who initiated treatment (372 patients in the rucaparib arm and 189 patients in the placebo arm). The starting dose for all rucaparib-treated patients was 600 mg BID. Study CO- 338-014 is ongoing; the data presented herein are based on all data available up to a visit cut-off of 15 April 2017.

Table 9: Summary of Study CO-338-014 for the Exposure-Response Analysis

Protocol	Description	Population	N	$N_{efficacy}$[a]	N_{safety}[b]	Treatment	Primary Endpoint
CO-338-014	Phase 3 study in patients with platinum-sensitive, high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer who had achieved a response to platinum-based chemotherapy	Placebo arm	189	189[d]	189[e]	600 mg BID (matching)	invPFS[c]
		Rucaparib arm	372	359[d]	359[e]	600 mg BID	

Source: Table 1 in Report QS-CLV-009 (Appendix 16.1.15 of Study CO-338-014 CSR, Section 5.3.5.1)

Abbreviations: AE = adverse event, BID = twice a day, inv = investigator, irr = independent radiologist reviewer, PFS = progression-free survival,

[a] $N_{efficacy}$ refers to the number of patients in the exposure-efficacy analysis

[b] N_{safety} refers to the number of patients in the exposure-safety analysis

[c] irrPFS was a key secondary endpoint

[d] The exposure-efficacy analysis dataset included all patients in the ITT population with available PK estimates (189/189 placebo and 359/375 375 rucaparib)

[e] The exposure-safety analysis dataset included all patients in the Safety population with available PK estimates (189/189 placebo and 359/372 rucaparib)

Exposure-Efficacy Analysis

The exposure-efficacy analysis dataset included all patients in the ITT population with available PK estimates (189/189 placebo and 359/375 rucaparib). PFS assessed by investigator (invPFS) and by IRR (irrPFS) were tested as efficacy endpoints. The model-predicted dose-averaged steady-state AUC ($AUC_{avg,ss*}$) was used as the exposure metric for which doses administered after disease progression were excluded. Exposure-PFS relationship and covariate effects were analysed using Cox regression models.

Table 10: Exposure summary for each endpoint in the exposure-efficacy analysis

Variable	invPFS	irrPFS	Though end of treatment
N[a]	375	375	375
N PK[b]	359	359	359
mean (SD), [min, max]			
Average/Nominal Dose Ratio	0.87 (0.13) [0.44,1]	0.88 (0.13) [0.44,1]	0.87 (0.13) [0.44,1]
$C_{min,avg,ss*}$ (ng/mL)	1260 (486) [494,4125]	1263 (488) [494,4125]	1258 (484) [494,4125]
$C_{max,avg,ss*}$ (ng/mL)	1593 (523) [683,4535]	1597 (526) [683,4535]	1590 (521) [683,4535]
$AUC_{avg,ss*}$ (ng/ml·hr)	34578 (12211) [14252.28,104611.54]	34678 (12268) [14252.28,104611.54]	34520 (12171) [14252.28,104611.54]

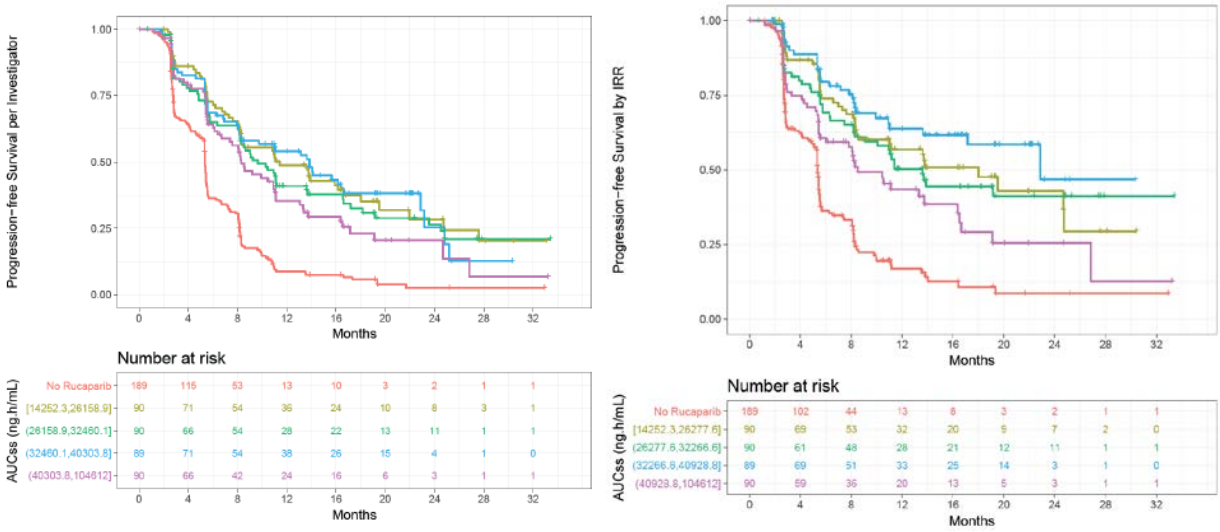
[a] Number of rucaparib group patients evaluable for the endpoint

[b] Number of rucaparib group patients evaluable for the endpoint with a measureable tumor volume at baseline and at least one evaluable PK concentration

$AUC_{avg,ss*}$ = average steady-state AUC, $C_{max,avg,ss}$* = average steady-state C_{max}, $C_{min,avg,ss*}$ = average steady-state C_{min}

Note: Continuous variables are reported as mean (SD), [min, max]. AUC refers to daily 0-24 hr AUC.

The invPFS and irrPFS data are presented below. The PFS data are presented by exposure quartile for rucaparib-treated patients, and for all placebo patients (no rucaparib).



The upper panel shows the Kaplan-Meier curves stratified by exposure quartile. The plus signs (+) indicate censored patients. The number of patients per quartile at risk is indicated in the lower panel.

Figure 5: Exposure-response relationship for invPFS and irrPFS

Covariates were tested in Cox models. Longer progression-free interval (PFI) following the penultimate platinum-based regimen (> 12 months) correlated with a reduced risk of disease progression as compared to shorter PFI (6-12 months), regardless of treatment received. The risk of disease progression was lowest in tBRCA patients, and increased in the remaining HRD analysis groups in the following order: tBRCA < non-tBRCA LOH+ < non-tBRCA LOH Unknown < nontBRCA LOH-. Following rucaparib treatment, the risk of disease progression was lower in patients with best response of CR (RECIST) to the platinum-based regimen administered immediately prior to initiation of rucaparib maintenance therapy than in patients with best response of PR (RECIST or reduction in CA-125); however, following placebo treatment, patients with a CR or PR had a comparable risk of progression (i.e., the effect was not statistically significant). As the models were tested with exposure forced into the model regardless of its statistical significance, the covariant effects estimated by the models were independent of rucaparib exposure.

Exposure-Safety Analysis

The primary analysis of exposure-safety included all safety events. A secondary analysis included safety events during the first 6 months of treatment only. This was intended to assess any bias introduced due to the longer duration of treatment observed for tBRCA patients.

For the analysis of time to the first dose reduction or dose modification, $AUC_{avg,ss*}$ until the time of event was selected. Patients without dose reduction or modification were not included in the analysis.

For the remaining safety endpoints, based on hepatic and haematological laboratory values and other qualitative safety endpoints, average $C_{max,ss}$ until the end of treatment ($C_{max,avg,ss*}$) was the selected exposure metric.

The exposure-safety analysis also included up to 548/564 patients with available PK estimates. Patient counts for individual endpoints were reduced if relevant post-baseline central laboratory data were not available.

Table 11: Summary of incidence of safety events by study arm

Endpoint	Placebo	Rucaparib 600 mg BID	N Total
Grade 3+ ALT	0/189 (0%)	24/359 (6.69%)	548
Grade 3+ AST	0/189 (0%)	3/359 (0.836%)	548
Grade 2+ Bilirubin	0/189 (0%)	9/359 (2.51%)	548
Grade 3+ Neutrophils	5/188 (2.66%)	23/359 (6.41%)	547
Grade 3+ Lymphocytes	5/188 (2.66%)	18/359 (5.01%)	547
Grade 3+ Platelets	0/189 (0%)	7/359 (1.95%)	548
Grade 3+ Hemoglobin	2/189 (1.06%)	46/359 (12.8%)	548
Grade 3+ Cholesterol	0/189 (0%)	15/359 (4.18%)	548
Grade 2+ Creatinine	7/189 (3.7%)	118/359 (32.9%)	548
Grade 3+ Fatigue	5/189 (2.65%)	24/359 (6.69%)	548
Grade 3+ Nausea	1/189 (0.529%)	14/359 (3.9%)	548

PK estimates (189/189 placebo and 359/372 rucaparib). The exposure-safety analysis tested the same safety endpoints as in the previous analysis (Report QS-CLV-007), including hepatic laboratory variables (Grade ≥ 3 ALT increase, Grade ≥ 3 AST increase, Grade ≥ 2 bilirubin increases), hematologic laboratory variables (Grade ≥ 3 decreases in neutrophils, platelets, lymphocytes, and hemoglobin, maximum hemoglobin reduction from baseline), other laboratory variables (Grade ≥ 3 cholesterol increase, Grade ≥ 2 creatinine increase), and other qualitative AEs (Grade ≥ 3 fatigue/asthenia, Grade ≥ 3 nausea). Laboratory parameters were based on the worst grade per standard CTCAE, Version 4.03.

In the first (primary) analysis, model-predicted dose-averaged steady-state C_{max} ($C_{max,avg*}$) throughout the rucaparib treatment period was used as the exposure endpoint. In the secondary analysis conducted the safety data and PK data were limited to only the first 6 months of treatment. In this analysis, the model-predicted dose-averaged $C_{max,avg*}$ was calculated up to the event of interest or 6 months if no event of interest occurred. In addition, the safety analysis also evaluated the time to first dose reduction and time to first dose modification with $AUC_{avg,ss*}$ as the exposure metric. Dose modifications included treatment interruption, dose reduction, or treatment discontinuation. Time-to-event endpoints (except time to first dose reduction/modification) were modeled with Cox regression, and other endpoints were modelled with linear or nonlinear regression.

Safety covariates included age (< 65 yrs vs ≥ 65 yrs), HRD analysis subgroup (tBRCA, nontBRCA LOH+, non-tBRCA LOH-, non-tBRCA LOH unknown), number of prior chemotherapies (2 or > 2), ECOG PS (0 or 1), baseline albumin value, and baseline haemoglobin value (tested on hemoglobin change from baseline endpoint only). To assess covariate effects, the ER relationship was forced into the model regardless of significance. Rucaparib exposures in the placebo arm were assigned as 0. Covariates were tested at $p < 0.05$ in a multivariate forward step-wise approach. Binary endpoints were modeled with linear logistic regression, time-to-event endpoints (except time to first dose reduction/modification) were modeled with Cox regression, and other endpoints were modeled with linear or nonlinear regression.

Table 12: Exposure-safety relationships with covariates

Exposure Metric	Safety Endpoint	AIC_{ER}> AIC_{trt}?	p-value for exposure [a]		Statistically Significant Covariates [b] (p<0.05)
			No covariate	Covariate adjusted	
$C_{max,avg,ss*}$	ALT Grade 3+	No	0.01	0.003	Baseline Albumin
$C_{max,avg,ss*}$	AST Grade 3+	No	0.146	--	--
$C_{max,avg,ss*}$	Bilirubin Grade 2+	No	0.048	0.068	HRD analysis group [c]
$C_{max,avg,ss*}$	Neutrophils Grade 3+	No	0.156	--	--
$C_{max,avg,ss*}$	Lymphocytes Grade 3+	No	0.529	0.44	HRD analysis group [c]
$C_{max,avg,ss*}$	Platelets Grade 3+	No [d]	0.012	--	--
$C_{max,avg,ss*}$	Hemoglobin Grade 3+	Yes	<0.001	<0.001	HRD analysis group [c]
$C_{max,avg,ss*}$	Hemoglobin, CFB [e]	Yes	<0.001	<0.001	Baseline Hb, Baseline albumin
$C_{max,avg,ss*}$	Creatinine Grade 2+	Yes	<0.001	<0.001	HRD analysis group [c]
$C_{max,avg,ss*}$	Cholesterol Grade 3+	Yes	<0.001	<0.001	Age
$C_{max,avg,ss*}$	Fatigue Grade 3+	No	0.095	0.162	Age
$C_{max,avg,ss*}$	Nausea Grade 3+	No	0.366	--	--

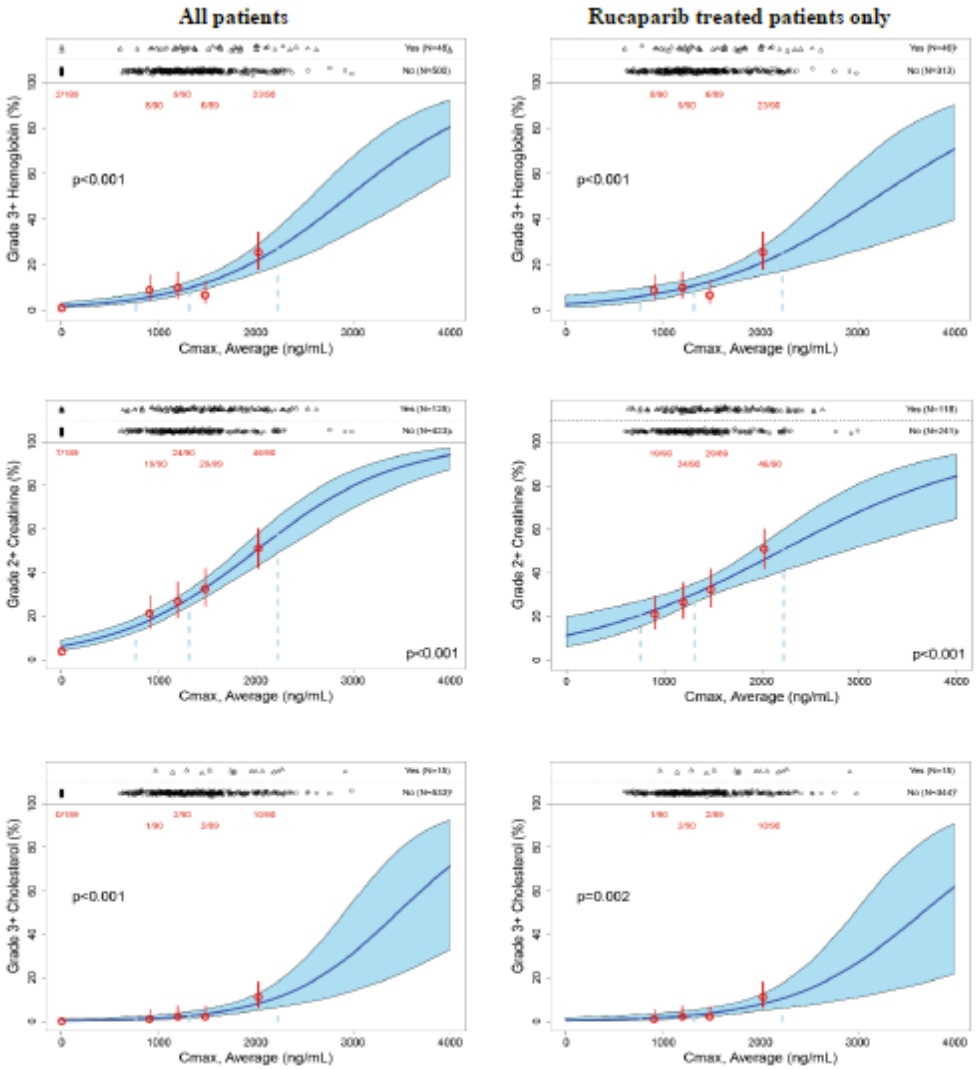
Note: The "AICER<AICtrt?" column indicates whether an exposure-response relationship provided a better fit to the data compared to the model with a treatment effect. "AICER<AICtrt?" is "Yes" if the AIC of the model with the exposure-response relationship and covariates was lower than that of the model with the treatment effect and covariates. "Covariate adjusted" means that the model includes statistically significant covariates. --: not applicable

[a] The p-value is the significance level of the exposure-response relationship in the model.
[b] Details of levels for each categorical covariate evaluated and methods for inclusion of covariates in the model were as described in the Exposure-Response report.
[c] The HRD analysis groups include tBRCA, non-tBRCA LOH+, non-tBRCA LOH- and non-tBRCA LOH unknown.
[d] For the Grade 3+ platelets model, the AIC for the exposure-response model was lower than the treatment effect model; however, the magnitude of the difference (0.4) suggested limited improvement
[e] Emax relationship with covariate effects on EC50.

In this analysis, treatment effect (i.e., placebo vs. rucaparib treatment) and linear $C_{max,ss*}$-safety relationships were tested. For the maximum haemoglobin change from baseline, saturable ER relationships (e.g., Emax) were also tested.

A treatment effect (placebo vs. rucaparib) was observed for many safety endpoints; however, when the analysis was limited to patients treated with rucaparib, statistically significant relationships ($p < 0.05$) with $C_{max,ss*}$ were observed only for Grade ≥ 3 haemoglobin decrease, Grade ≥ 2 creatinine increase, and Grade ≥ 3 cholesterol increase (Figure 6), with model-predicted incidences of 16.5%, 36.5%, and 1.2%, respectively, following rucaparib 600 mg BID.

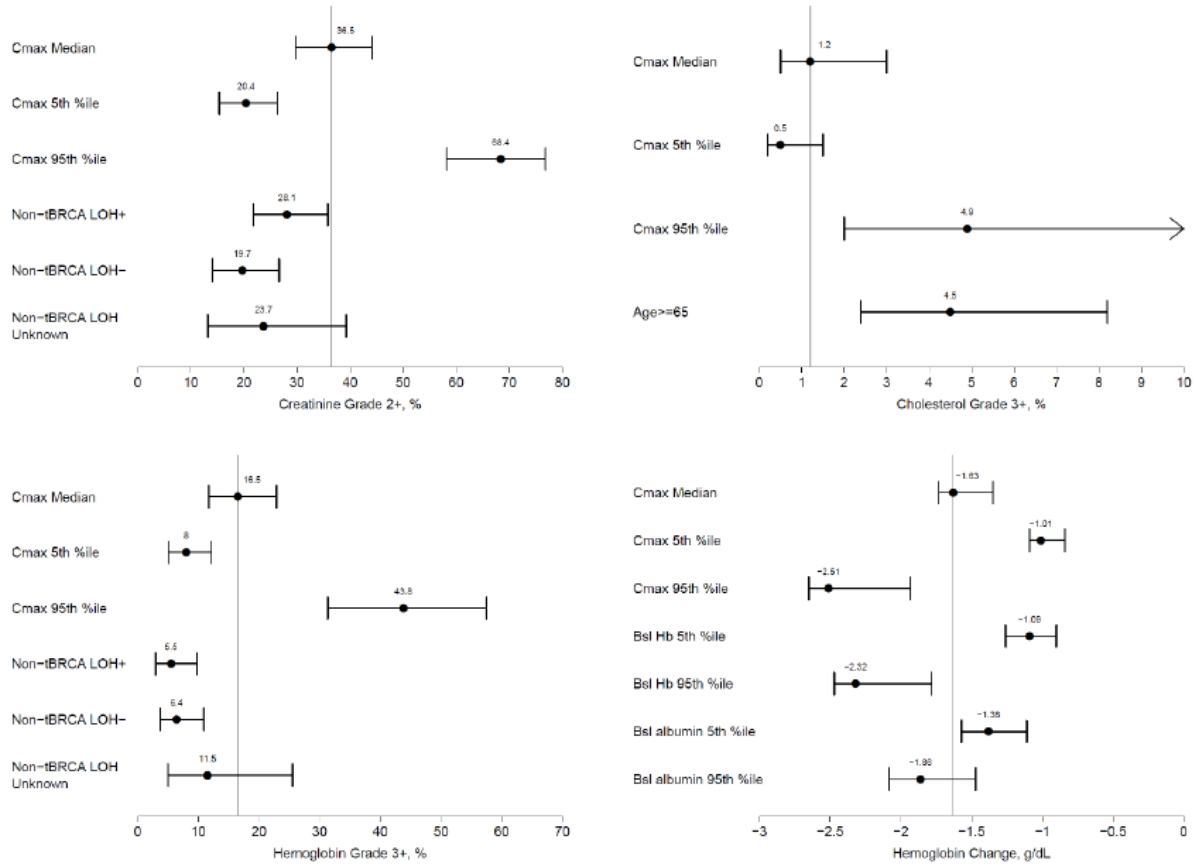
For haemoglobin, the model predicted a decrease of 1.63 g/dL from baseline at rucaparib 600 mg BID. Caution should be used for the correlation with Grade ≥ 3 cholesterol increase due to the low incidence. No statistically-significant ER relationships were observed for Grade ≥ 3 ALT increase, Grade ≥ 3 AST increase, Grade ≥ 2 bilirubin increase, Grade ≥ 3 neutrophil decrease, Grade ≥ 3 lymphocyte decrease, Grade ≥ 3 platelet decrease, Grade ≥ 3 fatigue, or Grade ≥ 3 nausea in rucaparib-treated patients.



Note: In the shaded polygon plots, red points represent the mean exposure and event rates in placebo treated patients or patients stratified by rucaparib exposure quartile. Vertical red bars represent the 5th to 95th percentile confidence intervals on the event rate. Event numbers (patients with event/total patients) are displayed above each vertical bar. The solid blue line is the logistic regression model fit when the p-value is ≤0.05. The shaded blue region represents the 5th to 95th percentile confidence intervals on the modeled event rate. The p-value for the slope is indicated. The horizontal line shows the average response rate, when the p-value is >0.05. The dashed vertical blue lines represent the 5th, 50th, and 95th percentile exposures. The data points (triangle-yes, circle-no) are shown above the plots.
Source: Figure 10 and Figure 12, Report QS-CLV-009, Appendix 16.1.15, Study CO-338-014 CSR

Figure 6: Rucaparib Exposure-Safety Relationship in the Primary Exposure-Safety Analysis (Study CO-338-014)

In the primary analysis, HRD analysis group appeared to be associated with increased creatinine and decreased haemoglobin levels during treatment. Compared with tBRCA patients, incidences of Grade ≥ 2 creatinine increase and Grade ≥ 3 hemoglobin decrease were lower and the decrease in haemoglobin was smaller in non-tBRCA LOH+, non-tBRCA LOH-, and non-tBRCA LOH unknown groups. Higher baseline hemoglobin and albumin level were correlated with larger haemoglobin decrease from baseline. Older patients (≥ 65 years old) showed higher incidence of Grade ≥ 3 cholesterol than younger patients (<65 years old). The covariate effects are presented in Figure 7.



Source: Figure 16, Report QS-CLV-009, Appendix 16.1.15, Study CO-339-014 CSR, Section 5.3.5.1

Abbreviations: Cmax = the daily steady-state C_{max}, corrected from the nominal dose to the average dose, tBRCA = tumor BRCA mutation, LOH = loss of heterozygosity, Bsl Hb = baseline hemoglobin, Bsl albumin = baseline albumin

Note: The vertical line of each forest plot represents the response rate in the patient with nominal characteristics: $C_{max,avg,ss*}$ = 1489 ng/mL, age < 65-yrs, HRD analysis group tBRCA, baseline hemoglobin of 11.8 g/dL, and baseline albumin of 44 g/L. The solid points represent estimated response rates in other populations, with horizontal bars to indicate 5th to 95th percentile confidence intervals.

Figure 7: Effect of Covariates on the Incidence of Safety Endpoints in Primary Exposure-Safety Analysis in Study CO-338-014

The secondary analysis was restricted to data in the first 6 months of treatment as mentioned above. Consistent correlations were observed, as in the primary exposure-safety analysis, for Grade ≥ 3 haemoglobin decrease, Grade ≥ 2 creatinine increase, Grade ≥ 3 cholesterol increase, and haemoglobin change from baseline. In addition, Grade ≥ 3 platelet decrease showed statistically significant correlation with rucaparib exposure. The model predicted 11.8% Grade ≥ 3 haemoglobin decrease, 8.8% Grade ≥ 2 creatinine increase, 0.9% Grade ≥ 3 cholesterol increase, and 0.8% Grade ≥ 3 platelet decrease. Caution should be used for the correlations with Grade ≥ 3 cholesterol increase and Grade ≥ 3 platelet decrease due to the low incidence rates.

In the secondary safety analysis with data up to 6 months, patients with age ≥ 65 years had increased incidences of Grade ≥ 2 creatinine increase and Grade ≥ 3 cholesterol increase. Patients with ECOG PS of 1 had increased incidences of Grade ≥ 2 creatinine increase as compared to patients with ECOG PS of 0. Similar to the primary analysis, patients with higher baseline haemoglobin values experienced larger haemoglobin changes from baseline. Non-tBRCA LOH+ and non-tBRCA LOH- patients had lower incidences of Grade ≥ 3 haemoglobin decrease.

Table 13: Secondary analysis of exposure-safety relationships with covariates

Exposure Metric	Safety Endpoint	AIC_{ER}< AIC_{trt}?	p-value for exposure [a]		Statistically Significant Covariates [b] (p<0.05)
			No covariate	Covariate adjusted	
$C_{max,avg,ss*}$	ALT Grade 3+	No	0.007	0.001	Baseline Albumin, HRD analysis group [c]
$C_{max,avg,ss*}$	AST Grade 3+	No	0.135	--	--
$C_{max,avg,ss*}$	Bilirubin Grade 2+	No	0.032	0.05	HRD analysis group [c]
$C_{max,avg,ss*}$	Neutrophils Grade 3+	No	0.177	--	--
$C_{max,avg,ss*}$	Lymphocytes Grade 3+	No	0.887	0.965	HRD analysis group [c]
$C_{max,avg,ss*}$	Platelets Grade 3+	Yes	0.004	--	--
$C_{max,avg,ss*}$	Hemoglobin Grade 3+	Yes	<0.001	<0.001	HRD analysis group [c]
$C_{max,avg,ss*}$	Hemoglobin, CFB [d]	Yes	<0.001	<0.001	Baseline Hb
$C_{max,avg,ss*}$	Creatinine Grade 2+	Yes	<0.001	<0.001	Age, ECOG
$C_{max,avg,ss*}$	Cholesterol Grade 3+	Yes	<0.001	<0.001	Age
$C_{max,avg,ss*}$	Fatigue Grade 3+	No	0.03	0.06	Age
$C_{max,avg,ss*}$	Nausea Grade 3+	No	0.27	--	--

[a] The p-value is the significance level of the exposure-response relationship in the model.
[b] Details of levels for each categorical covariate evaluated and methods for inclusion of covariates in the model were as described in Section 3.4.3.1.
[c] HRD analysis groups include tBRCA, non-tBRCA LOH+, non-tBRCA LOH-, and non-tBRCA LOH unknown.
[d] Linear relationship with covariate effects on the intercept.

No statistically significant relationship was observed between time to first dose reduction (p=0.085 for all patients; p=0.481 for rucaparib treated patients) or time to first dose modification (p=0.06 for all patients; p=0.146 for rucaparib treated patients) and rucaparib exposure ($AUC_{avg,ss*}$).

2.3.4. Discussion on clinical pharmacology

An overview of the clinical studies contributing to the summary of clinical pharmacology is provided in Table 2. Studies A4991014, CO-338-010 (Study 10), and CO-338-017 (ARIEL2) were previously submitted and assessed as part of the initial MA application. The update to the clinical pharmacology evaluation of rucaparib includes data from two ongoing studies for which enrollment has been completed: Study CO-338-044 (DDI study) evaluating PK DDI of rucaparib, followed by the optional continued treatment with rucaparib in patients with an advanced solid tumor; and Study CO-338-014 evaluating efficacy and safety of rucaparib in patients with EOC, FTC, or PPC in the maintenance setting. In support of this variation, the PPK model that was developed based on data from Studies A4991014, CO-338-010, and CO 338-017 and assessed as part of the initial MA was tested with data from Study CO-338-014. Individual post-hoc estimates of rucaparib exposures were then used in the ER analyses with selected efficacy and safety.

Pharmacokinetic interaction studies

The effect of rucaparib as drug-drug perpetrator was evaluated in a specific Phase I study (CO-338-044) at steady state conditions after the single administration of substrates of CYP1A2, CYP2C9, CYP2C19, CYP3A4 and P-gp in patients with advanced solid tumors. The results indicated that rucaparib is a moderate inhibitor of CYP1A2 (2.26-fold increase in $AUC_{0\text{-last}}$) and weak inhibitor of CYP2C9, CYP2C19, and CYP3A, and a marginal inhibitor of P-gp which is adequately reflected in the current SmPC (see SmPC section 4.5).

Pharmacokinetics in target population

The Applicant applied the population pharmacokinetic model that was previously developed using data from three clinical trials (A4991014, CO-338-010, and CO-338-017) to (i) assess the adequacy of the model to replicate the time-course profile of rucaparib in patients from study CO-33-014 through simulation-based exercise, and to (ii) obtain the individual estimates of exposure (AUC_{ss}, C_{maxss}) through bayesian analysis for the exposure-response evaluation. Results of the external validation demonstrates that, in general, the model is able to characterize the overall behaviour (5^{th}, 50^{th}, and 95^{th} percentiles) of rucaparib 600 mg BID. The model adequately describes the exposure of rucaparib at different treatment cycles and days post-administration. However, the inter-individual variability seems to be over-predicted, based on the 95% prediction intervals, as in the VPC results from studies A4991014, CO-330-010, and CO-338-017. Additional models were tested to assess the study effect on the final parameters. Other covariates that were collected in the primary analysis (A4991014, CO-330-010, and CO-338-017) could not be evaluated as they were missing in the current study (CO-338-014). The Applicant reported a 5% reduction in bioavailability and increased (10.7%) of CL for study CO-338-014, which lack of clinical relevance, considering the exposure-response analysis performed.

The Applicant provided a comparison between experimental and individual predicted $C_{min,ss}$ from Study CO-338-014. Due to the lack of intensive/rich sampling, AUC_{ss} and $C_{max,ss}$ could not be reported. The model under-predicts $C_{min,ss}$ and the bias is increased along the treatment cycles. In Study CO-338-014, patients were allowed to take rucaparib with or without food. No meal information has been recorded in the study database.

Overall, several limitations have been raised regarding the structural population pharmacokinetic model and thus results should be interpreted with caution.

Exposure-Efficacy Analysis

The exposure-efficacy analysis was carried out to evaluate the relation of $AUC_{ss,avg}$ to PFS assessed by investigator (invPFS) and by IRR (irrPFS). Exposure-PFS relationship and covariate effects were analysed using Cox regression models. No statistical relationship was observed between rucaparib $AUC_{ss,avg}$ and efficacy endpoints in patients receiving rucaparib 600 mg BID.

The risk of disease progression was lowest in tBRCA patients, and increased in the remaining HRD analysis groups in the following order: tBRCA < non-tBRCA LOH+ < non-tBRCA LOH Unknown < nontBRCA LOH-. The risk of disease progression was lower in patients with best response of CR (RECIST) to the platinum-based regimen administered immediately prior to initiation of rucaparib maintenance therapy than in patients with best response of PR (RECIST or reduction in CA-125) (statistically significant). Nevertheless, the covariate effects estimated were independent of rucaparib exposure, so the relationship cannot be attributed to rucaparib administration.

Exposure-Safety Analysis

The exposure-safety analysis showed statistically significant relationships ($p < 0.05$) between $C_{max,ss}$* and Grade ≥ 3 haemoglobin decrease, Grade ≥ 2 creatinine increase, and Grade ≥ 3 cholesterol increase. The model-predicted incidences of 16.5%, 36.5%, and 1.2%, respectively, following rucaparib 600 mg BID. The model predicted incidences in the extreme $C_{max,ss}$ percentiles (5^{th} and 95^{th}) were 8-43.8%, 20.4-68.4%, and 0.5-4.9% for Grade ≥ 3 haemoglobin decrease, Grade ≥ 2 creatinine increase, and Grade ≥ 3 cholesterol increase, respectively. However, the incidence in the recruited patients was low and all patients recovered. No dose reduction in those patients is recommended as the efficacy of rucaparib maintenance treatment has not been established at a starting rucaparib dose < 600 mg BID. The effects on haemoglobin and creatinine were also detected in the exposure-safety analysis carried out with studies CO-338-010 and CO-338-017, but the significant effects on Grade ≥ 3 ALT, Grade ≥ 3 AST and Fatigue/asthenia in studies CO-338-010 and CO-338-017 were not statistically significant in study CO-338-014.

Overall, from the exposure-safety analysis, statistically significant exposure-response relationships were observed for Grade 3+ haemoglobin, Grade 2+ creatinine, Grade 3+ cholesterol, and haemoglobin change from baseline in the primary and secondary safety analysis. Only the estimate for Grade 2+ creatinine change showed a marked difference between the primary and secondary analysis, suggesting an influence of the longer treatment duration in tBRCA patients on this outcome. tBRCA patients had higher rates of increased creatinine (Grade 2+) and haemoglobin AEs (Grade 3+ and change from baseline) compared to other the other HRD categories. tBRCA patients were not subdivided into germline and somatic groups.

Overall, the data submitted in this application do not lead to any changes in the SmPC. Two additional clinical pharmacology studies were ongoing at the time of this application: CO-338-045 (mass balance study) and CO-338-078 (hepatic impairment study). The mass balance study CO-338-045 will allow to further elucidate distribution, mean pathways of metabolism, routes of elimination and potential interactions of rucaparib and its metabolites and was already recommended to be submitted as soon as available at the time of the initial MA application. 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. Study CO-338-078 is an additional pharmacovigilance study included in the current RMP which will further investigate the impact of moderate hepatic impairment on rucaparib (considered as missing information). Results from part I of study CO-338-045 were submitted as part of variation EMEA/H/C/004272/II/0003. The expected deadline for CO-33-078 is Q3 2019.

2.3.5. Conclusions on clinical pharmacology

The modelling strategy performed using the existing population pharmacokinetic model developed with experimental data from three clinical trials (A4991014, CO-338-010, and CO-338-017) to predict the concentration time-course profiles and several pharmacodynamic endpoints of a new study (CO-338-014) based on a post-hoc analysis seems adequate. However, several issues were raised regarding the structural pharmacokinetic model developed (absorption model, covariate assessment, influence of food) that might limit the impact of its use to predict data for a new indication. Model predictions made based on the actual PK model could be biased and those results need to be considered with caution.

A weak exposure-efficacy/safety relationship has been established and efficacy/safety endpoints have been tested using that non-significant relationship. Over the range studied, rucaparib exposure did not significantly influence efficacy; extent and duration of prior platinum response and tBRCA mutation were most important. For safety, changes in haemoglobin, creatinine and cholesterol were influenced by exposure, with the effect on Grade 2+ creatinine being more marked with longer duration of Rubraca therapy. tBRCA mutation also influenced the rate of creatinine and haemoglobin AEs.

The clinical pharmacology of rucaparib is considered overall characterised. However there are outstanding studies which are expected to be submitted by the applicant as soon as available (see discussion on clinical pharmacology and RMP).

2.4. Clinical efficacy

2.4.1. Dose response study

No dose response study was submitted (see discussion on clinical efficacy).

2.4.2. Main study

Study CO-338-014 (ARIEL3)

Study CO-338-014 (ARIEL3) is an ongoing Phase 3 double-blind efficacy study of oral rucaparib in patients with platinum-sensitive, high-grade serous or endometrioid EOC, FTC, or PPC who receive either rucaparib or placebo as maintenance therapy following a response to platinum-based chemotherapy.

Methods

Study participants

Inclusion criteria

All patients enrolled into the study met all of the following inclusion criteria:

1. Informed consent.

2. ≥ 18 years of age at the time the ICF was signed

3. Have a histologically confirmed diagnosis of high-grade (Grade 2 or 3) serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer

- For mixed histology, >50% of the primary tumor must be confirmed to be high grade serous or endometrioid

- Grade 2 tumors classified under a 3-tier system should have been re-reviewed by local pathology and confirmed as high-grade under the 2-tier system

4. Received prior platinum-based therapy and have platinum-sensitive disease (ie, documented radiologic disease progression > 6 months following the last dose of the penultimate platinum administered).

- Received ≥ 2 prior platinum-based treatment regimens, including platinum-based regimen that must have been administered immediately prior to maintenance therapy in this trial. In addition, up to 1 non-platinum chemotherapy regimen was permitted.

- Prior hormonal therapy was permitted; this treatment was not counted as a non-platinum regimen.

- There was no upper limit on the number of prior platinum-based regimens that may have been received, but the patient must have been sensitive to the penultimate platinum-based regimen administered.

- If both neoadjuvant and adjuvant treatment were administered pre/post any debulking surgery, this was considered 1 treatment regimen

- Prior maintenance therapy following a prior treatment regimen was permitted, with the exception of the regimen received immediately prior to maintenance in this study. No anti-cancer therapy was permitted to be administered as maintenance treatment in the interval period between completion of the most recent platinum-based therapy and initiation of study drug in this trial.

5. Achieved best response of either CR or PR to the most recent platinum-based regimen administered and was randomized to study treatment within 8 weeks of the last dose of platinum received

- The most recent platinum-based regimen must have been a chemotherapy doublet. The choice of the platinum and the second chemotherapy agent was per investigator' discretion.

- A minimum of 4 cycles of platinum chemotherapy must have been administered. There was no cap on the maximum number of cycles; however, additional cycles of treatment administered following completion of

therapy for the specific purpose of enabling patient eligibility and randomization within 8 weeks of the last platinum dose was not permitted.

- A CR was defined as a complete radiologic response per RECIST v1.1, ie, absence of any detectable disease and CA-125 < upper limit of normal (ULN)*

- A PR was defined as either a partial response per RECIST v1.1 (if disease was measurable prior to chemotherapy) or a serologic response per GCIG CA-125 response criteria (if disease was not measurable according to RECIST v1.1)*

*Note: It was acceptable for sites to utilize local and contemporaneous clinical imaging reports to record lesion measurement history and define a burden of disease according to RECIST; it was not a requirement to re-read radiological scans to collect these data.

- CA-125 must also have been < ULN for all responses classified as a PR

- R0 surgery (no visible tumor) or R1 surgery (residual disease < 1 cm) as a component of the most recent treatment regimen was not permitted. The response assessment must have been determined solely in relation to the chemotherapy regimen administered. The presence of measurable disease or CA-125 > 2 x ULN immediately prior to the chemotherapy regimen was required.

- Responses must have been maintained through the completion of chemotherapy and during the interval period between completion of chemotherapy and entry in the study

- All disease assessments performed prior to and during this chemotherapy regimen must have been adequately documented in the patient's medical record.

6. Have had sufficient archival formalin-fixed paraffin-embedded (FFPE) tumor tissue (1 x 4 µm section for hematoxylin and eosin stain and approximately 8 to 12 x 10 µm sections, or equivalent) available for planned analyses.

- The most recently collected tumor tissue sample should have been provided, if available

- Submission of a tumor block was preferred; if sections were provided, these must all have been from the same tumor sample

- Sample must have been received at the central laboratory at least 3 weeks prior to planned start of treatment in order to enable stratification for randomization.

7. Have had CA-125 measurement that was < ULN

8. Have had Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1

9. Have had adequate organ function confirmed by the following laboratory values obtained within 14 days of the first dose of study drug

- Bone Marrow Function
  - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
  - Platelets $> 100 \times 10^9$/L
  - Hemoglobin ≥ 9 g/dL
- Hepatic Function
  - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq 3 \times$ ULN; if liver metastases, then $\leq 5 \times$ ULN
  - Bilirubin $\leq 1.5 \times$ ULN (< 2 x ULN if hyperbilirubinemia is due to Gilbert's syndrome)
- Renal Function
  - Serum creatinine $\leq 1.5 \times$ ULN or estimated glomerular filtration rate (GFR) $\geq$ 45 mL/min using the Cockcroft Gault formula

Exclusion Criteria

Patients were excluded from participation if any of the following criteria applied:

1. History of a prior malignancy except:

- Curatively treated non-melanoma skin cancer,

- Breast cancer treated curatively > 3 years ago, or other solid tumor treated curatively

> 5 years ago, without evidence of recurrence,

- Synchronous endometrioid endometrial cancer (Stage 1A G1/G2).

2. Prior treatment with any PARP inhibitor, including oral or intravenous rucaparib. Patients who previously received iniparib were eligible.

3. Required drainage of ascites during the final 2 cycles of their last platinum-based regimen and/or during the period between the last dose of chemotherapy of that regimen and randomization to maintenance treatment in this study.

4. Symptomatic and/or untreated central nervous system (CNS) metastases. Patients with asymptomatic previously treated CNS metastases were eligible provided they had been clinically stable for at least 4 weeks.

5. Pre-existing duodenal stent and/or any gastrointestinal disorder or defect that would, in the opinion of the Investigator, interfere with absorption of study drug.

6. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, or history of chronic hepatitis B or C.

7. Pregnant or breast feeding. Women of childbearing potential must have had a negative serum pregnancy test ≤ 3 days prior to first dose of study drug.

8. Received treatment with chemotherapy, radiation, antibody therapy or other immunotherapy, gene therapy, vaccine therapy, angiogenesis inhibitors, or experimental drugs ≤ 14 days prior to first dose of study drug and/or ongoing adverse effects from such treatment > National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade 1, with the exception of Grade 2 non-hematologic toxicity such as alopecia, peripheral neuropathy, and related effects of prior chemotherapy that were unlikely to be exacerbated by treatment with study drug.

Ongoing hormonal treatment for previously treated breast cancer was permitted. See also inclusion criteria 4.

9. Received administration of strong cytochrome P450 (CYP)1A2 or CYP3A4 inhibitors ≤ 7 days prior to first dose of study drug or had on-going requirements for these medications as described in the study protocol.

10. Non-study related minor surgical procedure ≤ 5 days, or major surgical procedure ≤ 21 days, prior to first dose of study drug; in all cases, the patient must have been sufficiently recovered and stable before treatment administration.

11. Presence of any other condition that may have increased the risk associated with study participation or may have interfered with the interpretation of study results, and, in the opinion of the investigator, would make the patient inappropriate for entry into the study.

Treatments

Patients initiated study treatment with 600 mg rucaparib or matched placebo BID, with or without food, and continued treatment in continuous 28-day cycles. Study treatment interruptions and/or dose reductions

were permitted due to events related to toxicity. Patients continued treatment until disease progression, unacceptable toxicity, patient or investigator request to discontinue, or death.

Objectives

The primary objective of the study is to evaluate progression-free survival (PFS) by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, as assessed by the investigator (invPFS), in molecularly-defined HRD subgroups, classified using the clinical trial assay (CTA), a well as in the overall ITT population.

A key, stand-alone secondary objective was to evaluate PFS by RECIST as assessed by independent radiology review (irrPFS). Other secondary objectives included evaluation of patient-reported outcome (PRO), both the disease-related symptoms – physical (DRS-P) subscale of National Comprehensive Cancer Network (NCCN) Functional Assessment of Cancer Therapy (FACT)-Ovarian Symptom Index (FOSI-18) and the complete [total score], as well as overall survival (OS), safety, and population pharmacokinetics (PPK) of rucaparib.

Exploratory objectives included assessment of cancer antigen-125 (CA-125), PFS on subsequent therapy (PFS2), overall response rate (ORR), duration of response (DOR), chemotherapy-free interval, time to first subsequent anti-cancer treatment, time to start of second subsequent anti-cancer treatment, PRO utilizing Euro-Quality of Life 5D (EQ-5D), and rucaparib exposure-efficacy/exposure safety relationships.

Outcomes / endpoints

Primary endpoints

1. PFS according to RECIST Version 1.1 (v1.1), as assessed by the investigator, or death from any cause (invPFS), in molecularly defined subgroups.

Secondary endpoints

1. Time to a 4-point decrease in the DRS-P subscale of the FOSI-18. The time to an event of worsening in the DRS-P subscale of the FOSI-18 was defined as the time from randomization to a 4-point reduction in the DRS-P subscale.
2. Time to an 8-point decrease in the total score of the FOSI-18. The time to an event of worsening in the total score of the FOSI-18 was defined as the time from randomization to an 8-point reduction in the total score. Additional clinical validation of this threshold was not undertaken.
3. Overall Survival defined as the time from randomization to date of death due to any cause
4. PFS according to RECIST v.1.1, as assessed by IRR, or death from any cause (irrPFS), in molecularly defined subgroups
5. Incidence of AEs, clinical laboratory abnormalities, and dose modifications
6. Individual model parameter estimates of rucaparib and covariates identification

Exploratory endpoints

1. Association between the change from baseline in CA-125 measurements and invPFS
2. PFS2 defined as time from randomization to the second event of disease progression as assessed by the investigator or death due to any cause. This second event of PFS may have been a documented event per RECIST guidelines or an event of symptomatic/clinical or CA-125 progression.
3. Chemotherapy free interval calculated as the time since the last dose of the most recent chemotherapy regimen to the date of the first dose of a subsequent chemotherapy after study drug + 1 day.

4. Time to start of first subsequent anti-cancer treatment, calculated in months as the time from randomization to the date of the first dose of the first subsequent anti-cancer treatment regimen after study drug + 1 day.
5. Time to start of second subsequent anti-cancer treatment, calculated in months as the time from randomization to the date of the first dose of the second subsequent anti-cancer treatment regimen after study drug + 1 day.
6. ORR per RECIST v1.1, as assessed by both investigator and IRR, in patients with measurable disease at study entry
7. DOR per RECIST Version 1.1, as assessed by both investigator and IRR
8. PRO as measured by the total score on the EQ-5D
9. Rucaparib PK, invPFS, irrPFS, CA-125, AEs, clinical laboratory abnormalities, and dose modifications

Sample size

Approximately 540 patients were planned to be randomized (2:1) to receive either rucaparib or placebo in this study, with a minimum of 180 and a maximum of 200 patients having a deleterious tBRCA mutation and a maximum of 150 patients with a known deleterious germline BRCA1/2 mutation (gBRCA) documented in their medical record. There was no minimum number of patients required for each of the nbHRD and biomarker negative subgroups; however, no more than 360 total patients were randomized for stratification into these subgroups combined.

Tumor HRD status by the CTA was determined after randomization, but before the final efficacy analysis. The primary endpoint (PFS in molecularly-defined HRD subgroups) was prospectively defined in this study.

The first patient was randomized into the study on 07 April 2014; randomization was completed on 19 July 2016, with 564 patients randomized (rucaparib [n = 375]; placebo [n = 189]) in total. In mid-April 2017, the IDMC notified the sponsor that the target number of PFS events in the tBRCA-mutant population had been achieved as of the visit cut-off of 15 April 2017. This notification led the sponsor to initiate activities to support the treatment blind break. In June 2017, the treatment assignment was unblinded to enable the primary analysis and evaluation of the study efficacy results.

Table 14: Estimated sample sizes and power calculations

Group	Hazard Ratio	Cumulative N	Minimum Number of Events (70%)	Median PFS Placebo vs Rucaparib (months)	Power	One-sided Alpha
tBRCA	0.50	180	126	6 vs 12	90%	0.025
All HRD (tBRCA + nbHRD)	0.60	300	210	6 vs 10	90%	0.025
ITT Population (tBRCA + nbHRD + Biomarker Negative)	0.70	540	378	6 vs 8.5	90%	0.025

The primary efficacy analysis was planned to end after 70% of the patients in the tBRCA subgroup have an observed event of investigator-determined disease progression or death. If the minimum number of tBRCA patients were enrolled, then the primary analysis was planned to be performed following the 126th event of investigator-determined disease progression or death. Similarly, if the maximum number of tBRCA patients

were enrolled then the primary analysis was planned to be performed following the 140th event of investigator-determined disease progression or death.

The Independent Data Monitoring Committee (IDMC) informed the sponsor when the required number of PFS events has been observed in order to ensure the sponsor remains blinded to which patients are in the tBRCA subgroup.

Randomisation

Patients were randomized (2:1) within 8 weeks following last dose of platinum-based chemotherapy and study treatment was initiated within 3 days of randomization.

At the time patients were stratified, the optimal LOH cutoff had not been determined, thus mutations in genes other than BRCA1 or BRCA2 were used as a method to identify patients with HRD tumors. Patients were stratified at randomization into one of 3 HRD subgroups (tBRCA [includes gBRCA and sBRCA], non-BRCA HRD [nbHRD], and biomarker negative) through analysis of homologous recombination gene mutations in DNA extracted from tumor tissue by the CTA developed by Foundation Medicine, Incorporated (FMI). The CTA identified deleterious mutations in 30 genes involved in HRR: BRCA1/2 (stratified into the tBRCA) and 28 other HRR genes (stratified into nbHRD). Patients with no deleterious mutations identified in any of the 30 HRR genes were stratified into the biomarker negative subgroup. Additional randomization stratification factors included: PFI following their penultimate platinum-based regimen (6 to 12 months or > 12 months), and best response (CR or PR) to their most recent platinum-based regimen.

Blinding (masking)

This was a double-blind study.

Statistical methods

The primary efficacy endpoint was PFS as assessed by the investigator (invPFS). The time to invPFS was calculated in months as the time from randomization to disease progression +1 day, as determined by RECIST v1.1 criteria or death due to any cause, whichever occurs first.

Only scans and deaths prior to the start of any subsequent anti-cancer treatment or within 90 days of treatment end date were included in the analysis. Patients without a documented event of progression were censored on the date of their last tumor assessment (i.e., radiologic assessment) prior to the start of any subsequent anti-cancer treatment or within 90 days of treatment end date. Patients who withdrew without a disease progression event and did not have any post-baseline tumor assessment were censored at date of randomization.

The stratified log rank test was considered the primary analysis for invPFS comparing rucaparib to placebo.

H0: HR (rucaparib/placebo) $\geq$ 1.
Ha: HR (rucaparib /placebo) < 1.

In addition, a stratified Cox proportional hazard model was used to calculate the hazard ratio (HR) between the treatment groups. The following randomization strata were used to estimate the treatment effect:

- HRD classification by the CTA (tBRCA, nbHRD, biomarker negative)
- Best response to most recent platinum-based regimen (CR, PR)
- Interval between completion of the penultimate platinum-based regimen and disease progression (6 to 12 months or > 12 months)

Sensitivity Analyses for PFS

Sensitivity analyses for invPFS were performed to evaluate the impact of censored patients. According to the study protocol, tumor scans were to continue to be performed during follow up for patients who discontinued without a documented disease progression event by RECIST v1.1. As such, a sensitivity analysis was performed in which all tumor scans or death events were included for assessment of PFS even if the patient discontinued study treatment or initiated a subsequent anticancer therapy. Patients who discontinued the study due to clinical progression were considered to have a PFS event on the date of their last dose of treatment.

In order to further evaluate the effectiveness of rucaparib in the HRD subgroups, the interaction between treatment and HRD status were tested using the Cox proportional hazards model for the primary endpoint of invPFs. The model included:

- Indicator variable for treatment with rucaparib;
- Categorical variable for HRD status; and
- Interaction between treatment and HRD status.

Secondary key efficacy endpoints

- Disease Related Symptoms – Physical Subscale of the FOSI-18

The time to an event of worsening in the DRS-P subscale of the FOSI-18 was defined as the time from randomization to a 4-point reduction in the DRS-P subscale. Patients without a documented event of a 4-point reduction were censored on the date of their last adequate FOSI-18 assessment or date of randomization if no FOSI-18 assessments had been completed. For patients without a baseline FOSI-18 assessment their values were censored at date of randomization.

- Total Score of the FOSI-18

The time to an event of worsening in the total score of the FOSI-18 was defined as the time from randomization to an 8-point reduction in the total score. Patients without a documented event of an 8-point reduction were censored on the date of their last adequate FOSI-18 assessment or date of randomization if no FOSI-18 assessments had been completed. For patients without a baseline FOSI-18 assessment their values were censored at date of randomization.

- Progression-free Survival by Independent Radiology Review (irrPFS)

The time to irrPFS was calculated in months as the time from randomization to disease progression + 1 day, as determined by the IRR or death due to any cause, whichever occurred first.

Only scans and deaths prior to the start of any subsequent anti-cancer treatment or within 90 days of treatment end date were included in the analysis. Patients without a documented event of progression were censored on the date of their last tumor assessment (i.e., radiologic assessment) prior to the start of any subsequent anti-cancer treatment or within 90 days of treatment end date. Patients who withdrew without a disease progression event and did not have any post-baseline tumor assessment were censored at date of randomization.

- Overall Survival

The time to overall survival was calculated in months as the time from randomization to date of death due to any cause. Patients who were still alive were censored on the date of their last available visit or last date known to be alive. It was anticipated that the data for overall survival would be heavily censored at the time of the primary endpoint analysis. In order to adjust for multiple analyses of overall survival at a later stage, a stopping rule was applied. The Haybittle-Peto stopping rule was applied where an overall survival result

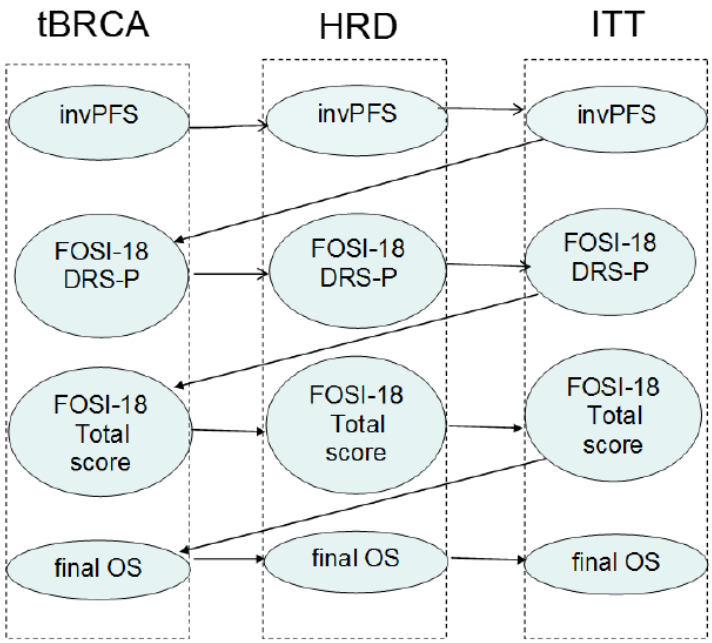
with a p-value <0.001 could be used to claim superiority of rucaparib compared to placebo. This meant that a p-value <0.05 could be utilized at the final analysis which was projected to be once 70% of the death events has been collected.

The same statistical test used for the primary endpoint (i.e., stratified log rank test and a stratified Cox proportional model) was used to compare rucaparib to placebo for all secondary endpoints.

The primary and key secondary endpoints were tested among the tBRCA, HRD, and ITT subgroups using an ordered step-down multiple comparisons procedure (Figure 8). Statistically significant differences between rucaparib and placebo groups were tested at a one-sided 0.025 significance level starting with invPFS in the tBRCA population, followed by the HRD and ITT populations. Once statistical significance was not achieved for one test, the statistical significance was not declared for all subsequent analyses in the ordered step-down procedure.

The primary and secondary efficacy endpoints were also evaluated in the non-nested, non-overlapping subgroups (tBRCA, non-tBRCA LOH+, non-tBRCA LOH-, and non-tBRCA LOH unknown) in order to ensure that 1) the results in the HRD subgroup were not solely driven by results in the tBRCA subgroup and 2) the results in the ITT subgroup were not solely driven by results of the tBRCA or HRD subgroups.

Figure 8: Ordered Step-down Procedure



Abbreviations: DRS-P = disease-related symptoms-physical subscale; FOSI-18 = Functional Assessment of Cancer Therapy (FACT)-Ovarian Symptom Index-18; invPFS = investigator-assessed progression-free survival; OS = overall survival.

Study population

HRD subgroups

The HRD subgroups within the Study CO-338-014 ITT population were based on analysis of tumour-extracted DNA by the NGS-based CTA developed by FMI. The pre-specified LOH cut-off of ≥ 16% was selected for prospective testing in Study CO-338-014.

The HRD-defined nested populations used for the primary efficacy analyses included:

- tBRCA: Patients with a tumour harboring a deleterious BRCA mutation (includes both germline and somatic);
- HRD (tBRCA or non-tBRCA LOH+): Patients who were found to have a tBRCA mutation and/or to have LOH ≥ 16%; and
- ITT Population: All patients randomized (HRD [tBRCA or non-tBRCA LOH+] or non-tBRCA LOH- and non-tBRCA LOH unknown).

In addition, the following non-nested subgroups were explored for efficacy:

- Non-tBRCA LOH+: Patients without a deleterious tBRCA mutation and with percent of tumor genome LOH ≥ 16%;
- Non-tBRCA LOH-: Patients without a deleterious tBRCA mutation and with percent of tumor genome LOH < 16%;
- Non-tBRCA LOH unknown: Patients without a deleterious tBRCA mutation and with percent of tumor genome LOH unknown.

BRCA mutation subgroups

The tumour-based CTA used in this study identifies deleterious mutations in the BRCA1 and BRCA2 genes; however, it does not distinguish between the BRCA mutation type, i.e., germline or somatic. In order to determine whether a BRCA mutation detected by the CTA was germline or somatic, DNA extracted from blood was sequenced using the BRCAnalysis test developed by Myriad Genetics. The germline and somatic designation for a tBRCA mutation was based on the results of both tumour and blood BRCA testing.

Table 15: Definition of population and patient's subgroups

Definitions of terms	
ITT population	The intent-to-treat (ITT) population consisted of all randomized patients.
Safety population	The Safety population consisted of all patients who received at least 1 dose of protocol-specified treatment.
Patient subgroups derived from a tissue next-generation sequencing (NGS)-based homologous recombination deficient (HRD) assay result:	
tBRCA	Patients who are classified as having a tumor with a deleterious BRCA mutation (includes both germline and somatic)
HRD	Patients who are classified as having HRD tumors. Within Study CO-338-014, the HRD subgroup consisted of tBRCA and non-tBRCA LOH+ patients (see non-tBRCA LOH+ definition below).
nbHRD	Within Study CO-338-014, patients with a tumor that did not contain a deleterious tBRCA mutation, but did have a deleterious mutation in 1 of the 28 pre-specified homologous recombination DNA repair (HRR) genes, were considered nbHRD for randomization stratification.
biomarker-negative	Within Study CO-338-014, patients with a tumor that did not contain a deleterious tBRCA mutation or deleterious mutation in 1 of the 28 the pre-specified HRR genes were identified as 'biomarker negative' for randomization stratification.
Non-tBRCA LOH+:	Patients without a deleterious tBRCA mutation and with percent of tumor genome loss of heterozygosity (LOH) ≥ 16%.
Non-tBRCA LOH-	Patients without a deleterious tBRCA mutation and with percent of tumor genome LOH < 16%.
Non-tBRCA LOHunknown	Patients who do not have a deleterious tBRCA mutation and for whom the LOH result is unknown.

Results

Participant flow

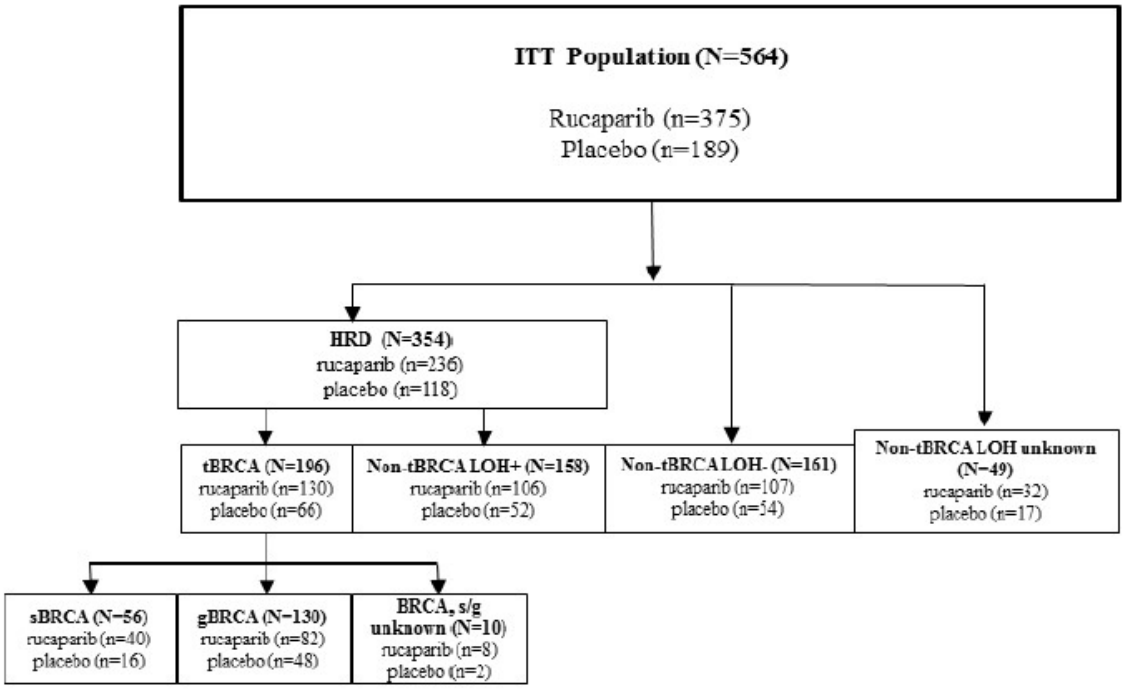


Figure 9: Disposition Flowchart of ITT Population and HRD Subgroups

Source: Figure 2, Study CO-338-014 CSR
Abbreviations: gBRCA = germline mutation in breast cancer gene; HRD = homologous recombination deficiency; ITT = intent-to treat; LOH = loss of heterozygosity; sBRCA = somatic mutation in breast cancer gene; tBRCA = deleterious tumor mutation in BRCA1 or BRCA2, includes gBRCA and sBRCA.

Table 16: Summary of Patient Disposition - ITT Population

Parameter	Rucaparib (N = 375) n (%)	Placebo (N = 189) n (%)	Overall (N = 564) n (%)
Patient Population			
Intent-to-treat population	375 (100.0)	189 (100.0)	564 (100.0)
Safety population	372 (99.2)	189 (100.0)	561 (99.5)
tBRCA population	130 (34.7)	66 (34.9)	196 (34.8)
HRD population	236 (62.9)	118 (62.4)	354 (62.8)
End-of-treatment Status			
Ongoing	60 (16.0)	5 (2.6)	65 (11.5)
Discontinued	315 (84.0)	184 (97.4)	499 (88.5)
Primary reason for discontinuation of study drug[a]			
Disease progression[b]	228 (72.4)	170 (92.4)	398 (79.8)
Clinical progression[b]	12 (3.8)	7 (3.8)	19 (3.8)
Adverse event[c]	52 (16.5)	1 (0.5)	53 (10.6)
Patient withdrew consent[c, d]	7 (2.2)	2 (1.1)	9 (1.8)
Investigator decision	3 (1.0)	0 (0.0)	3 (0.6)
Withdrew consent for treatment only[d]	9 (2.9)	4 (2.2)	13 (2.6)
Protocol non-compliance	1 (0.3)	0 (0.0)	1 (0.2)
Other	3 (1.0)	0 (0.0)	3 (0.6)

Source: Table 14.1.1.1
Abbreviations: HRD = homologous recombination deficiency; ITT = intent-to-treat; tBRCA = deleterious tumor mutatation in BRCA1 or BRCA2, includes gBRCA and sBRCA.
a Percentages based on the number of patients who discontinued study drug.

Recruitment

Study CO-338-014 is fully enrolled and ongoing.

The target number of PFS events in the tBRCA-mutant population was achieved as of the visit cut-off of 15 April 2017, and treatment assignment was unblinded in June 2017 following IDMC recommendation .

Efficacy analyses included all randomized patients and all data up to visit cut-off date of 15 April 2017.

Table 17: Summary of Study CO-338-014 and Cut-off Dates for Analysis of Efficacy

Study	Treatment Arm	N	Ovarian Cancer Type	Enrollment	Visit Cut-off
CO-338-014	Rucaparib (600 mg[a] BID)	375	EOC: N=312 FTC: N=32 PPC: N=31	First patient enrolled 07 April 2014; Enrollment completed 19 July 2016 All enrolled patients included	15 April 2017[b]
	Placebo	189	EOC: N=159 FTC: N=10 PPC: N=19		
Total number of patients		564	EOC: N=471 FTC: N=42 PPC: N=50		

Source: Table 10, Study CO-338-014 CSR
Abbreviations: BID = twice a day; EOC = epithelial ovarian cancer; FTC = fallopian tube cancer; PFS2 = PFS on a subsequent line of treatment; PPC = primary peritoneal cancer
a Rucaparib and placebo were administered as 120-mg tablets.
b Except PFS2, for which an updated data cut-off has been provided (ie, 31 December 2017).

Conduct of the study

The original protocol was dated 9 September 2013. As of 15 April 2017, the data cut-off date for the interim CSR, the protocol had been amended 3 times.

A total of 13 patients in the ITT population had deviations assessed as major protocol violations: 11 patients (2.9%) in the rucaparib group and 2 patients (1.1%) in the placebo group. In the rucaparib group, 7 patients had major protocol violations to inclusion criteria (2 had not achieved at least PR to their most recent platinum-based regimen, and 3 did not have the first dose of study drug within 8 weeks, and 1 had more than 1 non-platinum chemotherapy regimen received, and 1 had neutrophil count lower than required). Four patients in the rucaparib group had violations to exclusion criteria (2 had prior history of melanoma, 1 patient had a diagnosis of stage 1 colon cancer and 1 had recurrent breast cancer within 5 years of signing the ICF). In the placebo group, 1 patient had a violation to inclusion criteria (more than 1 non-platinum chemotherapy regimen received), and one to exclusion criteria (medical history of resolved chronic hepatitis B).

A total of 4 patients had major protocol violations due to incorrect study drug administration: 3 in the rucaparib group and 1 in the placebo group. In each case, the patient received one bottle of the incorrect study drug.

Baseline data

Table 18: Patient demographics – ITT population

	Rucaparib (N=375)	Placebo (N=189)	Overall (N=564)
Age (yr)			
n	375	189	564
Mean (StD)	60.5 (9.28)	60.7 (9.71)	60.6 (9.42)
Median	61.0	62.0	61.0
Min, Max	39.0, 84.0	36.0, 85.0	36.0, 85.0
Age Group, n (%)			
<65 yr	237 (63.2)	117 (61.9)	354 (62.8)
65-74 yr	113 (30.1)	64 (33.9)	177 (31.4)
75-85 yr	25 (6.7)	8 (4.2)	33 (5.9)
Race, n (%)			
American Indian or Alaska Native	3 (0.8)	1 (0.5)	4 (0.7)
Asian	14 (3.7)	7 (3.7)	21 (3.7)
Black or African American	6 (1.6)	2 (1.1)	8 (1.4)
Native Hawaiian or Other Pacific Islander	0	0	0
White	302 (80.5)	149 (78.8)	451 (80.0)
Other	3 (0.8)	3 (1.6)	6 (1.1)
Missing[a]	47 (12.5)	27 (14.3)	74 (13.1)
Geographic Region, n (%)			
North America	132 (35.2)	70 (37.0)	202 (35.8)
Western Europe	183 (48.8)	94 (49.7)	277 (49.1)
Australia/New Zealand	46 (12.3)	20 (10.6)	66 (11.7)
Israel	14 (3.7)	5 (2.6)	19 (3.4)
BMI (kg/m^2)			
n	373	187	560
Mean (StD)	27.9 (7.31)	26.6 (5.18)	27.4 (6.70)
Median	26.6	25.8	26.4
Min, Max	14.6, 113.1	16.2, 50.5	14.6, 113.1
ECOG at Baseline			
0	280 (74.7)	136 (72.0)	416 (73.8)
1	95 (25.3)	53 (28.0)	148 (26.2)

Source: Table 14.1.3.1
Abbreviations: BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; max = maximum; min = minimum; StD = standard deviation; yr = year.
a Missing information is due to national data protection laws prohibiting the collection of race information.

Table 19: Disease Characteristics - ITT Population

	Rucaparib (N=375)	Placebo (N=189)	Overall (N=564)
Time Since Cancer Diagnosis (months)			
n	375	189	564
Mean (StD)	48.3 (32.31)	46.4 (28.39)	47.7 (31.04)
Median	37.3	38.4	37.5
Min, Max	15.4, 265.2	15.0, 249.9	15.0, 265.2
Time Since Cancer Diagnosis Group, n (%)			
>12-24 months	52 (13.9)	25 (13.2)	77 (13.7)
>24 months	323 (86.1)	164 (86.8)	487 (86.3)
Type of Ovarian Cancer, n (%)			
Epithelial Ovarian Cancer	312 (83.2)	159 (84.1)	471 (83.5)
Fallopian Tube Cancer	32 (8.5)	10 (5.3)	42 (7.4)
Primary Peritoneal Cancer	31 (8.3)	19 (10.1)	50 (8.9)
Other	0	1 (0.5)	1 (0.2)
Histological Classification, n (%)			
Serous	357 (95.2)	179 (94.7)	536 (95.0)
Endometrioid	16 (4.3)	7 (3.7)	23 (4.1)
Mixed	1 (0.3)	3 (1.6)	4 (0.7)
Other	1 (0.3)	0	1 (0.2)
Histological Grade (Two Tier), n (%)			
High Grade	375 (100.0)	189 (100.0)	564 (100.0)
FIGO Stage at Diagnosis, n (%)			
FIGO Stage IA	0	2 (1.1)	2 (0.4)
FIGO Stage IB	1 (0.3)	1 (0.5)	2 (0.4)
FIGO Stage IC	11 (2.9)	4 (2.1)	15 (2.7)
FIGO Stage IIA	5 (1.3)	2 (1.1)	7 (1.2)
FIGO Stage IIB	7 (1.9)	1 (0.5)	8 (1.4)
FIGO Stage IIC	14 (3.7)	10 (5.3)	24 (4.3)
FIGO Stage IIIA	14 (3.7)	2 (1.1)	16 (2.8)
FIGO Stage IIIB	24 (6.4)	12 (6.3)	36 (6.4)
FIGO Stage IIIC	238 (63.5)	120 (63.5)	358 (63.5)
FIGO Stage IV	54 (14.4)	30 (15.9)	84 (14.9)
Other	4 (1.1)	2 (1.1)	6 (1.1)
Missing	3 (0.8)	3 (1.6)	6 (1.1)

Source: Table 14.1.4.1
Abbreviations: FIGO = International Federation of Gynecology and Obstetrics; max = maximum; min = minimum; StD = standard deviation.

Table 20: Disease Burden - ITT Population

	Rucaparib (N=375)	Placebo (N=189)	Overall (N=564)
Measureable Disease per Investigator, n (%)			
Yes	141 (37.6)	66 (34.9)	207 (36.7)
No	234 (62.4)	123 (65.1)	357 (63.3)
Number of Target Lesions per Investigator			
n	141	66	207
Mean (StD)	1.7 (0.88)	1.6 (0.94)	1.7 (0.89)
Median	1.0	1.0	1.0
Min, Max	1.0, 5.0	1.0, 5.0	1.0, 5.0
Sum of the Diameters of Target Lesions per Investigator (mm)			
n	141	66	207
Mean (StD)	33.6 (29.71)	33.1 (28.00)	33.5 (29.11)
Median	26.0	24.0	24.9
Min, Max	10.0, 221.0	10.0, 150.0	10.0, 221.0
Bulky Lesions (lesion >20 mm) per Independent Review, n (%)			
Yes	71 (18.9)	29 (15.3)	100 (17.7)
No	304 (81.1)	160 (84.7)	464 (82.3)

Source: Table 14.1.3.3
Abbreviations: max = maximum; min = minimum; StD = standard deviation

Table 21: Prior Anti-cancer Therapies - ITT Population

	Rucaparib (N=375)	Placebo (N=189)	Overall (N=564)
Number of Prior Chemotherapy Regimens			
n	375	189	564
Mean (StD)	2.5 (0.78)	2.5 (0.81)	2.5 (0.79)
Median	2.0	2.0	2.0
Min, Max	2.0, 6.0	2.0, 6.0	2.0, 6.0
Number of Prior Chemotherapy Regimens Group, n (%)			
2	231 (61.6)	124 (65.6)	355 (62.9)
3	108 (28.8)	42 (22.2)	150 (26.6)
4	23 (6.1)	17 (9.0)	40 (7.1)
5	11 (2.9)	5 (2.6)	16 (2.8)
>5	2 (0.5)	1 (0.5)	3 (0.5)
Number of Prior Platinum Regimens			
n	375	189	564
Mean (StD)	2.5 (0.71)	2.4 (0.66)	2.5 (0.69)
Median	2.0	2.0	2.0
Min, Max	2.0, 6.0	2.0, 5.0	2.0, 6.0
Number of Prior Platinum Regimens Group, n (%)			
2	236 (62.9)	126 (66.7)	362 (64.2)
3	109 (29.1)	47 (24.9)	156 (27.7)
>3	30 (8.0)	16 (8.5)	46 (8.2)
Penultimate Progression-free Interval after Last Dose of Platinum (months)			
n	375	189	564
Mean (StD)	18.9 (15.69)	21.0 (21.79)	19.6 (17.98)
Median	13.8	14.6	14.1
Min, Max	5.8, 120.0	6.0, 238.5	5.8, 238.5

Penultimate Progression-free Interval after Last Dose of Platinum Group[a], n (%)			
≥6-12 months	153 (40.8)	68 (36.0)	221 (39.2)
>12-24 months	140 (37.3)	74 (39.2)	214 (37.9)
>24 months	82 (21.9)	47 (24.9)	129 (22.9)
Best Response from Previous Platinum Therapy[a], n (%)			
RECIST CR	122 (32.5)	60 (31.7)	182 (32.3)
RECIST / CA-125 PR	252 (67.2)	129 (68.3)	381 (67.6)
Stable Disease[b]	1 (0.3)	0	1 (0.2)
Randomization Stratification: Best Response from Previous Platinum Therapy[c], n (%)			
RECIST CR	126 (33.6)	64 (33.9)	190 (33.7)
RECIST / CA-125 PR	249 (66.4)	125 (66.1)	374 (66.3)
Randomization Stratification: Penultimate Progression-free Interval[b], n (%)			
6-12 months	151 (40.3)	76 (40.2)	227 (40.2)
>12 months	224 (59.7)	113 (59.8)	337 (59.8)

Source: Table 14.1.4.1
Abbreviations: CA-125 = cancer antigen 125; CR = complete response; eCRF = electronic case report form; IVRS = Interactive Voice Response System; max = maximum; min = minimum; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; StD = standard deviation
a Collected via eCRF
b An additional patient in the rucaparib group had stable disease that was incorrectly captured on the eCRF as partial disease (see Section 10.2)
c Captured via IVRS

Table 22: Number of cycles of platinum-based chemotherapy in immediate prior regimen

Number of Platinum Containing Chemotherapy Cycles	Rucaparib n = 375	Placebo n = 189
	n (%)	
4	30 (8.0)	14 (7.4)
5	29 (7.7)	8 (4.2)
6	259 (69.1)	139 (73.5)
7	18 (4.8)	15 (7.9)
8	24 (6.4)	6 (3.2)
9	5 (1.3)	4 (2.1)
10 or more	10 (2.7)	3 (1.6)

Source: Listing 90.14.1.2.R11.2 T2V Day 90 RtQ
Abbreviations: RtQ = Response to Questions; T2V = Type II Variation

Prior bevacizumab therapy was reported for 22% of patients who received rucaparib and 23% of patients who received placebo.

BRCA status

Tumour tissue samples for all of the patients (N=564) were tested centrally to determine HRD positive status (as defined by the presence of a deleterious tumour BRCA [tBRCA] mutation or high genomic loss of heterozygosity). Blood samples for 95% (186/196) of the tBRCA patients were evaluated using a central blood germline BRCA (gBRCA) test. Based on these results, 70% (130/186) of the tBRCA patients had a gBRCA mutation and 30% (56/186) had a somatic BRCA mutation.

Numbers analysed

The population analysed for efficacy comprised all 564 patients (ITT) population randomised to either rucaparib (n=375) or placebo (n=189).

Outcomes and estimation

Primary efficacy endpoint

Table 23: Progression-free Survival per Investigator and IRR in Primary Analysis Populations and HRD Subgroups

Parameter	Investigator Assessment		IRR	
	Rucaparib	Placebo	Rucaparib	Placebo
Primary analysis subgroups				
ITT population[a]				
Patients, n	375	189	375	189
PFS events, n (%)	234 (62%)	167 (88%)	165 (44%)	133 (70%)
PFS, median in months (95% CI)	10.8 (8.3, 11.4)	5.4 (5.3, 5.5)	13.7 (11.0, 19.1)	5.4 (5.1, 5.5)
HR (95% CI)	0.36 (0.30, 0.45)		0.35 (0.28, 0.45)	
p-value[b]	< 0.0001		< 0.0001	
HRD Group[c]				
Patients, n	236	118	236	118
PFS events, n (%)	134 (57%)	101 (86%)	90 (38%)	74 (63%)
PFS, median in months (95% CI)	13.6 (10.9, 16.2)	5.4 (5.1, 5.6)	22.9 (16.2, NA)	5.5 (5.1, 7.4)
HR (95% CI)	0.32 (0.24, 0.42)		0.34 (0.24, 0.47)	
p-value[b]	< 0.0001		< 0.0001	
tBRCA Group[d]				
Patients, n	130	66	130	66
PFS events, n (%)	67 (52%)	56 (85%)	42 (32%)	42 (64%)
PFS, median in months (95% CI)	16.6 (13.4, 22.9)	5.4 (3.4, 6.7)	26.8 (19.2, NA)	5.4 (4.9, 8.1)
HR (95% CI)	0.23 (0.16, 0.34)		0.20 (0.13, 0.32)	
p-value[b]	< 0.0001		< 0.0001	
Exploratory analysis of non-nested subgroups				
nonBRCA LOH+ Group				
Patients, n	106	52	106	52
PFS events, n (%)	67 (63%)	45 (87%)	48 (45%)	32 (62%)
PFS, median in months (95% CI)	9.7 (7.9, 13.1)	5.4 (4.1, 5.7)	11.1 (8.2, NA)	5.6 (2.9, 2.8)
HR (95% CI)	0.44 (0.29, 0.66)		0.554 (0.35, 0.89)	
p-value[b]	< 0.0001		0.0135	
nonBRCA LOH- Group				
Patients, n	107	54	107	54
PFS events, n (%)	81 (73%)	50 (93%)	63 (59%)	46 (85%)
PFS, median in months (95% CI)	6.7 (5.4, 9.1)	5.4 (5.3, 7.4)	8.2 (5.6, 10.1)	5.3 (2.8, 5.5)
HR (95% CI)	0.58 (0.40, 0.85)		0.47 (0.31, 0.71)	
p-value[b]	0.0049		0.0003	

a. All randomised patients.
b. Two-sided p-value
c. HRD includes all patients with a deleterious germline or somatic BRCA mutation or non-tBRCA with high genomic loss of heterozygosity, as determined by the clinical trial assay (CTA).
d. tBRCA includes all patients with a deleterious germline or somatic BRCA mutation, as determined by the CTA.

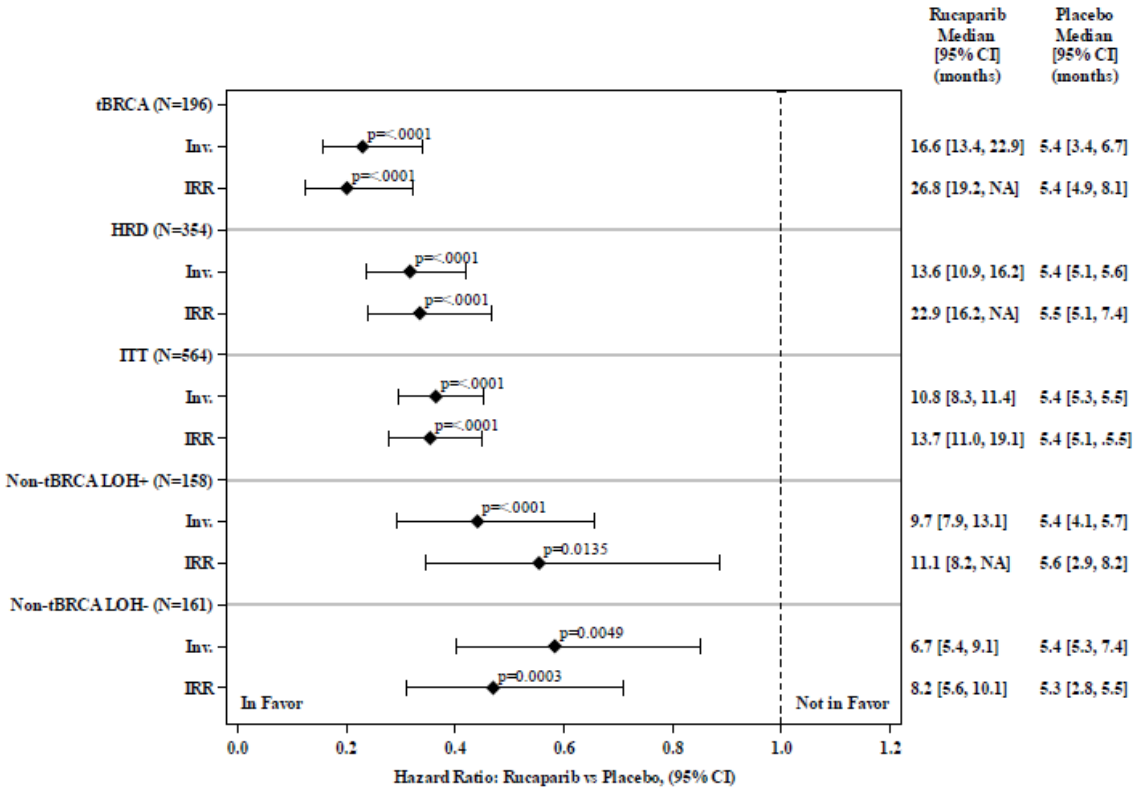


Figure 10: Progression-free Survival per Investigator and IRR in Primary Analysis Populations and HRD Subgroups

Source: Table 2.7.3-3; For invPFS and irrPFS, respectively, Figure 4 and Figure 10 (tBRCA), Figure 5 and Figure 11 (HRD), Figure 6 and Figure 12 (ITT), Figure 7 and Figure 13 (Non-tBRCA LOH+), Figure 8 and Figure 14 (Non-tBRCA LOH-) Study CO-338-014 CSR.
Abbreviations: CI = confidence interval; HRD = homologous recombination deficiency; Inv. = investigator; IRR = independent radiology review; ITT = intent-to-treat; LOH = loss of heterozygosity; NA = not assessable; PFS = progression-free survival; tBRCA = deleterious tumor mutation in BRCA1 or BRCA2, includes gBRCA and sBRCA
Note: p-values determined using stratified Cox proportional hazard model

Patients in Study CO-338-014 were treated for a median of 8.3 months (range 0-35 months). The majority of patients (58.9%) were treated with rucaparib for at least 6 months, and 34.9% were exposed over 1 year. For the ITT population, 44.6% of rucaparib patients were progression-free after 1 year of treatment as compared to just 8.8% in the placebo group. Persistence of effect continued to be observed at 18 and 24 months, where 32.0% and 26.0%, respectively, of ITT patients who received rucaparib remained progression-free as compared to 5.8% and 2.6%, respectively, in the placebo group.

Table 24: Percent of patients progression-free from 6 to 24 months

Time after Initiation of Treatment	PFS by Investigator Review (Primary Endpoint)		PFS by Blinded Independent Central Review (Key Secondary Endpoint)	
	Rucaparib	Placebo	Rucaparib	Placebo
	% of Patients			
tBRCA				
6 months	80.5	41.0	83.5	40.3
12 months	59.9	12.9	71.9	25.8
18 months	46.5	8.1	64.5	11.5
24 months	35.7	5.4	55.0	11.5
HRD				
6 months	74.9	38.2	76.8	43.2
12 months	51.4	11.8	60.5	24.6
18 months	40.3	8.0	55.3	14.8
24 months	32.6	2.4	49.4	11.1
ITT				
6 months	67.9	36.4	71.0.	36.3
12 months	44.6	8.8	53.0	16.9
18 months	32.0	5.8	45.1	10.8
24 months	25.6	2.6	40.1.	8.7
Non-tBRCA LOH+				
6 months	68.4	34.6	68.7	46.9
12 months	41.3	10.8	45.2	23.7
18 months	32.9	8.1	43.2	18.9
24 months	31.1	0	43.2	9.5
Non-tBRCA LOH-				
6 months	52.4	38.6	58.9	26.7
12 months	31.8	4.3	33.4	6.5
18 months	13.7	2.1	21.7	6.5
24 months	9.6	2.1	18.1	6.5

Source: Figures 2.7.3-4 to 2.7.3-11 T2V
Abbreviations: HRD = homologous recombination deficiency; IRR = independent radiology review; ITT = intent-to-treat; LOH = loss of heterozygosity; PFS = progression-free survival; tBRCA = deleterious tumor mutation in BRCA1 or BRCA2, includes gBRCA and sBRCA

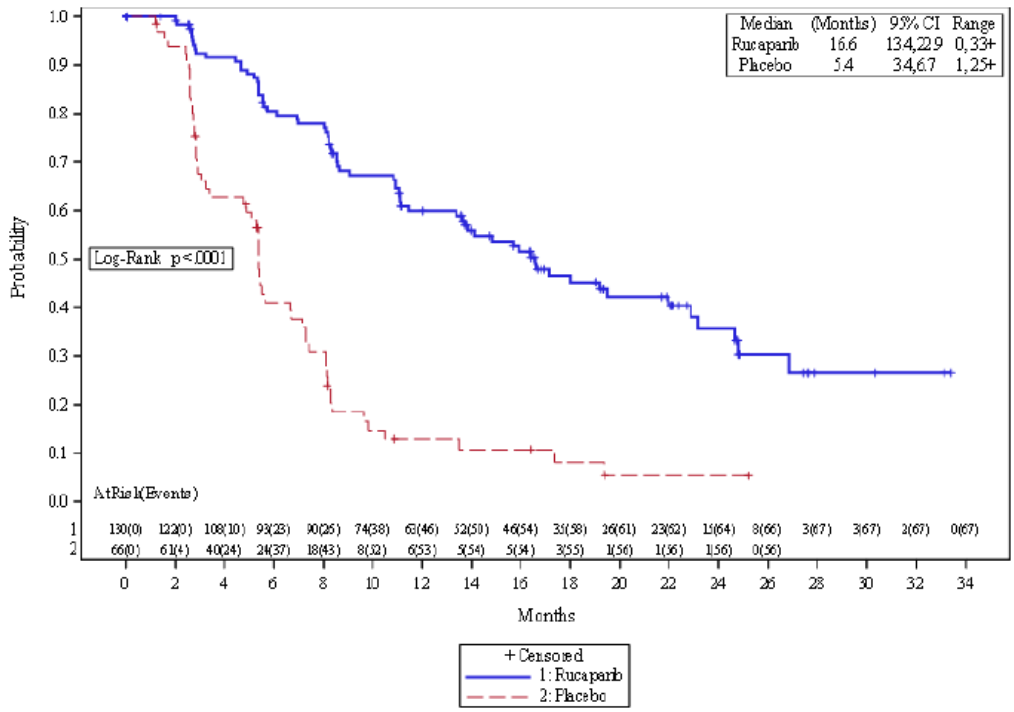


Figure 11: Progression-free Survival per Investigator – tBRCA population

Source: Figure 4, Study CO-338-014 CSR
Abbreviations: CI = confidence interval; tBRCA = deleterious tumor mutation in BRCA1 or BRCA2, includes gBRCA and sBRCA.
Note: Log-rank analysis was performed by randomization strata for best response and penultimate platinum progression-free interval.

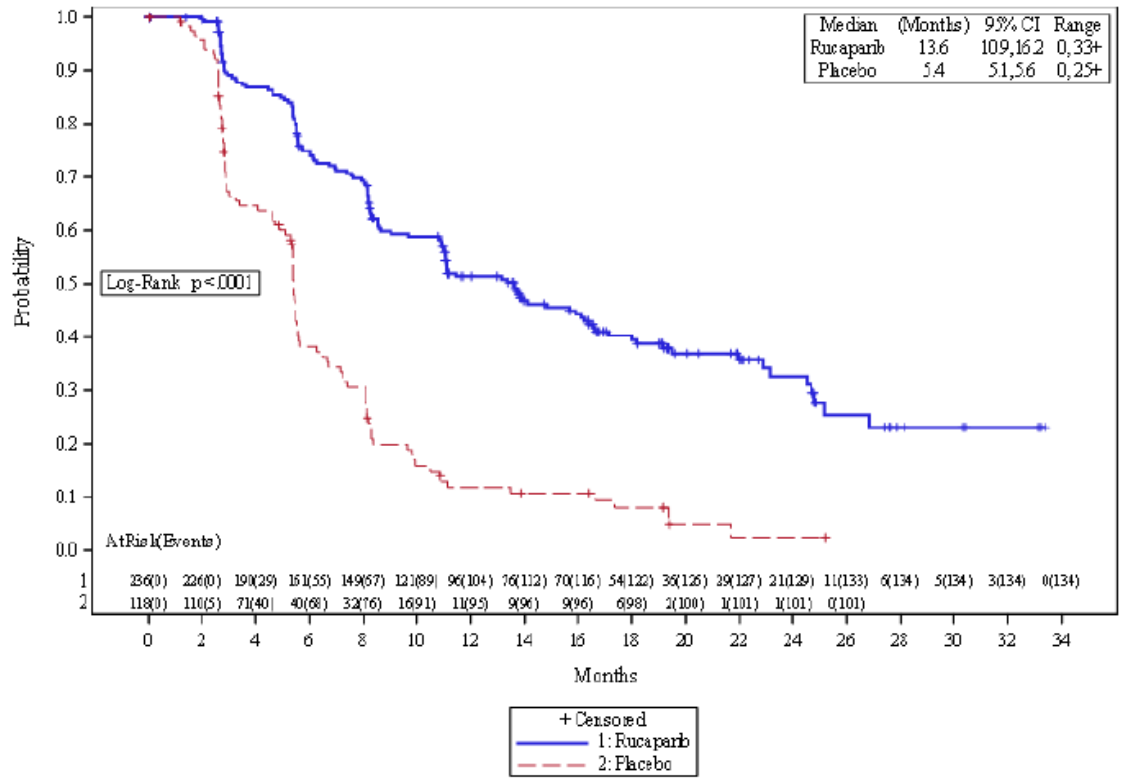


Figure 12: Progression-free Survival per Investigator – HRD population

Source: Figure 5, Study CO-338-014 CSR
Abbreviations: CI = confidence interval; CTA = clinical trial assay; HRD = homologous recombination deficiency
Note: Log-rank analysis was performed by randomization strata for HRD classification by CTA, best response, and penultimate platinum progressive-free interval.

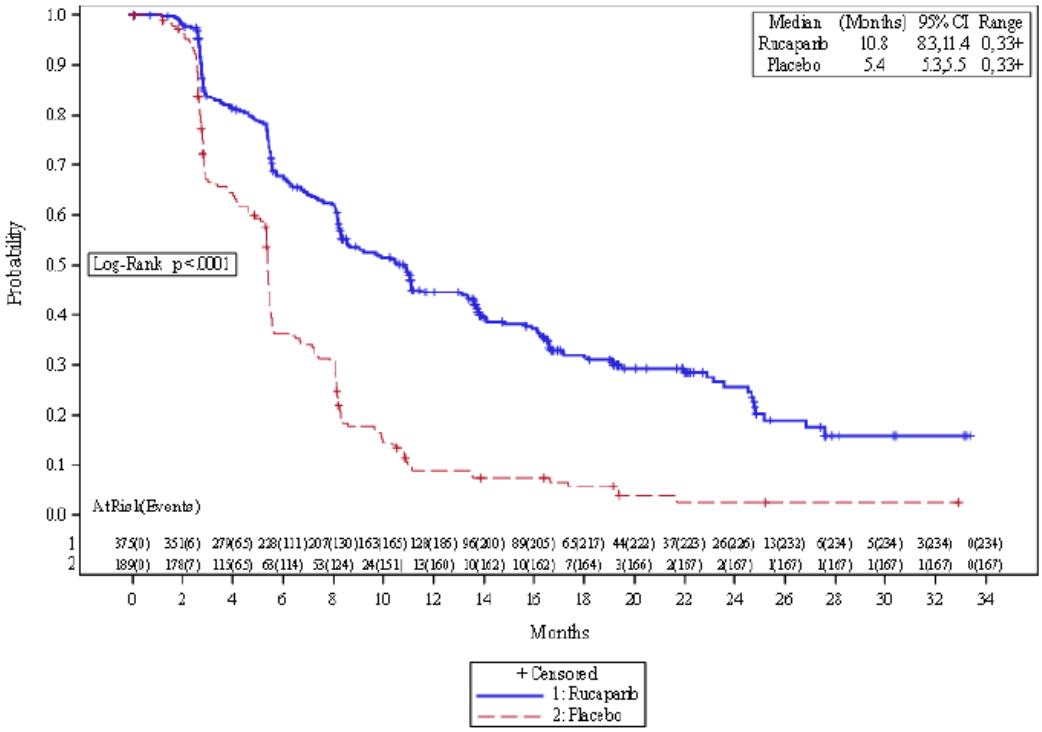


Figure 13: Progression-free Survival per Investigator – ITT Population

Source: Figure 6, Study CO-338-014 CSR
Abbreviations: CI = confidence interval; CTA = clinical trial assay; HRD = homologous recombination deficiency; ITT = intent-to-treat.
Note: Log-rank analysis was performed by randomization strata for HRD classification by CTA, best response, and penultimate platinum progressive-free interval.

Exploratory analyses of non-tBRCA LOH+, non-tBRCA LOH-, and non-tBRCA LOH unknown subgroups are presented below.

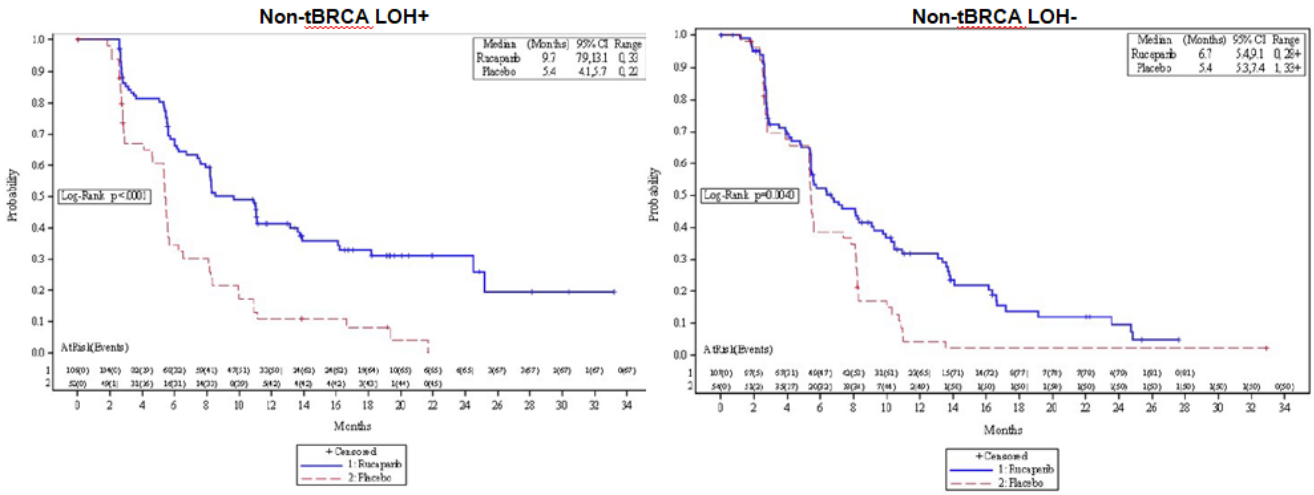


Figure 14: Progression-free Survival per Investigator – Non-tBRCA LOH+, Non-tBRCA LOH-

Source: Figure 7, Figure 8, Study CO-338-014 CSR
Abbreviations: CI = confidence interval; CTA = clinical trial assay; HRD = homologous recombination deficiency; ITT = intent-to-treat; LOH = loss of heterozygosity; tBRCA = deleterious tumor mutation in BRCA1 or BRCA2, includes gBRCA an sBRCA.
Note: Log-rank analysis was performed by randomization strata for HRD classification by CTA, best response and penultimate platinum progression-free interval

Sensitivity analyses, including censoring distribution, interaction between treatment and HRD status, and randomization stratification, were performed for the primary efficacy endpoint of invPFS. The results of these analyses are discussed in the Ancillary Analyses section.

Secondary efficacy endpoints

- **PFS assessed by independent radiology review**

PFS assessed by independent radiology review (irrPFS) was conducted as a key stand-alone secondary endpoint in support of the primary endpoint of invPFS.

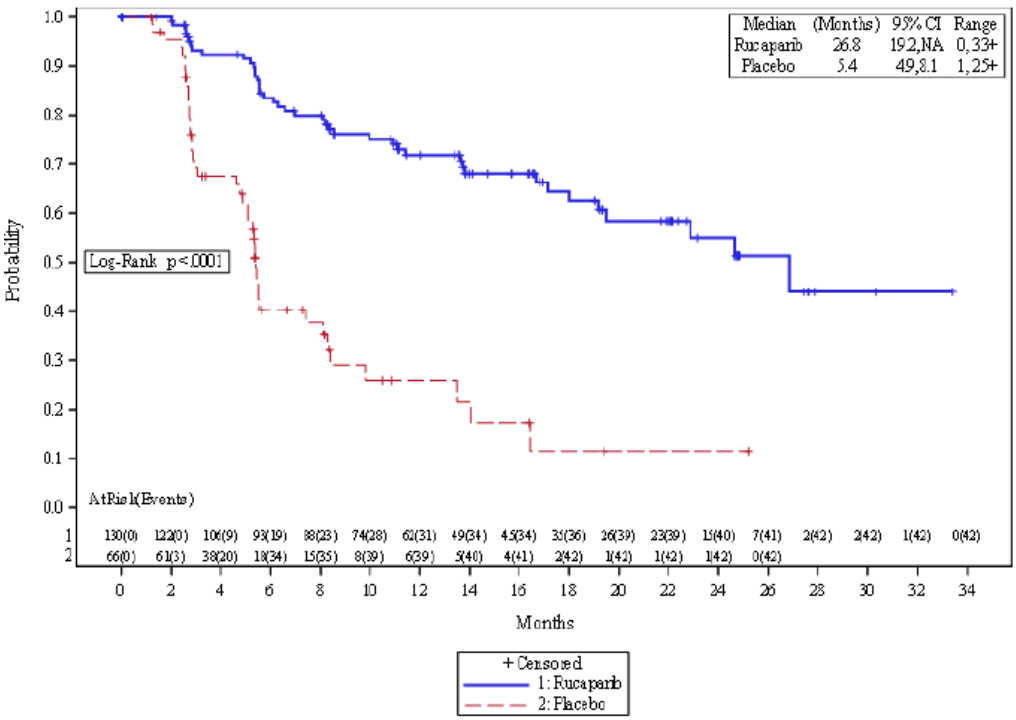


Figure 15: Progression free Survival by Independent Radiology Review – tBRCA Population

Source: Figure 10, Study CO-338-014 CSR
Abbreviations: CI = confidence interval; NA = not assessable; tBRCA = deleterious tumor mutation in BRCA1 or BRCA2, includes gBRCA and sBRCA.
Note: Log-rank analysis was performed by randomization strata for best response and penultimate platinum progression-free interval.

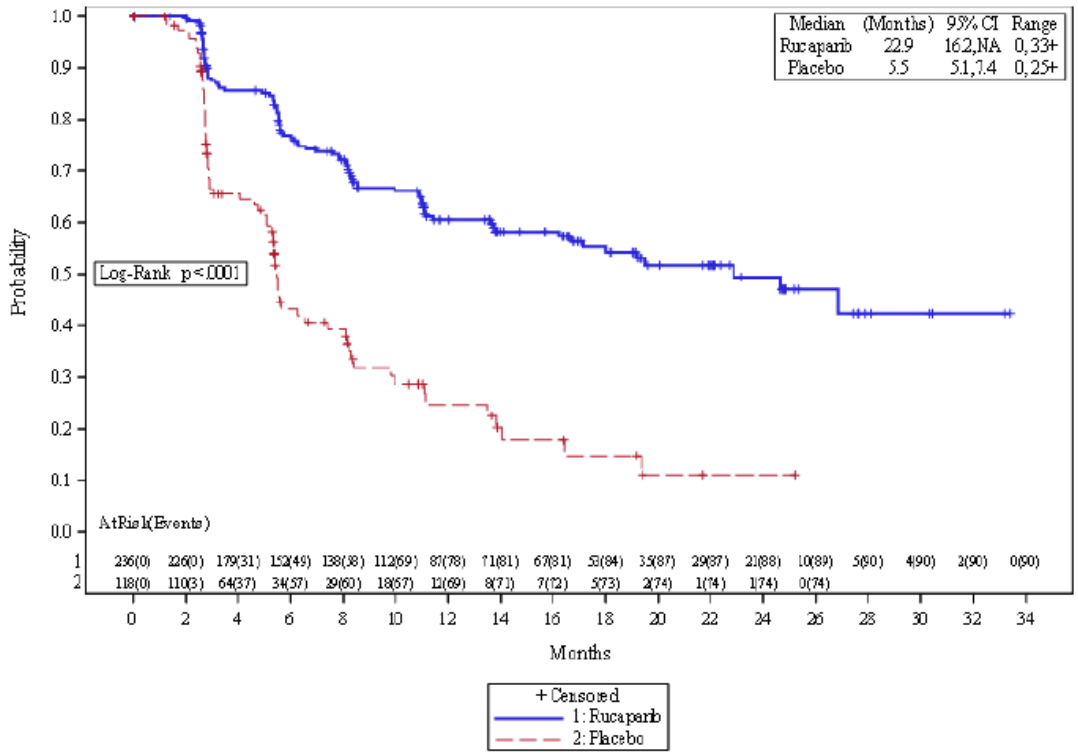


Figure 16: Progression free Survival by Independent Radiology Review – HRD Population

Source: Figure 11, Study CO-338-014 CSR
Abbreviations: CI = confidence interval; CTA = clinical trial assay; HRD = homologous recombination deficient
Note: Log-rank analysis was performed by randomization strata for HRD classification by CTA, best response, and penultimate platinum progression-free interval.

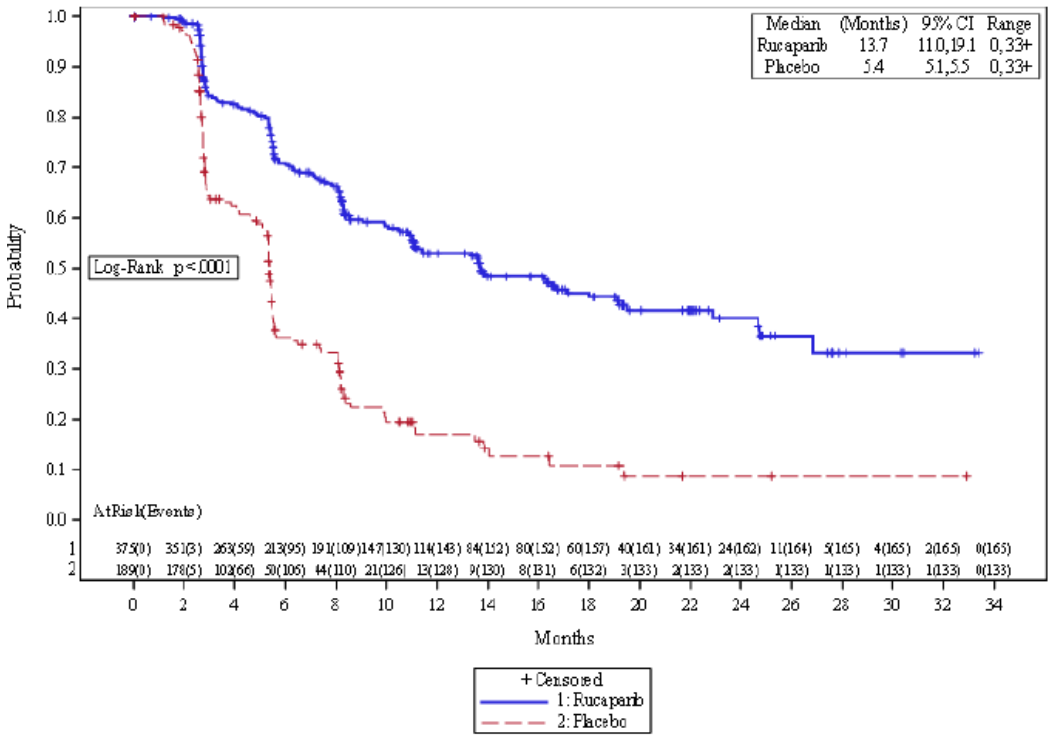


Figure 17: Progression free Survival by Independent Radiology Review –ITT Population

Source: Figure 12, Study CO-338-014 CSR
Abbreviations: CI = confidence interval; CTA = clinical trial assay; HRD = homologous recombination deficiency; ITT = intent-to-treat
Note: Log-rank analysis was performed by randomization strata for HRD classification by CTA, best response, and penultimate platinum progression-free interval.

- PRO using the Disease-related Symptoms – Physical subscale of the FOSI-18

Table 25: FOSI-18 Completion Rates (ITT Population)

	Completion Rate (%)			
	Rucaparib		Placebo	
Visit	Patients randomized[a]	Patients attending visit[b]	Patients randomized[a]	Patients attending visit[b]
Baseline	86.1 (323/375)	86.1 (323/375)	91.5 (173/189)	91.5 (173/189)
Cycle 2 Day 1	73.9 (277/375)	76.7 (277/361)	85.2 (161/189)	86.1 (161/187)
Cycle 3 Day 1	72.8 (273/375)	78.7 (273/347)	78.8 (149/189)	82.3 (149/181)
Cycle 4 Day 1	62.7 (235/375)	78.1 (235/301)	70.4 (133/189)	84.7 (133/157)
Cycle 5 Day 1	56.5 (212/375)	76.3 (212/278)	54.0 (102/189)	84.3 (102/121)
Cycle 6 Day 1	52.3 (196/375)	76.3 (196/257)	49.7 (94/189)	84.7 (94/111)
Cycle 7 Day 1	46.1 (173/375)	73.6 (173/235)	35.4 (67/189)	78.8 (67/85)
Cycle 8 Day 1	42.4 (159/375)	76.1 (159/209)	28.0 (53/189)	85.5 (53/62)

Source: Table 14, Study CO-338-014 CSR
a Completion rate calculated using a denominator of all patients randomized (ITT population).
b Completion rate calculated using a denominator of the number of patients attending the respective visit.

Questionnaires were only administered while patients were receiving study drug; thus, the completion rate of the FOSI-18 questionnaire declined incrementally at each study visit for both treatment groups with approximately 50% completion by Cycle 6, due to patients discontinuing treatment. The FOSI-18 completion rates determined for patients who were still ongoing at each respective visit ranged between ~75% to ~90% for the first 8 cycles; the completion rates were consistently higher for the placebo group compared to the rucaparib group. The difference was first observed at the pre-treatment baseline visit, suggesting that the difference results from a random imbalance at the time of treatment allocation, rather than from an effect of study treatment.

For patients in the tBRCA subgroup, the median time to worsening in the DRS-P subscale with rucaparib treatment (1.9 months [95% CI, 1.4-3.7 months]) showed no significant difference compared to placebo (4.2 months [95% CI, 2.8-9.2 months]; stratified log rank, p = 0.2893).

Since statistical significance for time to an event of worsening in the DRS-P subscale of the FOSI-18 for the tBRCA population was not reached, no further statistical significance of subsequent secondary endpoints can be claimed. Test and p-values are presented for the other efficacy endpoints descriptively.

The analysis of worsening DRS-P subscale for the HRD population showed a shorter median time to deterioration of 1.9 months (95% CI, 1.8-2.8 months) vs. 4.8 months (95% CI, 3.7-9.2 months). Similarly, there was a shorter median time to worsening in the DRS-P subscale for the ITT population: 1.9 months (95% CI, 1.8-2.8 months) vs. 6.4 months (95% CI, 4.6-9.2 months) for the ITT subgroup.

- **PRO using the Total Score of the FOSI-18**

The time to worsening in the total FOSI-18 score for patients in the tBRCA population who received rucaparib was less compared to placebo: 2.8 months (95% CI, 1.9-3.7) for rucaparib and 9.2 months (95% CI, 4.6-10.2) for placebo. Similar results were observed for both the HRD population (rucaparib, 3.0 months [95% CI, 2.6-4.6] vs. placebo, 10.2 months [95% CI, 8.3 months-NA]); and ITT population (rucaparib, 2.9 months [95% CI, 2.7-3.7] vs. placebo, 10.8 months [95% CI, 9.2-17.5]).

As with the DRS-P subscale, sensitivity analysis showed that the missing values had no substantial impact on the results of time to worsening in the FOSI-18 total score. An exploratory analysis of the change from baseline of the FOSI-18 subscales and total score by visit showed that the treatment differences observed for the FOSI-18 total score were driven primarily by the Physical and Treatment Side Effects subscales. The subscales capture symptoms associated with common AEs of rucaparib, including fatigue, lack of energy and nausea. In addition, a small cognitive debriefing study of FOSI-18 concluded that there is a significant overlap in patient understandings of lack of energy and fatigue.

- **Interim Overall Survival**

For the tBRCA population, the number of deaths was small (rucaparib, 23/130 [17.7%]; placebo, 12/66 [18.2%]), and the median survival could not be determined. Similarly, for the HRD population, the median survival could not be determined due to the small number of deaths: rucaparib, 42/236 (17.8%); placebo, 24/118 (20.3%). The ITT population was similar to the tBRCA and HRD populations with approximately 20% deaths in each treatment group (rucaparib, 81/375 [21.6%]; placebo, 42/189 [22.2%]), and the median survival was 29.6 months (95% CI, 28.6 months-NA) for the rucaparib group and not assessable for the placebo group.

There were no differences in survival between rucaparib and placebo treatments in any of the 3 populations, by stratified log-rank analysis or by stratified Cox proportional hazard model. Patient follow-up for survival is continuing in a blinded manner.

Exploratory efficacy endpoints

- **CA-125 – Percent change from baseline and association with invPFS**

Mean percent increases from baseline in CA-125 were observed for both treatment groups at each assessment; however, the percent changes observed for the rucaparib group were substantially suppressed compared to the placebo group. Rucaparib demonstrated significant benefit over placebo in terms of suppressing the percent increase in CA-125 from baseline in all 3 analysis populations. The onset and duration of rucaparib benefit varied depending on the population, with rucaparib benefit occurring as early as Cycle 4 (tBRCA and HRD) or Cycle 7 (ITT) and sustained through Cycle 10 (all populations). An association between invPFS and CA-125 minimum change from baseline, as well as between invPFS and change (or percent change) of CA-125 from baseline to the first post-baseline assessment, was observed. Since CA-125 is a clinically utilized biomarker of tumor recurrence (increase in CA-125 values) or effective treatment (decrease in CA-125 values), it was anticipated that observed changes in CA-125 would be associated with PFS (ie, the longer the PFS, the lack of disease progression, and thus, less of an increase in CA-125 and conversely the shorter the PFS, the greater the increase in CA-125).

- **PFS2**

At the time of the 15 April 2017 visit cut-off, a prolongation of the median time to PFS2 was observed with rucaparib treatment compared to placebo in all 3 analysis populations. Consistent with these results, a risk reduction by the stratified Cox proportional hazard model was observed.

Table 26: **Time to Second Event of Disease Progression (Visit Cut-off 15 April 2017)**

Population	Rucaparib N % censoring	Rucaparib median PFS2 (95%CI), months	Placebo N % censoring	Placebo median PFS2 (95%CI), months	p-value[a]	Rucaparib vs placebo Hazard Ratio[b]
tBRCA	n = 130 63.8%	26.1 (22.8, NA)	n = 66 42.4%	17.9 (15.6, 22.8)	p = 0.0002	0.442 (p = 0.0003)
HRD	n = 236 60.6%	24.7 (20.8, 27.0)	n = 118 44.1%	17.9 (15.8, 21.8)	p = 0.0005	0.567 (p = 0.0006)
ITT	n = 375 54.9%	21.1 (18.1, 23.7)	n = 189 41.8%	16.5 (14.6, 18.4)	p < 0.0001	0.617 (p = 0.0001)

Source: Figure 14.2.5.1 (tBRCA), Figure 14.2.5.2 (HRD), Figure 14.2.5.3 (ITT), and Table 14.2.1.2.10, Study CO-338-014 CSR
Abbreviations: CI = confidence interval, HRD = homologous recombination deficiency, ITT = intent-to-treat, NA = not assessable; PFS2 = second event of progression-free survival, tBRCA = deleterious tumor mutation in BRCA1 or BRCA2, includes gBRCA and sBRCA.
a Log-rank analysis was performed by randomization strata for HRD classification by CTA, best response, and penultimate platinum progression-free interval.
b Cox proportional hazard model.

Updated analyses of PFS2 have been performed for the updated safety data cut-off date (31 December 2017) for the T2V. A prolongation of the median time to PFS2 was observed with rucaparib treatment compared to placebo in all 3 analysis populations. Consistent with these results, a risk reduction by the stratified Cox proportional hazard model was observed.

Table 27 : Time to Second Event of Disease Progression (Visit Cut-off 31 December 2017)

Population	Rucaparib N % censoring	Rucaparib median PFS2 (95%CI), months	Placebo N % censoring	Placebo median PFS2 (95%CI), months	p-value[a]	Rucaparib vs placebo Hazard Ratio[b]
tBRCA	n = 130 50.8%	26.8 (23.4, 41.4)	n = 66 36.4%	18.4 (15.7, 23.6)	p = 0.0035	0.558 (p = 0.0040)
HRD	n = 236 47.0%	25.3 (21.9, 28.5)	n = 118 33.9%	18.4 (15.8, 22.1)	p = 0.0039	0.652 (p = 0.0042)
ITT	n = 375 40.5%	21.0 (18.9, 23.6)	n = 189 29.1%	16.5 (15.2, 18.4)	p = 0.0001	0.656 (p = 0.0002)

Source: Figure 14.2.5.1.1 (tBRCA), Figure 14.2.5.2.1 (HRD), Figure 14.2.5.3.1 (ITT), and Table 14.2.1.2.10.1, Study CO-338-014 Supporting Data T2V.
Abbreviations: CI = confidence interval, HRD = homologous recombination deficiency, ITT = intent-to-treat, NA = not assessable; PFS2 = second event of progression-free survival, T2V = Type II Variation; tBRCA = deleterious tumor mutation in BRCA1 or BRCA2, includes gBRCA and sBRCA.
a Log-rank analysis was performed by randomization strata for HRD classification by CTA, best response, and penultimate platinum progression-free interval.
b Cox proportional hazard model.

- **Chemotherapy-free interval**

At the time of the visit cut-off for this analysis (15 April 2017), the censoring rate for the chemotherapy-free interval ranged 43%-54% for the rucaparib group and 9%-19% for the placebo group.

Table 28: Time of Chemotherapy-free Interval

Population	Rucaparib N % censoring	Rucaparib median CFI (95%CI), months	Placebo N % censoring	Placebo median CFI (95%CI), months	p-value[a]	Rucaparib vs placebo Hazard Ratio[b]
tBRCA	n = 130 53.8%	20.8 (17.7, NA)	n = 66 19.7%	9.1 (7.2, 10.9)	p < 0.0001	0.291 (p < 0.0001)
HRD	n = 236 47.9%	18.2 (15.1, 21.1)	n = 118 18.6%	9.2 (8.1, 10.8)	p < 0.0001	0.411 (p < 0.0001)
ITT	n = 375 42.6%	15.0 (13.2, 17.5)	n = 189 17.5%	9.2 (8.1, 10.5)	p < 0.0001	0.443 (p < 0.0001)

Source: Figure 14.2.7.1 (tBRCA), Figure 14.2.7.2 (HRD), Figure 14.2.7.3 (ITT), and Table 14.2.1.2.12, Study CO-338-014 CSR
Abbreviations: CFI = chemotherapy-free interval, CI = confidence interval, HRD = homologous recombination deficiency, ITT = intent-to-treat, NA = not assessable, tBRCA = deleterious tumor mutation in BRCA1 or BRCA2, includes gBRCA and sBRCA.
a Log-rank analysis was performed by randomization strata for HRD classification by CTA, best response, and penultimate platinum progression-free interval.
b Cox proportional hazard model.

- **Time to start of first subsequent and second subsequent anti-cancer treatment**

The results for time to start of first subsequent anti-cancer treatment are similar to those in the previous section (chemotherapy-free interval), including high censoring rates for the rucaparib group. The time to start of first subsequent anti-cancer treatment after study drug was delayed by rucaparib treatment compared to placebo for all 3 HRD subgroups. For the tBRCA population, the median time (95% CI) to the start of the first subsequent anti-cancer treatment was 19.0 months (15.9-26.8 months) for the rucaparib group and 7.2 months (5.6-9.1 months) for the placebo group (stratified log rank p < 0.0001). For the HRD population, rucaparib treatment delayed the initiation of subsequent treatment compared to placebo: 16.4 months (12.7-19.1 months) vs. 7.6 months (6.5-9.1 months, p < 0.0001;). Similar results were observed for the ITT population with the median time to subsequent treatment as 12.5 months (11.5-15.5 months) for the rucaparib group and 7.4 months (6.5-8.7 months) for the placebo group (p < 0.0001). Analysis by stratified Cox proportional hazard model provided consistent results.

The median time to start of the second subsequent anti-cancer treatment after study drug discontinuation is preliminary and exploratory due to the high censoring rates in each population and treatment group. For the tBRCA population, the median time to the start of the second subsequent treatment could not be determined for patients who received rucaparib due to the high censoring rate (67.7%). For the tBRCA population treated with placebo, the median time to start of a second anti-cancer treatment was 19.4 months (95% CI, 15.1-24.8; censoring rate = 48.5%). The stratified log-rank analysis indicated a treatment effect (p = 0.0019). Censoring rates remained high for the HRD population (65.3% rucaparib and 48.3% placebo), but the preliminary results indicated that rucaparib treatment delayed the initiation of the second subsequent treatment compared to placebo: 26.5 months (95% CI, 22.2-NA months) vs. 19.4 months (15.8-22.8 months; stratified log rank p = 0.0016). Similar results were observed for the ITT population with high censoring rates (57.9% rucaparib and 48.1% placebo), and a median time to the second subsequent treatment as 22.2 months (19.1-24.5 months) for the rucaparib group and 18.6 months (15.7- 21.0 months) for the placebo group (stratified log rank p = 0.0060). Analysis by stratified Cox proportional hazard model provided consistent results.

- **ORR and DOR per RECIST – assessed by investigator**

Investigator-assessed ORR per RECIST v1.1 was analyzed in the subgroup of patients who had measurable disease (ie, measurable target lesions) at baseline, per investigator assessment. Patients who entered the study with residual disease and were treated with rucaparib demonstrated further reduction in tumor

burden, including achieving complete responses. Similar percentages of patients (~35%) had measurable disease at baseline in either the rucaparib and placebo groups for each of the 3 HRD populations.

Table 29: Confirmed Response Rate by Investigator – Patients with Measurable Disease at Baseline

	Rucaparib	Placebo
tBRCA Population	**n=40**	**n=23**
Confirmed Response Rate (n [%])	15 (37.5)	2 (8.7)
95% CI (%)	22.7 - 54.2	1.1 - 28.0
P-value[a]	0.0055	
Best Overall Confirmed Response per RECIST v1.1 (n [%])		
CR	7 (17.5)	0
PR	8 (20.0)	2 (8.7)
SD	19 (47.5)	8 (34.8)
PD	5 (12.5)	13 (56.5)
NE	1 (2.5)	0

	Rucaparib	Placebo
HRD Population	**n=85**	**n=41**
Confirmed Response Rate (n [%])	23 (27.1)	3 (7.3)
95% CI (%)	18.0 - 37.8	1.5 - 19.9
P-value[a]	0.0031	
Best Overall Confirmed Response per RECIST v1.1 (n [%])		
CR	10 (11.8)	0
PR	13 (15.3)	3 (7.3)
SD	43 (50.6)	17 (41.5)
PD	18 (21.2)	21 (51.2)
NE	1 (1.2)	0
ITT Population	**n=141**	**n=66**
Confirmed Response Rate (n [%])	26 (18.4)	5 (7.6)
95% CI (%)	12.4 - 25.8	2.5 - 16.8
P-value[a]	0.0069	
Best Overall Confirmed Response per RECIST v1.1 (n [%])		
CR	10 (7.1)	1 (1.5)
PR	16 (11.3)	4 (6.1)
SD	71 (50.4)	29 (43.9)
PD	38 (27.0)	32 (48.5)
NE	6 (4.3)	0

Source: Table 15, Study CO-338-014 CSR.
Abbreviations: CI = confidence interval; CMH = Cochran-Mantel-Haenszel; CR = complete response; CTA = clinical trial assay; HRD = homologous recombination deficiency; ITT = intent-to-treat; NE = not evaluable; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease; tBRCA = deleterious tumor mutation in BRCA1 or BRCA2, includes gBRCA and sBRCA.
a Calculated using a stratified CMH test comparing the confirmed response rate between treatments adjusting for the randomization strata of HRD classification by CTA (for HRD and ITT), best response and penultimate platinum progression-free interval and treatment as fixed effects.

Investigator-assessed DOR was analyzed in the subgroup of patients who had measurable disease at baseline, per investigator assessment, and had a confirmed response (CR or PR) by RECIST v1.1. Evaluation of treatment differences for DOR in the 3 analysis populations was limited due to the few responders in the placebo arm.

The median DOR for the patients who received rucaparib in the tBRCA population was 14.0 months (95% CI, 10.3-NA), and due to the limited number of placebo patients who had a confirmed response, the median duration of response could not be determined (stratified log rank, p = 0.5312). Similar results were observed for the HRD population (stratified log rank, p = 0.5295), and for the ITT population, no difference was observed in the duration of response for the rucaparib and placebo groups (stratified log rank, p = 0.3260).

Table 30: ORR in Non-nested LOH Populations

Population	Rucaparib n/total (%)	Placebo n/total (%)
Non-tBRCA LOH+	8/45 (17.8%) 95% CI: (8.0%, 32.1%)	1/18 (5.6%) 95% CI: (0.1%, 27.3%)
Non-tBRCA LOH-	3/45 (6.7%) 95% CI: (1.4%, 18.3%)	2/21 (9.5%) 95% CI: (1.2%, 30.4%)
Non-tBRCA LOH unknown	0/11 (0%) 95% CI: (0%, 28.5%)	0/4 (0%) 95% CI: (0%, 60.2%)

- **PRO outcome of EQ-5D**

There were no or marginal declines in the EQ-5D visual analogue scale (VAS) scores when comparing rucaparib to placebo treatment in patients in the HRD subgroups (data not shown).

Ancillary analyses

Comparison of PFS as assessed by the investigator and independent radiology review

In Study CO-338-014, all radiology scans were sent to IRR in order to assess the key, stand-alone secondary endpoint of irrPFS. As of the visit cut-off of 15 April 2017, all baseline scans had been read by independent radiologists, and only one of the post-baseline scan assessments was not obtained and read by the independent reviewers.

While the hazard ratios were consistent between investigator- and IRR-assessment of PFS, the median point estimates with 95% confidence intervals of irrPFS were longer than invPFS in the rucaparib arm for the primary analysis populations (tBRCA, HRD, and ITT), as well as the exploratory analysis in the non-nested sub-populations (non- BRCA LOH+ and non-BRCA LOH-). This phenomenon has been observed in other clinical studies of PARP inhibitors evaluated in the maintenance setting in patients with relapsed, platinum-sensitive ovarian cancer.

Among the patients in the ITT population with an event of disease progression by investigator assessment or death (rucaparib, n=234; placebo, n=167), 121 patients (rucaparib, n = 84; placebo, n = 37) were censored without a progression event by IRR. There were 274 patients (rucaparib, n = 145; placebo, n = 129) with an event of progression assessed by both investigator and IRR.

When comparing the type of events leading to radiologic progression (new lesion, non-target lesion progression, and target lesion progression), there was a similar distribution in the type of disease progression events between the subgroup of patients where both investigator and IRR deemed the patient had progressed (n = 274) and the subgroup of patients where progression was assessed only by the investigator (n = 121) and not by IRR. Overall in this study, the disease progression events were unequivocal, with the majority of progression events determined through the presence of new lesions. In addition, discordance between investigator- and IRR-assessed PFS was not attributable to a specific

investigative site or subset of sites and occurred in similar proportions in both the rucaparib and placebo arms.

The sponsor performed a sensitivity analysis to assess the potential effect of informative censoring on the IRR-assessed median PFS estimate. Patients with an investigator-assessed disease progression event, but no IRR-assessed disease progression event were re-analyzed as having a progression event at the next scheduled tumour assessment, or if no further tumour assessment existed then 12 weeks later was used as per protocol schedule for tumour assessments.

Table 31: Progression-free Survival per IRR Sensitivity Analysis

Analysis Population	PFS by Blinded Independent Central Review (Sensitivity Analysis[a])	
	Median PFS (months) rucaparib vs placebo[b]	Hazard Ratio[c]
tBRCA (rucaparib n = 130; placebo n = 66)	16.9 vs 5.4 (p < 0.0001)	0.219 (p < 0.0001)
HRD (rucaparib n = 236; placebo n = 118)	11.4 vs 5.4 (p < 0.0001)	0.345 (p < 0.0001)
ITT (rucaparib n = 375; placebo n = 189)	10.5 vs 5.4 (p < 0.0001)	0.389 (p < 0.0001)

Source: Figure 14.2.4.8.1, Figure 14.2.4.8.2, Figure 14.2.4.8.3, and Table 14.2.1.2.36, Study CO-338-014 Supporting Data T2V.
Abbreviations: HRD = homologous recombination deficiency; ITT = intent-to-treat; PFS = progression-free survival; T2V = Type II Variation; tBRCA = deleterious tumor mutation in BRCA1 or BRCA2, includes gBRCA and sBRCA
a Patients with an event by investigator assessment but censored by IRR set to have a disease progression event at the next scheduled tumor assessment, or 12 weeks later if no assessment was available.
b Stratified log-rank analysis
c Stratified Cox proportional hazard model

Comparison of results in sub-populations

- **Randomization stratification**

Table 32: Median PFS per Investigator by Randomization Strata – ITT Population

Population/ Subgroup	Rucaparib	Placebo	p-value[a]
	Median PFS (95% CI) (months)	Median PFS (95% CI) (months)	
ITT	n = 375 10.8 (8.3, 11.4)	n = 189 5.4 (5.3, 5.5)	p < 0.0001
tBRCA	n = 130 16.6 (13.4, 22.9)	n = 66 5.4 (3.4, 6.7)	p < 0.0001
nbHRD	n = 28 11.1 (5.6, 16.6)	n = 15 5.5 (3.9, 5.6)	p < 0.0001
Biomarker-negative	n = 217 8.1 (6.3, 9.2)	n = 108 5.3 (4.2, 5.5)	p < 0.0001
PFI 6-12 months	n = 151 8.2 (6.2, 9.0)	n = 76 4.1 (2.8, 5.3)	p < 0.0001
PFI >12 months	n = 224 13.6 (10.9, 16.4)	n = 113 5.6 (5.4, 8.1)	p < 0.0001
Best Response PR	n = 249 9.0 (8.2, 11.1)	n = 125 5.3 (3.0, 5.4)	p < 0.0001
Best Response CR	n = 126 11.1 (10.3, 17.2)	n = 64 5.6 (5.4, 8.1)	p < 0.0001

Source: Table 16, Study CO-338-014 CSR.
Abbreviations: CI = confidence interval; CR = complete response; ITT = intent-to-treat; nbHRD = non-BRCA homologous recombination deficiency assessed by single gene mutations; PFI = progression-free interval; PFS = progression-free survival; PR = partial response.
[a] *Stratified log-rank test*

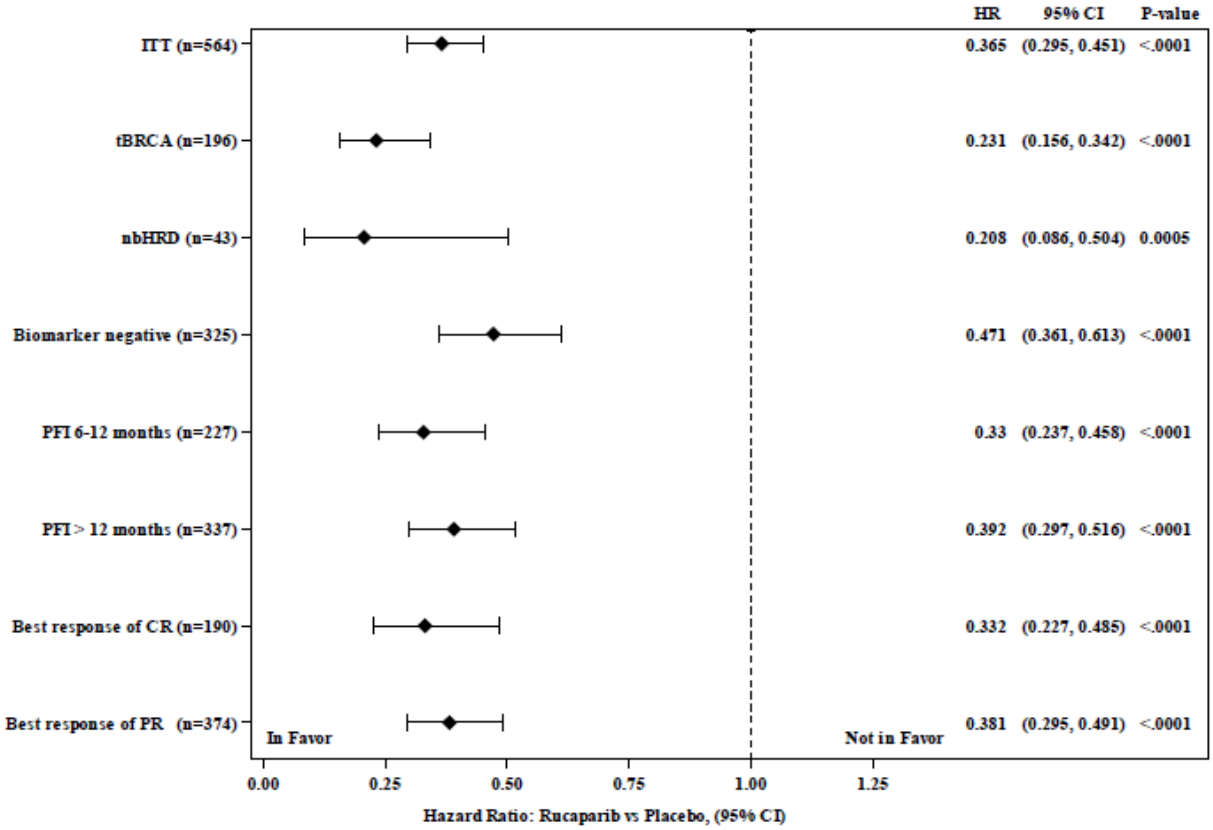


Figure 18: Forest Plot of PFS per Investigator by Randomization Strata – ITT Population

Source: Figure 22, Study CO-338-014 CSR.
Abbreviations: CI = confidence interval; CR = complete response; HR = hazard ration; ITT = intent-to-treat; nbHRD = non-BRCA homologous recombination deficiency assessed by single gene mutations; PFI = progression free interval; PFS = progression-free interval; PR = partial response; tBRCA = deleterious tumor mutation in BRCA1 or BRCA2, includes gBRCA and sBRCA.

- **HRD and gene mutation information**

Table 33: Median PFS per Investigator by HRD and Gene Mutation Information – ITT Population

Population/ Subgroup	Rucaparib Median PFS (95%CI) (months)	Placebo Median PFS (95%CI) (months)	p-value*
ITT	n = 375 10.8 (8.3, 11.4)	n = 189 5.4 (5.3, 5.5)	p < 0.0001
tBRCA	n = 130 16.6 (13.4, 22.9)	n = 66 5.4 (3.4, 6.7)	p < 0.0001
BRCA1 tBRCA	n = 80 14.1 (8.6, 16.6)	n = 37 5.4 (2.9, 8.1)	p < 0.0001
BRCA2 tBRCA	n = 50 24.7 (13.8, NA)	n = 29 5.4 (2.8, 6.7)	p < 0.0001
Germline tBRCA	n = 82 15.7 (10.9, 19.2)	n = 48 5.4 (4.7, 7.1)	p < 0.0001
Somatic tBRCA	n = 40 24.7 (11.1, NA)	n = 16 5.1 (2.6, 8.3)	p = 0.0002
HRD	n = 236 13.6 (10.9, 16.2)	n = 118 5.4 (5.1, 5.6)	p < 0.0001
Non-tBRCA LOH+	n = 106 9.7 (7.9, 13.1)	n = 52 5.4 (4.1, 5.7)	p < 0.0001
Non-tBRCA LOH-	n = 107 6.7 (5.4, 9.1)	n = 54 5.4 (5.3, 7.4)	p = 0.0040
Non-tBRCA LOH Unknown	n = 32 8.3 (5.6, 16.5)	n = 17 4.0 (2.6, 5.3)	p = 0.0003
nbHRD	n = 28 11.1 (5.6, 16.6)	n = 15 5.5 (3.9, 5.6)	p < 0.0001
Somatic tBRCA+ non-tBRCA LOH+	n = 146 11.1 (8.2, 14.8)	n = 68 5.4 (4.1, 5.6)	p < 0.0001
ITT excluding all germline tBRCA	n = 293 8.6 (8.1, 11.1)	n = 141 5.4 (4.6, 5.5)	p < 0.0001
All BRCA	n = 141 16.6 (13.4, 22.9)	n = 74 5.4 (4.7, 7.1)	p < 0.0001

Source: Table 17, Study CO-338-014 CSR.
Abbreviations: CI = confidence interval; CR = complete response; HRD = homologous recombination deficiency; ITT = intent-to-treat; LOH = loss of heterozygosity; nbHRD = non-BRCA HRD assessed by single gene mutations assessed by single gene mutations; NA = not assessed; PFI = progression-free interval; PFS = progression-free survival; PR = partial response; tBRCA = deleterious tumor mutation in BRCA1 or BRCA2, includes gBRCA and sBRCA.
a Stratified log-rank test

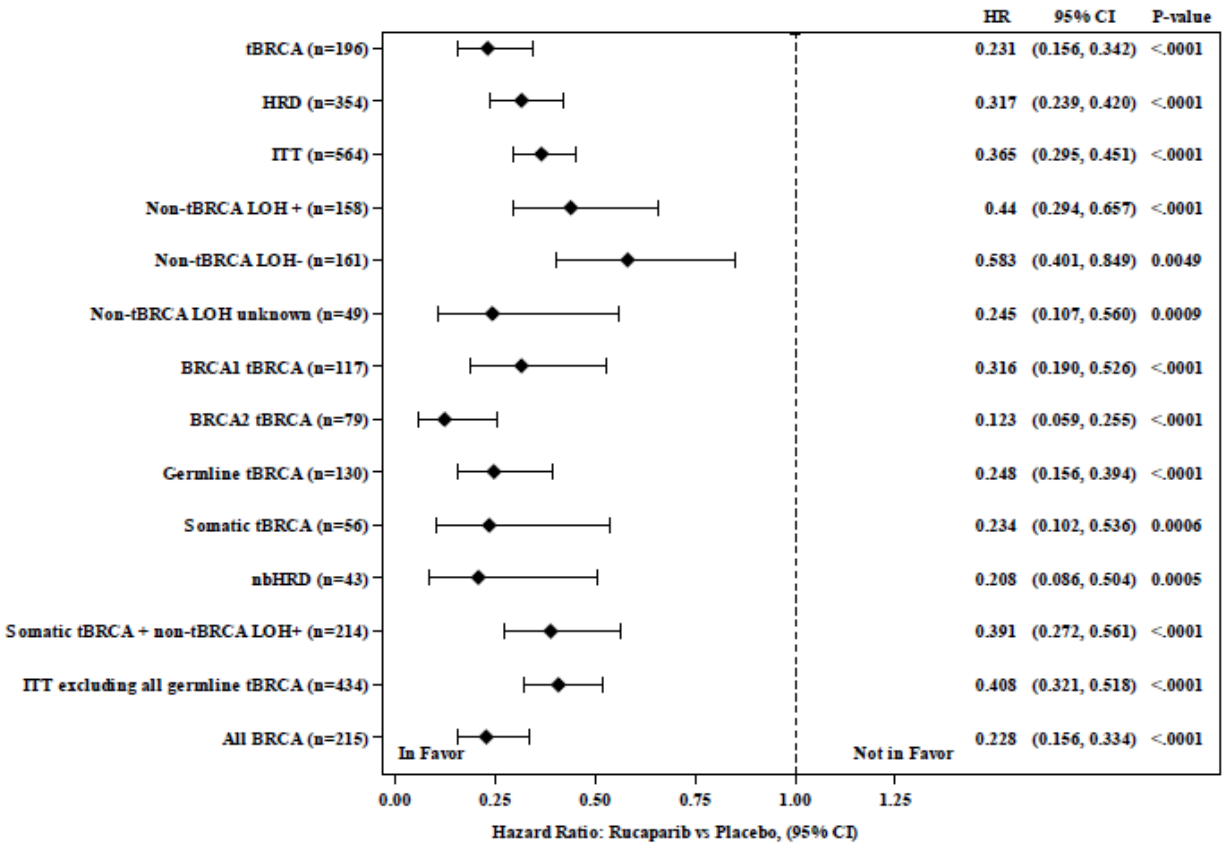


Figure 19: Forest Plot of PFS per Investigator by HRD and Gene Mutation Information – ITT Population

Source: Figure 23, Study CO-338-014 CSR
Abbreviations: CI = confidence interval; CR = complete response; ITT = intent-to-treat; nbHRD = non-BRCA homologous recombination deficiency; PFI = progression-free interval; PR = partial response; tBRCA = deleterious tumor mutation in BRCA1 or BRCA2, includes gBRCA and sBRCA

- **Demographics and disease burden at baseline**

Table 34: Median PFS per Investigator by Demographics and Baseline Disease Burden – ITT Population

Population/ Subgroup	Rucaparib Median PFS (95%CI) (months)	Placebo Median PFS (95%CI) (months)	p-value[a]
ITT	n = 375 10.8 (8.3, 11.4)	n = 189 5.4 (5.3, 5.5)	p < 0.0001
Age <65 yr	n = 237 11.1 (8.5, 13.7)	n = 117 5.4 (5.3, 5.6)	p < 0.0001
Age 65-74 yr	n = 113 8.3 (8.0, 11.1)	n = 64 5.3 (2.8, 5.6)	p < 0.0001
Age ≥75 yr	n = 25 9.2 (5.5, NA)	n = 8 5.5 (3.0, 11)	p = 0.1516
White	n = 302 10.8 (8.3, 13.1)	n = 149 5.4 (5.1, 5.5)	p < 0.0001
Non-White	n = 26 9.1 (5.3, 26.8)	n = 13 5.4 (2.6, 5.5)	p = 0.0071
Unknown Race	n = 47 11.0 (8.1, 16.1)	n = 27 5.5 (2.8, 8.3)	p = 0.0855
Measurable Disease	n = 141 8.2 (5.5, 9.2)	n = 5.3 5.3 (2.9, 5.4)	p < 0.0001
No Disease	n = 130 14.1 (10.9, 19.1)	n = 67 7.3 (5.4, 8.1)	p < 0.0001
Bulky Disease	n = 71 8.2 (5.4, 13.6)	n = 29 2.9 (2.6, 5.3)	p = 0.0007
No Bulky Disease	n = 304 11.0 (8.6, 13.6)	n = 160 5.4 (5.3, 5.6)	p < 0.0001

Source: Table 18, Study CO-338-014 CSR.
Abbreviations: CI = confidence interval; ITT = intent-to-treat; NA = not assessed.
a Stratified log-rank test

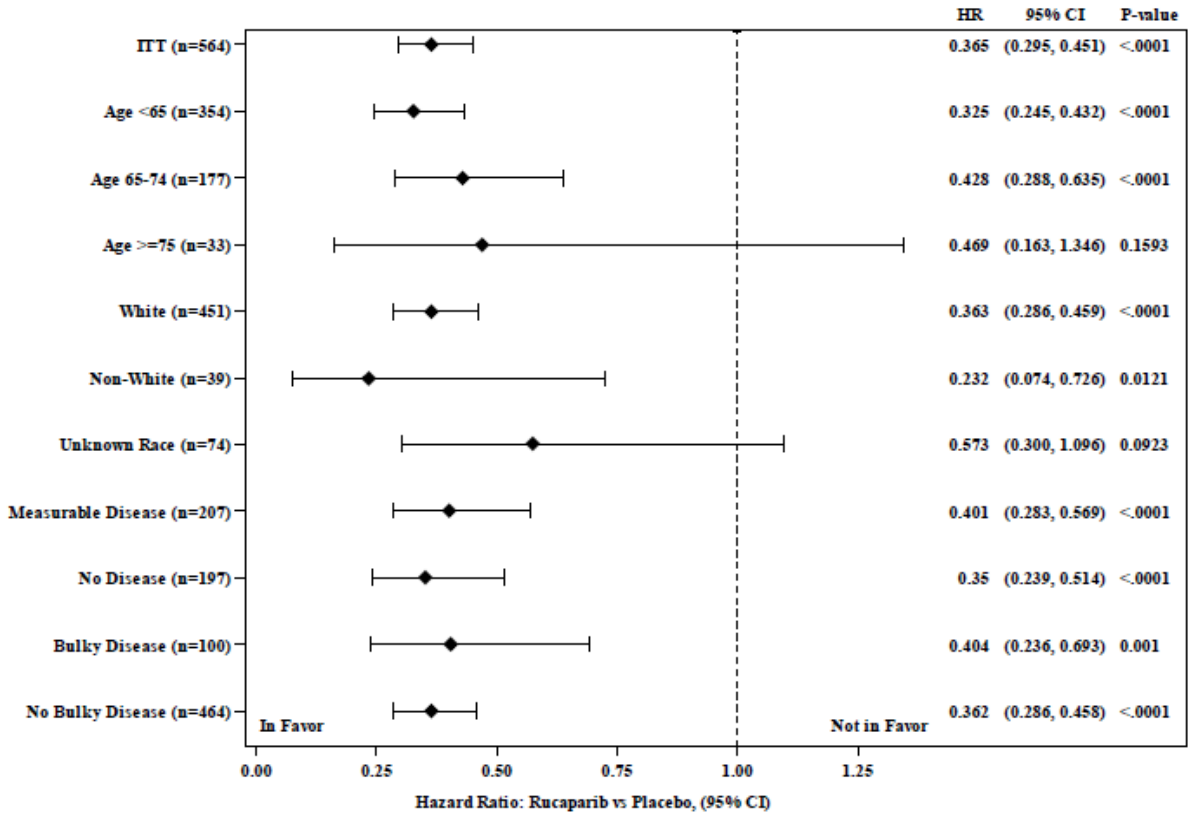


Figure 20: Forest Plot of PFS per Investigator by Demographics and Baseline Disease Burden – ITT Population

Source: Figure 24, Study CO-338-014 CSR.
Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; PFS = progression-free survival.

- **Other demographic variables**
- Patients by regions (EU and non-EU):

Table 35: Subgroup of Progression-free Survival per Investigator – ITT Subgroups by Region

Population	n	Median PFS (95% CI) (months)	p-value[a]	Hazard Ratio (95% CI)	p-value[b]
ITT subgroup from the EU					
rucaparib	183	10.9 (8.2-13.8)	< 0.0001	0.308 (0.224-0.423)	< 0.0001
placebo	94	5.4 (2.9-5.5)			
ITT subgroup from outside the EU (non-EU)					
rucaparib	192	10.4 (8.2-13.3)	< 0.0001	0.454 (0.336-0.614)	< 0.0001
placebo	95	5.4 (5.3-5.6)			

Source: Table 14.2.1.2.35, Figure 14.2.1.1.4, Figure 14.2.1.1.5, Study CO-338-014 Supporting Data T2V.
Abbreviations: CI = confidence interval; EU = European Union; ITT = intent-to-treat; NA = not assessable; PFS = progression-free survival; T2V = Type II Variation
a Stratified log-rank analysis
b Cox proportional hazard model

- Patients with fallopian tube or primary peritoneal cancer:

Table 36: Subgroup Analyses of Progression-free Survival per Investigator – ITT subgroup with either Fallopian Tube Cancer or Primary Peritoneal Cancer

Population	n	Median PFS (95% CI) (months)	p-value[a]	Hazard Ratio (95% CI)	p-value[b]
ITT subgroup with fallopian tube cancer					
rucaparib	32	13.1 (5.4-16.4)	0.2910	0.574 (0.203-1.625)	0.2956
placebo	10	5.5 (1.6-13.6)			
ITT subgroup with primary peritoneal cancer					
rucaparib	31	10.9 (8.0-NA)	0.0131	0.356 (0.153-0.830)	0.0168
placebo	19	5.3 (2.6-8.1)			

Source: Table 14.2.1.2.22, Figure 14.2.1.20.3, Table 14.2.1.2.23, Figure 14.2.1.21.3, Study CO-338-014 Supporting Data T2V.
Abbreviations: CI = confidence interval; ITT = intent-to-treat; NA = not assessable; PFS = progression-free survival.
a Stratified log-rank analysis
b Cox proportional hazard model

- Progression free survival by prior line of chemotherapy

Table 37: Subgroup Analyses of Progression-free Survival by prior line of chemotherapy

Cohort	Rucaparib n	Placebo n	invPFS		irrPFS	
			HR[a] (95% CI)	Median PFS (months); p value[b]	HR[a] (95% CI)	Median PFS (months); p value[b]
			rucaparib vs placebo		rucaparib vs placebo	
Patients with 2 prior chemotherapy regimens						
tBRCA	73	40	0.24 (0.14, 0.40)	21.9 vs 5.4; p < 0.0001	0.24 (0.13, 0.45)	26.8 vs 5.5; p < 0.0001
HRD	136	75	0.34 (0.23, 0.49)	14.1 vs 5.5; p < 0.0001	0.33 (0.21, 0.52)	26.8 vs 5.5; p < 0.0001
ITT	231	124	0.42 (0.32, 0.55)	10.4 vs 5.4; p < 0.0001	0.37 (0.27, 0.50)	17.1 vs 5.4; p < 0.0001
Patients with ⩾ 3 prior chemotherapy regimens						
tBRCA	57	26	0.21 (0.11, 0.40)	13.7 vs 5.4; p < 0.0001	0.17 (0.08, 0.35)	18.0 vs 5.4; p < 0.0001
HRD	100	43	0.27 (0.16, 0.44)	11.1 vs 5.4; p < 0.0001	0.30 (0.18, 0.52)	13.6 vs 5.4; p < 0.0001
ITT	144	65	0.28 (0.19, 0.41)	11.1 vs 5.3; p < 0.0001	0.36 (0.24, 0.53)	13.3 vs 5.3; p < 0.0001

Abbreviations: CI = confidence interval; gBRCA = germline mutation in BRCA; HR = hazard ratio; HRD = homologous recombination deficiency; invPFS = investigator-assessed PFS; irrPFS = independent radiology review of PFS; ITT = intent-to-treat; PFS = progression-free survival; RtQ = Response to Questions; sBRCA = somatic mutation in BRCA; tBRCA = deleterious tumor mutation in BRCA1 or BRCA2, includes gBRCA and sBRCA; T2V = Type II Variation.

[a] Cox proportional hazards model; p values for treatment-by-prior chemotherapy regimen subgroup interaction were nonsignificant for all analyses.

[b] Stratified log-rank p value.

- Comparison of FMI diagnostic test and clinical trial assay (CTA) test results

In Study CO-338-014, a NGS-based CTA was employed to detect deleterious mutations in BRCA1, BRCA2, and other HRR genes, as well as to determine the genome-wide LOH within patient tumor tissues samples. FMI's CTA (version T5) sequences the exons of 287 genes, including BRCA1/2 and 28 other HRR genes. The NGS-based assay also sequences ~3500 single nucleotide polymorphisms (SNPs) to determine genome-wide LOH.

Tumor DNA samples tested by the CTA were retrospectively tested by the FMI Diagnostic test. A total of 518 of 564 samples (92%) had sufficient DNA to generate a test result using the diagnostic test. The overall agreement for the HRD classification of the diagnostic test and CTA for all patients in Study CO-338-014 was 91.7% (95% CI, 89.0%-93.0%).

Summary of main study

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 38: Summary of Efficacy for trial CO-338-014

Title: 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.			
Study identifier	CO-338-014		
Design	Phase 3, double-blind, placebo-controlled, multicentre study. Switch maintenance treatment in patients with platinum-sensitive, relapsed, high-grade ovarian cancer patients who achieved a response to platinum-based chemotherapy.		
	Duration of main phase:		Continuous 28-day cycles.
	Duration of previous phase:		Completion of at least 2 prior courses of platinum-based treatment regimens. Disease progression greater than 6 months after completion of their last dose of penultimate platinum chemotherapy. Treatment within 8 weeks of completion of the final dose of the last platinum-containing regimen (minimum of 4 treatment cycles).
	Duration of Extension phase:		Follow-up for survival unless withdrawal of consent.
Hypothesis	Superiority		
Treatments groups	Rucaparib 600 mg BID		n=375
	Placebo		n=189
Endpoints and definitions	Primary endpoint	invPFS	Disease progression according to RECIST v1.1, as assessed by the investigator, or death from any cause, in molecularly defined subgroups
	Secondary endpoints		Decrease in the DRS-P subscale of FOSI-18, decrease in FOSI-18, OS, PFS by IRR, incidence of AEs, clinical laboratory abnormalities, and dose modifications, individual model parameter estimates of rucaparib and covariates identification.
	Exploratory endpoints		Association between CA-125 and invPFS, Time to next event of disease progression or death, ORR, DOR, EQ-5D, PK.
Database lock	Primary PFS analysis data cut-off: 15 April 2017		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	All randomised patients (ITT and HRD subgroups). 70% of PFS events in the tBRCA subgroup.		

Descriptive statistics and estimate variability	Treatment group	Rucaparib 600 mg	Placebo
	Number of subjects tBRCA	130	66
	Primary analysis Median invPFS tBRCA (months)	16.6	5.4
	95% CI	13.4, 22.9	3.4, 6.7
	Secondary analysis Time to worsening DRS-P FOS-18, tBRCA (months)	1.9	4.2
	95% CI	1.4 – 3.7	2.8 – 9.2
	Number of subject HRD	236	118
	Primary analysis Median invPFS HRD (months)	13.6	5.4
	95% CI	10.9, 16.2	5.1, 5.6
	Secondary analysis Time to worsening DRS-P FOS-18, HRD (months)	1.9	4.8
	95% CI	1.8 – 2.8	3.7 – 9.2
	Number of subject ITT	375	189
	Primary analysis Median invPFS ITT (months)	10.8	5.4
	95% CI	8.3, 11.4	5.3, 5.5
	Secondary analysis Time to worsening DRS-P FOS-18, ITT (months)	1.9	6.4
	95% CI	1.8 – 2.8	4.6 – 9.2
Effect estimate per comparison		Comparison groups	Rucaparib – placebo
	Primary endpoint (invPFS tBRCA)	HR	0.231
		95% CI	0.156, 0.342
		P-value	< 0.0001
	Secondary endpoint (Time to worsening) DRS-P FOSI-18, tBRCA)	HR	1.239
		95% CI	0.824, 1.861
		P-value	0.3031
	Primary endpoint (invPFS HRD)	HR	0.317
		95% CI	0.239, 0.420
		P-value	<0.0001
	Secondary endpoint (Time to worsening) DRS-P FOSI-18, HRD)	HR	1.642
		95% CI	1.192, 2.263
		P-value	0.0024
	Primary endpoint (invPFS ITT)	HR	0.365
		95% CI	0.295, 0.451
		P-value	<0.0001
	Secondary endpoint (Time to worsening) DRS-P FOSI-18, ITT)	HR	1.817
		95% CI	1.408, 2.344
		P-value	<.0001

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The application is based on the results of study CO-338-014 (ARIEL3) which is an ongoing Phase 3, randomised, double-blind efficacy study of rucaparib in patients with advanced platinum-sensitive high-grade serous ovarian cancer who had received 2 or more previous platinum-based chemotherapy.

No new dose-response study was submitted. In the pivotal study (ARIEL 3) the starting dose of 600 mg rucaparib twice a day (BID) was selected as the recommended dose for Phase 2 and Phase 3 studies based on safety, tolerability, overall PK, and the preliminary efficacy profile observed in Study CO-338-010, which evaluated monotherapy rucaparib in patients with advanced solid tumours. This dose is the approved dose for the currently approved indication for the treatment for relapsed or progressive EOC, FTC, or PPC.

At the time of the study design (the original protocol was dated 9 September 2013) there were no other therapeutic agents approved for maintenance treatment of ovarian cancer patients in response to platinum-based chemotherapy. In this context, using placebo as a comparator to determine the efficacy of rucaparib was considered acceptable. Currently approved agents in the maintenance setting of platinum-sensitive ovarian cancer include bevacizumab (for first recurrence, in combination with platinum-based chemotherapy), olaparib (for recurrent high grade ovarian cancer in patients with platinum-sensitive disease who are in response to platinum-based chemotherapy) and niraparib (for recurrent high grade ovarian cancer in patients with platinum-sensitive disease who are in response to platinum-base chemotherapy).

Rucaparib has shown activity in BRCA wild-type models, suggesting that it is active in cells with other mutations involved in HRD, and/or with high percentage of LOH, which is a phenotypic consequence of HRD. At the time of recruitment the optimal percentage LOH cut-off had not been defined, and patients were stratified at randomization according to HRD status using single mutations to classify patients. The results of the ARIEL2 study, which prospectively tested a 14% LOH cut-off may suggest that tumour with LOH could be used to identify patients with or without a BRCA mutation who may benefit from rucaparib (see clinical pharmacology section). In study ARIEL2, PFS was significantly longer in the BRCA mutant (HR 0.27 [95% CI 0.16-0.44]) and LOH-high subgroups (HR 0.62 [95% CI 0.42-0.90]), compared to the LOH-low subgroup. For the analysis of populations in the Phase 3 Study CO-338-014, patients were allocated to subgroups using the LOH genomic scarring method to classify nbHRD mutations, using a revised ≥16% LOH cut-off based on mature clinical data of ARIEL2. Analysis of mature PFS and LOH data from Study CO-338-017 Part 1, which enrolled platinum-sensitive patients, allowed optimization of the cut-off.

According to the scientific advice (EMEA/H/SA/2392/1/FU/2/2015/PA/SME/II), the 14% threshold would have been more recommendable from a clinical perspective, even though from a regulatory point of view, a higher cutoff (>14%) was understood. Agreement between the FMI CTA and FMI diagnostic test was assessed, finding a high overall agreement between the results of the 2 assays.

Study CO-338-014 excluded patients with prior treatment with a PARP inhibitor in order to assess rucaparib efficacy without the potential confounding effect of prior PARP inhibitor therapy. It is unknown if prior PARP inhibitor treatment would affect the efficacy or safety of subsequent lines of PARP inhibitor therapy, since this approach has not been investigated. A warning already exists in section 4.4 of the SmPC stating that efficacy of Rubraca as treatment for relapsed or progressive EOC, FTC, or PPC has not been investigated in patients who have received prior treatment with a PARP inhibitor and therefore the use in this patient population is not recommended (see SmPC section 4.4.). For the maintenance setting, this is adequately addressed with information included in section 5.1 of the SmPC taking into account that there are currently no PARP inhibitors approved in the frontline setting or as maintenance after first line platinum-based chemotherapy. Section 5.1 of the SmPC has been updated to reflect that efficacy of Rubraca in patients who

have received prior treatment with a PARP inhibitor in the maintenance setting, has not been investigated and cannot be extrapolated from the available data.

The main inclusion/exclusion criteria allowed the inclusion of patients in PR as defined by CA-125 (provided the disease was not measurable according to RECIST 1.1). However, taking into account the small number of patients (5%) with PR as GCIG CA-125 response criteria and the quite consistent outcome in these patients with regard to the PR according to RECIST or CA-125 (HR 0.296 CI95% 0.067-1.302 vs HR 0.381 CI95% 0.295-0.491 respectively) this was not considered a concern. Interestingly, patients were allowed to enrol even if they had residual bulky disease (≥2 cm).

Patients were randomised 2:1 to receive rucaparib or placebo. HRD (tBRCA, nbHRD, or biomarker negative), platinum sensitive (6 to 12 or >12 months PFI to their penultimate platinum-based regimen) and best response to previous platinum-based-chemotherapy (CR or PR) were stratification factors. Biomarker negative was defined as patients with a tumour that did not contain a deleterious tBRCA mutation or deleterious mutation in 1 of the 28 the prespecified HRR genes were identified as 'biomarker negative' for randomization stratification. However, HRD positivity was determined in DNA extracted from tumour tissue by the CTA developed by FMI (Foundation Medicine). The CTA identified deleterious mutations in 30 genes involved in HRR (homologous recombination repair). The use of this methodology does not allow the discrimination between somatic and germline mutations, so a central germline blood test was carried out to identify the germline BRCA mutations.

The primary endpoint for the study was PFS defined by RECIST and assessed by investigator (increased CA 125 concentrations alone were not sufficient to indicate disease progression unless confirmed by RECIST). Despite the fact that the trial was double-blind, a secondary analysis by IRR was also included in the study.

In order to adjust for multiple testing among the secondary endpoints and nested study populations in Study CO-338-014, an ordered step-down procedure was defined in the protocol. The final OS endpoint is the last step of this ordered step-down procedure and even though statistical significance was not achieved for the prior secondary endpoints, a robust exploratory analysis of final OS is proposed. In order to account for multiple analyses of OS, the Haybittle-Peto stopping rule has been specified for the final analysis. This stopping rule was specified so that if only one interim analysis of OS is performed, then a p-value very close to 0.05 can be utilized to guide the interpretation of the OS results.

The stratified long rank test and stratified Cox proportional model will be used to compare rucaparib and placebo for the primary endpoint (PFS per investigator) and secondary endpoints (FOSI-18 scores and Overall survival). The methodology and endpoints are endorsed.

The multiplicity adjustments were applied following an ordered step-down procedure. Primary endpoint (invPFS) was tested at a one-sided 0.025 significance among the defined nested populations: tBRCA, HRD and ITT.

Secondary endpoints (DRS-P FOSI-18, Total Score FOSI-18 and final OS) were globally and subsequently tested at a one-sided 0.025 significance among the defined nested populations: tBRCA, HRD and ITT. Efficacy endpoints results could evaluate if the HRD or ITT were not completely driven by results in the tBRCA subgroup. PFS2, time to start of the first subsequent anti-cancer treatment and chemotherapy-free interval were considered exploratory endpoints.

The ordered fashion of the procedure did not allow declaring statistical significance in the subsequent analyses once statistical significance was not achieved for the previous tests. However, the defined Haybittle-Peto stopping rule for Overall Survival results would not be applicable for the final OS due to the type I error rate adjustment defined in the step-down procedure.

There were 3 protocol amendments as of the time of the data cut-off for efficacy (15 April 2018). No critical findings were identified in the amendments.

Efficacy data and additional analyses

Although the number of patients with known BRCA mutation was limited by study protocol, the proportion of patients with BRCA mutations is higher than that described in the general population with almost 35% of patients being tBRCA positive. In an unselected population, the proportion of mutation is 15% for gBRCA and 6-8% for sBRCA, whereas in the study population it is 23% for gBRCA (22% rucaparib arm and 25% placebo) and 9.9% for sBRCA (10.7% and 8.5%). A similar observation is made with the nbHRD population (patients with a tumour that did not contain a deleterious tBRCA mutation, but did have a deleterious mutation in 1 of the 28 pre-specified homologous recombination DNA repair genes). According to the literature, mutation in a homologous recombination gene other than BRCA1/2 represents approximately 16% of ovarian cancer, whereas in Study CO-338-014 there are only 43 patients (8%). However, the higher proportion of patients tBRCA in the Study CO-338-014 (vs in the general population with OC) can be understood as rucaparib is believed to mainly act in these patients, so it is not surprising that the maximum number of tBRCA mutated allowed in the study was achieved (200).

Regarding the apparently lower proportion of patients with nbHRD in the study than in the general population, this was initially estimated considering the TCGA source, which would not be totally applicable to the study, since EMSY and PTEN genes are not critical for HRR or PARPi action, and epigenetic (methylation) alterations of BRCA1 and RAD51C genes were not identified by sequencing of tumours from patients in Study CO-338-014.

There were 564 patients randomized into this study (i.e., the ITT population): 375 patients in the rucaparib group and 189 patients in the placebo group. The data cut-off for efficacy was 15 April 2017. At that date, 90 (24%) patients in the rucaparib group and nine (5%) in the placebo group were still receiving treatment.

The primary reason for discontinuation was disease progression (71.6% rucaparib vs 91.1% placebo), which is in favour of rucaparib being an effective drug. On the other hand, the second most frequent reason for treatment discontinuation in the rucaparib arm was an adverse event (16.1%), which was only described for 1 patient (0.6%) in the placebo arm.

Most patients were <65 years-old and White, reflective of recruitment sites. The most common type of cancer was epithelial ovarian cancer, with serous histology. Most patients had advanced disease classified as FIGO stage IIIC (63.5% both arms), or IV (14.4% and 15.9%). Slightly more patients had measurable disease (37.6% and 34.9%) and bulky disease (18.9% and 15.3%) in the rucaparib arm of the study compared to placebo. Other demographic and baseline disease characteristics were generally balanced between treatment arms. Prior anticancer therapies were balanced, with a median of 2 prior chemotherapy regimens in both arms. Most patients received 2 or 3 previous lines of chemotherapy. The penultimate Progression-free Interval after Last Dose of Penultimate Platinum (>6-12; >12-24 and >24 months) was evenly balanced between groups. All relevant baseline characteristics have been reflected in section 5.1 of the SmPC.

Evidence of efficacy of rucaparib in ARIEL3 was provided mainly for patients with high grade serous ovarian cancer. However, recent evidence suggests that serous and endometrioid carcinomas arise from the tubal fimbrae, suggesting similar biology and origin for the high grade epithelial histologies (Jayson et al 2014). Pennington et al reported in their study that contrary to the common belief of homologous recombination deficiencies being characteristic of high-grade serous ovarian cancer only, DNA repair deficiencies were found equally commonly in carcinomas with non-serous histology (Pennington et al 2014). In view of this and considering the mechanism of action of rucaparib, it is considered that the indication does not need to be restricted to the serous histology.

Prior administration of bevacizumab was balanced between the rucaparib and placebo arms. About 22% of patients (n=126) received prior bevacizumab, including ~4% (n=23) who were treated with bevacizumab in addition to chemotherapy immediately prior to enrolment in ARIEL 3. Prior bevacizumab resulted in a shorter

median PFS by investigator assessment (primary endpoint) in both treatment arms and a reduced relative benefit of rucaparib over placebo, with larger confidence intervals (all still <1) due to the smaller patient numbers. Importantly, the relative benefit of rucaparib over placebo was maintained regardless of prior bevacizumab use.

The primary efficacy endpoint was met. Statistically significant differences between rucaparib and placebo were observed in the nested populations, with differences observed early in the treatment period, with separation of the curves noted by cycle 3.

Exploratory analyses in the non-nested populations (non-tBRCA LOH+ and non-tBRCA LOH- subgroups) were performed in order to demonstrate that the effect in the nested subgroups was not solely driven by the BRCA or HRD groups. These exploratory analyses found statistically significant differences between study arms, with differences observed later in the treatment period in the non-tBRCA LOH- subgroup.

The positive result seen in the non-BRCA LOH- could suggest a benefit in patients with low LOH, even though this conclusion should be cautiously taken due to the exploratory nature of this analysis. Potential unknown mechanisms of action other than the one ascribed to rucaparib, could be behind this finding. Alternatively, LOH as a time-dependent biomarker may also partially explain these results.

LOH+ could be understood as a phenotypic consequence of HRD (genomic scars), however, the sample size of the subgroup with a tumour that did not contain a deleterious tBRCA mutation, but did have a deleterious mutation in 1 of the 28 pre-specified homologous recombination DNA repair (HRR) genes (nbHRD; n=43) does not mimic the sample size of the patients without a deleterious tBRCA mutation and with percent of tumor genome loss of heterozygosity (LOH) ≥ 16% (Non-tBRCA LOH + n=158). This fact can be understood since the epigenetic alterations are not captured by nbHRD, even though they are by LOH (along with genetic alterations).

Two sensitivity analyses of invPFS were presented, one with ‘all’ on study scans used in the PFS analysis and one with clinical progression used as an event. These results were consistent with the primary efficacy analysis. The first sensitivity analysis of the primary PFS endpoint follows the EMA “Guideline on the evaluation of anticancer medicinal products in man” and uses the first date when there is documented evidence of progression, even if this is after missed treatments, treatment discontinuations or the start of a new anticancer therapy. All sensitivity analyses were consistent with the primary endpoint.

PFS results per Investigator by Randomization Strata showed consistency with the main results (even in the biomarker negative stratum; HR 0.471 95%CI 0.361-0.613 n=325). Likewise, positive results were observed for each of the HRD and gene mutation subgroups along with PFS by demographics and baseline disease burden. Importantly, both the investigator assessment and the Independent radiology review, showed consistent results in the three subgroups (tBRCA, HRD and ITT) regardless of the number of previous chemotherapy regimens used (2 or >3). Although no information is shown in the rest of subgroups of interest (LOH, nbHRD) dissimilar results are not expected according to the number of previous regimens

Consistency was observed among the different subgroups in the analysis of invPFS based on HRD and gene mutation, with an expected lesser activity in the non-tBRCA LOH negative. Interestingly, the co-existence of BRCA and nbHRD mutations in the same tumour (either in the same cell population or in different clones due to intra-tumoural heterogeneity) could theoretically define an important subgroup with 'exquisite sensitivity' to rucaparib. However, this “intuitive” idea does not seem to be reflected in the results.

The effect of rucaparib over placebo on invPFS was seen across all subgroups by demographics (age <65 years, 65-74 years, ≥ 75 years and race White, non-White and unknown) and by baseline disease burden. The rucaparib population was split into bulky disease (n=71, median invPFS 8.2 months) and no bulky disease (n=304, median inv PFS 11.0 months) and into measurable disease (n=141) and no disease (n=130).

The invPFS results in the ITT population were consistent between the EU and non-EU patients and for the subgroups with primary peritoneal and fallopian tube cancers. The number of patients with PPC and FTC are small but consistently represented throughout the nested populations.

PFS by IRR was consistently higher in the rucaparib arm compared to the placebo arm. This difference is particularly apparent in the tBRCA group (invPFS 16.6 months vs irrPFS 26.8 months) and diminishes progressively in the HRD and ITT groups. This difference is not seen in the placebo group, were the results of invPFS and irrPFS correlate across all nested populations. The phenomenon of reporting a higher median PFS by blinded independent radiology review (IRR) as compared to investigator assessment has been consistently observed in all 3 of the pivotal studies of PARP inhibitors in the maintenance treatment of ovarian cancer. Moreover, in all of the pivotal PARP inhibitor studies, the median PFS for the placebo arms, as reported by both investigator and IRR, is consistently 5.5 months approximately across all patient subgroups.

The first secondary endpoint to be analysed in the hierarchical step-down procedure was the disease-related symptoms, physical subscale (DRS-P) of the FOSI-18, a PRO questionnaire designed for ovarian cancer patients, in the tBRCA population. There was no statistically significant difference in median time to a 4-point worsening in the DRS-P subscale for rucaparib compared to placebo-treated patients in the tBRCA population (median time 1.9 vs. 4.2 months, respectively, p= 0.2893) with the trend favouring placebo. Therefore, for all subsequent endpoints nominal p values only are presented. The median time to worsening in the DRS-P subscale was shorter for rucaparib compared to placebo in the HRD population (1.9 vs. 4.8 months; HR 1.642, p=0.0024 in favour of placebo) and in the ITT population (1.9 vs 6.4 months, HR 1.817, p<0.0001 in favour of placebo).

The change from baseline in FOSI-18 DRS-P over time is difficult to interpret across the different populations. The mean change from baseline, although small (<5), is consistently negative for rucaparib and is more fluctuant for placebo. The confidence intervals gradually increase over time due to the limited number of patients remaining on treatment (in all populations by Cycle 11 there are 8 patients assessed in the placebo arm, with no patients in the non tBRCA LOH unknown population).

The median time to a 4-point worsening in the DRS-P subscale in the placebo arm varies slightly for the three analysis populations (ITT - 6.4 months; HRD - 4.8 months; tBRCA - 4.2 months) whilst the median PFS on placebo is consistently 5.4 months. Conversely, consistent median time to worsening was observed across analysis populations in the rucaparib arm (1.9 months), which is consistent with the early toxicity of Rubraca.

Selection of the time from randomization to a 4-point reduction in the FOSI-18 disease-related symptom score physical (DRS-P) subscale as the first secondary endpoint in the step down procedure was not carefully planned, given that the patients had all responded to previous treatment at baseline and the first assessment was at 4 weeks when patients would likely experience the toxicity of rucaparib without symptoms of progression on placebo. Poor data quality or chance may have contributed to the results. Therefore, presentation of these data in the SmPC is not recommended.

The exploration of QoL endpoints in the ITT population showed that the QoL outcomes were not affected by age or baseline disease burden.

The OS data for interim analysis was heavily censored at the visit cut-off for primary endpoint analysis. About 20% of deaths had occurred across in the nested population. Median survival could only be determined for the rucaparib arm in the ITT population. As of the updated safety data cut-off of 31 December 2017, a death event had been reported in only 30% of patients. The demonstration of a survival benefit is important in the setting of maintenance therapy, especially in the case of a placebo-controlled. It is acknowledged that subsequent therapies received after progression may make it difficult the interpretation of OS data. However, further evidence of lack of detrimental effect on OS and/or PFS2 should be provided.

The final analysis of OS will occur when 70% of death events have been collected and will be provided by the MAH to further investigate the efficacy of rucaparib in this setting (see PAES in Annex II condition).

Time to next line therapy was presented and time to chemotherapy was presented separately. Time to next line therapy was shorter than time to chemotherapy, as patients received other treatments (presumably including PARP inhibitors in the placebo arm). A few patients withdrew consent to follow up in the rucaparib (n=7) and placebo arms (n=2), whilst 53 (17.2%) and 18 (9.9%) in the rucaparib and placebo arms, respectively, received no subsequent therapy. Most patients in both arms received platinum-based therapy or a non-platinum chemotherapy. Unsurprisingly, a high proportion of placebo treated patients in the tBRCA population (25.8%) received a subsequent PARPi, mainly olaparib alone or in combination.

Of the patients with measurable disease at baseline (~35% of the total population) 18.4% of those treated with rucaparib in the ITT population (26/ 141) had a confirmed response compared to 7.6% (5/66) of those who received placebo. In the tBRCA population treated with Rubraca (N=130), a response was noted in 15 of 40 patients with measurable disease at baseline (ORR 37.5%). There were few/ no responses in the non-tBRCA LOH negative and LOH unknown populations.

Exploratory efficacy endpoints analyses suggest that CA-125 is suppressed in all nested populations, with a benefit seen earlier in the tBRCA and HRD groups, and that this suppression is associated with PFS results. The remaining exploratory endpoints analyses are limited by the heavy rate of censoring, especially in the rucaparib arm. PFS2, chemotherapy-free survival and time to start of first (and second) subsequent anti-cancer treatment analyses suggest that rucaparib treatment may prolong median time to subsequent progression and treatment, with benefit seen in all the analysis populations. The MAH will provide updates of these analyses in all populations at the time of the final OS analysis (see PAES Annex II condition).

2.4.4. Conclusions on the clinical efficacy

The use of Rucaparib for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy has shown a statistically significant improvement in PFS as compared with placebo in the ITT population which is considered clinically meaningful. This delay in tumour progression is not uniformly observed (size of the effect) according to the HRD positivity, although PFS in the rucaparib arm was always better than in the placebo arm.

Although a detrimental effect on OS is considered unlikely, the final OS analysis together with analyses of PFS2, chemotherapy-free survival and time to start of first (and second) subsequent anti-cancer treatment are required to further investigate the efficacy of rucaparib in this setting.

The CHMP considers the following measures necessary to address issues related to efficacy:

Description	**Due date**
PAES: In order to further investigate the efficacy of rucaparib maintenance treatment in patients with relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy, the MAH should submit the final analysis of OS and updated analyses of PFS2, chemotherapy-free interval and time to start of subsequent anti-cancer treatment of the phase 3, randomised, double-blind study CO-338-014	31 December 2022

2.5. Clinical safety

Introduction

The clinical study report (CSR) from the pivotal Phase 3 Study CO-338-014 (ARIEL3) supporting the maintenance indication was previously submitted during the conditional marketing authorisation (CMA) application to provide additional safety data with the 15 April 2017 visit cut-off date (CSR visit cut-off date). Updated safety data with a visit cut-off of 31 December 2017 (T2V visit cut-off date) are submitted in this variation. Additional data collected from the studies which supported the CMA for the treatment indication were also submitted in this variation using the same visit cut-off of 31 December 2017:

- CO-338-010 (Study 10), 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
- CO-338-017 (ARIEL2), a Phase 2 open-label study of rucaparib in patients with platinum sensitive, relapsed, high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer.

Patient exposure

A total of 372 patients were exposed to rucaparib in Study CO-338-014 (ARIEL3). Over half of patients who received rucaparib were exposed for at least 6 months (58.9%), compared to 37.6% of placebo patients. Based on drug dispensation logs, a total of 56.2% of patients in the rucaparib group were dispensed a reduced dose, compared to 4.8% in the placebo group.

Patient disposition is detailed in the efficacy section of this report. At the 31 December 2017 cut-off, 52 patients (16.5%) had discontinued rucaparib and 1 patient (0.5%) discontinued placebo because of an adverse event.

Table 39: Study Drug Exposure: Safety Population CO-338-014, Visit cut off 31 December 2017

Parameter	**Rucaparib (N = 372)**	**Placebo (N = 189)**
Number of Cycles Initiated		
Mean (StD)	13.2 (11.06)	7.6 (6.38)
Median	9.0	6.0
Min, Max	1, 47	1, 48
Duration of Treatment (months)		
Mean (StD)	12.0 (10.29)	6.7 (5.87)
Median	8.3	5.5
Min, Max	0, 43	0, 44
Duration of Treatment, n (%)		
< 6 months	153 (41.1)	118 (62.4)
6-12 months	82 (22.0)	54 (28.6)
> 12 months	137 (36.8)	17 (9.0)
Dose Reductions [a, b], n (%)		
Only 1 dose reduction	132 (35.5)	9 (4.8)
≥ 2 dose reductions	77 (20.7)	0
Dose reduced to 480 mg BID	184 (49.5)	7 (3.7)
Dose reduced to 360 mg BID	88 (23.7)	2 (1.1)
Dose reduced to 240 mg BID	32 (8.6)	0

[a] Based on the dispensation log
[b] Dose reductions may not have necessarily been conducted in a sequential manner.

Table 40: Rucaparib Exposure: Safety Population (Combined Studies CO-338-010 and CO-338-017) Visit cut off 31 December 2017

	Ovarian Cancer Patients (N = 565) Starting dose 600 mg BID
Number of Cycles Initiated	
Mean (StD)	8.3 (8.69)
Median	6.0
Min, Max	1, 53
Duration of Treatment, n (%)	
< 6 months	326 (57.7)
6-12 months	142 (25.1)
> 12 months	97 (17.2)
Dose Intensity [a]	
Mean (StD)	0.89 (0.175)
Median	0.95
Min, Max	0.1, 1.9
Dose Reductions, n (%)	
Only 1 dose reduction	146 (25.8)
≥ 2 dose reductions	119 (21.1)
Any dose reduction	265 (46.9%)
Dose Reduced to Dose Level 1[b]	232 (41.1)
Dose reduced to 500 mg BID	121 (21.4)
Dose reduced to 480 mg BID	111 (19.6)
Dose Reduced to Dose Level 2[b]	121 (21.4)
Dose reduced to 400 mg BID	66 (11.7)
Dose reduced to 360 mg BID	55 (9.7)
Dose Reduced to Dose Level 3[b]	62 (11.0)
Dose reduced to 300 mg BID	44 (7.8)
Dose reduced to 240 mg BID	18 (3.2)

[a] Defined as the actual dose received divided by the planned first dose.
[b] Differences in the doses per level due to tablet strengths (40, 60 or 120 mg tablets) used in Part 2A of Study CO-338-010 and Part 1 of Study CO-338-017 differing from tablet strengths (200 and 300 mg) used in Parts 2B and 3 of Study CO-338-010 and Part 2 of Study CO-338-017.

Overall, 25 of the 565 patients (4.4%) were ongoing in Studies CO-338-010 and CO-338-017. The most common primary reason for discontinuation of rucaparib was disease progression (n=403, 74.6%), whilst 7% (n=38) discontinued due to clinical progression; 54/540 (10%) patients with ovarian cancer discontinued treatment due to AEs (all causality).

Adverse events

Table 41: Overall Summary of Treatment-emergent Adverse Events: Safety Population CO-338-014, 31 December 2017

Patients with one or more:	**Rucaparib (N = 372) n (%)**	**Placebo (N = 189) n (%)**
TEAEs	372 (100)	182 (96.3)
Treatment-related TEAEs	362 (97.3)	139 (73.5)
Serious TEAEs	83 (22.3)	20 (10.6)
Serious treatment-related TEAEs	35 (9.4)	3 (1.6)
TEAEs of Grade ≥3	222 (59.7)	30 (15.9)
Treatment-related TEAEs of Grade ≥3	171 (46.0)	9 (4.8)
TEAEs leading to death	7 (1.9)	2 (1.1)
Treatment-related TEAEs leading to death	2 (0.5)	0

Patients with one or more:	**Rucaparib (N = 372) n (%)**	**Placebo (N = 189) n (%)**
TEAEs leading to study drug discontinuation Treatment-related TEAEs leading to study drug discontinuation	61 (16.4) 49 (13.2)	4 (2.1) 1 (0.5)
TEAEs leading to study drug interruption Treatment-related TEAEs leading to study drug interruption	243 (65.3) 205 (55.1)	19 (10.1) 9 (4.8)
TEAEs leading to study drug dose reduction Treatment-related TEAEs leading to study drug dose reduction	206 (55.4) 200 (53.8)	8 (4.2) 7 (3.7)
TEAEs leading to dose reduction or interruption Treatment-related TEAEs leading to dose reduction or interruption	267 (71.8) 239 (64.2)	20 (10.6) 11 (5.8)

Nearly all patients in the Safety population experienced at least 1 TEAE (100% rucaparib; 96.3% placebo), with treatment-related TEAEs reported for 97.3% and 73.5% of rucaparib and placebo patients, respectively. A larger proportion of patients in the rucaparib group had at least 1 SAE (22.3% rucaparib; 10.6% placebo). Fatal TEAEs occurred in 7 patients (1.9%) who received rucaparib and in 2 patients (1.1%) who received placebo; the fatal event assessed by the investigator as related to study treatment in 2 patients (AESI of AML and MDS). Compared to placebo, rucaparib treatment resulted in a greater incidence of Grade ≥3 TEAEs (59.7% rucaparib; 15.9% placebo), TEAEs leading to study drug discontinuation (16.4% rucaparib; 2.1% placebo), and TEAEs leading to study drug interruption or dose reduction (71.8% rucaparib; 10.6% placebo).

Table 42: Overall Summary of Treatment-emergent Adverse Events: Safety Population (Combined Studies CO-338-010 and CO-338-017), visit cut-off 31 December 2017

	600 mg BID Ovarian Cancer Patients (N = 565) n%
Number (%) of Patients with at Least 1:	
TEAE[a]	565 (100.0)
Treatment-related TEAE	536 (94.9)
Serious TEAE[a]	171 (30.3)
Treatment-related serious TEAE	64 (11.3)
≥ Grade 3 TEAE[a]	357 (63.2)
Treatment-related ≥ Grade 3 TEAE	264 (46.7)
TEAE with an outcome of death[a]	26 (4.6)
Treatment-related TEAE with an outcome of death	1 (0.2)
TEAE leading to discontinuation[a]	116 (20.5)
Treatment-related TEAE leading to discontinuation	53 (9.4)
TEAE leading to treatment interruption	340 (60.2)
Treatment-related TEAE leading to treatment interruption	290 (51.3)
TEAE leading to dose reduction	260 (46.0)
Treatment-related TEAE leading to dose reduction	250 (44.2)
TEAE leading to dose reduction or interruption	370 (65.5)
Treatment-related TEAE leading to dose reduction or interruption	328 (58.1)

[a] Included events of disease progression.

Treatment-emergent adverse events with an outcome of death were reported in 4.6% of the ovarian cancer patients, of which 1 TEAE (B-cell acute leukaemia) was considered treatment-related.

In study CO-338-014, the highest incidences of TEAEs in patients treated with rucaparib were observed in the following SOCs: GI disorders (92.5% rucaparib, 77.2% placebo), General disorders and administration site conditions (79.6% rucaparib, 57.1% placebo), and Nervous system disorders (65.6% rucaparib, 35.4% placebo).

The most common TEAEs that occurred in the rucaparib group were nausea (75.8%), combined asthenia/fatigue (70.7%), dysgeusia (39.8%), combined anaemia/low/decreased haemoglobin (39.0%), constipation (37.9%), vomiting (37.1%), combined ALT/AST increased (34.7%), diarrhoea (32.5%), and abdominal pain (30.1).

The most common TEAEs that occurred in the placebo group were combined asthenia/fatigue (44.4%), nausea (36.5%), abdominal pain (25.9%), constipation (24.3%), and diarrhoea (21.7%).

Table 43: TEAEs Reported in ≥ 20% of Patients in Any Treatment Group: Comparison with CSR – Safety Population (CO-338-014)

	CSR		T2V Update	
	Rucaparib (N = 372) n (%)	Placebo (N = 189) n (%)	Rucaparib (N = 372) n (%)	Placebo (N = 189) n (%)
Number of Patients With at Least One TEAE	**372 (100)**	**182 (96.3)**	**372 (100)**	**182 (96.3)**
Combined Preferred Terms				
Combined ALT/AST increased	126 (33.9)	7 (3.7)	129 (34.7)	8 (4.2)
Combined Anemia and/or low/decreased hemoglobin	139 (37.4)	11 (5.8)	145 (39.0)	10 (5.3)
Combined Asthenia/Fatigue	258 (69.4)	83 (43.9)	263 (70.7)	84 (44.4)
Combined Thrombocytopenia and/or low/decreased platelets	104 (28.0)	5 (2.6)	109 (29.3)	5 (2.6)
System Organ Class Preferred Term				
Blood and lymphatic system disorders	**172 (46.2)**	**16 (8.5)**	**177 (47.6)**	**16 (8.5)**
Anaemia	130 (34.9)	11 (5.8)	135 (36.3)	10 (5.3)
Gastrointestinal disorders	**343 (92.2)**	**145 (76.7)**	**344 (92.5)**	**146 (77.2)**
Abdominal pain	111 (29.8)	49 (25.9)	112 (30.1)	49 (25.9)
Constipation	136 (36.6)	45 (23.8)	141 (37.9)	46 (24.3)
Diarrhoea	118 (31.7)	41 (21.7)	121 (32.5)	41 (21.7)
Nausea	280 (75.3)	69 (36.5)	282 (75.8)	69 (36.5)
Vomiting	136 (36.6)	28 (14.8)	138 (37.1)	29 (15.3)
General disorders and administration site conditions	**292 (78.5)**	**107 (56.6)**	**296 (79.6)**	**108 (57.1)**
Asthenia	83 (22.3)	20 (10.6)	86 (23.1)	20 (10.6)
Fatigue	186 (50.0)	64 (33.9)	189 (50.8)	65 (34.4)
Infections and infestations	**170 (45.7)**	**64 (33.9)**	**174 (46.8)**	**65 (34.4)**
Investigations	**209 (56.2)**	**43 (22.8)**	**214 (57.5)**	**43 (22.8)**
Alanine aminotransferase increased	123 (33.1)	5 (2.6)	126 (33.9)	6 (3.2)
Aspartate aminotransferase increased	96 (25.8)	4 (2.1)	97 (26.1)	5 (2.6)
Metabolism and nutrition disorders	**171 (46.0)**	**48 (25.4)**	**176 (47.3)**	**49 (25.9)**
Decreased appetite	87 (23.4)	26 (13.8)	88 (23.7)	26 (13.8)
Musculoskeletal and connective tissue disorders	**166 (44.6)**	**85 (45.0)**	**172 (46.2)**	**86 (45.5)**
Nervous system disorders	**241 (64.8)**	**66 (34.9)**	**244 (65.6)**	**67 (35.4)**
Dysgeusia	146 (39.2)	13 (6.9)	148 (39.8)	13 (6.9)
Psychiatric disorders	**106 (28.5)**	**37 (19.6)**	**107 (28.8)**	**38 (20.1)**
Respiratory, thoracic and mediastinal disorders	**141 (37.9)**	**42 (22.2)**	**144 (38.7)**	**42 (22.2)**
Skin and subcutaneous tissue disorders	**208 (55.9)**	**69 (36.5)**	**214 (57.5)**	**70 (37.0)**
Vascular disorders	**71 (19.1)**	**32 (16.9)**	**77 (20.7)**	**33 (17.5)**

Note: CSR= Clinical study report; T2V=Type II Variation, data cut off 31 December 2017

Table 44: Treatment-related Adverse Events Reported in ≥ 20% of Patients in Any Treatment Group: Comparison with CSR – Safety Population (CO-338-014)

	CSR		T2V Update	
	Rucaparib (N = 372) n (%)	Placebo (N = 189) n (%)	Rucaparib (N = 372) n (%)	Placebo (N = 189) n (%)
Number of Patients With at Least One Treatment-related TEAE	**360 (96.8)**	**139 (73.5)**	**362 (97.3)**	**139 (73.5)**
Combined Preferred Terms				
Combined ALT/AST Increased	120 (32.3)	6 (3.2)	121 (32.5)	7 (3.7)
Combined Anemia and/or low/decreased hemoglobin	132 (35.5)	7 (3.7)	135 (36.3)	7 (3.7)
Combined Asthenia/Fatigue	228 (61.3)	59 (31.2)	233 (62.6)	59 (31.2)
Combined Thrombocytopenia and/or low/decreased platelets	95 (25.5)	4 (2.1)	101 (27.2)	4 (2.1)
System Organ Class Preferred Term				
Blood and lymphatic system disorders	**161 (43.3)**	**10 (5.3)**	**166 (44.6)**	**10 (5.3)**
Anaemia	124 (33.3)	7 (3.7)	127 (34.1)	7 (3.7)
Gastrointestinal disorders	**305 (82.0)**	**83 (43.9)**	**305 (82.0)**	**83 (43.9)**
Nausea	263 (70.7)	51 (27.0)	265 (71.2)	51 (27.0)
Vomiting	99 (26.6)	8 (4.2)	100 (26.9)	8 (4.2)
General disorders and administration site conditions	**242 (65.1)**	**67 (35.4)**	**247 (66.4)**	**67 (35.4)**
Fatigue	167 (44.9)	45 (23.8)	169 (45.4)	45 (23.8)
Investigations	**193 (51.9)**	**31 (16.4)**	**197 (53.0)**	**31 (16.4)**
Alanine aminotransferase increased	115 (30.9)	4 (2.1)	116 (31.2)	5 (2.6)
Aspartate aminotransferase increased	90 (24.2)	3 (1.6)	91 (24.5)	4 (2.1)
Metabolism and nutrition disorders	**118 (31.7)**	**25 (13.2)**	**120 (32.3)**	**27 (14.3)**
Decreased appetite	76 (20.4)	13 (6.9)	76 (20.4)	14 (7.4)
Nervous system disorders	**182 (48.9)**	**25 (13.2)**	**182 (48.9)**	**25 (13.2)**
Dysgeusia	137 (36.8)	13 (6.9)	137 (36.8)	13 (6.9)
Skin and subcutaneous tissue disorders	**154 (41.4)**	**39 (20.6)**	**157 (42.2)**	**39 (20.6)**

In study CO-338-014 the highest incidences of TEAEs assessed by the investigator as related to rucaparib were in the following SOCs: GI disorders (82.0% rucaparib, 43.9% placebo), General disorders and administration site conditions (66.4% rucaparib, 35.4% placebo), Investigations (53.0% rucaparib, 16.4% placebo), and Nervous system disorders (48.9% rucaparib, 13.2% placebo).

Nausea was the most common TEAE considered related to rucaparib (71.2% vs. 27.0% with placebo). Combined asthenia/fatigue (62.6% rucaparib, 31.2% placebo), dysgeusia (36.8% rucaparib, 6.9% placebo), and combined anaemia/low/decreased haemoglobin (36.3% rucaparib, 3.7% placebo), were also among the highest incidences of treatment-related TEAEs in Study CO-338-014.

The most common TEAEs in the treatment setting (Studies CO-338-010 and CO-338-017) were nausea (77.7%), combined asthenia/fatigue (74.7%), vomiting (45.8%), combined anaemia/decreased haemoglobin (44.2%), combined ALT/AST increased (39.5%), decreased appetite (38.8%), constipation (38.1%), dysgeusia (36.1%), abdominal pain (32.9%) and diarrhoea (32.6%). The most common

treatment-related TEAEs were nausea (67.8%), combined asthenia/fatigue (66.7%), combined anaemia/low/decreased haemoglobin (39.3%), combined ALT/AST increased (37.0%), dysgeusia (33.6%) and vomiting (31.9%).

A higher incidence of 'Skin and subcutaneous disorders' was observed in Study CO-338-014 (42.2%) compared to ovarian cancer patients in combined Studies CO-338-010 and CO-338-017 (25.1%). There were generally more reports of rash, pruritus and photosensitivity reaction in Study CO-338-014 rucaparib patients (8.6%, 9.9%, 15.1%, respectively) as compared to combined Studies CO-338-010 and CO-338-017 (4.6%, 3.7%, 9.4%, respectively).

Adverse drug reactions

Safety data reviewed for identification of ADRs presented in section 4.8 of the SmPC include safety data from the placebo-controlled Study CO-338-014 as well as updated treatment-setting safety data from Study CO-338-010 and Study CO 338 017. The total safety population of ovarian cancer patients in clinical studies evaluating rucaparib monotherapy is 937 (n=372 in the maintenance setting; n=565 in the treatment setting).

Each TEAE was reviewed for frequency of total reported events as well as frequency of events assessed as causally-related by the investigator, and comparisons between rucaparib and placebo arms were examined. Overall frequency of events in the rucaparib arm was evaluated to initially identify adverse reactions, whereby ≥ 10% overall frequency was used to determine very common adverse reactions, ≥ 1 to < 10% for common adverse reactions, and ≥0.1 to < 1% for uncommon adverse reactions. Frequency difference between rucaparib treatment group and placebo treatment group ≥ 5% (where rucaparib treatment group is higher) was deemed a clinically meaningful difference in the selection of adverse reactions. Other criteria used during assessment of TEAEs as possible adverse reactions included consistency with pharmacology/biological plausibility, temporal relationship of event relative to dosing, plausible alternative etiology, class effect, and dechallenge/rechallenge response (when applicable). TEAEs occurring in low frequencies (< 0.1%) were also reviewed considering these criteria as well as incidences of causally-related events.

The two tables below present adverse reactions for rucaparib with their corresponding frequencies and categorization. Adverse reactions that represent the same medical concept (synonymous PTs) but have two different categories (e.g. very common vs common) were categorized using the frequency of the PT that has a higher frequency (very common).

Three terms were removed from the ADR table in the SmPC following review of the placebo-controlled data from Study CO-338-014, as only minor differences were seen between the frequencies of events in patients receiving rucaparib compared with placebo. These were dermatitis, rash erythematous and pruritus. Two terms have been included further to the review of available data: dehydration and abdominal pain (combined PT: abdominal pain, abdominal pain upper or abdominal pain lower).

Overall, adverse reactions occurring in ≥ 20% of patients receiving rucaparib were nausea, fatigue/asthenia, vomiting, anaemia, abdominal pain, dysgeusia, ALT elevations, AST elevations, decreased appetite, diarrhoea, thrombocytopenia and creatinine elevations. The majority of adverse reactions were mild to moderate (Grade 1 or 2).

The ≥ Grade 3 adverse reactions occurring in > 5% of patients were anaemia (23%), ALT elevations (10%), fatigue/asthenia (10%), neutropenia (8%), thrombocytopenia (6%), and nausea (5%). The only serious adverse reaction occurring in > 2% of patients was anaemia (5%).

Adverse reactions that most commonly led to dose reduction or interruption were anaemia (20%), fatigue/asthenia (18%), nausea (16%), thrombocytopenia (15%), and AST/ALT elevations (10%). Adverse reactions leading to permanent discontinuation occurred in 10% of patients, with thrombocytopenia,

nausea, anaemia, and fatigue/asthenia being the most frequent adverse reactions leading to permanent discontinuation.

Table 45: Frequencies and Categorization of Adverse Reactions (All Grades, All Causality) Occurring in Patients from Studies CO-338-014, CO-338-010 and CO-338-017

Events	All Grades								
	CO-338-014				CO-338-010 and CO-338-017 N=565		Total of patients on Rucaparib N=937		Category
	Rucaparib N=372		Placebo N=189						
	n	%	n	%	n	%	n	%	
MDS/AML	3	0.8	0	0.0	2	0.4	5	0.5	Common (based on events observed in overall patient population of 1321)
AML	1	0.3	0	0.0	1	0.2	2	0.3	
MDS	2	0.5	0	0.0	1	0.2	3	0.2	
Anaemia (combined terms)	145	39.0	10	5.3	250	44.2	395	42.2	very common (using the highest frequency which is the combined frequency of 42.2%)
Anaemia	135	36.3	10	5.3	243	43.0	378	40.3	
Haemoglobin decreased	10	2.7	0	0.0	13	2.3%	23	2.5	
Thrombocytopenia (combined terms)	109	29.3	5	2.6	136	24.1	245	26.1	very common
Platelet count decreased	51	13.7	3	1.6	63	11.2	114	12.2	
Thrombocytopenia	64	17.2	2	1.1	84	14.9	148	15.8	
Neutropenia (combined terms)	72	19.4	9	4.8	80	14.2	152	16.2	very common (using the highest frequency which is the combined frequency of 16.2%)
Neutropenia	47	12.6	3	1.6	45	8.0	92	9.8	
Neutrophil count decreased	27	7.3	6	3.2	36	6.4	63	6.7	
Leukopenia	15	4.0	0	0.0	12	2.1	27	2.9	common
White blood cell count decreased	22	5.9	8	4.2	32	5.7	54	5.8	
Febrile neutropenia	5	1.3	0	0.0	8	1.4	13	1.4	common
Lymphopenia	5	1.3	0	0.0	14	2.5	19	2.0	common
Lymphocyte count decreased	4	1.1	2	1.1	5	0.9	9	1.0	
Decreased appetite	88	23.7	26	13.8	219	38.8	307	32.8	very common
Blood creatinine increased	61	16.4	3	1.6	125	22.1	186	19.9	very common
Blood cholesterol increased	16	4.3	7	3.7	34	6.0	50	5.3	common
Hypercholesterolaemia	27	7.3	4	2.1	21	3.7	48	5.1	
Dehydration	15	4.0	0	0.0	49	8.7	64	6.8	common
Dysgeusia	148	39.8	13	6.9	204	36.1	352	37.6	very common
Dizziness	57	15.3	15	7.9	91	16.1	148	15.8	very common
Dyspnoea	53	14.2	14	7.4	127	22.5	180	19.2	very common
Nausea	282	75.8	69	36.5	439	77.7	721	76.9	very common
Vomiting	138	37.1	29	15.3	259	45.8	397	42.4	very common
Diarrhoea	121	32.5	41	21.7	184	32.6	305	32.6	very common

Events	All Grades								
	CO-338-014				CO-338-010 and CO-338-017 N=565		Total of patients on Rucaparib N=937		Category
	Rucaparib N=372		Placebo N=189						
	n	%	n	%	n	%	n	%	
Dyspepsia	54	14.5	9	4.8	50	8.8	104	11.1	very common
Abdominal Pain	149	40.1	63	33.3	239	42.3	388	41.4	very common (using the highest frequency which is the combined frequency of 41.4%)
Abdominal pain	112	30.1	49	25.9	186	32.9	298	31.8	
Abdominal pain lower	12	3.2	7	3.7	28	5.0	40	4.3	
Abdominal pain upper	54	14.5	11	5.8	72	12.7	126	13.4	
ALT/AST increased (combined)	129	34.7	8	4.2	223	39.5	352	37.6	very common
Alanine aminotransferase increased	126	33.9	6	3.2	200	35.4	326	34.8	very common
Aspartate aminotransferase increased	97	26.1	5	2.6	197	34.9	294	31.4	very common
Transaminases increased	12	3.2	0	0	8	1.4	20	2.1	common
Photosensitivity reaction	68	18.3	1	0.5	57	10.1	125	13.3	very common
Rash	50	13.4	17	9.0	45	8.0	95	10.1	very common
Rash maculo-papular	13	3.5	3	1.6	15	2.7	28	3.0	common
Palmar-plantar erythrodysaesthesia syndrome	9	2.4	0	0.0	8	1.4	17	1.8	common
Erythema	33	8.9	5	2.6	25	4.4	58	6.2	common
Asthenia/ Fatigue (combined)	263	70.7	84	44.4	422	74.7	685	73.1	very common
Asthenia	86	23.1	20	10.6	105	18.6	191	20.4	
Fatigue	189	50.8	65	34.4	345	61.1	534	57.0	
Pyrexia	45	12.1	9	4.8	74	13.1	119	12.7	very common
Legend: Grey boxes – synonymous PTs representing the same medical concept									

Table 46: Frequencies and Categorization of Adverse Reactions (CTCAE Grade ≥3, All Causality) Occurring in Patients from Studies CO-338-014, CO-338-010 and CO-338-017

Events	CTCAE Grade ≥3								
	CO-338-014				CO-338-010 and CO-338-017 N=565		Total of patients on Rucaparib N=937		Final Category
	Rucaparib N=372		Placebo N=189						
	n	%	n	%	n	%	n	%	
MDS/AML	3	0.8	0	0.0	2	0.4	5	0.5	Common (based on events observed in overal patient population of 1321)
AML	1	0.3	0	0.0	1	0.2	2	0.3	
MDS	2	0.5	0	0.0	1	0.2	3	0.2	
Anaemia (combined terms)	80	21.5	1	0.5	137	24.2	217	23.2	very common

Events	CTCAE Grade ≥3								
	CO-338-014				CO-338-010 and CO-338-017 N=565		Total of patients on Rucaparib N=937		Final Category
	Rucaparib N=372		Placebo N=189						
	n	%	n	%	n	%	n	%	
Anaemia	73	19.6	1	0.5	131	23.2	204	21.8	(using the highest frequency which is the combined frequency of 23.2%)
Haemoglobin decreased	7	1.9	0	0.0	9	1.6	16	1.7	
Thrombocytopenia (combined terms)	20	5.4	0	0.0	36	6.4	56	6.0	common (using the highest frequency which is the combined frequency of 6.0%)
Platelet count decreased	8	2.2	0	0.0	10	1.8	18	1.9	
Thrombocytopenia	12	3.2	0	0.0	26	4.6	38	4.1	
Neutropenia (combined terms)	29	7.8	2	1.1	45	8.0	74	7.9	common
Neutropenia	19	5.1	1	0.5	28	5.0	47	5.0	
Neutrophil count decreased	11	3.0	1	0.5	17	3.0	28	3.0	
Leukopenia	2	0.5	0	0.0	3	0.5	5	0.5	common (using the highest frequency which is the 1.1%)
White blood cell count decreased	5	1.3	0	0.0	5	0.9	10	1.1	
Febrile neutropenia	5	1.3	0	0.0	8	1.4	13	1.4	common
Lymphopenia	0	0.0	0	0.0	4	0.7	4	0.4	uncommon
Lymphocyte count decreased	2	0.5	0	0.0	3	0.5	5	0.5	
Decreased appetite	3	0.8	0	0.0	16	2.8	19	2.0	common
Blood creatinine increased	1	0.3	0	0.0	3	0.5	4	0.4	uncommon
Blood cholesterol increased	1	0.3	0	0.0	3	0.5	4	0.4	uncommon
Hypercholesterolaemia	1	0.3	0	0.0	2	0.4	3	0.3	
Dehydration	4	1.1	0	0.0	16	2.8	20	2.1	common
Dysgeusia	0	0.0	0	0.0	1	0.2	1	0.1	uncommon
Dizziness	0	0.0	1	0.5	2	0.4	2	0.2	uncommon
Dyspnoea	0	0.0	0	0.0	5	0.9	5	0.5	uncommon
Nausea	14	3.8	1	0.5	29	5.1	43	4.6	common
Vomiting	15	4.0	2	1.1	25	4.4	40	4.3	common
Diarrhoea	2	0.5	2	1.1	13	2.3	15	1.6	common
Dyspepsia	1	0.3	0	0.0	2	0.4	3	0.3	uncommon
Abdominal Pain	13	3.5	1	0.5	27	4.8	40	4.3	common (using the highest frequency which is the combined frequency of 4.3%)
Abdominal pain	11	3.0	1	0.5	23	4.1	34	3.6	
Abdominal pain lower	0	0.0	0	0.0	1	0.2	1	0.1	
Abdominal pain upper	2	0.5	0	0.0	4	0.7	6	0.6	
ALT/AST increased (combined)	38	10.2	0	0.0	61	10.8	99	10.6	very common
Alanine aminotransferase increased	37	9.9	0	0.0	56	9.9	93	9.9	common
Aspartate aminotransferase increased	7	1.9	0	0.0.	19	3.4	26	2.8	common

Events	CTCAE Grade ≥3								
	CO-338-014				CO-338-010 and CO-338-017 N=565		Total of patients on Rucaparib N=937		Final Category
	Rucaparib N=372		Placebo N=189						
	n	%	n	%	n	%	n	%	
Transaminases increased	5	1.3	0	0.0	3	0.5	8	0.9	uncommon
Photosensitivity reaction	2	0.5	0	0.0	0	0.0	2	0.2	uncommon
Rash	1	0.3	0	0.0	1	0.2	2	0.2	uncommon
Rash maculo-papular	0	0.0	0	0.0	2	0.4	2	0.2	uncommon
Palmar-plantar erythrodysaesthesia syndrome	1	0.3	0	0.0	0	0.0	1	0.1	uncommon
Erythema	0	0.0	0	0.0	0	0.0	0	0.0	Not applicable
Asthenia/ Fatigue (combined)	26	7.0	5	2.6	64	11.3	90	9.6	common
Asthenia	10	2.7	1	0.5	26	4.6	36	3.8	
Fatigue	16	4.3	4	2.1	41	7.3	57	6.1	
Pyrexia	0	0.0	0	0.0	2	0.4	2	0.2	uncommon
Legend: Grey boxes – synonymous PTs representing the same medical concept									

Grade 3 or higher TEAEs (Study CO-338-014)

The highest incidences of Grade ≥3 TEAEs for patients treated with rucaparib were in the SOCs of Blood and lymphatic disorders and Investigations (25.5%). The most frequent Grade ≥3 TEAEs in patients treated with rucaparib relative to placebo were combined anaemia/decreased/low haemoglobin (21.5% vs. 0.5%) and combined ALT/AST increased (10.2% vs. 0%).

Table 47: Grade 3 or Higher TEAEs Reported in ≥ 5% of Patients in Any Treatment Group: Comparison with CSR – Safety Population (CO-338-014)

	CSR		T2V Update	
	Rucaparib (N = 372) n (%)	Placebo (N = 189) n (%)	Rucaparib (N = 372) n (%)	Placebo (N = 189) n (%)
Number of Patients With at Least One Grade 3[a] or Higher TEAE	**209 (56.2)**	**28 (14.8)**	**222 (59.7)**	**30 (15.9)**
Combined Preferred Terms				
Combined ALT/AST increased	39 (10.5)	0 (0.0)	38 (10.2)	0 (0.0)
Combined Anemia and/or low/decreased hemoglobin	70 (18.8)	1 (0.5)	80 (21.5)	1 (0.5)
Combined Asthenia/Fatigue	25 (6.7)	5 (2.6)	26 (7.0)	5 (2.6)
Combined Neutropenia and/or low/decreased ANC	25 (6.7)	2 (1.1)	29 (7.8)	2 (1.1)
Combined Thrombocytopenia and/or low/decreased platelets	19 (5.1)	0 (0.0)	20 (5.4)	0 (0.0)
System Organ Class Preferred Term				
Blood and lymphatic system disorders	**87 (23.4)**	**2 (1.1)**	**95 (25.5)**	**3 (1.6)**
Anaemia	65 (17.5)	1 (0.5)	73 (19.6)	1 (0.5)
Neutropenia	18 (4.8)	1 (0.5)	19 (5.1)	1 (0.5)
Gastrointestinal disorders	**47 (12.6)**	**12 (6.3)**	**49 (13.2)**	**12 (6.3)**
General disorders and administration site conditions	**29 (7.8)**	**6 (3.2)**	**31 (8.3)**	**6 (3.2)**
Investigations	**72 (19.4)**	**1 (0.5)**	**77 (20.7)**	**1 (0.5)**
Alanine aminotransferase increased	38 (10.2)	0 (0.0)	37 (9.9)	0 (0.0)
Metabolism and nutrition disorders	**15 (4.0)**	**1 (0.5)**	**19 (5.1)**	**1 (0.5)**

Most Grade ≥3 TEAEs were considered by the investigator to be related to study drug treatment, with combined anaemia/low/decreased haemoglobin being most common in rucaparib patients (20.7% rucaparib, 0.5% placebo). An exception was Grade ≥3 GI disorders, with 5.9% considered related compared to 13.2% irrespective of relationship.

Table 48: Treatment-related Grade 3 or Higher Adverse Events Reported in ≥ 5% of Patients in Any Treatment Group: Comparison with CSR – Safety Population (CO-338-014)

	CSR		T2V Update	
	Rucaparib (N = 372) n (%)	Placebo (N = 189) n (%)	Rucaparib (N = 372) n (%)	Placebo (N = 189) n (%)
Number of Patients With at Least One Treatment-related Grade 3[a] or Higher TEAE	**162 (43.5)**	**9 (4.8)**	**171 (46.0)**	**9 (4.8)**
Combined Preferred Terms				
Combined ALT/AST Increased	38 (10.2)	0 (0.0)	37 (9.9)	0 (0.0)
Combined Anemia and/or low/decreased hemoglobin	69 (18.5)	1 (0.5)	77 (20.7)	1 (0.5)
Combined Asthenia/Fatigue	25 (6.7)	3 (1.6)	26 (7.0)	3 (1.6)
Combined Neutropenia and/or low/decreased ANC	21 (5.6)	1 (0.5)	24 (6.5)	1 (0.5)
System Organ Class Preferred Term				
Blood and lymphatic system disorders	**82 (22.0)**	**1 (0.5)**	**89 (23.9)**	**1 (0.5)**
Anaemia	64 (17.2)	1 (0.5)	71 (19.1)	1 (0.5)
Gastrointestinal disorders	**22 (5.9)**	**1 (0.5)**	**22 (5.9)**	**1 (0.5)**
General disorders and administration site conditions	**27 (7.3)**	**4 (2.1)**	**28 (7.5)**	**4 (2.1)**
Investigations	**66 (17.7)**	**1 (0.5)**	**69 (18.5)**	**1 (0.5)**
Alanine aminotransferase increased	37 (9.9)	0 (0.0)	36 (9.7)	0 (0.0)

The updated most common Grade ≥3 or higher TEAEs in the treatment setting studies were combined anaemia/low/decreased haemoglobin (24.2%), combined asthenia/fatigue (11.3%), combined ALT/AST increased (10.8%), combined neutropenia/low/decreased ANC (8.0%), combined thrombocytopenia/ low platelets (6.4), nausea (5.1%) and malignant neoplasm progression (5.0%). The most common treatment-related Grade ≥3 TEAEs were combined anaemia/ low/decreased haemoglobin (21.8%), combined ALT/AST increased (9.2%), combined asthenia/fatigue (8.7%) and combined neutropenia/ low/decreased ANC (7.4%).

Dose adjustments

Dose reductions

The most commonly reported TEAEs leading to rucaparib dose reduction were combined anaemia/low or decreased haemoglobin (12.6%), combined ALT/AST increased (11.0%), combined thrombocytopenia/ low/decreased platelets (10.8%) and nausea (9.9%). The only TEAE leading to dose reduction in > 2 patients on placebo was combined asthenia/fatigue in 4 patients. Mostly, the TEAEs leading to dose reduction were considered by the investigator to be treatment related.

Table 49: Treatment-emergent Adverse Events that Led to Dose Reduction in ≥ 5% of Patients in Any Treatment Group: Comparison with CSR - Safety Population (CO-338-014)

	CSR		T2V Update	
	Rucaparib (N = 372) n (%)	Placebo (N = 189) n (%)	Rucaparib (N = 372) n (%)	Placebo (N = 189) n (%)
Number of Patients With at Least One TEAE Leading to Study Drug Dose Reduction	**203 (54.6)**	**8 (4.2)**	**206 (55.4)**	**8 (4.2)**
Combined Preferred Terms				
Combined ALT/AST increased	41 (11.0)	0 (0.0)	41 (11.0)	0 (0.0)
Combined Anemia and/or low/decreased hemoglobin	45 (12.1)	0 (0.0)	47 (12.6)	0 (0.0)
Combined Asthenia/Fatigue	33 (8.9)	4 (2.1)	33 (8.9)	4 (2.1)
Combined Thrombocytopenia and/or low/decreased platelets	39 (10.5)	0 (0.0)	40 (10.8)	0 (0.0)
System Organ Class Preferred Term				
Blood and lymphatic system disorders	**66 (17.7)**	**0 (0.0)**	**69 (18.5)**	**0 (0.0)**
Anaemia	41 (11.0)	0 (0.0)	43 (11.6)	0 (0.0)
Thrombocytopenia	20 (5.4)	0 (0.0)	21 (5.6)	0 (0.0)
Gastrointestinal disorders	**47 (12.6)**	**1 (0.5)**	**48 (12.9)**	**1 (0.5)**
Nausea	37 (9.9)	1 90.5)	37 (9.9)	1 (0.5)
General disorders and administration site conditions	**33 (8.9)**	**6 (3.2)**	**33 (8.9)**	**6 (3.2)**
Fatigue	25 (6.7)	4 (2.1)	24 (6.5)	4 (2.1)
Investigations	**85 (22.8)**	**0 (0.0)**	**88 (23.7)**	**0 (0.0)**
Alanine aminotransferase increased	39 (10.5)	0 (0.0)	39 (10.5)	0 (0.0)
Platelet count decreased	20 (5.4)	0 (0.0)	20 (5.4)	0 (0.0)

In the update of Studies CO-338-010 and CO-338-017, the most commonly reported TEAEs leading to rucaparib dose reduction for all ovarian cancer patients were combined anaemia/low/ decreased haemoglobin (17.2%), combined asthenia/fatigue (14.0%), and nausea (10.4%).

Treatment interruption

The most commonly reported TEAEs leading to rucaparib treatment interruption were combined thrombocytopenia/low/decreased platelets (17.2%), combined anaemia/low/decreased haemoglobin (15.1%), combined ALT/AST increased (10.2%), and nausea (10.2%). The only TEAE reported with placebo treatment interruption > 2 patients was asthenia/fatigue (n=6, 3.2%). Mostly, the TEAEs leading to treatment interruption were considered by the investigator to be treatment related.

The median time to first TEAE leading to dose modification (i.e. dose reduction, treatment interruption, or study drug discontinuation) was shorter for patients who received rucaparib as compared to patients who received placebo (1.0 months [95% CI 0.7, 1.2] vs 3.2 months [95% CI 1.9, 4.2]; 'treatment related; 0.9 months [95% CI 0.6, 1.0] vs. 1.9 [95% CI 0.7, 3.5]).

Table 50: Treatment-emergent Adverse Events that Led to Treatment Interruption in ≥ 5% of Patients in Any Treatment Group: Comparison with CSR - Safety Population (CO-338-014)

	CSR		T2V Update	
	Rucaparib (N = 372) n (%)	Placebo (N = 189) n (%)	Rucaparib (N = 372) n (%)	Placebo (N = 189) n (%)
Number of Patients With at Least One TEAE Leading to Treatment Interruption	**237 (63.7)**	**19 (10.1)**	**243 (65.3)**	**19 (10.1)**
Combined Preferred Terms				
Combined ALT/AST increased	39 (10.5)	0 (0.0)	38 (10.2)	0 (0.0)
Combined Anemia and/or low/decreased hemoglobin	51 (13.7)	1 (0.5)	56 (15.1)	1 (0.5)
Combined Asthenia/Fatigue	32 (8.6)	6 (3.2)	33 (8.9)	6 (3.2)
Combined Neutropenia and/or low/decrease ANC	23 (6.2)	0 (0.0)	24 (6.5)	1 (0.5)
Combined Thrombocytopenia and/or low/decreased platelets	64 (17.2)	0 (0.0)	64 (17.2)	0 (0.0)
System Organ Class Preferred Term				
Blood and lymphatic system disorders	**89 (23.9)**	**1 (0.5)**	**91 (24.5)**	**1 (0.5)**
Anaemia	47 (12.6)	1 (0.5)	52 (14.0)	1 (0.5)
Thrombocytopenia	39 (10.5)	0 (0.0)	38 (10.2)	0 (0.0)
Gastrointestinal disorders	**78 (21.0)**	**7 (3.7)**	**81 (21.8)**	**7 (3.7)**
Nausea	38 (10.2)	2 (1.1)	38 (10.2)	2 (1.1)
Vomiting	32 (8.6)	2 (1.1)	32 (8.6)	2 (1.1)
General disorders and administration site conditions	**42 (11.3)**	**7 (3.7)**	**43 (11.6)**	**7 (3.7)**
Fatigue	23 (6.2)	6 (3.2)	24 (6.5)	6 (3.2)
Infection and infestations	**22 (5.9)**	**5 (2.6)**	**24 (6.5)**	**5 (2.6)**
Investigations	**88 (23.7)**	**1 (0.5)**	**90 (24.2)**	**1 (0.5)**
Alanine aminotransferase increased	39 (10.5)	0 (0.0)	38 (10.2)	0 (0.0)
Platelet count decreased	26 (7.0)	0 (0.0)	27 (7.3)	0 (0.0)

In the update of Studies CO-338-010 and CO-338-017, the most commonly reported TEAEs leading to rucaparib interruption for all ovarian cancer patients were combined anaemia/low/ decreased haemoglobin (17.7%), combined asthenia/fatigue (14.0%); nausea (12.9), vomiting (12.0%), and combined thrombocytopenia/low/decreased platelets (11.9%).

Serious adverse event / deaths / other significant events

Fatal Treatment Emergent Adverse Events

Fatal TEAEs that occurred while being treated or within 28 days of the last dose are presented in the table below.

Table 51: TEAEs with an Outcome of Death: Comparison with CSR – Safety Population (CO-338-014)

System Organ Class Preferred Term	CSR		T2V Update	
	Rucaparib (N = 372) n (%)	Placebo (N = 189) n (%)	Rucaparib (N = 372) n (%)	Placebo (N = 189) n (%)
Number of Patients With at Least One TEAE Leading to Death	**6 (1.6)**	**2 (1.1)**	**7 (1.9)**	**2 (1.1)**
Blood and lymphatic system disorders	**1 (0.3)**	**0 (0.0)**	**1 (0.3)**	**0 (0.0)**
Histiocytosis haematophagic	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)
Cardiac disorders	**1 (0.3)**	**0 (0.0)**	**1 (0.3)**	**0 (0.0)**
Cardiac arrest	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**4 (1.1)**	**1 (0.5)**	**5 (1.3)**	**1 (0.5)**
Acute myeloid leukaemia	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)
B-cell unclassifiable lymphoma high grade	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Malignant neoplasm progression[a]	1 (0.3)	0 (0.0)	2 (0.5)	0 (0.0)
Metastases to meninges	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)
Metastases to peritoneum[a]	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Myelodysplastic syndrome	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	**0 (0.0)**	**1 (0.5)**	**0 (0.0)**	**1 (0.5)**
Pulmonary embolism	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)

[a] Patient 17003-302 was summarized in the CSR as having died due to metastases to the peritoneum. The AE to which this event should have been coded was malignant neoplasm progression, which has been corrected for this Type II Variation.

Two patients who received rucaparib (malignant neoplasm progression) and 1 patient who received placebo (meningeal metastases) had fatal TEAEs resulting from their underlying disease with onset while being treated or within 28 days of their last dose.

The two treatment-related fatal TEAEs in rucaparib patients were AESIs (AML and MDS).

Of the remaining 3 patients in the rucaparib group with a fatal TEAE, 1 patient had a fatal event of haematophagic histiocytosis which the investigator assessed as not related to rucaparib. One patient had unclassifiable high-grade B cell lymphoma and 1 patient had a fatal cardiac arrest, with a history of left bundle branch block, congenital heart disease and congestive heart failure. Both events were considered by the investigator as unrelated to rucaparib.

The remaining placebo patient with a fatal TEAE had a pulmonary embolism considered by the investigator as unrelated to treatment.

Table 52: TEAEs with an Outcome of Death: Safety Population (Combined Studies CO-338-010 and CO-338-017)

System Organ Class Preferred Term	600 mg BID Ovarian Cancer Patients (N = 565)
	n (%)
Number of Patients With at Least One TEAE Leading to Death	**26 (4.6)**
Gastrointestinal disorders	**1 (0.2)**
Intestinal obstruction	1 (0.2)
General disorders and administration site conditions	**4 (0.7)**
General physical health deterioration	4 (0.7)
Infections and infestations	**2 (0.4)**
Sepsis	1 (0.2)
Septic shock	1 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**17 (3.0)**
B-cell type acute leukaemia	1 (0.2)
Malignant neoplasm progression	15 (2.7)
Metastatic neoplasm	1 (0.2)
Nervous system disorders	**2 (0.4)**
Cerebral artery embolism[a]	1 (0.2)
Cerebrovascular accident	1 (0.2)

[a] One patient experienced an SAE of cerebral artery embolism leading to death. Subsequent to the visit cut-off date for this Type II Variation, the investigator confirmed that cerebral artery embolism was a symptom of the patient's SAE of pulmonary embolism and not a separate SAE.

The most frequently reported fatal TEAE in the updated treatment studies was malignant neoplasm progression (15 patients, 2.7%). All other TEAEs with an outcome of death, apart from general physical health deterioration, were reported for single patients. The patient with septic shock also had febrile neutropaenia. One patient with a treatment-related fatal TEAE (B-cell type acute leukaemia in Study CO-338-010) had prior systemic neoadjuvant/adjuvant treatment with carboplatin and paclitaxel.

Other Serious Adverse Events

Combined anaemia/low/decreased haemoglobin was the most common SAE reported in patients treated with rucaparib (4.3%) relative to placebo (0.5%); all were assessed by the investigator as related to study drug.

The next most common serious TEAEs were vomiting (n=7) and pyrexia (n=6); of these 3 patients (0.8%) had vomiting and 2 patients (0.5%) had pyrexia assessed by the investigator as related to study drug.

A serious TEAE of acute kidney injury (AKI) was experienced by 4 patients in the rucaparib arm (1.1%), and no patients in placebo arm; of these 2 patients (0.5%) had the event assessed by the investigator as related to study drug. For one patient, a concurrent treatment-related TEAE of Grade 3 decreased GFR resulted in discontinuation of study treatment and the AKI resolved. For the other patient it was possible that rucaparib may have indirectly contributed to AKI, secondary to concurrent serious TEAEs of nausea and vomiting and TEAEs of poor intake, anemia and diarrhoea.

A serious TEAE of febrile neutropenia was experienced by 5 patients (independent of the pyrexia cases) treated with rucaparib; of these, 4 patients had the event assessed by the investigator as related to study drug. All 4 serious TEAEs of thrombocytopenia/or low/decreased platelets were assessed by the investigator as study drug-related.

Of the 4 SAEs in the metabolism and nutrition disorders SOC, 3 were due to dehydration and 1 decreased appetite.

Table 53: Treatment-emergent SAEs Reported in ≥ 1% of Patients in Any Treatment Group: Comparison with CSR – Safety Population (CO-338-014)

	CSR		T2V Update	
	Rucaparib (N = 372) n (%)	**Placebo (N = 189) n (%)**	**Rucaparib (N = 372) n (%)**	**Placebo (N = 189) n (%)**
Number of Patients With at Least One Serious TEAE	**78 (21.0)**	**20 (10.6)**	**83 (22.3)**	**20 (10.6)**
Combined Preferred Terms				
Combined Anemia and/or low/decreased hemoglobin[a]	16 (4.3)	1 (0.5)	16 (4.3)	1 (0.5)
Combined Thrombocytopenia and/or low/decreased platelets	4 (1.1)	0 (0.0)	4 (1.1)	0 (0.0)
System Organ Class Preferred Term				
Blood and lymphatic system disorders	**23 (6.2)**	**1 (0.5)**	**23 (6.2)**	**1 (0.5)**
Anaemia	16 (4.3)	1 (0.5)	16 (4.3)	1 (0.5)
Febrile neutropenia	5 (1.3)	0 (0.0)	5 (1.3)	0 (0.0)
Gastrointestinal disorders	**22 (5.9)**	**9 (4.8)**	**24 (6.5)**	**9 (4.8)**
Abdominal pain	5 (1.3)	0 (0.0)	5 (1.3)	0 (0.0)
Constipation	5 (1.3)	2 (1.1)	5 (1.3)	2 (1.1)
Intestinal obstruction	3 (0.8)	2 (1.1)	3 (0.8)	2 (1.1)
Small intestinal obstruction	3 (0.8)	3 (1.6)	4 (1.1)	3 (1.6)
Vomiting	6 (1.6)	2 (1.1)	7 (1.9)	2 (1.1)
General disorders and administration site conditions	**9 (2.4)**	**0 (0.0)**	**11 (3.0)**	**0 (0.0)**
Pyrexia	6 (1.6)	0 (0.0)	6 (1.6)	0 (0.0)
Infections and infestations	**10 (2.7)**	**5 (2.6)**	**11 (3.0)**	**5 (2.6)**
Injury, poisoning and procedural complications	**3 (0.8)**	**3 (1.6)**	**4 (1.1)**	**3 (1.6)**
Investigations	**6 (1.6)**	**0 (0.0)**	**7 (1.9)**	**0 (0.0)**
Metabolism and nutrition disorders	**1 (0.3)**	**1 (0.5)**	**4 (1.1)**	**1 (0.5)**
Musculoskeletal and connective tissue disorders	**3 (0.8)**	**0 (0.0)**	**5 (1.3)**	**0 (0.0)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**10 (2.7)**	**1 (0.5)**	**9 (2.4)**	**1 (0.5)**
Nervous system disorders	**5 (1.3)**	**0 (0.0)**	**6 (1.6)**	**0 (0.0)**
Renal and urinary disorders	**6 (1.6)**	**0 (0.0)**	**6 (1.6)**	**0 (0.0)**
Acute kidney injury	4 (1.1)	0 (0.0)	4 (1.1)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	**6 (1.6)**	**1 (0.5)**	**7 (1.9)**	**1 (0.5)**

Table 54: Treatment-related SAEs Reported in ≥ 1% of Patients Any Treatment Group: Comparison with CSR – Safety Population (CO-338-014)

	CSR		T2V Update	
	Rucaparib (N = 372) n (%)	**Placebo (N = 189) n (%)**	**Rucaparib (N = 372) n (%)**	**Placebo (N = 189) n (%)**
Number of Patients With at Least One Treatment-related Serious TEAE	34 (9.1)	3 (1.6)	35 (9.4)	3 (1.6)
Combined Preferred Terms				
Combined Anemia and/or low/decreased hemoglobin	16 (4.3)	1 (0.5)	16 (4.3)	1 (0.5)
Combined Thrombocytopenia and/or low/decreased platelets	4 (1.1)	0 (0.0)	4 (1.1)	0 (0.0)
System Organ Class Preferred Term				
Blood and lymphatic system disorders	**21 (5.6)**	**1 (0.5)**	**21 (5.6)**	**1 (0.5)**
Anaemia	16 (4.3)	1 (0.5)	16 (4.3)	1 (0.5)
Febrile neutropenia	4 (1.1)	0 (0.0)	4 (1.1)	0 (0.0)
Gastrointestinal disorders	**4 (1.1)**	**0 (0.0)**	**4 (1.1)**	**0 (0.0)**
General disorders and administration site conditions	**4 (1.1)**	**0 (0.0)**	**4 (1.1)**	**0 (0.0)**
Investigations	**5 (1.3)**	**0 (0.0)**	**6 (1.6)**	**0 (0.0)**

In the updated studies in the treatment setting (CO-338-010 and CO-338-017), SAEs were reported in 30.3% of ovarian cancer patients treated with rucaparib, most commonly anaemia/low/decreased haemoglobin (5.0%) and malignant neoplasm progression (4.8%). Treatment-related SAEs were experienced by 11.3% of ovarian cancer patients overall, most commonly anaemia/low/decreased haemoglobin (4.2%).

New Primary Malignancies (excluding MDS/ AML)

As of 31 December 2017, 7 of 1186 patients who received rucaparib in Clovis-sponsored clinical trials developed a new primary malignancy (excluding MDS/ AML). Two malignancies, a B-cell acute lymphocytic leukaemia (ALL) and a T-cell lymphoma, were assessed as related to rucaparib therapy. The remaining 5 malignancies (2 malignant melanoma, 2 lung cancer, and 1 B-cell unclassifiable lymphoma high grade) were all considered unrelated to rucaparib treatment by the investigator. Confounding risk factors, including prior cytotoxic chemotherapy, BRCA mutations, and former smoking history may have contributed.

AESI – MDS and AML

Cumulatively, 14 cases of MDS/AML reported amongst the 1186 patients (1.2%) who received rucaparib in clinical trials. These include 6 cases (~0.5%) reported whilst patients received rucaparib or within 28 days of rucaparib discontinuation; 1 case of MDS in Study CO-338-010, 1 case of MDS, 1 case of AML, and 1 case of MDS evolving to AML in Study CO-338-014 and 1 case each of MDS and AML in Study CO-338-017.

A further 8 rucaparib-treated patients developed MDS/AML more than 28 days after discontinuing rucaparib, including 1 case of MDS in Study CO-338-010; 2 cases of MDS, 2 cases of AML, and 1 case of MDS evolving to AML in Study CO-338-014; and 1 case each of MDS and AML in Study CO-338-017. This includes 1 case of MDS reported after the 31 December visit cut-off and therefore not included in the source summary tables. One patient in Study CO-338-014 developed AML more than 28 days after discontinuing placebo.

All the patients diagnosed with MDS/ AML had received multiple regimens and cycles of prior chemotherapy, including platinum- and/or taxane-containing regimens. One patient had received a prior alkylating agent (cyclophosphamide) for breast cancer and treatment with cisplatin and trabectedin after rucaparib discontinuation. Data indicate that patients exposed to DNA-damaging therapies for the treatment of ovarian and breast cancer have an increased risk of developing MDS or AML (Fulcher et al; ASCO; JCO abstract 2017). One patient had received olaparib for over 1 year during the intervening period between discontinuing rucaparib and being diagnosed with MDS.

Between 31 December 2017 and 27 June 2018, 3 more cases of MDS and AML were reported, resulting in a total of 18 cases of MDS/AML. Of the 18 patients with MDS or AML, 17 received rucaparib and 1 received placebo.

Overall, the rate of MDS/AML is 1.3% (common) for all patients including during the long term safety follow up (rate is calculated based on overall safety population of 1321 patients exposed to at least one dose of oral rucaparib in all clinical studies) including cases that were fatal. The duration of therapy with rucaparib in patients who developed MDS/AML varied from less than 1 month to approximately 28 months. The cases were typical of secondary, cancer therapy-related MDS/AML. All patients had potential contributing factors for the development of MDS/AML; in all cases, patients had received previous platinum- containing chemotherapy regimens and/or other DNA damaging agents. Additional cases have been reported post-marketing.

Laboratory findings

The most common laboratory abnormalities with rucaparib treatment were increased creatinine, increased ALT, increased AST, increased cholesterol and myelosuppression (mainly decreased haemoglobin and platelets, with lesser decreases in lymphocytes and neutrophils). Laboratory abnormalities were consistent with the TEAEs reported; shifts in toxicity grade for laboratory abnormalities were consistent with Grade 3 or higher TEAEs reported.

Clinical Chemistry

Table 55: Shifts in Key Clinical Chemistry Parameters: Comparison with CSR – Safety Population (CO-338-014)

	CSR				T2V Update			
	Rucaparib		Placebo		Rucaparib		Placebo	
Shift in CTCAE Grade (n [%])[a]								
	Grade 1-4	**Grade 3-4**	**Grade 1-4**	**Grade 3-4**	**Grade 1-4**	**Grade 3-4**	**Grade 1-4**	**Grade 3-4**
Increase in ALT[b, c]	267 (72.8)	24 (6.5)	7 (3.7)	0	268 (73.0)	24 (6.5)	7 (3.7)	0
Increase in AST[d, e]	223 (60.9)	3 (0.8)	7 (3.7)	0	223 (60.9)	3 (0.8)	7 (3.7)	0
Increase alkaline phosphatase[b, c]	116 (31.6)	1 (0.3)	10 (5.3)	0	117 (31.9)	1 (0.3)	10 (5.3)	0
Increase bilirubin[b, c]	34 (9.3)	1 (0.3)	3 (1.6)	0	35 (9.5)	1 (0.3)	3 (1.6)	0
Increase in cholesterol[b, c]	152 (41.4)	15 (4.1)	39 (20.6)	0	155 (42.2)	15 (4.1)	40 (21.2)	0
Hyperglycemia[b, c]	125 (34.1)	6 (1.6)	54 (28.6)	0	134 (36.5)	7 (1.9)	54 (28.6)	0
Increase in creatinine[b, c, f]	156 (42.5)	1 (0.3)	14 (7.4)	0	158 (43.1)	1 (0.3)	14 (7.4)	0

Table 56: Shifts from Baseline to a Worsening Toxicity of Grade 2, 3, or 4 in Clinical Chemistry Parameters with Incidence of Toxicity Shift ≥ 5% Higher in Rucaparib As Compared to Placebo: Comparison with CSR - Safety Population (CO-338-014)

	CSR						T2V Update					
	Rucaparib			Placebo			Rucaparib			Placebo		
Shift in CTCAE Grade (n [%])[a]												
	Grade 2	**Grade 3**	**Grade 4**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 2**	**Grade 3**	**Grade 4**
Increase in ALT[b, c]	55 (15.0)	24 (6.5)	0	1 (0.5)	0	0	56 (15.3)	24 (6.5)	0	1 (0.5)	0	0
Increase in AST[d, e]	29 (7.9)	3 (0.8)	0	1 (0.5)	0	0	29 (7.9)	3 (0.8)	0	1 (0.5)	0	0
Increase in cholesterol[b, c]	70 (19.1)	11 (3.0)	4 (1.1)	8 (4.2)	0	0	71 (19.3)	11 (3.0)	4 (1.1)	8 (4.2)	0	0
Increase in creatinine[b, c]	117 (31.9)	1 (0.3)	0	7 (3.7)	0	0	120 (32.7)	1 (0.3)	0	7 (3.7)	0	0
Decrease in phosphate[b, c]	68 (18.5)	6 (1.6)	0	14 (7.4)	1 (0.5)	0	71 (19.3)	6 (1.6)	0	14 (7.4)	1 (0.5)	0

a Shifts are based on worst grade experienced on treatment and patients who at least a 1 grade shift from baseline.
b Rucaparib n = 367
c Placebo n = 189
d Rucaparib n = 366
e Placebo n = 188
f Evaluated using modified CTCAE criteria (ie, Version 5.0) where Grade 1 is >ULN-1.5 ULN; Grade 2 is >1.5 x baseline to 3.0 x baseline or >1.5 x ULN to 3.0 x ULN; Grade 3 is >3.0 x baseline or >3.0 x ULN to 6.0 x ULN; and Grade 4 is >6.0 x ULN.

The highest incidence of shift to Grade 2 toxicity was an increase in creatinine (32.7%) and to Grade 3 toxicity was an increase in ALT (6.5%) in rucaparib patients. The largest difference in toxicity shift at any grade in rucaparib compared to placebo patients was Grade 2 increased creatinine with a difference of 29.0% between rucaparib (32.7%) and placebo patients (3.7%).

Serum creatinine

Elevation in serum creatinine was graded according to the recently-approved CTCAE Version 5.0, in addition to Version 4.03. In CTCAE Version 5.0, Grade 1 creatinine elevation is based on values above the ULN instead of any increase from baseline, per CTCAE v4.03.

Based on CTCAE, v4.03, nearly all patients had a shift to a worsening serum creatinine grade (97.5% rucaparib, 87.8% placebo) with most shifts from normal at baseline to Grade 1 (64.6% rucaparib, 84.1% placebo) or Grade 2 (30.5% rucaparib, 3.7% placebo) post-baseline.

Per CTCAE, Version 5.0, 43.1% of patients on rucaparib had a shift to a worsening serum creatinine grade compared to 7.4% on placebo; most shifts were from normal at baseline to Grade 1 (10.1% rucaparib, 3.7% placebo) or Grade 2 (30.5% rucaparib, 3.7% placebo).

Few creatinine increases were reported as TEAEs (16.4% rucaparib; 1.6% placebo). Only 1 rucaparib – treated patient had a TEAE of Grade 3 increased blood creatinine (and fever), having had a normal baseline blood creatinine level. Renal ultrasound, urine and blood cultures were normal. The event resolved without treatment; study drug was interrupted and resumed at a reduced dose. Within a few weeks, Grade 1 increased blood creatinine was reported, which resolved without treatment interruption or dose reduction.

Creatinine increases based on laboratory assessment occurred early in treatment (by Day 15 of Cycle 1) and then plateaued; most elevations remained in the normal range, were mild (Grade 1), and not accompanied by changes in blood urea nitrogen.

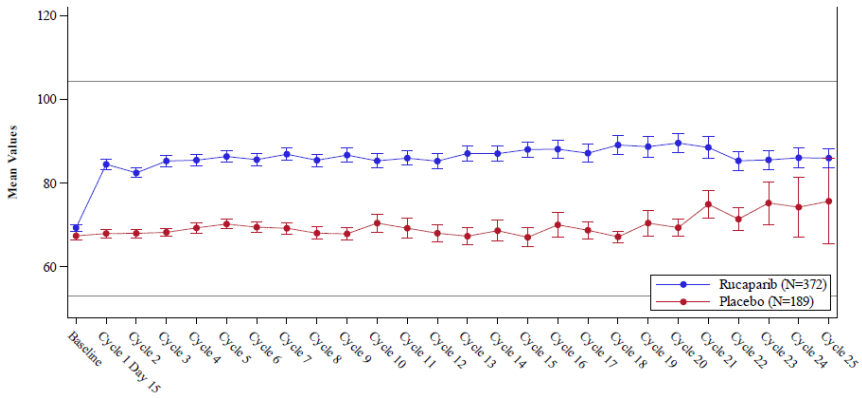


Figure 21: Mean (+/-SE) Values at Day 1 of Cycle, Baseline and On-treatment Values for Creatinine (umol/L), Safety Population CO-338-014 (Normal range 53-104.3 umol/L), Data cut-off 31 December 2017

Note: The on-treatment period is defined as the time from first dose of study drug to 28 days after the last dose of study drug. Only lab assessments performed by the central lab are included.

Liver Function Tests: AST/ ALT

Based on laboratory assessments, ALT/AST increased early in treatment and levels were approximately 2.5 to 4 times over the mean baseline value for the rucaparib group by Cycle 1 Day 15. The increase was transient, and the mean values subsequently decreased over time during continued rucaparib treatment to be within normal limits, although, higher in value than in the placebo group.

Grade≥3 toxicity in ALT and AST from laboratory testing occurred in 24 (6.5%) and 3 (0.8%) rucaparib-treated patients. The incidence of Grade ≥3 TEAEs of increased ALT/AST was 10.2% with rucaparib treatment compared to 0% with placebo. Two patients discontinued study drug due to increases in ALT/AST. No elevation of ALT or AST (or combined terms) resulted in a serious outcome.

An analysis of ALT/AST elevations for patients in Study CO-338-014, using a visit cutoff of 31 December 2017, were based on treatment-emergent adverse events (TEAEs) and/or central laboratory data assessed at protocol-specified time points. In addition to the 38 patients (10.2%) who had TEAEs of Grade 3 ALT/AST, there were 4 additional patients who had a Grade 3 ALT/AST value per the central laboratory values, without corresponding TEAEs, resulting in a total of 11.3% (42/372) rucaparib treated patients who had a Grade 3 ALT/AST value based on TEAEs and/or central laboratory data.

Grade 3 ALT measurements (9.1%) were more common than Grade 3 AST measurements (0.3%) and that only a small percentage (1.9%) of patients experienced concomitant Grade 3 ALT and AST elevations. All Grade 3 elevations assessed as related to study drug resolved or improved to Grade 1, for those patients for whom follow-up laboratory results are available. There were no patients who experienced repeat Grade 3 increased ALT and/or AST elevations.

There was a single patient who had a TEAE of Grade 4 with a preferred term of drug induced liver injury that occurred 194 days after starting treatment that was assessed by the Investigator to be due to concomitant use of Augmentin Duo Forte and atorvastatin and not related to rucaparib. The patient discontinued these drugs but continued with rucaparib for 2 more cycles with ALT/AST values ≤Grade 1 (central labs).

The median time to onset of first TEAE of a Grade 3 AST/ALT elevations event was 15 days and the increase was typically transient. The profiles of the AST and ALT values, based on central laboratory data, are similar to what was observed in the treatment setting and increases were generally not accompanied by concomitant elevation in bilirubin. Overall, the increases in ALT and/or AST were asymptomatic and there were no events that met Hy's Law for drug-induced liver injury (3 x ULN ALT/AST and 2 x ULN bilirubin).

The Study CO-338-014 protocol was amended on 07 July 2016 to allow patients to continue dosing in the event of Grade 3 ALT/AST, in the absence of other signs of liver dysfunction. However, the last patient enrolled shortly thereafter (19 July 2016). Given the early onset of the ALT/AST elevations and the timing of the amendment, this guidance was not applied to these early onset events. However, there were 7 patients who had a Grade 3 ALT event without any dose modification, highlighting that the treating Investigator did not consider the laboratory abnormality to be clinically significant. The resolution of ALT/AST increases was similar regardless of action being taken with rucaparib.

Overall, 97.6% (41/42) of patients who had a ≥ Grade 3 ALT and/or AST TEAE or lab result had a subsequent central laboratory measurement in order to assess an improvement. The majority of patients had ALT and AST levels that either resolved or improved to Grade 1 and the outcome was similar regardless of whether action was taken with rucaparib or not. Only 2 patients had an ongoing Grade 3 event of ALT and/or AST at the end of treatment. One patient had Grade 3 elevated AST at the end of treatment and was subsequently found to have a new liver metastasis. One patient had Grade 3 ALT/AST elevations associated with cholestasis and discontinued due to disease progression in the liver.

Thirty-eight patients with a ≥ Grade 3 ALT and/or AST measurement were re-challenged with rucaparib and, of these, none of them had another ≥ Grade 3 measurement based on the central laboratory data.

Risk factors for elevated transaminases were also evaluated. A logistic regression model was used to identify predictors to any grade of elevated transaminase and elevated transaminase events grade 3 or higher. The model included common demographic and medical history variables. The potential risk factor that qualified ($p < 0.2$) into the model, besides treatment with rucaparib ($p < 0.0001$), were HRD group and age at baseline; however, neither HRD group ($p=0.1597$) nor age at baseline ($p=0.0798$) met statistical significance ($p < 0.05$) of increased risk of elevated transaminases of any grade. There was no evidence from the logistic regression model that any patient group was at greater risk of elevated transaminases during rucaparib treatment.

Haematology

Table 57: Shifts in Key Haematology Parameters: Comparison with CSR – Safety Population (CO-338-014)

	CSR				T2V Update			
	Rucaparib		Placebo		Rucaparib		Placebo	
Shift in CTCAE Grade (n [%])[a]								
	Grade 1-4	**Grade 3-4**	**Grade 1-4**	**Grade 3-4**	**Grade 1-4**	**Grade 3-4**	**Grade 1-4**	**Grade 3-4**
Decrease in hemoglobin[b, c]	224 (61.0)	46 (12.5)	24 (12.7)	2 (1.1)	224 (61.0)	47 (12.8)	24 (12.7)	2 (1.1)
Decrease in lymphocytes[b, d]	87 (23.7)	17 (4.6)	31 (16.5)	5 (2.7)	94 (25.6)	19 (5.2)	31 (16.5)	5 (2.7)
Decrease in neutrophils[b, d]	128 (34.9)	23 (6.3)	32 (17.0)	4 (2.1)	131 (35.7)	25 (6.8)	32 (17.0)	4 (2.1)
Decrease in platelets[b, d]	145 (39.5)	8 (2.2)	15 (8.0)	0	148 (40.3)	8 (2.2)	15 (8.0)	0

[a] Shifts are based on worst grade experienced on treatment and patients who had at least a 1 grade shift from baseline.
[b] Rucaparib n = 367
[c] Placebo n = 189
[d] Placebo n = 188

The most common haematology laboratory finding and haematologic TEAE was decreased haemoglobin (anaemia). The incidence of the TEAE of combined terms of anaemia/low/decreased haemoglobin was 39.0% for patients treated with rucaparib and 5.3% for patients treated with placebo. Patients treated with rucaparib had the largest shift in any toxicity grade for decrease in haemoglobin (61.0%) as compared to placebo (12.7%) and similarly for shifts to Grade 3 or 4 (12.8% vs. 1.1%). There was a higher incidence of the TEAE of Grade ≥3 combined anaemia/low/decreased haemoglobin (21.5%) compared to the incidence

by central laboratory testing of Grade ≥3 decrease in haemoglobin (12.8%), presumably as TEAEs involved reports from central and local laboratories.

Increased shifts in worsening toxicity grades with rucaparib treatment as compared to placebo were also observed for the other key haematology parameters.

Table 58: Shifts from Baseline to a Worsening Toxicity of Grade 2, 3, or 4 in Haematology Parameters with Incidence of Toxicity Shift ≥ 5% Higher in Rucaparib As Compared to Placebo: Comparison with CSR - Safety Population (CO-338-014)

	CSR						T2V Update					
	Rucaparib			Placebo			Rucaparib			Placebo		
Shift in CTCAE Grade (n [%])[a]												
	Grade 2	**Grade 3**	**Grade 4**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 2**	**Grade 3**	**Grade 4**
Decrease in hemoglobin[b, c]	92 (25.1)	46 (12.5)	0	7 (3.7)	2 (1.1)	0	92 (25.1)	47 (12.8)	0	7 (3.7)	2 (1.1)	0
Decrease in leukocytes[b, c]	49 (13.4)	11 (3.0)	1 (0.3)	12 (6.3)	0	0	52 (14.2)	11 (3.0)	1 (0.3)	12 (6.3)	0	0
Decrease in lymphocytes[b, d]	53 (14.4)	17 (4.6)	0	18 (9.6)	5 (2.7)	0	58 (15.8)	19 (5.2)	0	18 (9.6)	5 (2.7)	0
Decrease in neutrophils[b, d]	63 (17.2)	19 (5.2)	4 (1.1)	14 (7.4)	2 (1.1)	2 (1.1)	63 (17.2)	21 (5.7)	4 (1.1)	14 (7.4)	2 (1.1)	2 (1.1)
Decrease in platelets[b, d]	29 (7.9)	6 (1.6)	2 (0.5)	0	0	0	30 (8.2)	6 (1.6)	2 (0.5)	0	0	0

[a] Shifts are based on worst grade experienced on treatment and patients who had at least a 1 grade shift from baseline.
[b] Rucaparib n = 367
[c] Placebo n = 189
[d] Placebo n = 188

The highest incidences of shifts to Grade 2 or Grade 3 toxicity were for a decrease in haemoglobin in rucaparib patients (25.1% Grade 2 and 12.8% Grade 3). The largest difference in toxicity shift of any grade with rucaparib compared to placebo was Grade 2 decrease in haemoglobin with a difference of 21.4% between rucaparib (25.1%) and placebo patients (3.7%).

Decreased Haemoglobin (Anaemia)

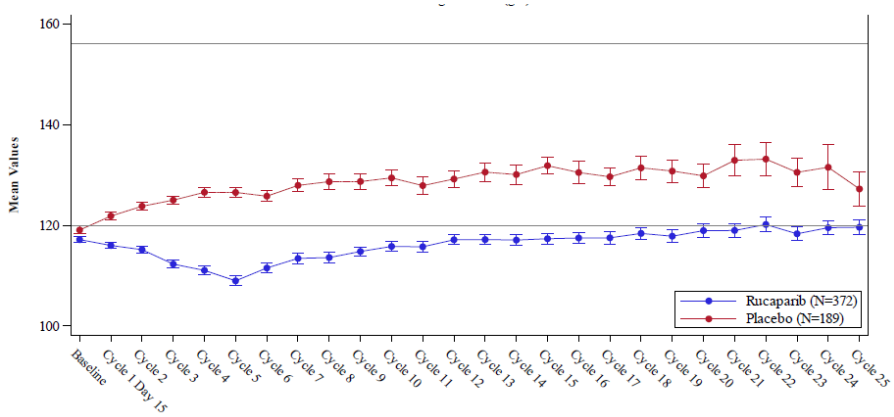


Figure 22: Mean (+/-SE) Values at Day 1 of Cycle Baseline and On-treatment Values for Haemoglobin (g/L) Safety Population CO-338-014 (Normal range 120-156 g/L), Data cut-off 31 December 2017

Note: The upper horizontal line represents the upper limit of normal, and the lower horizontal line represents the lower limit of normal.

Mean haemoglobin values in the rucaparib group were lower than mean values in the placebo group by Cycle 1 Day 15, with a nadir at Cycle 5 that was consistent with the median time to onset for TEAEs of anaemia/low/ decreased haemoglobin that led to treatment discontinuation (3.9 months). Mean

haemoglobin values remained lower in the rucaparib than in the placebo group throughout the study. For MCV and MCH, mean values in the rucaparib group increased over baseline throughout the study, with no increase in reticulocytes, indicating macrocytic anaemia.

The median time to onset of the first event of Grade ≥3 anaemia/ decreased haemoglobin was 2.8 months (95% CI, 2.7-3.5) in the rucaparib group (Study CO-338-014 CSR). Most of the TEAEs of combined anaemia/low/decreased haemoglobin were managed with dose reduction or treatment interruption and blood transfusions. After combined thrombocytopenia/low/ decreased platelets (3.0%, 11 patients), anaemia/low/ decreased haemoglobin was the second most common TEAE leading to study drug discontinuation (2.7%, 10 patients) with a median time to onset of 3.9 months (95% CI, 1.9-5.1).

In the rucaparib group 79 patients (21.2%) received at least one blood transfusion; the mean (standard deviation) number of blood transfusions was 2.2 (1.46).

In the treatment setting (Studies CO-338-010 and CO-338-017), 30.0% of patients had a blood transfusion, mostly for ≥ Grade 3 combined anaemia/low/decreased haemoglobin whilst erythropoietin was administered infrequently (1.9% patients).

Decreased platelets and neutrophils

A decrease in mean/median platelets was observed with rucaparib treatment by Cycle 2 which was sustained but did not decrease further with additional treatment cycles. Four patients (1.1% [4/372]) treated with rucaparib required a platelet transfusion for thrombocytopenia.

There were minimal changes from baseline in neutrophil count for either treatment group.

Platelet transfusions and use of granulocyte colony stimulating factor (GCSF) were described for ovarian cancer patients in the treatment setting (n=377; Studies CO-338-010 and CO-338-017). Platelet transfusions (1.3% of patients) and GCSF (2.1% patients) were administered infrequently. Treatment interruption and/or dose reduction were the typical management strategies used.

Changes from baseline in other haematology parameters were generally small or within normal limits.

Table 59: Shifts in Key Haematology Parameters in Patients Treated with 600 mg Rucaparib: Safety Population (studyCO-338-014)

	CSR						T2V Update					
	Rucaparib			Placebo			Rucaparib			Placebo		
Shift in CTCAE Grade (n [%])[a]												
	Grade 2	**Grade 3**	**Grade 4**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 2**	**Grade 3**	**Grade 4**
Decrease in hemoglobin[b, c]	92 (25.1)	46 (12.5)	0	7 (3.7)	2 (1.1)	0	92 (25.1)	47 (12.8)	0	7 (3.7)	2 (1.1)	0
Decrease in leukocytes[b, c]	49 (13.4)	11 (3.0)	1 (0.3)	12 (6.3)	0	0	52 (14.2)	11 (3.0)	1 (0.3)	12 (6.3)	0	0
Decrease in lymphocytes[b, d]	53 (14.4)	17 (4.6)	0	18 (9.6)	5 (2.7)	0	58 (15.8)	19 (5.2)	0	18 (9.6)	5 (2.7)	0
Decrease in neutrophils[b, d]	63 (17.2)	19 (5.2)	4 (1.1)	14 (7.4)	2 (1.1)	2 (1.1)	63 (17.2)	21 (5.7)	4 (1.1)	14 (7.4)	2 (1.1)	2 (1.1)
Decrease in platelets[b, d]	29 (7.9)	6 (1.6)	2 (0.5)	0	0	0	30 (8.2)	6 (1.6)	2 (0.5)	0	0	0

Source: Table 14.3.4.1.1, Study CO-338-014 Supporting Data T2V

Abbreviations: CSR = clinical study report; CTCAE = Common Terminology Criteria for Adverse Events; T2V = Type II Variation

[a] Shifts are based on worst grade experienced on treatment and patients who at least a 1 grade shift from baseline.

[b] Rucaparib n = 367

[c] Placebo n = 189

[d] Placebo n = 188

Table 60: Shifts in Key Haematology Parameters in Patients Treated with 600 mg Rucaparib: Safety Population (Combined Studies CO-338-010 and CO-338-017)

	600 mg BID Ovarian Cancer Patients (N = 565)	
	n (%)[a]	
Shift from Baseline in CTCAE Grade[b]		
	Grade 1-4[a]	**Grade 3-4**
Decrease in hemoglobin	381 (68.3)	133 (23.8)
Decrease in lymphocytes	287 (51.8)	61 (11.0)
Decrease in neutrophils	189 (34.2)	57 (10.3)
Decrease in platelets	241 (43.2)	46 (8.2)

a Percentages are based on the number of patients with assessments in the subgroup for the haematology test.
b Shifts are based on worst grade experienced on treatment and patients who had at least a 1 grade shift from baseline.

QT prolongation

ECGs were collected at screening, end of treatment and when clinically indicated in Study CO-338-014. There were no cases in the rucaparib or placebo treatment groups of TEAEs that might be associated with QT prolongation.

Rucaparib can be expected to cause mild QT prolongation (estimated to 11.5 ms [90% CI: 8.77 to 14.2 msec] at the $C_{max,ss}$ of 2079 ng/mL) in some patients, but the risk for clinically significant QT prolongation (i.e. > 20 msec) appears to be low. ECG monitoring may be warranted in high-risk patients receiving rucaparib, such as those with unstable cardiac conditions.

Safety in special populations

Older population

Of the 372 patients receiving rucaparib in Study CO-338-014 evaluating rucaparib in the maintenance setting, 137 patients (36.8%) were 65 years or older. Older patients (≥ 65 years old) experienced a higher incidence of SAEs, Grade ≥3 TEAEs, and TEAEs leading to study drug discontinuation or dose modifications compared to the younger subgroup (< 65 years old). However, the incidence was similar across age subgroups for the commonly experienced TEAEs (myelosuppression, nausea, vomiting and asthenia/ fatigue) and in the SOCs of interest for older patients, including cardiac disorders, infections and infestations, nervous system disorders, psychiatric disorders and vascular disorders.

Table 61: Summary of Safety in Elderly Patients with Ovarian Cancer - Study CO-338-014 (Safety Population)

	Rucaparib			Placebo		
	Age Group (years)			Age Group (years)		
	< 65 N = 235	65-74 N = 113	75-84[a] N = 24	< 65 N = 117	65-74 N = 64	75-85[a] N = 8
Number of Patients	n (%)			n (%)		
Patients with 1 or more TEAEs	235 (100.0)	113 (100.0)	24 (100.0)	112 (95.7)	62 (96.9)	8 (100.0)
Patients with 1 or more treatment related TEAEs	227 (96.6)	112 (99.1)	23 (95.8)	79 (67.5)	53 (82.8)	7 (87.5)
Patients with 1 or more serious TEAEs	47 (20.0)	29 (25.7)	7 (29.2)	13 (11.1)	7 (10.9)	0 (0.0)
Hospitalization/prolonged hospitalization	37 (15.7)	25 (22.1)	7 (29.2)	12 (10.3)	6 (9.4)	0 (0.0)
Life-threatening	2 (0.9)	2 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Disability/incapacity	2 (0.9)	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)
Other medically significant	11 (4.7)	3 (2.7)	1 (4.2)	2 (1.7)	1 (1.6)	0 (0.0)
Unknown	1 (0.4)	2 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patients with 1 or more TEAEs leading to death	5 (2.1)	1 (0.9)	1 (4.2)	0 (0.0)	2 (3.1)	0 (0.0)
Patients with 1 or more serious treatment related TEAEs	20 (8.5)	15 (13.3)	0 (0.0)	2 (1.7)	1 (1.6)	0 (0.0)
Patients with 1 or more treatment related TEAEs leading to death	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAE leading to drop out (discontinuation)	32 (13.6)	24 (21.2)	5 (20.8)	2 (1.7)	2 (3.1)	0 (0.0)
Treatment related TEAE leading to drop out (discontinuation)	25 (10.6)	21 (18.6)	3 (12.5)	1 (0.9)	0 (0.0)	0 (0.0)
TEAEs (by SOC or PT where relevant)						
Psychiatric disorders	64 (27.2)	36 (31.9)	7 (29.2)	24 (20.5)	13 (20.3)	1 (12.5)
Nervous system disorders	153 (65.1)	75 (66.4)	16 (66.7)	41 (35.0)	21 (32.8)	5 (62.5)
Injury, poisoning and procedural complications[b]	32 (13.6)	15 (13.3)	2 (8.3)	13 (11.1)	5 (7.8)	2 (25.0)
Cardiac disorders	21 (8.9)	13 (11.5)	1 (4.2)	2 (1.7)	4 (6.3)	0 (0.0)
Vascular disorders	52 (22.1)	20 (17.7)	5 (20.8)	23 (19.7)	9 (14.1)	1 (12.5)
Cerebrovascular disorders[c]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	114 (48.5)	47 (41.6)	13 (54.2)	46 (39.3)	18 (28.1)	1 (12.5)
Anticholinergic syndrome (PT)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Quality of life decreased (PT)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Combined: postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	36 (15.3)	27 (23.9)	7 (29.2)	16 (13.7)	4 (6.3)	4 (50.0)
Combined Anemia and/or low/decreased hemoglobin	84 (35.7)	52 (46.0)	9 (37.5)	8 (6.8)	1 (1.6)	1 (12.5)
Combined Neutropenia and/or low/decreased ANC	46 (19.6)	22 (19.5)	4 (16.7)	6 (5.1)	3 (4.7)	0 (0.0)
Combined Thrombocytopenia and/or low/decreased platelets	62 (26.4)	42 (37.2)	5 (20.8)	2 (1.7)	3 (4.7)	0 (0.0)

Other TEAEs appearing more frequently in older patients[d]						
	Rucaparib			Placebo		
	Age Group (years)			Age Group (years)		
	< 65 N = 235	65-74 N = 113	75-84 N = 24	< 65 N = 117	65-74 N = 64	75-85 N = 8
	n (%)			n (%)		
Abdominal pain	68 (28.9)	33 (29.2)	11 (45.8)	34 (29.1)	13 (20.3)	2 (25.0)
Abdominal pain upper	36 (15.3)	13 (11.5)	5 (20.8)	5 (4.3)	4 (6.3)	0 (0.0)
Arthralgia	39 (16.6)	14 (12.4)	6 (25.0)	15 (12.8)	8 (12.5)	1 (12.5)
Asthenia	52 (22.1)	25 (22.1)	9 (37.5)	12 (10.3)	6 (9.4)	2 (25.0)
Blood creatinine increased	29 (12.3)	1 (0.9)	5 (20.8)	2 (1.7)	1 (1.6)	0 (0.0)
Bronchitis	5 (2.1)	3 (2.7)	2 (8.3)	3 (2.6)	1 (1.6)	0 (0.0)
Constipation	87 (37.0)	43 (38.1)	11 (45.8)	27 (23.1)	17 (26.6)	2 (25.0)
Decreased appetite	49 (20.9)	32 (28.3)	7 (29.2)	14 (12.0)	11 (17.2)	1 (12.5)
Diarrhoea	70 (29.8)	40 (35.4)	11 (45.8)	28 (23.9)	11 (17.2)	2 (25.0)
Dizziness	28 (11.9)	23 (20.4)	6 (25.0)	10 (8.5)	3 (4.7)	2 (25.0)
Dry skin	24 (10.2)	6 (5.3)	4 (16.7)	11 (9.4)	5 (7.8)	1 (12.5)
Eczema	1 (0.4)	0 (0.0)	2 (8.3)	1 (0.9)	1 (1.6)	0 (0.0)
Haemoglobin decreased	3 (1.3)	5 (4.4)	2 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	52 (22.1)	13 (11.5)	6 (25.0)	23 (19.7)	8 (12.5)	0 (0.0)
Hypercholesterolaemia	12 (5.1)	12 (10.6)	3 (12.5)	3 (2.6)	1 (1.6)	0 (0.0)
Hypertension	21 (8.9)	11 (9.7)	4 (16.7)	11 (9.4)	5 (7.8)	0 (0.0)
Influenza	20 (8.5)	2 (1.8)	3 (12.5)	4 (3.4)	0 (0.0)	0 (0.0)
Lethargy	7 (3.0)	2 (1.8)	2 (8.3)	2 (1.7)	0 (0.0)	0 (0.0)
Neuropathy peripheral	7 (3.0)	2 (1.8)	2 (8.3)	4 (3.4)	2 (3.1)	0 (0.0)
Oedema peripheral	23 (9.8)	13 (11.5)	5 (20.8)	7 (6.0)	6 (9.4)	1 (12.5)
Pain in extremity	11 (4.7)	4 (3.5)	3 (12.5)	12 (10.3)	3 (4.7)	0 (0.0)
Pain of skin	0 (0.0)	0 (0.0)	2 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)
Pelvic pain	4 (1.7)	1 (0.9)	2 (8.3)	3 (2.6)	1 (1.6)	0 (0.0)
Pruritus	26 (11.1)	16 (14.2)	9 (37.5)	11 (9.4)	9 (14.1)	0 (0.0)
Pyrexia	31 (13.2)	8 (7.1)	6 (25.0)	7 (6.0)	2 (3.1)	0 (0.0)
Renal failure	0 (0.0)	6 (5.3)	2 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)
Transaminases increased	8 (3.4)	2 (1.8)	2 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)
Vertigo	7 (3.0)	2 (1.8)	2 (8.3)	0 (0.0)	2 (3.1)	0 (0.0)
Weight decreased	10 (4.3)	12 (10.6)	3 (12.5)	1 (0.9)	1 (1.6)	0 (0.0)

[a] No patients in Study CO-338-014 aged ≥ 85 years received rucaparib. An age category ≥ 85 years old was not included; the single placebo patient who was 85 years old was added to the group of placebo patients who were 75 to 84 years old, creating an age category of patients 75 to 85 years old.
[b] The SOC of Injury, poisoning and procedural complications represents the category of Accidents and Injuries, including the preferred terms that are Accidents and Injuries.
[c] To include preferred terms of cerebrovascular accident, hemiparesis, cerebral haemorrhage, intracranial haemorrhage basilar artery thrombosis, transient ischaemic attack.
[d] Greater than 5% increase in frequency of the TEAE in patients ≥ 75 years as compared to < 75 years who received rucaparib.

The number of patients ≥ 75 years old was small. In patients ≥ 75 years old, incidences of abdominal pain (45.8%), constipation (45.8%), diarrhoea (45.8%), asthenia (37.5%), pruritus (37.5%) and dizziness (25.0%) were higher than in patients < 75 years old (29.0%, 37.4%, 31.6%, 22.1%, 12.1%, and 14.7% respectively). There was an increase in the incidence of combined postural hypotension, falls, black outs, syncope, dizziness, ataxia, and fractures in older patients treated with rucaparib (15.3% in patients < 65 years old, 23.9% in patients 65 to 74 years old, and 29.2% in patients ≥ 75 years old). This may have been driven by dizziness (11.9%, 20.4% and 25.0% in the three respective age categories).

Of the 565 patients with ovarian cancer treated with rucaparib in the treatment setting (Studies CO-338-010 and CO-338-017), 243 patients (43.0%) were 65 years or older. Results were consistent with those for the maintenance setting, in that older patients (≥ 65 years old) experienced greater incidences of SAEs, Grade 3 or higher TEAEs, and TEAEs leading to study drug discontinuation or dose modification compared to the younger patients (< 65 years old), with similar incidences across age subgroups for commonly experienced TEAEs.

When referring to the overall safety population (937 patients in clinical trials in ovarian cancer treated with rucaparib monotherapy), frequencies of some adverse reactions increased patients ≥ 75 years old: increased blood creatinine (32%), dizziness (20%), pruritus (15%), and memory impairment (4%) were higher than in patients < 75 years old (18%, 15%, 9% and 1% respectively).

HRD and BRCA (tBRCA) Mutation Subgroups

Table 62: Summary of Treatment Emergent Adverse Events tBRCA and HRD Safety Populations (CO-338-014)

Patients with one or more:	**tBRCA**		**HRD**	
	Rucaparib (N = 129) n (%)	**Placebo (N =66) n (%)**	**Rucaparib (N = 235) n (%)**	**Placebo (N =118) n (%)**
TEAEs Treatment-related TEAEs	129 (100) 127 (98.4)	65 (98.5) 55 (83.3)	235 (100) 230 (97.9)	112 (94.9) 89 (75.4)
Serious TEAEs Serious treatment-related TEAEs	30 (23.3) 12 (9.3)	11 (16.7) 2 (3.0)	54 (23) 22 (9.4)	15 (12.7) 2 (1.7)
TEAEs of Grade ≥3 Treatment-related TEAEs of Grade ≥3	80 (62.0) 62 (48.1)	12 (18.2) 5 (7.6)	138 (58.7) 107 (45.5)	20 (16.9) 8 (6.8)
TEAEs leading to death Treatment-related TEAEs leading to death	5 (3.9) 2 (1.6)	1 (1.5) 0	6 (2.6) 2 (0.9)	1 (0.8) 0
TEAEs leading to study drug discontinuation Treatment-related TEAEs leading to study drug discontinuation	18 (14.0) 14 (10.9)	3 (4.5) 0	36 (15.3) 27 (11.5)	3 (2.5) 0
TEAEs leading to study drug interruption Treatment-related TEAEs leading to study drug interruption	88 (68.2) 71 (55.0)	9 (13.6) 4 (6.1)	152 (64.7) 125 (53.2)	16 (13.6) 8 (6.8)
TEAEs leading to study drug dose reduction Treatment-related TEAEs leading to study drug dose reduction	73 (56.6) 71 (55.0)	4 (6.1) 4 (6.1)	131 (55.7) 126 (53.6)	7 (5.9) 6 (5.1)
TEAEs leading to dose reduction/ interruption Treatment-related TEAEs leading to dose reduction or interruption	96 (74.4) 85 (65.9)	10 (15.2) 6 (9.1)	168 (71.5) 148 (63.0)	17 (14.4) 10 (8.5)

Germline and Somatic BRCA Mutation

Table 63: Summary of Treatment Emergent Adverse Events tBRCA germline and somatic Safety Populations (CO-338-014)

Patients with one or more:	**tBRCA germline**		**tBRCA somatic**	
	Rucaparib (N = 82) n (%)	**Placebo (N =48) n (%)**	**Rucaparib (N = 40) n (%)**	**Placebo (N =16) n (%)**
TEAEs Treatment-related TEAEs	82 (100) 81 (98.8)	48 (100) 39 (81.3)	40 (100) 39 (97.5)	15 (93.8) 14 (87.5)
Serious TEAEs Serious treatment-related TEAEs	23 (28.0) 9 (11.0)	9 (18.8) 2 (4.2)	6 (15) 2 (5.0)	1 (6.3) 0
TEAEs of Grade ≥3 Treatment-related TEAEs of Grade ≥3	52 (63.4) 42 (51.2)	11 (22.9) 5 (10.4)	23 (57.5) 16 (40.0)	1 (6.3) 0
TEAEs leading to death Treatment-related TEAEs leading to death	4 (4.9) 2 (2.4)	1 (2.1) 0	0 0	0 0
TEAEs leading to study drug discontinuation Treatment-related TEAEs leading to study drug discontinuation	15 (18.3) 12 (14.6)	3 (6.3) 0	2 (5.0) 2 (5.0)	0 0
TEAEs leading to study drug interruption Treatment-related TEAEs leading to study drug interruption	55 (67.1) 41 (50.0)	9 (18.8) 4 (8.3)	26 (65.0) 23 (57.5)	0 0
TEAEs leading to study drug dose reduction Treatment-related TEAEs leading to study drug dose reduction	46 (56.1) 44 (53.7)	4 (8.3) 4 (8.3)	22 (55.0) 22 (55.0)	0 0
TEAEs leading to dose reduction/ interruption Treatment-related TEAEs leading to dose reduction or interruption	60 (73.2) 51 (62.2)	10 (20.8) 6 (12.5)	29 (72.5) 27 (67.5)	0 0

Renal impairment

A statistically significant exposure-response relationship ($p < 0.05$) was observed for Grade ≥ 2 increased creatinine, with a model-predicted incidence of 36.5% following treatment with 600 mg rucaparib BID. Increased creatinine is likely due to the potent inhibition by rucaparib of the multidrug and toxin extrusion (MATE)1 and MATE2-K renal transporters. In the secondary analysis, older patients (≥ 65 years) and those with poorer performance status (ECOG = 1) appeared to have a higher incidence of Grade ≥ 2 increased creatinine.

Rucaparib studies required serum creatinine ≤ 1.5 x ULN for inclusion; thus, some patients with mild renal impairment (defined using the NCI Organ Dysfunction Working Group criteria as an estimated creatinine clearance [CLcr] of 40-59 mL/min) were enrolled.

Table 64: Overall Summary of Treatment-emergent Adverse Events: Comparison of Patients by Renal Function defined according to the EMA guideline – Safety Population (CO-338-014)

Parameter	Normal Renal Function[a, d]		Mild Renal Impairment[b, d]		Moderate Renal Impairment[c,d]	
	Rucaparib (N = 162) n%	Placebo (N = 80) n%	Rucaparib (N = 158) n%	Placebo (N = 83) n%	Rucaparib (N = 52) n%	Placebo (N = 26) n%
Patients with one or more TEAEs[e]	162 (100.0)	78 (97.5)	158 (100.0)	79 (95.2)	52 (100.0)	25 (96.2)
Patients with one or more treatment-related TEAEs[e]	158 (97.5)	58 (72.5)	153 (96.8)	60 (72.4)	51 (98.1)	21 (80.8)
Patients with one or more serious TEAEs	33 (20.4)	10 (12.5)	32 (20.3)	7 (8.4)	18 (34.6)	3 (11.5)
Patients with one or more serious treatment-related TEAEs	18 (11.1)	0 (0.0)	7 (4.4)	2 (2.4)	10 (19.2)	1 (3.8)
Patients with one or more TEAEs of Grade 3 or higher	84 (51.9)	13 (16.3)	95 (60.1)	12 (14.5)	43 (82.7)	5 (19.2)
Patients with one or more treatment-related TEAEs of Grade 3 or higher	69 (42.6)	1 (1.3)	68 (43.0)	5 (6.0)	34 (65.4)	3 (11.5)
Patients with one or more TEAEs leading to death	4 (2.5)	2 (2.5)	2 (1.3)	0 (0.0)	1 (1.9)	0 (0.0)
Patients with one or more treatment-related TEAEs leading to death	2 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patients with one or more TEAEs leading to study drug discontinuation	24 (14.8)	2 (2.5)	27 (17.1)	1 (1.2)	10 (19.2)	1 (3.8)
Patients with one or more treatment-related TEAEs leading to study drug discontinuation	21 (13.0)	0 (0.0)	21 (13.3)	0 (0.0)	7 (13.5)	1 (3.8)
Patients with one or more TEAEs leading to study drug interruption	93 (57.4)	6 (7.5)	105 (66.5)	8 (9.6)	45 (86.5)	5 (19.2)
Patients with one or more treatment-related TEAEs leading to study drug interruption	76 (46.9)	1 (1.3)	86 (54.4)	4 (4.8)	43 (82.7)	4 (15.4)
Patients with one or more TEAEs leading to study drug dose reduction	74 (45.7)	1 (1.3)	90 (57.0)	4 (4.8)	42 (80.8)	3 (11.5)
Patients with one or more treatment-related TEAEs leading to study drug dose reduction	72 (44.4)	1 (1.3)	88 (55.7)	4 (4.8)	40 (76.9)	2 (7.7)

[a] Patients with normal renal function had CLcr ≥ 90 mL/min according to EMA guideline.

[b] Patients with mild renal impairment had CLcr ≥ 60 mL/min to < 90 mL/min according to EMA guideline.

[c] Patients with moderate renal impairment had CLcr ≥ 30 mL/min to < 60 mL/min according to EMA guideline.

[d] Guideline on the Evaluation of the Pharmacokinetics of Medicinal Products in Patients with Decreased Renal Function. 2016. at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/02/WC500200841.pdf.)

[e] Included events of disease progression.

In patients with moderate renal impairment (CLcr of 30-59 mL/min), frequencies of some adverse reactions increased: Grade 3 or 4 anaemia (31%), Grade 3 or 4 thrombocytopenia (12%), and Grade 3 fatigue/asthenia (15%) were higher than in patients with mild renal impairment (CLcr > 60-90 mL/min) or normal renal function (CLcr > 90 mL/min) (21%, 5%, and 8%).

Hepatic Impairment

A dedicated study in patients with moderate hepatic impairment, Study CO-338-078, is ongoing with a report due Q3 2019. Entry to studies CO-338-014, CO-338-010 and CO-338-017 was restricted to patients with normal hepatic function or mild hepatic impairment with ALT and AST ≤ 3 × ULN (≤ 5 × ULN if liver metastases) and bilirubin ≤ 1.5 × ULN (< 2 × ULN if Gilbert's syndrome). Therefore, some patients with mild hepatic impairment (defined using the NCI Organ Dysfunction Working Group criteria as AST > ULN with total bilirubin ≤ ULN or any AST level with total bilirubin > 1.0-1.5 × ULN) were enrolled.

The exposure-safety analysis conducted for 359/372 patients treated with rucaparib in Study CO-338-014 found no statistically significant exposure-response relationships for Grade ≥ 3 ALT increased, Grade ≥ 3 AST increased or Grade ≥ 2 total bilirubin increased. ALT/ AST elevations are a known effect of rucaparib.

Table 65: Overall Summary of Treatment-emergent Adverse Events: Comparison of Patients by Hepatic Function – Safety Population (CO-338-014)

Parameter	No Hepatic Impairment[a, c]		Mild Hepatic Impairment[b, c]	
	Rucaparib (N = 353) n%	Placebo (N = 183) n%	Rucaparib (N = 19) n%	Placebo (N = 6) n%
Patients with one or more TEAEs[d]	353 (100.0)	176 (96.2)	19 (100.0)	6 (100.0)
Patients with one or more treatment-related TEAEs[d]	343 (97.2)	134 (73.2)	19 (100.0)	5 (83.3)
Patients with one or more serious TEAEs	79 (22.4)	20 (10.9)	4 (21.1)	0 (0.0)
Patients with one or more serious treatment-related TEAEs	33 (9.3)	3 (1.6)	2 (10.5)	0 (0.0)
Patients with one or more TEAEs of Grade 3 or higher	210 (59.5)	30 (16.4)	12 (63.2)	0 (0.0)
Patients with one or more treatment-related TEAEs of Grade 3 or higher	161 (45.6)	9 (4.9)	10 (52.6)	0 (0.0)
Patients with one or more TEAEs leading to death	7 (2.0)	2 (1.1)	0 (0.0)	0 (0.0)
Patients with one or more treatment-related TEAEs leading to death	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Patients with one or more TEAEs leading to study drug discontinuation	57 (16.1)	4 (2.2)	4 (21.1)	0 (0.0)
Patients with one or more treatment-related TEAEs leading to study drug discontinuation	46 (13.0)	1 (0.5)	3 (15.8)	0 (0.0)
Patients with one or more TEAEs leading to study drug interruption	232 (65.7)	19 (10.4)	11 (57.9)	0 (0.0)
Patients with one or more treatment-related TEAEs leading to study drug interruption	196 (55.5)	9 (4.9)	9 (47.4)	0 (0.0)
Patients with one or more TEAEs leading to study drug dose reduction	194 (55.0)	8 (4.4)	12 (63.2)	0 (0.0)
Patients with one or more treatment-related TEAEs leading to study drug dose reduction	189 (53.5)	7 (3.8)	11 (57.9)	0 (0.0)

a Patients with no hepatic impairment had AST and total bilirubin ≤ ULN.
b Patients with mild hepatic impairment had AST > ULN with total bilirubin ≤ ULN or any AST level with total bilirubin > 1.0-1.5 x ULN).
c Cancer Therapy Evaluation Program (CTEP) Protocol Template for Organ Dysfunction Studies. 5 June 2015. (Accessed 18 April 2016, at http://ctep.cancer.gov/protocolDevelopment/docs/CTEP_Organ_Dysfunction_Protocol_Template.docx.)
d Included events of disease progression.

The proportions of patients who received rucaparib and reported SAEs, Grade ≥3 TEAEs and TEAEs leading to study drug discontinuation were similar between patients with normal hepatic function and with mild hepatic impairment. Incidences of treatment-related Grade ≥3 TEAEs were higher in patients with mild hepatic impairment (52.6%) compared to patients without hepatic impairment (45.6%). Additionally, the incidence of TEAEs leading to dose reduction was higher in rucaparib-treated patients with mild hepatic impairment (63.2%) as compared to no hepatic impairment (55.0%). Conversely, the incidence of TEAEs in rucaparib-treated patients leading to treatment interruption was higher in patients without hepatic impairment (65.7%) as compared to mild hepatic impairment (57.9%).

Safety related to drug-drug interactions and other interactions

In a DDI study in cancer patients at steady state following 600 mg BID, rucaparib was found to be a moderate inhibitor of CYP1A2, and a weak inhibitor of CYP2C9, CYP2C19, and CYP3A. Rucaparib also marginally inhibits P-gp in the gut (see Rubraca EPAR).

Discontinuation due to adverse events

The most common TEAEs leading to discontinuation of rucaparib were within the SOC of Blood and lymphatic system disorders (5.6% rucaparib, 0.0% placebo). By PT these were most commonly combined thrombocytopenia/low/decreased platelets (3.0% patients), combined anaemia/or low/decreased haemoglobin (2.7% patients), and nausea (2.7% patients). No patient in the placebo arm discontinued study treatment due to these events.

Table 66: TEAEs Leading to Study Drug Discontinuation in ≥ 2 Patients in Any Treatment Group: Comparison with CSR - Safety Population (CO-338-014)

	CSR		T2V Update	
	Rucaparib (N = 372) n (%)	**Placebo (N = 189) n (%)**	**Rucaparib (N = 372) n (%)**	**Placebo (N = 189) n (%)**
Number of Patients With at Least One TEAE Leading to Study Drug Discontinuation	**53 (14.2)**	**5 (2.6)**	**61 (16.4)**	**4 (2.1)**
Combined Preferred Terms				
Combined ALT/AST Increased	2 (0.5)	0 (0.0)	2 (0.5)	0 (0.0)
Combined Anemia and/or low/decreased hemoglobin	11 (3.0)	0 (0.0)	10 (2.7)	0 (0.0)
Combined Asthenia/Fatigue	6 (1.6)	0 (0.0)	6 (1.6)	0 (0.0)
Combined Neutropenia and/or low/decreased ANC	2 (0.5)	0 (0.0)	4 (1.1)	0 (0.0)
Combined Thrombocytopenia and/or low/decreased platelets	10 (2.7)	0 (0.0)	11 (3.0)	0 (0.0)
System Organ Class Preferred Term				
Blood and lymphatic system disorders	**21 (5.6)**	**0 (0.0)**	**21 (5.6)**	**0 (0.0)**
Anaemia	11 (3.0)	0 (0.0)	10 (2.7)	0 (0.0)
Febrile neutropenia	3 (0.8)	0 (0.0)	3 (0.8)	0 (0.0)
Neutropenia	1 (0.3)	0 (0.0)	2 (0.5)	0 (0.0)
Thrombocytopenia	8 (2.2)	0 (0.0)	8 (2.2)	0 (0.0)
Cardiac disorders	**2 (0.5)**	**0 (0.0)**	**2 (0.5)**	**0 (0.0)**
Gastrointestinal disorders	**12 (3.2)**	**3 (1.6)**	**14 (3.8)**	**3 (1.6)**
Nausea	9 (2.4)	1 (0.5)	10 (2.7)	1 (0.5)
Vomiting	5 (1.3)	1 (0.5)	6 (1.6)	1 (0.5)

General disorders and administration site conditions	**6 (1.6)**	**0 (0.0)**	**6 (1.6)**	**0 (0.0)**
Asthenia	2 (0.5)	0 (0.0)	2 (0.5)	0 (0.0)
Fatigue	4 (1.1)	0 (0.0)	4 (1.1)	0 (0.0)
Investigations	**7 (1.9)**	**0 (0.0)**	**10 (2.7)**	**0 (0.0)**
Alanine aminotransferase increased	2 (0.5)	0 (0.0)	2 (0.5)	0 (0.0)
Aspartate aminotransferase increased	2 (0.5)	0 (0.0)	2 (0.5)	0 (0.0)
Neutrophil count decreased	1 (0.3)	0 (0.0)	2 (0.5)	0 (0.0)
Platelet count decreased	2 (0.5)	0 (0.0)	3 (0.8)	0 (0.0)
Weight decreased	2 (0.5)	0 (0.0)	2 (0.5)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**6 (1.6)**	**2 (1.1)**	**8 (2.2)**	**1 (0.5)**
Malignant neoplasm progression	2 (0.5)	1 (0.5)	4 (1.1)	0 (0.0)
Myelodysplastic syndrome	2 (0.5)	0 (0.0)	2 (0.5)	0 (0.0)
Nervous system disorders	**2 (0.5)**	**0 (0.0)**	**3 (0.8)**	**0 (0.0)**
Seizure	1 (0.3)	0 (0.0)	2 (0.5)	0 (0.0)
Renal and urinary disorders	**3 (0.8)**	**0 (0.0)**	**3 (0.8)**	**0 (0.0)**
Acute kidney injury	2 (0.5)	0 (0.0)	1 (0.3)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	**2 (0.5)**	**0 (0.0)**	**2 (0.5)**	**0 (0.0)**
Skin and subcutaneous tissue disorders	**2 (0.5)**	**0 (0.0)**	**3 (0.8)**	**0 (0.0)**

In the update of studies CO-338-010 and CO-338-017 the most common TEAEs leading to discontinuation of rucaparib by PT were malignant neoplasm progression (3.5% patients), combined asthenia/fatigue (3.0% patients), and small intestinal obstruction (1.9% patients).

Post marketing experience

Rucaparib was approved for use in the treatment setting in the US on 19 December 2016. Using data derived from speciality pharmacies and distributers, approximately 1400 patients have been prescribed Rubraca commercially from approval until 19 December 2017. The US label was expanded to include the maintenance setting on 6 April 2018; therefore, patient experience in the US clinical setting has not yet been captured.

As of 19 December 2017, there were 854 individual SAEs reported from post-marketing sources out of 6180 post-marketing events reported; 540 SAEs were unexpected per the USPI. Unlisted AEs reported in at least 10 patients included: bone marrow failure, ascites, intestinal obstruction, small intestinal obstruction, death, blood count abnormal, dehydration, malignant neoplasm progression and renal impairment.

Amongst the listed serious events, there were 4 cases of AML, 2 of leukaemia and 5 of MDS.

2.5.1. Discussion on clinical safety

Safety data is based on updated data of studies CO-338-014 (maintenance indication), CO-338-010 and CO-338-017 (treatment indication) and post marketing safety information in the United States (US). Safety data of studies CO-338-014, CO-338-010 and CO-338-017 were submitted under the initial conditional marketing authorisation (CMA) application with the 15 April 2017 visit cut-off date (CSR visit cut-off date). In this report the updated data of those studies correspond with the 31 December 2017 visit cut-off (T2V visit cut-off dates).

Safety data were presented from 372 patients exposed to rucaparib in the maintenance setting (ARIEL 3, study CO-338-014) in addition to updated data from 565 patients in the treatment setting (studies

CO-338-010 and CO-338-017). The safety profile was consistent across both settings and with the results previously presented.

In the maintenance setting, the most common TEAEs occurring with rucaparib included GI toxicity [nausea (75.8%), constipation (37.9%), vomiting (37.1%), diarrhoea (32.5%) and abdominal pain (30.1%)], as well as combined asthenia/fatigue (70.7%), dysgeusia (39.8%), combined anaemia/low/decreased haemoglobin (39.0%) and combined ALT/AST increased (34.7%). Nausea (71.2%), asthenia/ fatigue (62.6%), dysgeusia (36.8%) and anaemia (36.3%) were also the most frequent treatment-related TEAEs.

Gastrointestinal toxicities (nausea and vomiting) are frequently reported with rucaparib, are generally low grade (CTCAE Grade 1 or 2), and may be managed with dose reduction or interruption; antiemetics, such as 5-HT3 antagonists, dexamethasone, aprepitant, and fosaprepitant can be used as treatment for nausea/vomiting and may also be considered for prophylactic (i.e., preventative) use prior to starting Rubraca. It is important to proactively manage these events to avoid prolonged or more severe events of nausea/vomiting which have the potential to lead to complications such as dehydration or hospitalisation (see SmPC section 4.4). Dehydration has also been included in the tabulated list of ADRs in section 4.8 of the SmPC.

For rucaparib combined ALT/ AST increased was 34.7%, compared to 33.9% increased ALT and 26.1% increased AST in study CO-338-014. In the overall safety population, events related to increases in ALT and AST were observed in 38% (all grades) and 11% (≥ CTCAE Grade 3) of patients. These events occurred within the first few weeks of treatment with rucaparib, were reversible, and were rarely associated with increases in bilirubin. Increased ALT was observed in 34.8% (all grades) and 9.9% (≥ CTCAE Grade 3) of patients, increased AST in 31.4% (all grades) and 2.8% (≥ CTCAE Grade 3) of patients and increased ALT and AST in 28.6% (all grades) and 2.1% (≥ CTCAE Grade 3) of patients. No events met Hy's Law criteria for drug-induced liver injury. Most patients could continue rucaparib with or without treatment modification without recurrence of Grade ≥ 3 LFT abnormalities. Adequate dose modifications for ALT/ AST elevation in accordance with protocol Amendment 3 (July 2016) of Study CO-338-014 have been included in the SmPC. Grade 1-3 elevations in AST/ALT can be managed without change to the rucaparib dose, or with treatment modification (interruption and/or dose reduction). Grade 4 reactions require treatment modification (see SmPC section 4.2). For Grade 3 without other signs of liver dysfunction, it is recommended to monitor LFTs weekly until resolution to Grade ≤ 2 and continue rucaparib provided bilirubin is < ULN and alkaline phosphatase (ALP) is < 3 x ULN. Interruption of treatment is recommended if AST/ALT levels do not decline within 2 weeks until Grade ≤ 2, then rucaparib can be resumed at the same or at a reduced dose. For Grade 4, it is recommended to interrupt rucaparib until values return to Grade ≤ 2; then to resume rucaparib with a dose reduction and monitor LFTs weekly for 3 weeks.

Regarding abdominal pain (combined PT of: abdominal pain, abdominal pain upper, and abdominal pain lower), the overall incidence was higher in patients treated with rucaparib compared to placebo (40.1% vs. 33.3%), especially for those considered related to study treatment (16.4% vs. 4.8%). Despite abdominal pain being a symptom that can be associated with ovarian cancer, it has been included in section 4.8 of the SmPC considering differences observed compared to placebo.

The MAH initially proposed to delete four ADRs from the tabulated list of adverse reactions in section 4.8 of the SmPC after reviewing data from study CO-338-014. TEAE were reported as follows in this study: pruritus 13.7% vs. 10.6%; dermatitis (inc. dermatitis acneform, allergic, bullous) 3.2% vs. 1.6%, rash erythematous 1.6% vs. 0%, pyrexia 12.1 % [1.6% assessed as causally-related] vs 4.8%. Given the difference in incidence of pyrexia between rucaparib and placebo (7.3%), the CHMP considered that pyrexia may be causally related to rucaparib and has been kept in the list of ADRs in the SmPC.

The most common Grade ≥ 3 TEAEs in patients treated with rucaparib relative to placebo were combined anaemia/low/decreased haemoglobin (21.5% rucaparib, 0.5% placebo) and combined ALT/AST increased (10.2% rucaparib, 0% placebo).

Serious TEAEs occurred in 22.3% of rucaparib-treated patients and 10.6% of placebo-treated patients; most commonly anaemia (4.3%). The next most common serious TEAEs were vomiting (1.9% rucaparib, 0.8% related to study drug; 1.1% placebo) and pyrexia (1.6% rucaparib, 0.5% related to study drug; 0.0% placebo).

A serious TEAE of acute kidney injury was experienced by 4 patients in the rucaparib arm (1.1%), and no patients in placebo arm; of these 2 patients (0.5%) had the event assessed by the investigator as related to study drug. Potential relation with study drug cannot be ruled out. Information about cases of elevations in serum creatinine has been updated in section 4.8 of the SmPC and reflects that across 937 OC patients from Studies CO-338-010, CO-338-017, and CO-338-017 four (0.4%) patients reported a CTCAE Grade 3 reaction

A serious TEAE of febrile neutropenia was experienced by 5 patients (1.3%) (independent of the pyrexia cases) treated with rucaparib, and no patients in placebo arm; of these, 4 patients each (1.1%) had the event assessed by the investigator as related to study drug. Neutropenia is adequately addressed in the SmPC. In general, supportive care and institutional guidelines should be implemented for the management of low blood counts (see SmPC section 4.4). Neutropenia, anaemia and thrombocytopenia may be managed through dose interruptions and/or dose reductions for moderate to severe reactions (i.e. CTCAE Grade 3 or 4) (see SmPC section 4.2).

Similarly, all 4 patients (1.1%) with a serious TEAE of combined thrombocytopenia and/or low/decreased platelets were assessed by the investigator as having study drug-related (rucaparib in all cases) serious TEAEs. Thrombocytopenia and/or low/decreased platelets are adequately addressed in the SmPC.

TEAEs with an outcome of death occurred in 7 patients treated with rucaparib; of these, 2 events (1 of AML, 1 of MDS) were assessed as related to rucaparib. Most of the 'on treatment deaths' and all of the 'treatment related TEAEs of death' were in the tBRCA population, albeit small patient numbers. In case of 1 patient with hematophagic histiocytosis, biopsy results obtained after the patient's death showed T-cell lymphoma, which the investigator assessed, along with anaemia, as being related to rucaparib.

The safety profile, including TEAEs, SAEs and TEAEs by CTCAE grade was similar among patients with a tBRCA mutation as compared to the wider HRD subgroup in patients treated with rucaparib or placebo. The summary of TEAEs for the gBRCA subgroup was similar to the tBRCA population, as most BRCA mutations were germline origin (n = 82 rucaparib). The smaller number of sBRCA patients (n = 40 rucaparib) limits the comparisons between treatment groups. The proportion of patients with an SAE was higher for the tBRCA germline than somatic subgroup for both placebo and rucaparib. There were 5 TEAEs leading to death in the tBRCA population treated with rucaparib, with 4 in the germline, none in the somatic subgroups and one with unknown germline/somatic tBRCA status.

There are insufficient patients to determine whether the toxicity profile differs between patients with germline and somatic BRCA mutations. It could be speculated that patients with gBRCA mutations would be more prone to toxicity as all cells should be more sensitive to PARP inhibitors.

Myelodysplastic syndrome/acute myeloid leukaemia (MDS/AML), including cases with fatal outcome, have been reported in patients who received rucaparib. The duration of therapy with rucaparib in patients who developed MDS/AML varied from less than 1 month to approximately 28 months. MDS/AML are serious adverse reactions that occur uncommonly (0.5%) in patients on treatment and during the 28 day safety follow up, and commonly (1.3%) for all patients including during the long term safety follow up (rate is calculated based on overall safety population of 1321 patients exposed to at least one dose of oral rucaparib in all clinical studies). In the pivotal Phase 3 study (ARIEL3, Study CO-338-014), the incidence of MDS/AML during therapy in patients who received rucaparib was 0.8%. Although no cases were reported during therapy in patients who received placebo, one case has been reported in a placebo - treated patient during the long term safety follow up. All patients had potential contributing factors for the development of

MDS/AML; in all cases, patients had received previous platinum-containing chemotherapy regimens and/or other DNA damaging agents.

Cytogenetic analysis revealed that some of the rucaparib treated patients diagnosed with MDS/ AML had complex karyotypes with > 3 abnormalities or aberrations in chromosomes 5 and 7, consistent with therapy-related myeloid neoplasm (t-MN). This can result from prior treatment with multiple cycles of platinum-chemotherapy; however, a relationship between rucaparib and t-MN cannot be excluded. The current RMP includes MDS/AML as an important potential risk for rucaparib. If MDS/AML is suspected, the patient should be referred to a haematologist for further investigations, including bone marrow analysis and blood sampling for cytogenetics. If, following investigation for prolonged haematological toxicity, MDS/AML is confirmed, Rubraca should be discontinued (see SmPC section 4.4).

Changes from baseline in laboratory results were consistent with the reported TEAEs, predominantly anaemia, thrombocytopenia, abnormal liver function tests and, to a lesser extent, elevated creatinine. The reported elevations in ALT/AST with rucaparib treatment were not associated with any events of drug-induced liver injury.

It should be also pointed out that the CTCAE criteria for assessing serum creatinine have been modified from CTCAE version 4.03 to CTCAE version 5.0. In CTCAE Version 5.0, the Grade 1 creatinine criteria is recommended to be based only on values greater than the ULN instead of any increase in creatinine from baseline as in CTCAE v4.03. This fact led to significant changes on incidence of shifts in increase in creatinine, due to the lower incidence of grade 1 with version 5.0 [*A shift to a worsening serum creatinine grade*: Version 4.03 (97.5% rucaparib, 87.8% placebo) vs Version 5.0 (43.1% rucaparib, 7.4% placebo); *Grade 1*: Version 4.03 (64.6% rucaparib, 84.1% placebo) vs (Version 5.0: (10.1% rucaparib, 3.7% placebo) and *Grade 2:* Version 4.03 and Version5.0 (30.5% rucaparib, 3.7% placebo)].

Older patients (≥ 65 years old) experienced a higher incidence of SAEs, Grade ≥3 TEAEs, and TEAEs leading to study drug discontinuation or dose modifications compared to the younger subgroup (< 65 years old). There are limited clinical data in patients aged 75 or over. However available data showed that the frequencies of some adverse reactions increased (see SmPC section 4.8). No adjustment is recommended to the starting dose for elderly patients (≥ 65 years of age).

In patients with mild and moderate renal dysfunction (classified per the EMA guideline) rucaparib treatment resulted in an increased incidence of Grade ≥3 TEAEs and TEAEs leading to study drug interruption or dose reduction compared to patients with normal renal function. In patients with moderate renal impairment rucaparib treatment also led to an increased incidence of SAEs and treatment-related Grade ≥ 3 TEAEs. No starting dose adjustment is required in patients with mild or moderate renal impairment (see SmPC section 4.2). There are no clinical data in patients with severe renal impairment (CLcr less than 30 mL/min), therefore rucaparib is not recommended for use in patients with severe renal impairment. Rucaparib may only be used in patients with severe renal impairment if the potential benefit outweighs the risk. Patients with moderate or severe renal impairment should be carefully monitored for renal function and adverse reactions.

Incidences of treatment-related Grade 3 or higher TEAEs in patients taking rucaparib were slightly higher in patients with mild hepatic impairment as compared to patients without hepatic impairment. However, the number of patients with mild hepatic impairment was limited. A dedicated study in patients with moderate hepatic impairment, Study CO-338-078, is currently ongoing. Further data will be available in hepatic impairment when this study is completed (see RMP). There are limited clinical data in patients with moderate or severe hepatic impairment (i.e., any total bilirubin greater than 1.5 times ULN), therefore rucaparib is not recommended for use in patients with moderate or severe hepatic impairment (see SmPC section 4.2).

No clinically meaningful differences in the TEAEs, SAEs and TEAEs by CTCAE grade occurred with rucaparib treatment in patients with mild hepatic impairment as compared to those with normal hepatic function;

however, the number of patients with mild hepatic impairment was small and limits the interpretation of data. Rucaparib is not recommended for use in patients with moderate or severe hepatic impairment (i.e. any total bilirubin greater than 1.5 times ULN).

Risks commonly observed across PARP inhibitors class of medicinal products include myelosuppression (anaemia, thrombocytopaenia and neutropaenia), gastrointestinal effects (nausea, vomiting), asthenia/fatigue, MDS/AML and embryo-foetal toxicity. Differences in the safety profile have also been noted and photosensitivity and increased ALT/AST are more often reported in association with rucaparib.

No new safety concerns were identified based on the data from study ARIEL3, and the list of important identified or potential risks has not been changed, apart from a slight rewording of the potential risk for DDI.

The interaction with CYP1A2, CYP2C9 and CYP3A substrates is considered an identified risk, as drug-interaction studies have been performed to characterise the risk and there are no additional pharmacovigilance activities concerning this risk. However, it is not considered an *important* risk as the risk can be handled by SmPC warnings, and it was therefore removed from the list of safety concerns.

As the risk for transporter interactions is yet uncharacterised and there are ongoing pharmacovigilance activities concerning this risk, this risk should remain in the list of safety concerns.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics. The RMP has also been updated adequately.

2.5.2. Conclusions on clinical safety

The available safety data allowed further characterisation of the safety profile of rucaparib in ovarian cancer patients. No new safety concern was identified from the submitted data. Adverse drug reactions of interest for rucaparib include haematological toxicity, GI effects and AST/ ALT elevations. The latter are more noticeable with rucaparib than other authorised PARP inhibitors.

The close monitoring of the incidence of AML/ MDS should continue. There is a targeted adverse events data collection form for MDS/AML and ARIEL4 (current specific obligation in Annex II) should provide further information.

2.5.3. PSUR cycle

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

2.6. Risk management plan

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

The PRAC considered that the risk management plan version 2.1 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

At the December 2018 meeting, the CHMP requested the applicant to include a post-authorisation efficacy study (PAES) in the RMP.

The applicant implemented the changes as requested by CHMP in the RMP version 2.2.

The CHMP endorsed the Risk Management Plan version 2.2 with the following content:

Safety concerns

Table 67: Summary of safety concerns

Summary of important risks and missing information	
Important identified risks	Myelosuppression Nausea and vomiting
Important potential risks	MDS/AML New primary malignancy QTc interval prolongation Photosensitivity Embryotoxicity and teratogenicity DDI with metformin, DDI with substrates of BCRP, e.g., rosuvastatin
Missing information	Use in patients for longer than 18 months Effects of rucaparib on fertility The effect on an infant of a nursing mother receiving rucaparib Safety in patients with severe renal impairment Safety in patients with moderate or severe hepatic impairment Characterisation of metabolites of rucaparib DDI with oral contraceptives Efficacy and safety of rucaparib in patients previously treated with olaparib or another PARP inhibitor

Pharmacovigilance plan

Table 68: On-going and planned additional pharmacovigilance activities

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
CO-338-043 (ARIEL4) Started	Primary: To compare the anti tumour 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.	Myelosuppression Nausea and vomiting MDS/AML New primary malignancy QTc interval prolongation Photosensitivity Use in patients for longer than 18 months	Final report	Q2 2023
Category 3 - Required additional pharmacovigilance activities				
CO-338-078 Planned	A Phase 1, open-label, parallel group study to determine the PK, safety and tolerability of rucaparib in patients with an advanced solid tumour and	Effect of moderate hepatic impairment on rucaparib PK	Final Part I report	Q3 2019

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	either moderate hepatic impairment or normal hepatic function			
CO-338-095 Arm B: In vivo DDI study with oral contraceptives Planned	A Phase 1, open label, DDI study to determine the effect of rucaparib on the PK of oral contraceptives in female patients with advanced solid tumours	DDI with oral contraceptives	Protocol	Q3 2018
CO-338-095 Arm A: In vivo DDI study with BCRP substrate Planned	A Phase 1, open label, DDI study to determine the effect of rucaparib on the PK of oral rosuvastatin in patients with advanced solid tumours	DDI with BCRP substrates	Protocol	Q3 2018

Risk minimisation measures

Table 69: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern.

Safety concern	Routine risk minimisation activities	Pharmacovigilance activities
Important identified risk 1: Myelosuppression	**Routine risk communication:** *SmPC section: 4.2, 4.4, 4.8* *Product leaflet (PL) section: 2, 4* **Routine risk minimisation activities recommending specific clinical measures to address the risk:** *SmPC section: 4.2* *PL section: 2* **Other routine risk minimisation measures beyond the Product Information**: Prescription only medicine	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: *None* **Additional pharmacovigilance activities**: *Periodic review of collection and assessment of data emerging from the ongoing clinical programme CO-338-043 (ARIEL4)*
Important Identified risk 2: Nausea and vomiting	**Routine risk communication:** *SmPC section: 4.2, 4.4, 4.7, 4.8* *PL section: 4* **Routine risk minimisation activities recommending specific clinical measures to address the risk:** *None*	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: *None* **Additional pharmacovigilance activities**:

	Other routine risk minimisation measures beyond the Product Information: Prescription only medicine	*Periodic review of collection and assessment of data emerging from the ongoing clinical programme CO-338-043 (ARIEL4)*
Important Potential risk 1: MDS/AML	**Routine risk communication:** *SmPC section: 4.4, 4.8* *PL section: 2* **Routine risk minimisation activities recommending specific clinical measures to address the risk:** *None* **Other routine risk minimisation measures beyond the Product Information**: Prescription only medicine	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: *Targeted follow up questionnaire* **Additional pharmacovigilance activities**: *Periodic review of collection and assessment of data emerging from the ongoing clinical programme CO-338-043 (ARIEL4). After last dose of study drug, all patients will be monitored for MDS/AML until death, lost to follow up, withdrawal of consent or study closure.*
Important Potential risk 2: New primary malignancy	**Routine risk communication:** *None* **Routine risk minimisation activities recommending specific clinical measures to address the risk:** *None* **Other routine risk minimisation measures beyond the Product Information**: Prescription only medicine	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: *None* **Additional pharmacovigilance activities**: *Periodic review of collection and assessment of data emerging from the ongoing clinical programme CO-338-043 (ARIEL4). After last dose of study drug, all patients will be monitored for new primary malignancy until death, lost to follow up, withdrawal of consent or study closure.*
Important Potential risk 3: QTc interval prolongation	**Routine risk communication:**	**Routine pharmacovigilance activities beyond adverse**

	None **Routine risk minimisation activities recommending specific clinical measures to address the risk:** *None* **Other routine risk minimisation measures beyond the Product Information**: Prescription only medicine	**reactions reporting and signal detection**: *None* **Additional pharmacovigilance activities**: *None*
Important Potential risk 4: Photosensitivity	**Routine risk communication:** *SmPC section: 4.4, 4.8* *PL section: 2, 4* **Routine risk minimisation activities recommending specific clinical measures to address the risk:** *None* **Other routine risk minimisation measures beyond the Product Information**: Prescription only medicine	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: *None* **Additional pharmacovigilance activities**: *Periodic review of collection and assessment of data emerging from the ongoing clinical programme CO-338-043 (ARIEL4)*
Important Potential risk 5: Embryotoxicity and teratogenicity	**Routine risk communication:** *SmPC section: 4.4,4.6, 5.3* *PL section: 2* **Routine risk minimisation activities recommending specific clinical measures to address the risk:** *None* **Other routine risk minimisation measures beyond the Product Information**: Prescription only medicine	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: *None* **Additional pharmacovigilance activities**: *None*
Important Potential risk 6: DDI with metformin, DDI with substrates of BCRP, e.g.,	**Routine risk communication:** *SmPC section: 4.5, 5.2*	**Routine pharmacovigilance activities beyond adverse reactions reporting and**

rosuvastatin	*PL section: 2* **Routine risk minimisation activities recommending specific clinical measures to address the risk:** *None* **Other routine risk minimisation measures beyond the Product Information**: Prescription only medicine	**signal detection**: *None* **Additional pharmacovigilance activities**: *Study CO-338-095 Arm A: A Phase 1, open label, DDI study to determine the effect of rucaparib on the PK of oral rosuvastatin in patients with advanced solid tumours*
Missing information 1: Use in patients for longer than 18 months	**Routine risk communication:** *SmPC section: 4.8* **Routine risk minimisation activities recommending specific clinical measures to address the risk:** *None* **Other routine risk minimisation measures beyond the Product Information**: Prescription only medicine	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: *None* **Additional pharmacovigilance activities**: *Periodic review of collection and assessment of data emerging from the ongoing clinical programme CO-338-043 (ARIEL4)*
Missing information 2: Effects of rucaparib on fertility	**Routine risk communication:** *SmPC section: 4.6, 5.3* **Routine risk minimisation activities recommending specific clinical measures to address the risk:** *None* **Other routine risk minimisation measures beyond the Product Information**: Prescription only medicine	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: *None* **Additional pharmacovigilance activities**: *None*
Missing information 3: The effect on an infant of a nursing mother receiving rucaparib	**Routine risk communication:** *SmPC section: 4.3, 4.6* *PL section: 2* **Routine risk minimisation**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**:

	activities recommending specific clinical measures to address the risk: *None* **Other routine risk minimisation measures beyond the Product Information**: Prescription only medicine	*None* **Additional pharmacovigilance activities**: *None*
Missing information 4: Safety in patients with severe renal impairment	**Routine risk communication:** *SmPC section: 4.2, 5.2* **Routine risk minimisation activities recommending specific clinical measures to address the risk:** *None* **Other routine risk minimisation measures beyond the Product Information**: Prescription only medicine	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: *None* **Additional pharmacovigilance activities**: *None*
Missing information 5: Safety in patients with moderate or severe hepatic impairment	**Routine risk communication:** *SmPC section: 4.2, 5.2* **Routine risk minimisation activities recommending specific clinical measures to address the risk:** *None* **Other routine risk minimisation measures beyond the Product Information**: Prescription only medicine	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: *None* **Additional pharmacovigilance activities**: *Study CO-338-078: A Phase 1, open-label, parallel group study to determine the PK, safety and tolerability of rucaparib in patients with an advanced solid tumour and either moderate hepatic impairment or normal hepatic function*
Missing information 6: Characterisation of metabolites of rucaparib	**Routine risk communication:** *None* **Routine risk minimisation activities recommending**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**:

	specific clinical measures to address the risk: *None* **Other routine risk minimisation measures beyond the Product Information**: Prescription only medicine	*None* **Additional pharmacovigilance activities**: *None*
Missing information 7: DDI with oral contraceptives	**Routine risk communication:** *SmPC section: 4.5* **Routine risk minimisation activities recommending specific clinical measures to address the risk:** *None* **Other routine risk minimisation measures beyond the Product Information**: Prescription only medicine	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: *None* **Additional pharmacovigilance activities**: *Study CO-338-095 Arm B: A Phase 1, open label, DDI study to determine the effect of rucaparib on the PK of oral contraceptives in female patients with advanced solid tumours*
Missing information 8: Efficacy and safety of rucaparib in patients previously treated with olaparib or another PARP inhibitor	**Routine risk communication:** *SmPC section: 5.1* **Routine risk minimisation activities recommending specific clinical measures to address the risk:** *None* **Other routine risk minimisation measures beyond the Product Information**: Prescription only medicine	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: *None* **Additional pharmacovigilance activities**: *None*

No additional risk minimisation measures are foreseen for the important safety concerns.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated. In addition the MAH took the opportunity to make minor corrections in the SmPC. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The minor changes to the PIL associated with this variation without changes to the PIL design and layout are considered acceptable for not repeat the PIL User Testing.

2.7.2. 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, was not contained in any medicinal product authorised in the EU and it is approved under a conditional marketing authorisation.

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

3.1.1. Disease or condition

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

3.1.2. Available therapies and unmet medical need

Standard therapy includes surgical debulking and platinum and taxane-based chemotherapy, resulting in complete clinical remission in up to 75% of patients, however only 30% of patients will be cured. Once recurrent, ovarian cancer generally does not exhibit the same level of chemo-sensitivity, highlighting the need for rational therapies directed toward specific molecular targets. The vascular endothelial growth factor (VEGF) inhibitor, bevacizumab, was proven to have benefit in epithelial ovarian cancer (EOC), fallopian tube cancer (FTC), or primary peritoneal cancer (PPC) in the maintenance setting and is approved in the European Union (EU), as well as in the US, in combination with carboplatin and gemcitabine for treatment of first recurrence of platinum-sensitive EOC, FTC, or PPC.

Two other PARP inhibitors, olaparib and niraparib, have been approved as monotherapy in the EU and US for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade EOC, FTC, or PPC who are in response (complete response [CR] or partial response [PR]) to platinum-based chemotherapy.

3.1.3. Main clinical studies

This application is mainly based on the Study CO-338-014 (ARIEL3). A fully-enrolled, ongoing Phase 3, randomized, double-blind study of monotherapy oral rucaparib versus placebo as switch maintenance treatment in patients with platinum-sensitive, relapsed, high-grade ovarian cancer who achieved a response to platinum-based chemotherapy.

3.2. Favourable effects

- tBRCA population (n=196)

The median invPFS in the tBRCA population was 16.6 months (95% CI, 13.4-22.9) for the rucaparib group and 5.4 months (95% CI, 3.4-6.7) for the placebo group (stratified log rank, p < 0.0001). Consistent with the primary analysis of this population, the stratified Cox proportional hazard model showed a statistically significant improvement in invPFS with rucaparib treatment compared to placebo (HR 0.231 [95% CI, 0.156-0.342]; p < 0.0001).

- HRD population (n=354)

In the HRD population, the median invPFS was 13.6 months (95% CI, 10.9-16.2 months) for the rucaparib group and 5.4 months (95% CI, 5.1-5.6 months) for the placebo group (stratified log rank, p < 0.0001). The stratified Cox proportional hazard model was consistent with the stratified log-rank results (HR 0.317 [95% CI, 0.239-0.420]; p < 0.0001).

- ITT population (n=564)

In the ITT population, the median invPFS was 10.8 months (95% CI, 8.3-11.4 months) for the rucaparib group and 5.4 months (95% CI, 5.3-5.5 months) for the placebo group (stratified log rank, p < 0.0001). A positive treatment effect of rucaparib over placebo was also determined by the stratified Cox proportional hazard model (HR 0.365 [95% CI, 0.295-0.451]; p < 0.0001).

Exploratory analyses in the non-nested populations (non-tBRCA LOH+ and non-tBRCA LOH- subgroups) were performed in order to demonstrate that the effect in the nested subgroups was not solely driven by the BRCA or HRD groups. These exploratory analyses found statistically significant differences between study arms, with differences observed later in the treatment period in the non-tBRCA LOH- subgroup.

Following the ordered step-down procedure, the secondary endpoint time to an event of worsening in the DRS-P subscale of the FOSI-18 was analysed. Median time to worsening in the DRS-P subscale was shorter in the rucaparib arm than in the placebo arm, but the difference was not statistically significant (1.9 months, 95% CI 1.4-3.7 and 4.8 months, 95% CI 3.7-9.2). Since statistical significance for the secondary endpoint in the tBRCA population was not reached, no further statistical significance of subsequent secondary endpoints can be claimed in the ordered step-down procedure.

OS data are immature. About 20% of deaths had occurred across in the nested population. Median survival could only be determined for the rucaparib arm in the ITT population (29.6 months). For the tBRCA population, the number of deaths was small (rucaparib, 23/130 [17.7%]; placebo, 12/66 [18.2%]). Similar results were observed in the HRD population (rucaparib, 42/236 [17.8%]; placebo, 24/118 [20.3%]) and in the ITT (rucaparib, 81/375 [21.6%]; placebo, 42/189 [22.2%]).

3.3. Uncertainties and limitations about favourable effects

The OS data for interim analysis was heavily censored at the visit cut-off for primary endpoint analysis. As of the updated safety data cut-off of 31 December 2017, a death event had been reported in 30% of patients. Although a detrimental effect on OS seems unlikely, the lack of maturity of OS hampers proper conclusion. To further investigate the efficacy of rucaparib, results from the final OS analysis will be provided by 31 December 2022 (see Annex II condition, PAES).

Some exploratory endpoints analyses were also limited by the heavy rate of censoring, especially in the rucaparib arm. PFS2, chemotherapy-free survival and time to start of first (and second) subsequent anti-cancer treatment analyses suggested that rucaparib treatment may prolong median time to subsequent progression and treatment, with benefit observed in all the analysis populations. However, considering the

lack of maturity of the data, updated analyses are required to be provided at the time of the final OS analysis (see Annex II condition, PAES).

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. This is adequately addressed in the SmPC especially for the use of Rubraca in the treatment for relapsed or progressive EOC, FTC, or PPC.

3.4. Unfavourable effects

In maintenance setting, the most common adverse reactions related to rucaparib, occurring in ≥ 20% of patients, were nausea, asthenia/fatigue, dysgeusia, anemia, ALT/AST increased, thrombocytopenia, vomiting, decreased appetite. The majority of adverse reactions were Grade 1 or 2.

The most common Grade ≥3 or higher TEAEs were combined anaemia/low/decreased haemoglobin (21.5%), combined ALT/AST increased (10.2%), combined neutropenia/low/decreased ANC (7.8%), combined asthenia/fatigue (7.0%) and combined thrombocytopenia/ low platelets (5.4%).

Serious adverse reaction occurring in >1% of patients was anaemia, vomiting, pyrexia, febrile neutropenia, abdominal pain, constipation, thrombocytopenia, small intestinal obstruction, acute kidney injury, small intestinal obstruction.

Treatment-related fatal TEAEs were 1 case of AML and 1 case of MDS (AESI). For each event, a rucaparib relationship could not be ruled out. In overall safety data, MDS/AML occur in 0.5% rate for patients on treatment and during the 28 day safety follow up, and 1.3% for all patients including during the long term safety follow up. The differential incidence of AML/ MDS between the rucaparib and placebo group make the development of these haematological malignancies likely influenced by rucaparib rather than only prior platinum-based chemotherapy. Initial results suggest that patients with gBRCA mutation maybe particularly susceptible to development of AML/ MDS. This risk will continue to be closely monitored and is adequately addressed in the RMP and SmPC.

The most common TEAEs leading to discontinuation of rucaparib were thrombocytopenia, anemia and nausea. The most commonly reported TEAEs leading to rucaparib dose reduction or treatment interruption were anemia, ALT/AST increased, thrombocytopenia and nausea. The guidelines in place to manage dose modification appear appropriate due to relatively low number of discontinuation in comparison with dose reduction or treatment interruption of above mentioned TEAEs.

The most notable laboratory abnormalities in maintenance setting were decreased haemoglobin, increased ALT, increased AST and increased serum creatinine. Decreased platelets, neutrophils, leukocytes, lymphocytes; increased cholesterol, alkaline phosphatase, bilirubinwere observed to a lesser extent.

Rucaparib is expected to cause very mild QT prolongation at the plasma levels and the risk for clinically significant QT prolongation (i.e., > 20 msec) appears to be low. Caution should be practiced in patients with special QT prolongation risk.

Greater sensitivity of some elderly patients ≥ 65 years of age to adverse events cannot be ruled out. There are limited clinical data in patients aged 75 or over. This is addressed in the SmPC.

Photosensitivity is an identified potential risk of rucaparib treatment as reflected in the current RMP.

Overall no new safety concern was identified for rucaparib. The risks associated with rucaparib are adequately covered in the current RMP. The SmPC has been adequately revised to update the safety information on rucaparib.

3.5. Uncertainties and limitations about unfavourable effects

There were no clinically meaningful differences in the TEAEs, SAEs, and TEAEs by CTCAE grade that occurred with rucaparib in the patients with mild renal impairment as compared to those with normal renal function. However, there appeared to be a generally higher incidence of these events in patients with moderate renal impairment. There are no clinical data in patients with severe renal impairment (CLcr less than 30 mL/min). Therefore rucaparib is not recommended for use in patients with severe renal impairment. Rucaparib may only be used in patients with severe renal impairment if the potential benefit outweighs the risk. Patients with moderate or severe renal impairment should be carefully monitored for renal function and adverse reactions (see SmPC section 4.2).

Incidences of treatment-related Grade 3 or higher TEAEs in patients taking rucaparib were slightly higher in patients with mild hepatic impairment as compared to patients without hepatic impairment. However, number of patients with mild hepatic impairment is limited. A dedicated study in patients with moderate hepatic impairment, Study CO-338-078, is currently ongoing. Further data will be available in hepatic impairment when this study is completed (see RMP).

3.6. Effects Table

Table 70: Effects Table for Rucaparib in Maintenance therapy in Ovarian Cancer (data cut-off: 15 April 2017 for efficacy and 31 December 2017 for safety)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence
Favourable Effects					
Primary Analysis Groups					
mPFS tBRCA	Median delay in tumor progression or death	months	16.6	5.4	According to investigator review ($p < 0.0001$) n=196
mPFS HRD	Median delay in tumor progression or death	months	13.6	5.4	According to investigator review ($p < 0.0001$) n=354
mPFS ITT	Median delay in tumor progression or death	months	10.8	5.4	According to investigator review ($p < 0.0001$) n=564
Exploratory Analysis of Non-nested Subgroups					
mPFS Non-tBRCA LOH+	Median delay in tumor progression or death	months	9.7	5.4	According to investigator review ($p < 0.0001$) n=158

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence
mPFS Non-tBRCA LOH-	Median delay in tumor progression or death	months	6.7	5.4	According to investigator review ($p < 0.0040$) n=161
Unfavourable Effects: Treatment n=372; Control n=189					
Treatment-related TEAE	All Grade ≥ 3	%	97.346.0	73.5 4.8	
Treatment-related TEAE with an outcome of death		%	0.5	0.0	
Nausea	All Grade ≥ 3	%	75.8 3.8	36.5 0.5	
Fatigue/Asthenia	All Grade ≥ 3	%	70.77.0	44.4 2.6	
Dysgeusia	All Grade ≥ 3	%	39.8 0	6.9 0	
Vomiting	All Grade ≥ 3	%	37.1 4.0	15.3 1.1	
Decreased appetite	All Grade ≥ 3	%	23.7 0.8	13.8 0.0	
Anemia	All ≥ Grade 3	%	39.0 21.5	5.3 0.5	
ALT/AST increased	All ≥ Grade 3	%	34.710.2	4.2 0.0	
Thrombocytopenia	All ≥ Grade 3	%	29.3 5.4	2.6 0.0	
Neutropenia	All ≥ Grade 3	%	19.4 7.8	4.8 1.1	
MDS/AML	Grade ≥ 3	%	0.8	0.0	
Decreased haemoglobin	Laboratory abnormalities Shifts Grade 1-4 Grade 3-4	%	 61.0 12.8	 12.7 1.1	
Increased ALT	Laboratory abnormalities Shifts Grade 3-4	%	 6.5	 0.0	
Increased AST	Laboratory abnormalities	%			

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence
	Shifts Grade 3-4		0.8	0.0	
Increased serum creatinine	Laboratory abnormalities Shifts Grade 3-4	%	0.3	0.0	

Abbreviations: HRD = homologous recombination deficiency; ITT = intent-to-treat; LOH = loss of heterozygosity; PFS = progression-free survival; tBRCA = deleterious tumor mutation in BRCA1 or BRCA2, includes gBRCA and sBRCA; ALT (alanine aminotransferase), AST (aspartate aminotransferase), MDS (myelodysplastic syndrome), AML (acute myeloid leukaemia), TEAE (treatment-emergent adverse event), AR (Adverse Reaction), AE (Adverse Event)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The use of rucaparib as maintenance therapy in patients considered platinum-sensitive (6 to 12 or >12 months PFI to their penultimate platinum-based regimen) and who received ≥ 2 prior platinum-based treatment regimens has shown a clinically meaningful delay in the progression of the disease, with a gain in mPFS from 5.4 months to 11.2 months, depending on the population analysed. Consistency was observed across the different analyses and subgroups investigated (including in the biomarker negative stratum; HR 0.471 95%CI 0.361-0.613 n=325), even though the IRR analysis reported even a higher benefit for the rucaparib arm compared to the investigator analysis.

The adverse events associated with rucaparib use are generally manageable with supportive treatment, and dose interruptions or modifications if required.

3.7.2. Balance of benefits and risks

The clinical meaningful benefits observed with rucaparib in Study CO-338-014 and the sufficiently characterised safety profile support a positive benefit-risk balance of rucaparib as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

3.7.3. Additional considerations on the benefit-risk balance

Although most patients in Study CO-338-014 were patients with high grade serous ovarian cancer it is considered that the indication does not need to be restricted to the serous histology in view of recent evidence suggesting that serous and endometrioid carcinomas arise from the tubal fimbrae, suggesting similar biology and origin for the high grade epithelial histologies, and in view of the mechanism of action and biological rationale suggesting benefit in high grade tumours.

The robustness of the data in patients considered biomarker negative overcomes doubts based on the mechanism of action of rucaparib. This is consistent with external data, where a clinically significant PFS

benefit was observed after treating patients without HRD positivity with another PARP inhibitor (niraparib) in the maintenance setting. Even in the non-tBRCA LOH negative population, another way of defining lack of Homologous Recombinant Deficiency, a gain of 4 months in mPFS was observed compared to placebo in Study CO-338-014. Taken together, a broader indication (i.e. irrespective of BRCA status) in patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy is supported.

3.8. Conclusions

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

The CHMP considers the following measures necessary to address issues related to efficacy:

Description	Due date
PAES: In order to further investigate the efficacy of rucaparib maintenance treatment in patients with relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy, the MAH should submit the final analysis of OS and updated analyses of PFS2, chemotherapy-free interval and time to start of subsequent anti-cancer treatment of the phase 3, randomised, double-blind study CO-338-014	31 December 2022

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include new indication for Rubraca as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated with the expanded clinical efficacy and safety data. In addition the MAH took the opportunity to make minor corrections in the SmPC. The Package Leaflet is also updated in accordance. Annex II was updated to include a new PAES.
The updated RMP version 2.2 has also been approved.

This CHMP recommendation is subject to the following new conditions:

Conditions and requirements of the marketing authorisation

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
PAES: In order to further investigate the efficacy of rucaparib maintenance treatment in patients with relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy, the MAH should submit the final analysis of OS and updated analyses of PFS2, chemotherapy-free interval and time to start of subsequent anti-cancer treatment of the phase 3, randomised, double-blind study CO-338-014	31 December 2022

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.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication to include new indication for Rubraca as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated with the expanded clinical efficacy and safety data. In addition the MAH took the opportunity to make minor corrections in the SmPC. The Package Leaflet is also updated in accordance. Annex II was updated to include a new PAES.
The updated RMP version 2.2 has also been approved.

Summary

Please refer to Scientific Discussion 'Rubraca-H-C-004272-II-001'