European Union (EU) Risk Management Plan (RMP) for Rucaparib

RMP Version number	8.1
Data lock point (DLP) for this RMP	**Clinical data**: 04 Apr 2022 for Study CO-338-014 (ARIEL3) Study CO-338-010 (Clinical study report (CSR) date: 29 Aug 2019) Study CO-338-017 (ARIEL2) (CSR date: 12 Sep 2019) Study CO-338-043 (ARIEL4): 30 Sep 2020 Study CO-338-087 (ATHENA-MONO): 23 Mar 2022 SAE cut-off date: 30 May 2023 **Post marketing experience**: 30 May 2023
Date of final sign off	30 Jun 2023
Rationale for submitting an updated RMP	Submission of Study CO-338-087 (ATHENA-MONO) CSR Reclassification of "Myelodysplastic syndrome/Acute myeloid leukaemia" as Important Identified Risk
Summary of significant changes in this RMP	**Part I: Product(s) Overview** MAH change to zr pharma& **Part II: Module SI – Epidemiology of the indication** Inclusion of indication as monotherapy treatment for the maintenance treatment of adult patients with advanced (FIGO Stages III and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to first-line platinum-based chemotherapy. **Part II: Module SIII - Clinical trial exposure** Exposure in Study CO-338-087 (ATHENA-MONO) was included according to the cutoff date of 23 Mar 2022 and data summarised for the Safety Population (CO-338-010, CO-338-017, CO-338-014, CO-338-43, and CO-338-087 [ATHENA-MONO]). **Part II: Module SIV - Populations not studied in clinical trials** This section was aligned with data from the Safety Population (CO-338-010, CO-338-017, CO-338-014, CO-338-43, and CO-338-087 [ATHENA-MONO]). **Part II: Module SV - Post-authorisation experience** This section was updated to align with the Periodic Safety Update Report (PSUR)#8 (DLP 19 Dec 2022). **Part II: SVII.2 New safety concerns and reclassification with a submission of an updated RMP** Reclassification of "Myelodysplastic syndrome/Acute myeloid leukaemia" as Important Identified Risk **Part II: Module SVII.3.1 Presentation of important identified risks and important potential risks** and **Module SVII.3.2 Presentation of the missing information** The characterisation of risks was updated. **Part II: Module SVIII** Reclassification of "Myelodysplastic syndrome/Acute myeloid leukaemia" as Important Identified Risk **Part IV: Plans for post-authorisation efficacy studies** CO-338-087 (ATHENA) added **Part V: Module V.1 Routine Risk Minimisation Measures** and **V.3 Summary of risk minimisation measures**

	Reclassification of "Myelodysplastic syndrome/Acute myeloid leukaemia" as Important Identified Risk **Part VI: Summary of the risk management plan** Updated with changes described above

Other RMP versions under evaluation

RMP Version number	N/A
Submitted on	N/A
Procedure number	N/A

Details of the currently approved RMP

Version number	8.0
Approved with procedure	EMEA/H/C/004272/II/0037
Date of approval (opinion date)	22 Jun 2023

Qualified Person Responsible For Pharmacovigilance (QPPV)

QPPV name	Stefan Zohmann
QPPV signature	[redacted]

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List of Abbreviations

ADP	adenosine diphosphate
ADR	adverse drug reaction
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
AML	acute myeloid leukaemia
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under the concentration-time curve
BCRP	breast cancer resistant protein
BID	twice daily
BMI	body mass index
BRCA	breast cancer gene
BRIP1	BRCA1 interacting protein C-terminal helicase 1
CI	confidence interval
C_{max}	maximum plasma drug concentration
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CLcr	creatinine clearance
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DDI	drug-drug-interaction
DLP	data lock point
DNA	deoxyribonucleic acid
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report

ESMO	European Society for Medical Oncology
EU	European Union
EU-27	27 EU member states
gBRCA	germline mutation in BRCA (BRCA1 and BRCA2)
GI	gastrointestinal
GLP	Good Laboratory Practice
hERG	human Ether-a-go-go-Related Gene
HIV	human immunodeficiency virus
HLT	high level term
HR	hazard ratio
HRD	homologous recombination deficiency
5-HT_3	5-hydroxytryptamine $_3$
IC_{50}	half maximal inhibitory concentration
IIT	Investigator-initiated trials
INN	International Non-proprietary Name
invPFS	investigator-assessed PFS
ISS	integrated safety summary
ITT	intent-to-treat
IV	intravenous
MAH	Marketing Authorisation Holder
MATE	multidrug and toxic compound extrusion
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
N	number of patients
NCI	National Cancer Institute
NPP	Named Patient Program
OCT	organic cation transporter
ODWG	Organ Dysfunction Working Group

OR	odds ratio
ORR	objective response rate
PARP	Poly (ADP-ribose) polymerase
PFS	progression free survival
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PO	per os
PSUR	Periodic Safety Update Report
PT	Preferred Term
PTAM	Post Trial Access Management
QD	once daily
QPPV	Qualified Person for Pharmacovigilance
QT	The time between the start of the Q wave and the end of the T wave in the heart's electrical cycle.
QTc	Corrected QT Interval
QTcF	Fridericia's formula
RAD5	BRCA1/BRCA2-containing complex, subunit 5
RAP	Rucaparib Access Program
RECIST	Response Evaluation Criteria in Solid Tumours
RMP	Risk Management Plan
RP2D	recommended Phase 2 dose
RR	relative risk
SAE	serious adverse event
sBRCA	somatic mutations in BRCA (BRCA1 or BRCA2)
SEER	Surveillance, Epidemiology, and End Results
SIR	standardised incidence ratio
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Queries
SOC	System organ class

SPF	sun protection factor
SPM	second primary malignancy
tBRCA	tumour tissue alteration in BRCA1 or BRCA2, includes gBRCA and sBRCA
TEAE	treatment-emergent adverse event
TMZ	temozolomide
UGT	uridine 5'-diphospho-glucuronosyltransferase
UK	United Kingdom
ULN	upper limit of normal
US	United States
USAN	United States Adopted Name

Part I: Product(s) Overview

Active substance(s) (International nonproprietary name (INN) or common name)	Rucaparib (CO-338) (formerly known as AG 014447 and PF-01367338)
Pharmacotherapeutic group(s) (Anatomical Therapeutic Chemical (ATC) Code)	Other antineoplastic agents L01XK03
Marketing Authorisation Holder (MAH)	zr pharma&
Medicinal products to which this RMP refers	Rucaparib
Invented name(s) in the European Economic Area (EEA)	Rubraca
Marketing authorisation procedure	Centralised
Brief Description of the Product Including:	**Chemical class and mode of action**: Rucaparib (CO 338), 8-fluoro-2-{4-[(methylamino)methyl]phenyl}-1,3,4,5-tetrahydro-6H-azepino[5,4,3-cd]indol-6-one ((1S,4R)-7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methanesulfonic acid is a potent small molecule inhibitor of poly-adenosine diphosphate (ADP) ribose polymerase (PARP) enzymes, including PARP-1, PARP-2, and PARP-3.
	Important information about its composition: None
Hyperlink to the Product Information	
Indication(s) in the EEA	Current: 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.
	Proposed: Rubraca is indicated as monotherapy for the maintenance treatment of adult patients with advanced (FIGO Stages III and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to first-line platinum-based chemotherapy. 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.
Dosage in the EEA	Current: The recommended dose of Rubraca is 600 mg taken twice daily, equivalent to a total daily dose of 1,200 mg, until disease progression or unacceptable toxicity.
	Proposed: The recommended dose of Rubraca is 600 mg taken twice daily, equivalent to a total daily dose of 1,200 mg.

	Duration of treatment *First-line maintenance treatment of advanced ovarian cancer* Patients can continue treatment until disease progression, unacceptable toxicity or completion of 2 years treatment. *Maintenance treatment of platinum-sensitive relapsed ovarian cancer* Patients can continue treatment until disease progression or unacceptable toxicity.
Pharmaceutical Form(s) and Strengths	Current: Film-coated tablets: 200 mg, 250 mg, and 300 mg
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Indication

Rubraca is indicated as monotherapy for the maintenance treatment of adult patients with advanced (FIGO Stages III and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to first-line platinum-based chemotherapy.

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.

Incidence and prevalence:

- The majority of cases of ovarian cancer are of epithelial origin (~90%).[1]
- Based upon estimates obtained from Globocan 2020, the 5-year prevalence of ovarian cancer in women in the 27 EU member states (EU-27) population is 49.58 per 100,000.[2]
- Using the Globocan 2020 database, the incidence of ovarian cancer in females in EU-27 is 45,470. The 5-year prevalence are 12,824.[2]
- Based on European data, the prevalence of ovarian cancer provided in the 2016 Orphanet Report is 30.0 per 100,000.[4]
- The incidence of ovarian cancer varies across the continent with the highest incidence rates (> 15.7 per 100,000) reported in Latvia, Poland, Bulgaria, Lithuania, United Kingdom (UK), and Estonia; and the lowest incidence rates (< 10.3 per 100,000) reported in Portugal, Netherlands, Cyprus, Germany, and Austria. A similar pattern was reported for prevalence.[1,5]
- Based on data recorded by Surveillance, Epidemiology, and End Results (SEER) between 2009 and 2013, the age-adjusted number of new cases of ovarian cancer in the United States (US) was 11.9 per 100,000 women per year.[6]
- Approximately 1.3% of women will be diagnosed with ovarian cancer at some point during their lifetime, based on 2010 to 2012 SEER data.[6]

Breast cancer gene (BRCA)1/2 mutations:

- Approximately 10% to 15% of all cases of ovarian malignancies are associated with germline mutations in BRCA1 and BRCA2. Somatic mutations occur less frequently in 5% to 10% of ovarian cancers.[7]
- The estimated lifetime risk of ovarian cancer is 25% to 65% among BRCA1 mutation carriers and 15% to 20% among BRCA2 mutation carriers, which is dramatically increased compared to that of the general population (1.5%).[8,9]

Non-BRCA homologous recombination deficiency (HRD) Mutations:

- Mutations in non-BRCA HRD genes have also been associated with an increased risk of ovarian cancer. For example, germline mutations in BRCA1 interacting protein C-terminal helicase 1 (BRIP1), BRCA1/BRCA2-containing complex, subunit 5 (RAD5)1C and RAD51D confer a lifetime risk up to age 70 of 5.8%, 5.2%, and 12.0%, respectively.[10-12]

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

- Ovarian cancer is predominantly a disease of older, post-menopausal women with the majority (> 80%) of cases being diagnosed in women over 50 years.[1]
- The age-adjusted incidence of new ovarian cases per 100,000 women is slightly higher among Whites (12.5) and Non-Hispanics (12.0) than Hispanics (10.6), American Indian/Alaskan Natives (10.4), Blacks (9.6), and Asian/Pacific Islanders (9.3).[6]

Risk factors

- Approximately 90% of ovarian cancer cases are thought to be sporadic.[8] However, women with a family history of ovarian cancer have an increased risk for the disease.[6,13] Women with a first-degree relative who has ovarian cancer have more than a two-fold increase in risk of ovarian cancer compared with women with no family history.[1]
- In women with a BRCA1 mutation, risk of ovarian cancer onset begins to increase by age 36 to 39 years with a 2% to 3% risk by 40 years of age. For BRCA2 mutations, risk begins to increase by 44 to 46 years, with a 2% to 3% risk by 50 years of age.[8]
- There is a higher incidence of BRCA1 or BRCA2 mutations in individuals with Ashkenazi Jewish heritage, conferring a 16% lifetime risk for ovarian cancer.[8,13,14]
- Mutations in non-BRCA HRD genes have also been associated with an increased risk of ovarian cancer. For example, germline mutations in BRIP1, RAD51C and RAD51D confer a lifetime risk up to age 70 of 5.8%, 5.2%, and 12.0%, respectively.[10-12]
- Use of oral contraceptives is associated with a reduction in ovarian cancer risk of 40% to 50% after 3 years' cumulative use.[8]
- In a matched case-control study of 3223 women, the use of oral contraceptives reduced the risk of ovarian cancer in BRCA1 mutation carriers (odds ratio [OR] = 0.56; 95% confidence interval [CI], 0.45-0.71; p < 0.0001) and BRCA2 mutation carriers (OR = 0.39; 95% CI, 0.23-0.66; p = 0.0004). Parity was associated with a reduced risk for carriers of BRCA1 mutations (OR = 0.67; 95% CI, 0.46-0.96; p = 0.03), but with an increased risk for those with BRCA2 mutations (OR = 2.74; 95% CI, 1.18-6.41; p = 0.02). Breastfeeding was associated with a reduced risk for carriers of BRCA1 mutations (OR = 0.74; 95% CI, 0.56-0.97; p = 0.03).[15]
- Significant positive association between inactivity and epithelial ovarian cancer risk (OR = 1.34; 95% CI, 1.14-1.57) has been reported.[16]
- There is a higher risk of relapse in patients for which surgical resection was not complete. In a retrospective review of data from 1895 patients with International Federation of Gynaecology and Obstetrics stage III epithelial ovarian cancer, compared with patients with microscopic residual disease, patients with 0.1 to 1.0 cm and > 1.0 cm residual disease had an increased risk of recurrence (hazard ratio [HR] = 1.96; 95% CI, 1.70-2.26; and HR = 2.36; 95% CI, 2.04-2.73, respectively) and death (HR =2.11; 95% CI, 1.78-2.49; p < 0.001; and HR = 2.47; 95% CI, 2.09-2.92, respectively).[17]

The main existing treatment options

The standard approach to treatment of advanced ovarian cancer is cytoreductive surgery (either at the time of diagnosis or interval debulking), with the goal of minimising residual tumour to no visible residual disease, a major prognostic indicator for improved survival. If initial cytoreduction is not performed, interval debulking surgery is considered. This surgery may be carried out after 3 or 4 cycles of primary chemotherapy, followed by a further 3 cycles of chemotherapy. Six to eight cycles of platinum- and taxane-based chemotherapy is the global standard of care.

Maintenance therapy:
The use of maintenance therapy following a response to standard treatment provides an opportunity to extend the progression-free period and delay the time to relapse. The anti-angiogenesis antibody, bevacizumab, given with chemotherapy in the first-line setting and then as maintenance showed significant improvements in PFS in two studies (GOG 0218 and ICON7), and as a result bevacizumab was incorporated into standard of care for first-line ovarian cancer.

PARP inhibitor maintenance therapy was initially approved as a strategy for improving outcomes in recurrent second line and beyond, platinum-sensitive ovarian cancer and more recently has been shown to be an effective strategy for improving outcomes in the first-line setting following cytoreductive surgery and platinum-based chemotherapy.

PARP inhibitor first-line maintenance therapy:
Olaparib is recommended as first-line maintenance therapy in the following indications:

- Maintenance treatment of adult patients with advanced (FIGO stages III and IV) BRCA 1/2-mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy, and
- Maintenance treatment of adult patients with advanced (FIGO stages III and IV) BRCA 1/2-mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a BRCA 1/2 mutation and/or genomic instability.

Niraparib has also been granted marketing authorisation as monotherapy for the maintenance treatment of adult patients with advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy.

Recurrent ovarian cancer:

- Surgery is rarely used for recurrent ovarian cancer.[1]
- The most common treatment for recurrent ovarian cancer is platinum-based combination chemotherapy (where likely to be tolerated) in platinum-sensitive relapsed disease, typically carboplatin or cisplatin in combination with paclitaxel, liposomal doxorubicin hydrochloride, or gemcitabine.[17,18]
- Patients who respond to platinum-based chemotherapy (in complete or partial response) may receive a PARP inhibitor as a later-line maintenance therapy.
    - Olaparib is indicted as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (compete response or partial response) to platinum-based chemotherapy.
    - Both rucaparib and niraparib are approved as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.
- Trabectedin in combination with pegylated liposomal doxorubicin is indicated for the treatment of patients with relapsed platinum-sensitive ovarian cancer.[19]

- Hormonal therapy with tamoxifen or an aromatase inhibitor can be used for women with recurrent, platinum-resistant ovarian cancer or in those wishing to avoid or delay further chemotherapy, particularly where their original tumour is expressing the oestrogen receptor.[18]
- Other therapy, including targeted therapy:
    - Anti-vascular endothelial growth factor antibody, bevacizumab, is approved in Europe for the treatment of advanced or recurrent epithelial ovarian cancer in combination with other agents including carboplatin and paclitaxel or gemcitabine.

Natural history of the indicated condition in the untreated population, including mortality and morbidity

- The age-standardised mortality rate of ovarian cancer in the EU-27 population in 2000 varied from 6.3 to 15.2 per 100,000 across EU countries, based upon estimates obtained from the European Cancer Information System.[20]
- Increasing age is associated with increased risks for disease progression (HR = 1.06; 95% CI, 1.02-1.11 for an increase every 10 years) and death (HR = 1.12; 95% CI, 1.06-1.18).[17] Based on SEER 2009 to 2013 data, the percent of ovarian cancer deaths in the US is highest among women aged 65 to 74 years (25.8%), 75 to 84 years (25.0%), and 55 to 64 years (21.4%).[6]
- The majority of patients diagnosed with ovarian cancer present with advanced stage disease. At the time of diagnosis, 14.8% of ovarian cancers were localised, 19% were regional, and 60% were distant. The 5-year relative survival rates for localised, regional, and distant ovarian cancers were 92.1%, 73.1%, and 28.8%, respectively.[6,21]

Important co-morbidities

As the incidence of ovarian cancer increases sharply with age, many patients have one or more other chronic diseases. Co-morbidity is an important predictor of prognosis in patients with chronic diseases, including cancer.[22] In a study of 1540 Danish women diagnosed with epithelial ovarian cancer between 2000 and 2011, the proportion of patients with co-morbidity was 25% between 2000 and 2002, and 35% between 2009 and 2011.[22]

Important co-morbidities in patients with relapsed ovarian cancer are presented in Table 1.

Table 1. Important Co-morbidities in Patients with Ovarian Cancer

Cardiovascular Disease	▪ A study of 10,174 elderly (≥ 66 years) women in the US with ovarian cancer, reported that 3- and 12-month incidence rates (per 1000 person-years) of most conditions were significantly higher in cancer than in matched cancer-free patients (5087 women in each group): hypertension (177.3 and 47.4, respectively); thromboembolic event (145.3 and 5.5, respectively); congestive heart failure (113.3 and 28.6, respectively); infection (664.4 and 55.2, respectively); and anaemia (408.3 and 33.1, respectively) at 12 months.[23] ▪ Cardiovascular diseases (myocardial infarction, congestive heart failure and peripheral vascular disease) were reported in 7.4% of newly diagnosed ovarian cancer cases in Denmark between 2000 and 2011.[22] ▪ In a German study of 1213 patients with recurrent ovarian cancer, cardiovascular disease was the most frequent co-morbidity (47.5%).[24] ▪ In a German open-label trial of 51 women aged 65 years or older with relapsed ovarian cancer after failure of platinum-containing therapy, blood pressure and heart were the sites of co-morbidity in 18 (14.8%) and 13 (10.7%) of the 122 concomitant diseases, respectively.[25]

Cerebrovascular Disease	Cerebrovascular disease was reported in 5.8% (89/1540) of newly diagnosed ovarian cancer cases in Denmark between 2000 and 2011.[22]
Respiratory Diseases	Chronic obstructive pulmonary disease (COPD) was reported in 5.3% (81/1540) of newly diagnosed ovarian cancer cases in Denmark between 2000 and 2011.[22]
Gastrointestinal (GI) Disease	The true incidence of malignant intestinal obstruction due to progressive disease (not a primary diagnosis) is not known.[18] In a German open-label trial of 51 women aged 65 years or older with relapsed ovarian cancer after failure of platinum-containing therapy, the lower GI tract was the site of co-morbidity in 11 (9.0%) of the 122 concomitant diseases.[25]
Other Cancers	In a Danish study of newly diagnosed ovarian cancer cases between 2000 and 2011, any cancer was the most prevalent co-morbidity, registered in 7.9% (121) of the ovarian cancer patients.[22] Patients with ovarian cancer are at increased risk of developing a second primary malignancies (SPM). In a nationwide, retrospective, population-based study in Taiwan, 12,127 patients with newly diagnosed ovarian cancer were followed between 1997 and 2010. The study period represented a follow-up of 56,214 person-years. During this time, 707 cancers developed. The Standardised Incidence Ratios (SIRs) for haematologic cancer and leukaemia after > 1 year follow-up were 1.72 (95% CI, 0.96-2.84) and 3.98 (95% CI, 1.99–7.12), respectively. Chemotherapy was an independent risk factor for SPM (HR = 1.27; 95% CI, 1.02–1.59, p = 0.033). Among the chemotherapy agents included (cyclophosphamide, gemcitabine, fluorouracil, platinum, anthracyclines, and taxanes), fluorouracil was associated with a significantly increased risk of SPM (HR = 5.18; 95% CI, 3.66–7.33, p < 0.001).[26] Female BRCA1 and BRCA2 mutation carriers have an increased risk of fallopian tube and breast cancer. An estimated 26% to 34% of female BRCA2 carriers will develop breast cancer by age 50. Other cancers associated with BRCA2 mutations are pancreatic cancer, gall bladder/bile duct cancer, stomach cancer, and melanoma.[18]
Myelodysplastic syndrome (MDS)/ acute myeloid leukaemia (AML)	Diagnoses of therapy-related myeloid leukaemia and MDS are recognised complications of cytotoxic therapy.[27] In patients with ovarian cancer receiving platinum-based treatment, a frequency of MDS/AML of 0.33% has been reported.[28] Fulcher et al. reported that the incidence of MDS and AML expressed as cases per 1,000 patient-years in the ovarian cancer cohort was 0.51 (0.2%) and 0.39 (0.1%) and in ovarian cancer-BRCA patients, 0.62 and 0.25, respectively. The incidence of MDS and AML in ovarian cancer patients was higher in patient subcohorts exposed to deoxyribonucleic acid (DNA) damaging agents than in the overall cohort.[29]
Menopause and Oestrogen Deficiency	Most women with ovarian cancer are post-menopausal at the time of diagnosis and others become menopausal due to surgical removal of ovaries, resulting in oestrogen deficiency–related health effects, such as increased risk of cardiovascular disease and hyperlipidaemia.[8]
Musculoskeletal Diseases	In a German open-label trial of 51 women aged 65 years or older with relapsed ovarian cancer after failure of platinum-containing therapy, the musculoskeletal system was the site of co-morbidity in 18 (14.8%) of the 122 concomitant diseases.[25]
Depression and Anxiety Related Disorders	Depression is a major outcome in cancer patients. In a study of 99 elderly (aged over 70 years) women with advanced ovarian cancer, undergoing first-line carboplatin chemotherapy, 15 (15%) were depressed according to the Diagnostic and Statistical Manual of Mental Disorders criteria for depression, and 39% were depressed according to psychiatric clinical interview.[30]

Part II: Module SII - Non-clinical part of the safety specification

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Nausea and vomiting The oral toxicity of rucaparib was evaluated in a total of 12 studies, including 10 studies in rats and dogs by single and repeated oral dose administration for up to 91 days of daily treatment. The GI system was one of the primary target organs identified in these studies. In the dog, GI manifested principally as clinical signs, which included abnormal stool (non-formed, water, liquid, mucoid) and vomiting. Nausea cannot be directly assessed in rats and dogs; however, the clinical signs associated with GI effects, which included emesis for dogs, is consistent with nausea. The GI effects in the dog were not dose-limiting and did not affect the general health of the animals, but were associated with some body weight loss. The toxicities induced in rats and dogs were generally reversible after a 4-week recovery period and no additional targets were identified in animals following prolonged oral dosing.	The GI system was one of the primary target organs identified in toxicology studies with oral rucaparib. Similarly, nausea and vomiting are common adverse drug reactions (ADRs) observed in patients.
Myelotoxicity The oral toxicity of rucaparib was evaluated in a total of 12 studies, including 10 studies in rats and dogs by single and repeated oral dose administration for up to 91 days of daily treatment. The findings in the rat and dog non-clinical studies with rucaparib included changes in the hematopoietic and lymphopoietic systems. Data from both the rat and dog 13-week studies established that, based on hematologic and histologic evaluations (bone marrow, spleen, liver, gut-associated lymphoid tissue, thymus, and lymph nodes), changes in hematopoietic tissues were not progressive over time. Partial to complete recovery occurred with all changes in hematologic parameters and bone marrow cellularity in both the rat and dog.	The hematopoietic system was one of the primary target organs identified in toxicology studies with oral rucaparib. Similarly, myelotoxicity is a common ADRs observed in patients.
Reproductive and developmental toxicity Rats were given oral rucaparib at doses ranging from 50 to 1000 mg/kg/day from Gestation Day 7 to 17 in a non-Good Laboratory Practice (GLP) dose range finding embryo-foetal development study. Rucaparib caused maternal toxicity at doses ≥ 500 mg/kg/day, and was embryotoxic (100% early resorptions) at doses ≥ 50 mg/kg/day. In addition, rucaparib induced structural chromosomal aberrations in cultured human peripheral blood lymphocytes, with or without metabolic activation. No animal studies have been performed regarding the excretion of rucaparib in breast milk.	Rucaparib can cause embryo or foetal harm when administered to a pregnant woman. Rucaparib should not be used during pregnancy. Embryotoxicity and teratogenicity are important potential risks for rucaparib. Appropriate warnings and precautions regarding use during pregnancy are provided in the Summary of Product Characteristics (SmPC) (SmPC; Sections 4.4 and 4.6). To minimise the risk of potential harm to an embryo or foetus, Section 4.6 of the SmPC advises female patients to use effective contraception during

	treatment and for 6 months following the last dose of rucaparib. A contraindication regarding use during breast feeding is provided in the SmPC (SmPC; Section 4.3).
Nephrotoxicity No evidence of nephrotoxicity was observed in general toxicology studies with rucaparib. Rucaparib is a potent inhibitor of multidrug and toxic compound extrusion (MATE)1 and MATE2-K.	These results suggest rucaparib has a limited potential for nephrotoxicity in humans. Rucaparib inhibits MATE1/2K transporters and consequently inhibits MATE1/2 K mediated tubular creatinine secretion. The clinical significance of increases in creatinine due to MATE1/2K transporter inhibition is currently unknown.
Hepatotoxicity No evidence of hepatotoxicity was observed in general toxicology studies with rucaparib.	Based on nonclinical studies, rucaparib has a low potential for causing hepatotoxicity in humans. Whilst elevations of alanine aminotransferase (ALT)/aspartate aminotransferase (AST) were seen in the clinical development programme, these were transient and most elevations resolved with or without modifications of rucaparib dosing. Hepatotoxicity is not considered to be an important safety concern in humans.
Genotoxicity Rucaparib camsylate generated by the current commercial manufacturing process was negative in a Bacterial Reverse Mutation (Ames) Assay. Rucaparib was clastogenic in an *in vitro* chromosomal aberration assay in cultured human lymphocytes.	The clastogenic response in mitotically-stimulated cells was anticipated based on the mechanism of action of rucaparib and indicates potential genotoxicity in humans. Appropriate warnings and precautions regarding pregnancy and a nursing mother are provided in the SmPC based on the positive genotoxicity results.
Carcinogenicity No carcinogenicity studies have been performed with rucaparib.	Carcinogenicity studies are typically not performed for therapeutics intended to treat patients with advanced cancer.

Fertility No standalone fertility study was conducted with rucaparib. Male reproductive assessment endpoints were evaluated in a 3-month repeat-dose study in rat and dog. No rucaparib-related effects on sperm total count, density, motility, or morphology, or effects on spermatogenesis were noted at 100 mg/kg/day in the rat and 20 mg/kg/day in the dog with systemic exposures of approximately 30% and 9%, respectively, of the human exposure (area under the concentration-time curve $(AUC)_{0\text{-}24h}$) at 600 mg twice daily (BID). The male and female reproductive organs were not identified as target organs with rucaparib dosing in rat or dog. However, based on published studies, PARP inhibitors may have the potential to impair spermatogenesis and reduce fertility.[31-34]	Cumulatively, there were no cases concerning the effects of rucaparib on fertility received from clinical trials sponsored by Clovis Oncology nor from post-marketing data.
General Safety Pharmacology **Cardiovascular** Rucaparib had a half maximal inhibitory concentration (IC_{50}) value of 22.6 µM in the human ether-a-go-go-related gene (hERG) assay; approximately 13-fold higher than the unbound maximum plasma drug concentration (C_{max}) of 1.79 µM in patients treated with 600 mg BID rucaparib. Cardiac effects, which were described as myocardial degeneration in the rat and a higher incidence of endocardial haemorrhage in dog, were observed at necropsy following intravenous (IV) administration of rucaparib whereas no effects were observed with oral dosing of rucaparib, the intended commercial formulation, in repeat-dose toxicity studies in rats and dogs. Exposure data indicated that cardiac lesion development following IV dosing was likely C_{max} driven as cardiac effects were correlated to high C_{max} values after IV dosing. The cardiac effects observed in nonclinical toxicology studies were shown to occur with use of the IV formulation and at doses delivering C_{max} values ≥5 fold greater than those observed in patients at the recommended oral dose of 600 mg BID. However, no cardiac effects were observed in any of the studies conducted with the oral formulation.	The results of the nonclinical studies suggest that when given orally, rucaparib poses a low risk for development of cardiac lesions in patients. However, a potential risk cannot be excluded (SmPC; Section 5.3), and QTc interval prolongation is considered an important potential risk.
Nervous system There were no neurobehavioural findings in the 91-day repeat-dose study in rat. In addition, there was a low uptake of [^{14}C] rucaparib in brain and spinal cord in rats and based on *in vitro* transporter studies, rucaparib is a substrate of P-glycoprotein (P-gp) and breast cancer resistant protein (BCRP).	It is unlikely that rucaparib activity in the central nervous system (CNS) would translate to any significant effects in patients.
Mechanisms for Drug-Drug Interactions (DDIs) <u>Rucaparib as a victim drug</u> Rucaparib showed slow *in vitro* enzymatic turnover rate in human liver microsomes and hepatocytes. In another *in vitro* study, recombinant human cytochrome P450 (CYP)2D6, and	<u>Rucaparib as a victim drug</u> Collective clinical CYP genotyping results and population pharmacokinetics (PK) analysis

to a lesser extent CYP1A2 and CYP3A4, could metabolise rucaparib. *In vitro*, rucaparib is a dual substrate of P-gp and BCRP. Rucaparib as a perpetrator drug *In vitro* studies showed that rucaparib is a reversible inhibitor of CYP1A2, CYP2C9, CYP2C19, and CYP3A4, and to a lesser extent of CYP2C8, CYP2D6, and uridine 5'-diphospho-glucuronosyltransferase (UGT)1A1. Rucaparib induced CYP1A2, and down regulated CYP2B6 and CYP3A4 in human hepatocytes at clinically relevant exposures. Rucaparib is a potent inhibitor of MATE 1 and MATE2-K, a moderate inhibitor of organic cation transporter (OCT)1, and a weak inhibitor of OCT2. In addition, rucaparib is an *in vitro* inhibitor of P-gp and BCRP.	showed that patients with different CYP2D6 and CYP1A2 genotypes had similar rucaparib PK. Contribution of CYP3A4 to rucaparib metabolism *in vivo* cannot be excluded. Clinical P-gp and BCRP-related DDIs with rucaparib as a substrate cannot be excluded. Rucaparib as a perpetrator drug Study CO-338-044 (Part I) showed that at steady state of 600 mg BID, rucaparib showed moderate inhibition of CYP1A2 (≥2 but <5-fold increase in AUC), mild inhibition of CYP2C9, CYP2C19, and CYP3A4 (≥1.25 but <2-fold), and marginal inhibition of P-gp transporter (>1 but <1.25-fold increase in AUC). When co-administering medicinal products metabolized by CYP1A2, CYP2C9, CYP3A4, particularly medicines which have a narrow therapeutic index, dose adjustments may be considered based on appropriate clinical monitoring. Study CO-338-095 (Part I) showed that rucaparib marginally increased C_{max} of ethinylestradiol and levonorgestrel (1.09- to 1.2-fold) and weakly increased the $AUC_{0\text{-last}}$ for both ethinylestradiol and levonorgestrel to 1.43- to 1.56-fold. Rucaparib is a potent inhibitor of MATE 1 and MATE2-K, a moderate inhibitor of OCT1, and a weak inhibitor of OCT2. As inhibition of these transporters could decrease metformin renal elimination and decrease liver uptake of metformin, caution is advised when metformin is co-administered with rucaparib. In addition, rucaparib is an inhibitor of the BCRP and Study CO-338-095 (Part I) showed that rucaparib weakly increased the exposure to rosuvastatin (a BCRP substrate) up to approximately 1.29- to 1.35-fold as measured by $C_{max,}$ $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$. The clinical relevance of

	UGT1A1 inhibition by rucaparib is not clear. Caution should be used when rucaparib is co-administered with UGT1A1 substrates (i.e. irinotecan) to patients with UGT1A1*28 (poor metabolizer) due to a possible increase in SN-38 exposure and associated toxicities.
Other Toxicity-related Information or Data • Local tolerance The distribution of radioactivity following a single oral dose of [^{14}C]-rucaparib in male pigmented Long-Evans rats was qualitatively similar to that in albino rats, with the exception of the uveal pigment of the eyes and the pigmented skin where a higher concentration of radioactivity was observed, suggesting an association of radioactive drug-related material with melanin. However, rucaparib was not found to be phototoxic in a study conducted in Long-Evans pigmented rats given rucaparib camsylate via oral gavage for 5 days at a dose of up to 750 mg/kg/day.	Although phototoxicity was not observed in nonclinical studies, photosensitivity has been observed in patients treated with rucaparib (SmPC; Section 4.8). Appropriate warnings and precautions regarding spending time in direct sunlight and the use of protective clothing and sunscreen are provided in the SmPC (SmPC; Section 4.4).
• Secondary pharmacology Rucaparib demonstrated limited activity in radioligand binding assays against 39 receptors, ion channels, and transporters, as well as by functional enzymatic profiling against 530 wild type and mutant kinases.	These results suggest rucaparib has a limited potential for off-target effects in humans.

Based on the above it is evaluated that there are no safety issues that should warrant additional non-clinical studies.

Conclusions on non-clinical data

Safety Concerns
Important Identified Risks (confirmed by clinical data) – None
Important Potential Risks (not refuted by clinical data or which are of unknown significance) – QTc interval prolongation – Embryotoxicity and teratogenicity
Missing Information – None

Part II: Module SIII - Clinical trial exposure

Rucaparib has been developed as an antineoplastic agent. Nonclinical evaluation has demonstrated sensitivity of BRCA1 and BRCA2 homozygous mutant cell lines to rucaparib, which is attributed to PARP inhibition alone, and provides a rationale for the clinical assessment of rucaparib as monotherapy in patients with hereditary (germline) and acquired (somatic) deficiencies of BRCA1 and BRCA2. The rucaparib clinical development programme also identified patients without BRCA mutations who had benefit from rucaparib through examination of molecular tumour characteristics identified by next generation sequencing of tumour DNA. Rucaparib is the INN and United States Adopted Name (USAN) for CO-338 and is used to indicate the active moiety.

As of 30 May 2023, 21 clinical studies (CO-338-010, CO-338-017 [ARIEL2], CO-338-078 Part 1 and Part 2, A4991002, A4991005, A4991014, CO-338-023 [RUCAPANC], CO-338-044 Part 1 and Part 2 [DDI], CO-338-045 Part 1 and Part 2 [Absorption, distribution, metabolism, excretion], CO-338-095 Part 1 Arm A and Arm B, CO-338-097 [ARIES], CO-338-014 [ARIEL3], CO-338-043 [ARIEL4], CO-338-052 [TRITON2], CO-338-081 [RUCA-J], CO-338-095 Part 2, CO-338-098 Arm A [SEASTAR], CO-338-100 [LODESTAR], CO-338-107 [RAMP], and CO-338-111 [CATCH-R] and CO-338-098 Arm B [SEASTAR]) had been completed and 2 studies (CO-338-063 [TRITON3] and CO-338-087 [ATHENA]) are ongoing.

Data from ARIEL3 are included in this RMP to support the indication for use of rucaparib as monotherapy 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.

Completed Studies

- Study A4991002: Phase 1 open-label, dose-escalation study of IV rucaparib in combination with temozolomide (TMZ) in patients with advanced solid tumours (Part 1) or malignant melanoma (Part 2).
- Study A4991005: Phase 2, open-label study of IV rucaparib in combination with TMZ in patients with metastatic melanoma.
- Study A4991014: Phase 1, open-label, dose-escalation study of IV and oral rucaparib administered with different chemotherapeutic agents in patients with advanced solid tumours.
- Study CO-338-023 (RUCAPANC): A Phase 2, single-arm, open-label study of monotherapy oral rucaparib as treatment for patients with previously treated locally advanced or metastatic pancreatic ductal adenocarcinoma and a known deleterious BRCA mutation.
- Study CO-338-044 (Part 1 and Part 2): A Phase 1, open-label, multiple-probe DDI study to determine the effect of rucaparib on PK of caffeine, S-warfarin, omeprazole, midazolam, and digoxin in patients with advanced solid tumours.
- Study CO-338-045 (Part 1 and Part 2): A Phase 1, single-dose study of the disposition of [^{14}C]-radiolabelled rucaparib in patients with advanced solid tumours).
- Study CO-338-010: 3-part, open-label, Phase 1/2 study of monotherapy oral rucaparib.
    - Part 1: A Phase 1 portion evaluating PK and safety of escalating doses of rucaparib in patients with solid tumours; this portion identified 600 mg BID as the recommended starting dose for future studies (N = 56).
    - Part 2: A Phase 2 portion evaluating the efficacy and safety of rucaparib in patients with relapsed, high-grade ovarian cancer associated with a BRCA mutation.
        - Part 2A enrolled patients with a germline BRCA mutation (gBRCA) who had received 2 to 4 prior treatment regimens (N= 42).

        - Part 2B enrolled patients with a gBRCA or somatic BRCA mutations (sBRCA) who received at least 3 prior chemotherapy regimens (N=12).
    - Part 3: A Phase 2 portion in patients with a relapsed solid tumour associated with a BRCA mutation in order to characterise the PK, food effect, and safety profile of a higher dose strength tablet (N = 26).
- Study CO-338-017 (ARIEL2): A 2-part open-label Phase 2 study of monotherapy oral rucaparib for treatment of relapsed, high-grade ovarian cancer patients. It was designed to identify tumour characteristics that may predict sensitivity to rucaparib. Patients were classified into molecularly-defined subgroups, including tumour BRCA (tumour tissue alteration in BRCA1 or BRCA2 (tBRCA), inclusive of both germline and somatic BRCA) and BRCA-like, by a prospectively defined genomic signature.
    - Part 1 enrolled patients with platinum-sensitive, relapsed disease who received ≥ 1 prior platinum regimen (N = 204).
    - Part 2 enrolled patients with relapsed disease who received at least 3 prior chemotherapy regimens (N=287).
- Study CO-338-078 (Part 1 and Part 2): A Phase 1, open-label, parallel group study to determine the PK, safety and tolerability of rucaparib in patients with advanced solid tumour and with moderate hepatic impairment or normal hepatic function.
- CO-338-095 (Part 1): A Phase 1, open- label, DDI study to determine the effect of rucaparib on the PK of oral rosuvastatin (Arm A) and oral contraceptives (ethinylestradiol and levonorgestrel) (Arm B) in patients with advanced solid tumours.
- CO-338-097 (ARIES): A Phase 2, open-label study to evaluate rucaparib in combination with nivolumab in patients with selected solid tumours.
- CO-338-098 Arm B (SEASTAR): A Phase 1b/2, open-label, parallel arm study of the safety, PK, and efficacy of oral rucaparib with other anticancer agents in patients with a solid tumour. In Arm B, patients received rucaparib and sacituzumab govitecan.
- Study CO-338-014 (ARIEL3): a Phase 3, randomised, 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 (N=561 (372 treated with rucaparib and 189 with placebo); Enrolment complete. A final CSR has been completed and provides safety and efficacy data for the indication of monotherapy 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.
- Study CO-338-043 (ARIEL4): A Phase 3 multicentre, randomised study of rucaparib versus chemotherapy in patients with relapsed, BRCA-mutant, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who had received at least 2 prior chemotherapy regimens. Enrolment complete. A final CSR has been completed and provides safety and efficacy data for the indication.
- Study CO-338-052 (TRITON2): A multicentre, open-label Phase 2 study of rucaparib in patients with metastatic castration-resistant prostate cancer associated with HRD. Enrolment complete.
- CO-338-081 (RUCA-J): A Phase 1, open-label study of rucaparib in Japanese patients with previously- treated solid tumour.
- CO-338-095 (Part 2): An optional rucaparib treatment phase following completion of Part 1 (DDI).
- CO-338-098 Arm A (SEASTAR): A Phase 1b/2, open-label, parallel arm study of safety, PK, and efficacy, of oral rucaparib with other anticancer agents in patients with a solid tumour. Patients in Arm A received rucaparib and lucitanib.
- CO-338-100 (LODESTAR): A Phase 2, multicenter, open-label study of rucaparib as treatment for solid tumors.

- CO-338-107 (RAMP): A Phase 1b, open-label, parallel arm study of safety, PK, and efficacy of rucaparib in combination with other anticancer agents in metastatic castration-resistant prostate cancer.
- CO-338-111 (CATCH-R): A rollover study to provide continued access to rucaparib.

Ongoing Studies

- Study CO-338-063 (TRITON3): A multicentre, randomized, open-label Phase 3 study of rucaparib versus physician's choice of therapy for patients with metastatic castration-resistant prostate cancer associated with HRD.
- CO-338-087 (ATHENA): A Phase 3, double-blind, randomized study of rucaparib and nivolumab as maintenance treatment following response to front-line platinum-based chemotherapy in patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer ATHENA consists of two separate treatment components: ATHENA-MONO and ATHENA-COMBO.

Clinical Study CO-338-014 (ARIEL3) supports the safety and efficacy of orally administered rucaparib for monotherapy 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. Safety and exposure data from Studies CO-338-010, CO-338-017 (ARIEL2), CO-338-014 (ARIEL3), and CO-338-043 (ARIEL4) are presented in this RMP.

Clinical study CO-338-087 (ATHENA-MONO) supports the safety and efficacy of rucaparib in patients with newly diagnosed epithelial ovarian, fallopian tube, or primary peritoneal cancer who have responded to their first-line platinum-based regimen.

Safety and exposure data from Studies CO-338-010, CO-338-017 (ARIEL2), CO-338-014 (ARIEL3), CO-338-043 (ARIEL4), and CO-338-087 (ATHENA-MONO) are presented in this RMP.

The clinical studies included in this RMP are summarised in Table 2.

Table 2. Clinical Studies Included in the RMP

Study Number	Study Phase/ Status/Follow-up	Primary Objective	Study Design	Test Product Dose, Route of Administration	Patient Population
Uncontrolled Studies					
CO-338-010	Phase 1 Complete Phase 2 (Part 2A, Part 2B, and Part 3) Complete Parts 1 and 3: follow-up evaluation for 28 days after the last dose of rucaparib. Long-term follow-up (Part 2B): every 12 weeks, and every 14 weeks after 18 months.	Part 1: 1.To evaluate the safety profile of escalating doses of continuous daily oral rucaparib in patients with advanced solid tumours, and to determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D). Parts 2A and 2B: To evaluate objective response rate (ORR) in patients with relapsed, high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer associated with a BRCA mutation. Parts 1 and 3: To characterise the PK profile of oral rucaparib when administered as a continuous daily dose.	A 3-part Phase 1/2 open-label, safety, PK, and preliminary efficacy study. Part 1 (Phase 1) included dose-escalation and RP2D expansion cohorts.	Oral rucaparib (21-day cycles); salt. Phase 1/Part 1: Escalating oral doses once daily (QD) or BID on Days 1–21 of every 21-day cycle 40 mg-500 mg QD (per os (PO)) 240 mg-840 mg BID (PO) Phase 2/Parts 2 and 3: RP2D of oral rucaparib established in Part 1, 600 mg BID on Days 1-21 of every 21-day cycle.	Phase 1: Patients with advanced solid tumour Phase 2 Part 2A: Patients with platinum-sensitive, relapsed, ovarian cancer associated with a gBRCA mutation who received 2-4 prior chemotherapy regimens. Part 2B: Patients with relapsed, ovarian cancer with a gBRCA or sBRCA mutation who received 3-4 prior chemotherapy regimens. Part 3: Patients with advanced solid tumour with evidence of a gBRCA or sBRCA mutation.

Study Number	Study Phase/ Status/Follow-up	Primary Objective	Study Design	Test Product Dose, Route of Administration	Patient Population
CO-338-017 (ARIEL2)	Phase 2 Complete Parts 1 and 2: follow-up evaluation for 28 days after the last dose of rucaparib. Long-term follow-up: every 8 and 12 weeks in Part 1 and 2, respectively.	Part 1: To determine progression free survival (PFS) in patients with relapsed platinum-sensitive ovarian cancer classified into molecularly-defined subgroups by a prospectively defined HRD signature. Part 2: To estimate ORR in heavily pre-treated patients with relapsed ovarian cancer classified into molecularly-defined subgroups by a prospectively defined HRD signature.	Single arm, open-label, two-part, multicentre safety and efficacy study	600 mg BID oral rucaparib on Days 1-28 of every 28-day cycle	Patients with relapsed, ovarian cancer. <u>Part 1:</u> Patients with platinum-sensitive ovarian cancer who received ≥ 1 platinum regimen. <u>Part 2:</u> Patients with ovarian cancer who received 3-4 prior chemotherapy regimens.
Randomised placebo-controlled study					
Study CO-338-014 (ARIEL3)	Phase 3 Enrolment complete; Follow up ongoing	To compare the anti-tumour efficacy of oral single agent rucaparib with that of placebo as measured by PFS, when administered as a switch maintenance treatment for platinum sensitive, relapsed high grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer following a response to platinum-based chemotherapy.	Double-blind, randomised, placebo-controlled	600 mg BID oral rucaparib on Days 1-28 of every 28-day cycle	Patients with relapsed, platinum-sensitive, ovarian cancer
CO-338-087 (ATHENA) Only ATHENA-MONO data presented in this RMP	Phase 3 enrollment complete; Follow up ongoing	To evaluate PFS by Response Evaluation Criteria in Solid Tumors (RECIST), as assessed by the investigator (invPFS), in HRD and intent-to-treat (ITT) subpopulations, using the following comparisons: <u>ATHENA-MONO</u> Monotherapy: Arm B (oral rucaparib + IV placebo) vs Arm D (placebo [oral and IV])	Double-blind, randomised, placebo-controlled	Arm B: 600 mg BID oral rucaparib daily Arm D: 600 mg BID oral placebo daily	Newly diagnosed ovarian cancer patients following response to first-line therapy (surgery and platinum-based chemotherapy)

Study Number	Study Phase/ Status/Follow-up	Primary Objective	Study Design	Test Product Dose, Route of Administration	Patient Population
Randomised comparator-controlled study					
Study CO-338-043 (ARIEL4)	Phase 3 enrollment complete; Follow up ongoing	To determine investigator assessed PFS for rucaparib versus chemotherapy.	Open-label, randomised, chemotherapy-controlled	600 mg BID oral rucaparib in 28 day cycles. Chemotherapy: weekly paclitaxel for patients with platinum resistant or partially sensitive disease. For patients with platinum-sensitive disease, platinum-based chemotherapy consisting of the Investigator's selection of monotherapy platinum (cisplatin or carboplatin) or platinum-based doublet chemotherapy (carboplatin/paclitaxel, carboplatin/gemcitabine, or cisplatin/gemcitabine).	Patients with relapsed, BRCA-mutant, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Abbreviations: BID = twice daily; BRCA = breast cancer gene; gBRCA = germline mutation in BRCA (BRCA1 and BRCA2); HRD = homologous recombination deficiency; invPFS = investigator assessed PFS; ITT = intent-to-treat; MTD = maximum tolerated dose; ORR = objective response rate; PFS = progression-free survival; PK = pharmacokinetic(s); QD = once daily; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended Phase 2 dose; sBRCA = somatic mutations in BRCA (BRCA1 and BRCA2).

Exposure data from the safety population in Studies CO-338-010, CO-338-017, CO-338-014 (ARIEL3), CO-338-043 (ARIEL4), and CO-338-087 (ATHENA-MONO) are presented in Table 3. Data from Studies CO-338-010 and CO-338-017 are pooled due to similar patient populations.

Table 3. Exposure by Study

Dose Group	Study	N
600 mg BID ovarian cancer (including BRCA mutant)	CO-338-010 Part 1	5
	CO-338-010 Part 2A	42
	CO-338-010 Part 2B	12
	CO-338-010 Part 3	15
	CO-338-017 Part 1	204
	CO-338-017 Part 2	287
	ARIEL3	372 (rucaparib) 189 (placebo)
	ARIEL4	232 (rucaparib)
	ATHENA-MONO	425 (rucaparib) 110 (placebo)
Total number of ovarian cancer patients treated		1,594 (rucaparib) 299 (placebo)

Source: 2.7.4 type II variation 28 Feb 2020, Table 2.7.4-2, CO-338-043 Table 2.1 (Data cut off 30 Sep 2020), and ATHENA-MONO Integrated safety summary (ISS), Table 2.1.
Abbreviations: BID = twice daily; BRCA = breast cancer gene; N = number of patients.

Duration of Exposure

Table 4. Duration of Exposure (Safety Population, Studies CO-338-010, CO-338-017, CO-338-014, CO-338-043, CO-338-087 [ATHENA-MONO])

	Rucaparib (N=1594)		Placebo (N=299)	
Duration of Exposure (At Least)	**Persons (N=1594)**	**Person Time (Years)**	**Persons (N=299)**	**Person Time (Years)**
1 month	1496 (93.9%)	124.7	294 (98.3%)	24.5
3 months	1196 (75.0%)	299.0	227 (75.9%)	56.8
6 months	915 (57.4%)	457.5	149 (49.8%)	74.5
12 months	533 (33.4%)	533.0	64 (21.4%)	64.0
18 months	368 (23.1%)	552.0	42 (14.0%)	63.0
24 months	243 (15.2%)	486.0	17 (5.7%)	34.0
30 months	91 (5.7%)	227.5	3 (1.0%)	7.5
36 months	71 (4.5%)	213.0	2 (0.7%)	6.0
Overall	1594 (100.0%)	1521.2	299 (100.0%)	217.6

Source: ATHENA-MONO Integrated safety summary (ISS), Table 2.1. Final data used for CO-338-010 (20 May 2019). Da cutoffs of 01 Feb 2019 (CO-338-017), 31 Dec 2019(CO-338-014), 30 Sep 2020 (CO-338-043), 23 Mar 2022 (CO-338-087 [ATHENA-MONO]).

Exposure by Dose

The dose of 600 mg BID rucaparib was selected as the appropriate starting dose for subsequent Phase 2 and Phase 3 studies based on the overall PK, safety, and preliminary efficacy profile observed in the Phase 1 dose-escalation portion of Study CO-338-010.

In the Phase 1 dose-escalation portion (Part 1) of Study CO-338-010, the initial rucaparib dose level evaluated was 40 mg QD. Dose escalation in a standard 3+3 design was based on toxicities appearing in the initial 21-day treatment period. In total, 10 dose levels (40, 80, 160, 300, and 500 mg QD and 240, 360, 480, 600, and 840 mg BID) were evaluated. Patients could then continue treatment with rucaparib in the optional treatment-extension period beyond Cycle 1.

In the Phase 2 portion of Study CO-338-010, the starting dose of rucaparib was 600 mg BID, the RP2D determined from Phase 1 (Part 1) of the study.

In Study CO-338-014 (ARIEL3), 561 patients initiated treatment with either 600 mg BID of rucaparib or placebo; 372 patients in the rucaparib group and 189 patients in the placebo group.

In Study CO-338-043 (ARIEL4), 345 patients initiated treatment with either 600 mg BID of rucaparib or chemotherapy; 232 patients in the rucaparib group and 113 patients in the chemotherapy group.

In Study CO-338-087 (ATHENA-MONO), 535 patients initiated treatment with either 600 mg BID of rucaparib or placebo; 425 patients in the rucaparib group and 110 patients in the placebo group.

Table 5. Exposure by Dose (Safety Population, Studies CO-338-010, CO-338-017, CO-338-014, CO-338-043, and CO-338-087 [ATHENA-MONO])

	Rucaparib (N=1594)		Placebo (N=299)	
Dose of Exposure	**Persons**	**Person Time (Years)**	**Persons**	**Person Time (Years)**
600 mg BID	1581 (99.2%)	837.1	299 (100.0%)	203.6
Dose Level -1 (500/480 mg BID	718 (45.0%)	308.7	16 (5.4%)	6.0
Dose Level -2 (400/360 mg BID)	369 (23.1%)	193.7	6 (2.0%)	4.0
Dose Level -3 (300/240 mg BID)	201 (12.6%)	102.9	4 (1.3%)	0.7
Dose Level -4 (200 mg BID)	72 (4.5%)	44.1	0	0

Source: ATHENA-MONO Integrated safety summary (ISS), Table 2.2. Final data used for CO-338-010 (20 May 2019). Data cutoffs of 01 Feb 2019 (CO-338-017), 31 Dec 2019 (CO-338-014), 30 Sep 2020 (CO-338-043), 23 Mar 2022 (CO-338-087 [ATHENA-MONO]).
Abbreviations: BID = twice daily.

Exposure by Age and Gender

Table 6. Exposure by Age Group and Gender (Safety Population, Studies CO-338-010, CO-338-017, CO-338-014, CO-338-043, and CO-338-087 [ATHENA-MONO])

	Rucaparib (N=1594)		Placebo (N=299)	
	Persons	**Person Time (Years)**	**Persons**	**Person Time (Years)**
Age Group				
< 65 years	1014 (63.6%)	1014.5	184 (61.5%)	134.8
65-74 years	454 (28.5%)	405.8	97 (32.4%)	65.8
≥ 75 years	126 (7.9%)	100.9	18 (6.0%)	16.9
Gender				
Male	0	0	0	0
Female	1594 (100.0%)	1521.2	299 (100.0%)	217.6

Source: ATHENA-MONO Integrated safety summary (ISS), Table 2.3. Final data used for CO-338-010 (20 May 2019). Data cutoffs of 01 Feb 2019 (CO-338-017), 31 Dec 2019 (CO-338-014), 30 Sep 2020 (CO-338-043), 23 Mar 2022 (CO-338-087 [ATHENA-MONO]).

Exposure by Ethnic or Racial Origin and Region

Table 7. Exposure by Ethnic or Racial Origin and Region (Safety Population, Studies CO-338-010, CO-338-017, CO-338-014, CO-338-043, and CO-338-087 [ATHENA-MONO])

	Rucaparib (N=1594)		Placebo (N=299)	
Ethnic/Racial Origin	**Persons**	**Person Time (Years)**	**Persons**	**Person Time (Years)**
White	1268 (79.5%)	1195.4	230 (76.9%)	165.5
Other	183 (11.5%)	195.5	40 (13.4%)	32.8
Unknown	143 (9.0%)	130.3	29 (9.7%)	19.4
Region				
US/Canada	630 (39.5%)	548.4	107 (35.8%)	72.6

	Rucaparib (N=1594)		Placebo (N=299)	
Ethnic/Racial Origin	**Persons**	**Person Time (Years)**	**Persons**	**Person Time (Years)**
Europe	596 (37.4%)	592.3	139 (46.5%)	96.5
Eastern Europe	164 (10.3%)	163.8	12 (4.0%)	15.4
Latin America	34 (2.1%)	25.4	0	0
Asia	72 (4.5%)	93.9	14 (4.7%)	16.3
Australia/New Zealand	98 (6.1%)	97.4	27 (9.0%)	16.8

Source: ATHENA-MONO Integrated safety summary (ISS), Table 2.4. Final data used for CO-338-010 (20 May 2019). Data cutoffs of 01 Feb 2019 (CO-338-017), 31 Dec 2019 (CO-338-014), 30 Sep 2020 (CO-338-043), 23 Mar 2022 (CO-338-087 [ATHENA-MONO]).

Exposure in Special Populations

Studies CO-338-010, CO-338-017, CO-338-014 (ARIEL3), CO-338-043 (ARIEL4), and CO-338-087 (ATHENA-MONO) excluded the enrolment of patients with pre-existing moderate to severe hepatic or renal impairment. The inclusion criteria for Studies CO-338-010, CO-338-017, CO-338-014 (ARIEL3), and CO-338-043 (ARIEL4) specified that for hepatic function, AST and ALT ≤ 3 × upper limit of normal (ULN) (if liver metastases, then ≤ 5 × ULN) (AST and ALT ≤ 1.5 x ULN in ATHENA-MONO); and bilirubin ≤ 1.5 × ULN (< 2 × ULN if hyperbilirubinaemia was due to Gilbert's syndrome) were required. For renal function, serum creatinine ≤ 1.5 × ULN was specified. In accordance with the National Cancer Institute (NCI) Organ Dysfunction Working Group (ODWG) criteria,[34] mild hepatic impairment is defined as AST > ULN with total bilirubin ≤ ULN or any AST level with total bilirubin > 1.0-1.5 × ULN. Renal impairment is defined according to European Medicines Agency (EMA)-specified renal impairment classifications: normal (creatinine clearance (CLcr ≥ 90 mL/min), mild (CLcr 60-89 mL/min), and moderate impairment (CLcr 30 to 59 mL/min). Study CO-338-078 (Part 1) included 8 patients with moderate hepatic impairment.

Table 8. Exposure by Hepatic and Renal Impairment (Safety Population, Studies CO-338-010, CO-338-017, CO-338-014, CO-338-043, and CO-338-087 [ATHENA-MONO])

	Rucaparib (N=1594)		Placebo (N=299)	
Hepatic Impairment	**Persons**	**Person Time (Years)**	**Persons**	**Person Time (Years)**
No Impairment	1486 (93.2%)	1459.4	289 (96.7%)	210.6
Mild	108 (6.8%)	61.8	10 (3.3%)	7.0
Renal Impairment				
No Impairment	653 (41.0%)	680.3	133 (44.5%)	97.8
Mild	656 (41.2%)	607.4	123 (41.1%)	88.3
Moderate	285 (17.9%)	233.6	43 (14.4%)	31.4

Source: ATHENA-MONO Integrated safety summary (ISS), Table 2.5. Final data used for CO-338-010 (20 May 2019). Data cutoffs of 01 Feb 2019 (CO-338-017, 31 Dec 2019 (CO-338-014), 30 Sep 2020 (CO-338-043), 23 Mar 2022 (CO-338-087 [ATHENA-MONO]).), 31 Dec 2019

Exposure by BRCA Mutation Status

Exposure by BRCA mutation status for patients with ovarian cancer is presented below.

Table 9. Exposure by BRCA Mutation Status (Safety Population, Studies CO-338-010, CO-338-017, CO-338-014, CO-338-043, and CO-338-087 [ATHENA-MONO])

	Rucaparib (N=1594)		Placebo (N=299)	
BRCA Mutation Status	**Persons**	**Person Time (Years)**	**Persons**	**Person Time (Years)**
Germline BRCA	469 (29.4%)	486.7	61 (20.4%)	45.9
Somatic BRCA	151 (9.5%)	195.4	24 (8.0%)	21.6
BRCA germline/somatic status unknown	57 (3.6%)	79.1	13 (4.3%)	8.3
Non-BRCA	917 (57.5%)	760.1	201 (67.2%)	141.7
Ovarian Cancer Overall	1594 (100.0%)	1521.2	299 (100.0%)	217.6

Source: ATHENA-MONO Integrated safety summary (ISS), Table 2.6. Final data used for CO-338-010 (20 May 2019). Data cutoffs of 01 Feb 2019 (CO-338-017), 31 Dec 2019 (CO-338-014), 30 Sep 2020 (CO-338-043), 23 Mar 2022 (CO-338-087 [ATHENA-MONO]).

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
History or active second malignancy	Residual effects of prior therapy could influence the interpretation of the study data, and there may be increased risk associated with study participation.	No	MDS/AML and new primary malignancy are important potential risks
Prior treatment with a PARP inhibitor (excluding iniparib)	Residual effects of prior therapy could influence the interpretation of the study data.	No	Use in this population is not predicted to be associated with additional risks of clinical significance
Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, or history of chronic hepatitis B or C	Concomitant conditions such as these could influence the interpretation of the study data. In addition, the effect of PARP inhibition on these diseases is not known.	No	Use in this population is not predicted to be associated with additional risks of clinical significance
Patients with untreated or symptomatic CNS metastases. Patients with asymptomatic CNS metastases that had been clinically unstable within the past 4 weeks.	Concomitant conditions such as these could influence the interpretation of the study data.	No	Use in this population is not predicted to be associated with additional risks of clinical significance
Treatment with prohibited medication or radiation ≤ 14 days prior to treatment with rucaparib	Use of certain systemic therapies could influence the interpretation of the study data.	No	Use in this population is not predicted to be associated with additional risks of clinical significance
Received administration of strong CYP1A2 or CYP3A4 inhibitors ≤7 days prior to first dose of study drug or have on-going requirements for these medications	Although in vitro rucaparib metabolism mediated by CYP3A4 was slow, a significant contribution of CYP3A4 in vivo cannot be excluded. Caution should be used for concomitant use of strong CYP3A4 inhibitors or inducers.	No	The SmPC states that enzymes responsible for rucaparib metabolism have not been identified. Based on in vitro data, CYP2D6, and to a lesser extent CYP1A2 and CYP3A4, were able to metabolize rucaparib. Although in vitro rucaparib metabolism mediated by CYP3A4 was slow, a significant contribution of CYP3A4 in vivo cannot be excluded.

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
			Use in this population is not predicted to be associated with additional risks of clinical significance
Minor surgical procedures ≤ 5 days or major surgical procedure ≤ 21 days prior to administration of rucaparib	Recovery or secondary effects from surgical procedures could influence interpretation of the study data.	No	Use in this population is not predicted to be associated with additional risks of clinical significance
Pre-existing duodenal stent and/or any GI disorder or defect, abnormality or surgery that could interfere with absorption	Concomitant conditions such as these could influence the interpretation of the study data.	No	Use in this population is not predicted to be associated with additional risks of clinical significance
Females who are pregnant or breast-feeding	There are no adequate and well controlled studies in pregnant women using rucaparib. There are no data pertaining to the effects of rucaparib during pregnancy and breast-feeding.	No	Embryotoxicity and teratogenicity are important potential risks
Presence of any serious or unstable concomitant systemic disorder incompatible with the clinical study.	Concomitant disorders such as these could influence interpretation of the study data.	No	Use in this population is not predicted to be associated with additional risks of clinical significance
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 randomisation to maintenance treatment in this study.	Recovery or secondary effects from the procedure could influence interpretation of the study data.	No	Use in this population is not predicted to be associated with additional risks of clinical significance
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 > 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.	Prior therapy could influence the interpretation of the study data.	No	Use in this population is not predicted to be associated with additional risks of clinical significance

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

In Studies CO-338-010 and CO-338-017, a total of 565 patients were exposed to rucaparib, in Study CO-338-014 (ARIEL3), a total of 372 were exposed to rucaparib, in Study CO-338-043 (ARIEL4), a total of 232 were exposed to rucaparib, and in Study CO-338-087 (ATHENA-MONO), a total of 425 patients were exposed to rucaparib.

Overall, with exposure of a total of 1,594 patients, ADRs with a frequency of between 1/100 to 1/1000 (ie, uncommon) could be detected.

Overall, in the Pooled Ovarian Cancer Safety Population (Studies CO-338-010, CO-338-017, CO-338-014, CO-338-043, and CO-338-087 [ATHENA-MONO]), 368 (23.1%) patients who were exposed to rucaparib had a duration of exposure of at least 18 months corresponding to a person time of 552.0 years. A total of 243 (15.2%), 91 (5.7%), and 71 (4.5%) patients were exposed for at least 24, 30, and 36 months, respectively, corresponding to person time of 486.0, 227.5 and 213.0 years, respectively.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 10. Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Paediatric population	Not included in the clinical development programme
Pregnant women	Not included in the clinical development programme
Breastfeeding women	Not included in the clinical development programme
Patients with hepatic impairment	In the Pooled Ovarian Cancer Safety Population, 108 (6.8%) patients who were exposed to rucaparib had mild hepatic impairment. Patients with moderate (defined as any ALT/AST level and total bilirubin > 1.5-3 × ULN) or severe hepatic impairment (defined as any ALT/AST level and total bilirubin > 3 × ULN) were not included in the clinical development. Study CO-338-078 (Part 1) included 8 patients with moderate hepatic impairment.
Patients with renal impairment	Among the patients in the Pooled Ovarian Cancer Safety Population who received rucaparib, there were 653 (41.0%) patients with no renal impairment, 656 (41.2%) with mild renal impairment, and 285 (17.9%) with moderate renal impairment. No patients with severe renal impairment or on dialysis were enrolled in rucaparib trials.
Patients previously treated with olaparib or another PARP Inhibitor	Not included in the clinical development programme
Population with relevant different ethnic origin	In the Pooled Ovarian Cancer Safety Population, the majority of patients who were exposed to rucaparib were White (79.5%). The remaining patients were Other (11.5%) or Unknown (9.0%).
Subpopulations carrying relevant genetic polymorphisms	CYP1A2 and CYP2D6 play a limited role in rucaparib metabolism.

Type of special population	Exposure
Elderly	In the Pooled Ovarian Cancer Safety Population, 454 (28.5%) of the patients who were exposed to rucaparib were 65 to 74 years of age, and 126 (7.9%) patients were 75 years of age or older.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

With the exception of EU, UK, Israel, and Switzerland commercial exposure data, patient exposure from marketing experience is presented by the number of individual patients exposed to Rubraca since the marketing authorisation was granted in the US on 19 December 2016.

For EU territories, Israel, Switzerland, and the UK where Rubraca is commercially available, zr pharma& has entered into agreements with appointed contractual partners who directly distribute Rubraca to patients via a health care provider. In addition, Rubraca is distributed directly to wholesalers or health care providers and exposure data for individual patients is not available. Due to these methods of product distribution for Rubraca, the exposure data are limited to the amount (number of packs) of Rubraca provided to the contractual partners and does not include individual patients exposed to Rubraca. Due to this method of distribution for Rubraca, the exposure data are limited to the amount (number of packs) of Rubraca provided to the contractual partners and does not include individual patients exposed to Rubraca. This contrasts with the US method of distribution, where Rubraca is provided to health care providers and their patients directly using an in-office dispensing pharmacy or a Specialty Pharmacy. As a result, EU and UK commercial Rubraca exposure has been calculated as treatment days.

SV.1.2 Exposure

Cumulative number of patients up to 19 December 2022 who have been exposed worldwide to Rubraca, as well as the number of "treatment days" within the [redacted], are presented in Table 11 and Table 12.

Table 11. Cumulative number of patients exposed to Rubraca (excluding commercial exposure in the [redacted])

Country	Source	No. of patients
[redacted]	Named patient use (NPU)	2
	Rucaparib access program (RAP)	10
	Post Trial Access Management (PTAM)	1
	PTAM	1
	Investigator initiated trials (IITs)[6]	170
	NPU	1
	IIT[6]	56
	RAP	36
	PTAM	3
	PTAM	2
	RAP	49
	Free Of Charge (FOC)	17
	IITs[6]	255
	RAP	22
	PTAM	3
	NPU	40
	IITs[6]	42
	RAP	2
	NPU	1
	NPU	2
	PTAM	1
	PTAM	1
	IITs[6]	52
	RAP	68

Country	Source	No. of patients
[redacted]	PTAM	5
	FOC	6
	NPU	1
	IITs[6]	178
	RAP	185
	NPU	31
	FOC	29
	PTAM	3
	Commercial	7,093
	IITs [6]	650
	NPU	25
Total		**9,043**

[redacted]

Table 12. Cumulative commercial exposure to Rubraca® supplied in the [redacted]

	Cumulative exposure to Rubraca		
[redacted]	**200 mg**	**250 mg**	**300 mg**
No. of Rubraca packs sold	4,016	4,468	10,115
No. of tablets sold (mg) (Each pack of Rubraca contains 60 tablets)	240,960	268,080	606,900
Amount of Rubraca sold (mg)	48,192,000	67,020,000	182,070,000
Total amount of Rubraca sold (mg)	= 48,192,000 mg + 67,020,000 mg + 182,070,000 mg = 297,282,000 mg		
Total no. of treatment days (Rubraca daily dosage: 1200 mg[b])	= 297,282,000 mg / 1,200 mg **= 247,735 treatment days[a]**		
	Cumulative		
[redacted]	**200 mg**	**250 mg**	**300 mg**
No. of Rubraca packs sold	902	1,079	5,305
No. of tablets sold (mg) (Each pack of Rubraca contains 60 tablets)	54,120	64,740	318,300
Amount of Rubraca sold (mg)	10,824,000	16,185,000	95,490,000
Total amount of Rubraca sold (mg)	= 10,824,000 mg + 16,185,000 mg + 95,490,000 mg = 122,499,000 mg		
Total no. of treatment days (Rubraca daily dosage: 1200 mg[b])	= 122,499,000 mg / 1,200 mg **= 102,082.5 treatment days[a]**		
	Cumulative		
[redacted]	**200 mg**	**250 mg**	**300 mg**
No. of Rubraca packs sold	932	1,594	6,411
No. of tablets sold (mg) (Each pack of Rubraca contains 60 tablets)	55,920	95,640	384,660
Amount of Rubraca sold (mg)	11,184,000	23,910,000	115,398,000
Total amount of Rubraca sold (mg)	= 11,184,000 mg + 23,910,000 mg + 115,398,000 mg = 150,492,000 mg		
Total no. of treatment days (Rubraca daily dosage: 1200 mg[b])	= 150,492,000 mg / 1,200 mg **= 125,410 treatment days[a]**		
	Cumulative		
[redacted]	**200 mg**	**250 mg**	**300 mg**

	Cumulative exposure to Rubraca		
No. of Rubraca packs sold	892	926	2,481
No. of tablets sold (mg) (Each pack of Rubraca contains 60 tablets)	53,520	55,560	148,860
Amount of Rubraca sold (mg)	10,704,000	13,890,000	44,658,000
Total amount of Rubraca sold (mg)	= 10,704,000 mg + 13,890,000 mg + 44,658,000 mg = 69,252,000 mg		
Total no. of treatment days (Rubraca daily dosage: 1200 mg[b])	= 69,252,000 mg / 1,200 mg **= 57,710 treatment days[a]**		
	Cumulative		
[redacted]	**200 mg**	**250 mg**	**300 mg**
No. of Rubraca packs sold	139	247	687
No. of tablets sold (mg) (Each pack of Rubraca contains 60 tablets)	8,340	14,820	41,220
Amount of Rubraca sold (mg)	1,668,000	3,705,000	12,366,000
Total amount of Rubraca sold (mg)	= 1,668,000 mg + 3,705,000 mg + 12,366,000 = 17,739,000 mg		
Total no. of treatment days (Rubraca daily dosage: 1200 mg[b])	= 17,739,000 mg / 1,200 mg **= 14,782.5 treatment days[a]**		
	Cumulative		
[redacted]	**200 mg**	**250 mg**	**300 mg**
No. of Rubraca packs sold	1,938	1,874	4,928
No. of tablets sold (mg) (Each pack of Rubraca contains 60 tablets)	116,280	112,440	295,680
Amount of Rubraca sold (mg)	23,256,000	28,110,000	88,704,000
Total amount of Rubraca sold (mg)	= 23,256,000 mg + 28,110,000 mg + 88,704,000 mg = 140,070,000 mg		
Total no. of treatment days (Rubraca daily dosage: 1200 mg[b])	= 140,070,000 mg / 1,200 mg **= 116,725 treatment days[a]**		
[redacted]	**200 mg**	**250 mg**	**300 mg**
No. of Rubraca packs sold	--	1	35
No. of tablets sold (mg) (Each pack of Rubraca contains 60 tablets)	--	60	2,100
Amount of Rubraca sold (mg)	--	15,000	630,000
Total amount of Rubraca sold (mg)	= 15,000 mg + 630,000 mg = 645,000 mg		
Total no. of treatment days (Rubraca daily dosage: 1200 mg[b])	= 645,000 mg / 1,200 mg **= 537.5 treatment days[a]**		
[redacted]	**200 mg**	**250 mg**	**300 mg**
No. of Rubraca packs sold	16	--	44
No. of tablets sold (mg) (Each pack of Rubraca contains 60 tablets)	960	--	2,640
Amount of Rubraca sold (mg)	192,000	--	792,000
Total amount of Rubraca sold (mg)	= 192,000 mg + 792,000 mg = 984,000 mg		
Total no. of treatment days (Rubraca daily dosage: 1200 mg[b])	= 984,000 mg / 1,200 mg **= 820 treatment days[a]**		

[a] Due to the data recorded being limited to the number of Rubraca packs distributed, [redacted] commercial exposure is calculated as the number of treatment days. Individual patient exposure data was not available.

[b] Total daily dosage of 1200 mg is provided within the approved EU SmPC at 600 mg BID.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes
Given the pharmacological class of rucaparib and the absence of psychotropic effects, there is no expected potential for drug abuse and the potential for misuse for illegal purposes is low.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission
The below list of safety concerns is considered the "initial submission" and is locked moving forward.

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Risk	Reason not considered an important risk
Metabolism and nutrition disorders Very common: Decreased appetite, Increased blood creatinine Common: Hypercholesterolaemia, Dehydration	The clinical impact of these risks on patients is considered minimal in relation to the severity of the indication
Nervous system disorders Very common: Dysgeusia, Dizziness	
Respiratory, thoracic and mediastinal disorders Common: Dyspnoea	
GI disorders Very common: Diarrhoea, Dyspepsia, Abdominal pain	
Hepatobiliary disorders Very common: Increased ALT, Increased AST Common: Increased transaminases	
Skin and subcutaneous tissue disorders Very common: Rash Common: Rash maculo-papular, Palmar-plantar erythrodysaesthesia syndrome, Erythema	
General disorders and administration site conditions Very common: Fatigue, Pyrexia	
DDI with substrates of CYP1A2, CYP2C9, and CYP3A with a narrow therapeutic index	

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP
Important Identified Risk 1: Myelosuppression
Risk-benefit impact: Myelosuppression was a common ADR; however, the rate of serious myelosuppression was low. Myelosuppression can be managed with routine medical care and/or dose interruption and/or dose reductions for more severe cases. The risk of myelosuppression can be serious and potentially life-threatening, and proper monitoring and treatment is required to minimise the risk of the consequences of myelosuppression and to ensure an acceptable risk-benefit balance.

Important Identified Risk 2: Nausea and vomiting
Risk-benefit impact: Nausea and vomiting were the most common ADR; however, the rate of serious nausea and vomiting was low. Nausea and vomiting can be managed with routine medical care and/or dose interruption and/or dose reductions or antiemetics for more severe cases. Nausea/vomiting for a prolonged duration can be a serious condition and it may result in malnutrition and electrolyte disturbances and thus proper treatment is required to minimise the risk and its consequences and to ensure an acceptable risk-benefit balance.

Important Potential Risk 1: MDS/AML
Risk-benefit impact: During clinical development, there were a few events of MDS/AML; however, there is insufficient scientific evidence to conclude that MDS and AML were causally related to rucaparib treatment. 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. This potential risk will be further evaluated in the post-marketing period.

Important Potential Risk 2: New primary malignancy
Risk-benefit impact: During clinical development, there were a few events of new primary malignancy; however, most of them were deemed not related to rucaparib. This potential risk will be further evaluated in the post-marketing period.

Important Potential Risk 3: QTc interval prolongation
Risk-benefit impact: During clinical development, there were a few events that were associated with QT prolongation but all were confounded by other factors. This potential risk will be further evaluated in the post-marketing period.

Important Potential Risk 4: Photosensitivity
Risk-benefit impact: Events of photosensitivity were reported in 11-21% of the patients. Patients should avoid spending time in direct sunlight because they may burn more easily during rucaparib treatment; when outdoors, patients should wear a hat and protective clothing, and use sunscreen and lip balm with sun protection factor (SPF) of 50 or greater. This risk will be further evaluated in the post-marketing period.

Important Potential Risk 5: Embryotoxicity and teratogenicity
Risk-benefit impact: Rubraca can cause foetal harm when administered to a pregnant woman based on its mechanism of action and findings from animal studies. No cases were reported during the clinical development programme and the risk will be further evaluated in the post-marketing period.

Important Potential Risk 6: DDI with metformin, DDI with substrates of BCRP, e.g., rosuvastatin
Risk-benefit impact: Rucaparib is a potent inhibitor of MATE 1 and MATE2-K, a moderate inhibitor of OCT1, and a weak inhibitor of OCT2. As inhibition of these transporters could decrease metformin renal elimination and decrease liver uptake of metformin, caution is advised when metformin is co-administered with rucaparib. In addition, rucaparib is an inhibitor of the BCRP with IC_{50} value suggesting potential BCRP inhibition and increased exposures of medicinal products that are BCRP substrate (e.g., rosuvastatin). This risk will be further evaluated in, a Phase 1, open label, DDI study to determine the impact of rucaparib on PK of oral rosuvastatin patients with advanced solid tumours (Study CO-338-095 Arm A).

Missing information 1: Use in patients for longer than 18 months
Risk-benefit impact: In the safety population in Studies CO-338-010 and CO 338 017, 52 (9.2%) patients had duration of exposure of at least 18 months. Only 25 (4.4%) and 13 (2.3%) of the patients were exposed for at least 24 and 30 months, respectively. In Study CO-338-014 (ARIEL3) 93 (25.0%) patients that were exposed to rucaparib had duration of exposure of at least 18 months corresponding to a person time of 139.5 years. Sixty-four (17.2%) and 31 (8.3%) patients were exposed for at least 24 and 30 months, respectively. The risks of long-term exposure (longer than 18 months) cannot be defined and thus the safety profile for this population will be derived from routine and additional pharmacovigilance activities.

Missing information 2: Effects of rucaparib on fertility
Risk-benefit impact: There are no data on the effect of rucaparib on human fertility. The effects of rucaparib on fertility cannot be defined based on available evidence and thus the safety profile will be derived from routine pharmacovigilance activities.

Missing information 3: The effect on an infant of a nursing mother receiving rucaparib
Risk-benefit impact: Lactating women were excluded from enrolment in the clinical development programme. The risk to an infant of a nursing mother receiving rucaparib cannot be defined based on available evidence and thus the safety profile in this population will be derived from routine pharmacovigilance activities.

Missing information 4: Safety in patients with severe renal impairment
Risk-benefit impact: Rucaparib has not been evaluated in patients with severe renal impairment. Rucaparib may only be used in patients with severe renal impairment if the benefit outweighs the potential risk, in which case the patient should be carefully monitored for renal function and adverse reactions. The risk of use in patients with severe renal impairment cannot be defined based on available evidence and thus the safety profile in this population will be derived from routine pharmacovigilance activities.

Missing information 5: Safety in patients with moderate or severe hepatic impairment
Risk-benefit impact: Rucaparib has not been evaluated in patients with moderate or severe hepatic impairment. The risk of use in patients with moderate and severe hepatic impairment cannot be defined based on available evidence and thus the safety profile in this population will be derived from routine pharmacovigilance activities and 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 (Study CO-338-078).

Missing information 6: Characterisation of metabolites of rucaparib
Risk-benefit impact: The metabolites of rucaparib are not fully known. The characterisation of rucaparib's metabolites, and enzymes responsible for the metabolism is ongoing. The effect of strong CYP3A4 inhibitors and inducers on rucaparib PK is not available.

Missing information 7: DDI with oral contraceptives
Risk-benefit impact: Interactions between rucaparib and oral contraceptives and BCRP substrates have not been studied. Results from Study CO-338-044 suggest that steady state rucaparib is likely to have a limited impact on the exposure of oral contraceptives. DDI with oral contraceptives cannot be defined based on available evidence. A Phase 1, open label, DDI study is planned to determine the impact of rucaparib on PK of oral contraceptives in female patients with advanced solid tumours (Study CO-338-095 Arm B).

Missing information 8: Efficacy and safety of rucaparib in patients previously treated with olaparib or another PARP inhibitor
Risk-benefit impact: Patients who received prior treatment with a PARP inhibitor were excluded from the clinical development programme. Efficacy and safety of rucaparib in patients previously treated with olaparib or another PARP inhibitor cannot be defined based on available evidence and thus the safety profile in this population will be derived from routine pharmacovigilance activities.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Myelodysplastic syndrome (MDS)/Acute myeloid leukaemia (AML) previously classified as an important potential risk is to be reclassified as important identified risk. In conclusion of PSUSA/00010694/202206 procedure, given that the risk is listed as an ADR in the SmPC and considering that MDS/AML is an identified risk in the RMPs for olaparib and niraparib, the MAH was recommended by PRAC to reclassify MDS/AML as an important identified risk.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

Important Identified Risk 1: Myelodysplastic syndrome (MDS)/Acute myeloid leukaemia (AML)
Medical Dictionary for Regulatory Activities (MedDRA) Terms: Preferred Term (PTs) from the High Level Term (HLT) Leukaemias acute myeloid: Acute myeloid leukaemia, and Acute myeloid leukaemia recurrent (current MedDRA Version) PTs from the HLT Myelodysplastic syndromes: 5q minus syndrome, Chronic myelomonocytic leukaemia, Chronic myelomonocytic leukaemia (in remission), Myelodysplastic syndrome, Myelodysplastic syndrome transformation, Myelodysplastic syndrome unclassifiable, Myelodysplastic syndrome with an excess of blasts, Myelodysplastic syndrome with ringed sideroblasts, Myelodysplastic syndrome with multilineage dysplasia, and Myelodysplastic syndrome with unilineage dysplasia (current MedDRA Version).
Potential mechanisms: The mechanism(s) contributing to or driving the occurrence of secondary malignancies have not been identified. It is possible that DNA-repair deficiencies resulting from PARP inhibition and/or BRCA mutations may be involved; however, patients with relapsed ovarian cancer have typically been heavily pretreated with cytotoxic chemotherapy which makes it difficult to determine the causality of secondary malignancies.
Evidence source(s) and strength of evidence: During clinical development, some events of MDS/AML were reported. However, there is insufficient scientific evidence to conclude that the cases of MDS and AML were causally related to rucaparib. MDS/AML is serious, potentially life-threatening and would require medical intervention and hence it is an important potential risk.
Characterisation of the risk: ***Frequency*** **Clinical (cumulative up to DLP of 30 May 2023)** Analysis of events that occurred on or after rucaparib treatment and had an onset date on or prior to 30 May 2023 showed that in a total of approximately 3,025 patients treated with oral rucaparib (includes the number of patients who received rucaparib in ongoing studies as well as completed studies, but excluding IITs), there were 38 patients (1.2%) who developed MDS or AML (including MDS transforming into AML), including long-term follow-up. These included: • Study CO-338-010 (N=2): two patients with MDS; • ARIEL3 (N=14): five patients with MDS, including refractory anaemia with excess blasts; five patients AML, and four patients with MDS transforming into AML; • ARIEL2 (N=7): five patients with MDS and two patients with AML; • ARIEL4 (N=7): six patients with MDS and one patient with AML; • ATHENA (N=8): two patients with MDS and two patients with AML in ATHENA-MONO and two patients with MDS and two patients with AML in ATHENA-COMBO (treatment blinded). For these 38 patients, the duration of rucaparib treatment prior to the diagnosis of MDS/AML ranged from 1.9 months to approximately 71.9 months. Fifteen patients (two patients from Study CO-338-010, two patients from ARIEL2, six patients from ARIEL3, three patients from ARIEL4, and two patients from ATHENA-MONO) had an event with an onset during treatment or during the 28-day safety follow up. Six placebo-treated patients in ARIEL3 developed MDS (n = 5) or AML (n = 1) more than 28 days after discontinuing placebo.

Important Identified Risk 1: Myelodysplastic syndrome (MDS)/Acute myeloid leukaemia (AML)

Events of MDS/AML were typically considered treatment related in patients who had received rucaparib, often due to the inability to rule out rucaparib as a contributing factor (due to temporal association or the knowledge of the occurrence of MDS/AML in other PARP inhibitor treated patients). However, causality assessment is confounded by factors such as history of prior platinum-based chemotherapy, also known to be associated with MDS/AML.

All of the patients diagnosed with MDS or AML had received prior chemotherapy, and many patients received multiple platinum- and/or taxane-containing regimens. Treatment with chemotherapy could be considered an alternative aetiology to the events.

Post-marketing experience (cumulative up to DLP of 30 May 2023)

From the time of first launch of Rubraca in the US on 19 December 2016 to the DLP of 30 May 2023, there were 31 cases reporting 36 serious events that included 14 events of MDS, including one of MDS with excess blasts, and 13 events of AML.

Severity and Nature of Risk:

Depending on the subtype of MDS the disease can range from mild to severe. About a third of patients with MDS develop AML. Based on the International Prognostic Scoring System median survival ranges from 5 months to 5.7 years.[49]

Risk factors and risk groups:

Therapy-related myeloid leukaemia and MDS are recognised complications of cytotoxic therapy.[27] Therapy-related leukaemia is a complication of chemoradiotherapy used to treat a variety of primary malignancies including ovarian cancer.[50] Travis et al reported a case-control study of secondary leukaemia in a population-based cohort in North America and Europe. Between 1980 and 1993, 28,971 patients with invasive ovarian cancer were followed.[28] It was concluded that platinum-based treatment increases the risk of secondary leukaemia in patients with ovarian cancer. Among the patients who received platinum-based combination chemotherapy, the relative risk (RR) of leukaemia was 4.0 (95% CI, 1.4-11.4).

In a Danish study of newly diagnosed ovarian cancer cases between 2000 and 2011, any other concomitant cancer was the most prevalent co-morbidity, registered in 7.9% (121) of the ovarian cancer patients.[22]

In the placebo arm of a randomised, Phase 3 maintenance study of niraparib in patients who had received two or more previous lines of cytotoxic chemotherapy, MDS/AML occurred in 1.2% of patients.[51,52]

The majority of patients with AML and MDS are elderly. Based on data from the Haematological Malignancy Research Network, in a cohort of patients with a newly diagnosed haematological malignancy, between 2004 and 2009, the median age at diagnosis for AML and MDS was 68.7 and 76.1 years, respectively. These diseases are more common in men. The sex-rate ratio (male/female) for AML and MDS was 1.25 (95% CI, 1.07–1.45) and 2.09 (95% CI, 1.78–2.48), respectively.[53]

Obesity is a risk factor for AML. In a meta-analysis of prospective cohort studies, seven studies reported on the correlation between AML and body mass index (BMI). Obesity was associated with a significantly increased incidence of AML (RR = 1.53; 95% CI, 1.26–1.85; $p < 0.001$).[54]

There were 5 treatment-emergent adverse events (TEAEs) leading to death in the tBRCA population treated with rucaparib. Of these, 4 occurred in the gBRCA group and 1 occurred in a patient for whom the germline/somatic status was unknown. Three of these TEAEs were assessed as not related to rucaparib, including 2 of the TEAEs (malignant neoplasm progression [n=1] and cardiac arrest [n=1]) within the germline subgroup and 1 TEAE (histiocytosis haematophagic) within the germline/somatic unknown group.

Within the gBRCA group, there were TEAEs of AML and MDS that led to death (n=1 each). Both patients had received multiple regimens and cycles of prior chemotherapy, including platinum- and/or taxane-containing regimens.

While there appeared to be a difference within the gBRCA population as compared to those with somatic or unknown germline/somatic BRCA status, the TEAEs leading to death were either assessed

Important Identified Risk 1: Myelodysplastic syndrome (MDS)/Acute myeloid leukaemia (AML)
as unrelated to rucaparib or, for the TEAEs of MDS and AML, the causality was confounded by the exposure to prior chemotherapy. Despite the very small number of patients involved, it remains possible/plausible that patients with gBRCA mutations are more likely to develop (fatal) haematological malignancies.
Preventability: Section 4.4 of the SmPC advises that 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 < 2 months to approximately 6 years. 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. Section 4.8 of the SmPC advises that 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 (1.1%) for all patients including during the long-term safety follow up (rate is calculated based on overall safety population of 3,025 patients exposed to at least one dose of oral rucaparib in all clinical studies). In the placebo-controlled Phase 3 studies, ARIEL3 and ATHENA-MONO, the incidence of MDS/AML during therapy in patients who received rucaparib was 1.6% and 0.5%, respectively. Although no cases were reported during therapy in patients who received placebo, six cases have been reported in placebo-treated patients 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.
Impact on the risk-benefit balance of the product: Routine pharmacovigilance activities will further characterise the risk of MDS/AML with respect to number of reports, seriousness, outcome, and risk factors and that the data are consistent with the information already known for this risk. Routine risk minimisation will be used to communicate information regarding this potential risk.
Public health impact: Minimal impact due to the rarity of the risk.

Important Potential Risk 1: New primary malignancy
MedDRA Terms: System organ class (SOC) of Neoplasms benign, malignant and unspecified (including cysts and polyps)
Potential mechanisms: The increased concentration of DNA damage marker in tissues of patients treated with PARP inhibitors implies an accumulation of double strand breaks in normal tissues that could lead to an increased risk of cancer secondary to DNA damage. [55] PARP inhibition impairs the ability of cells to repair DNA single strand breaks and, in cells that have a deficient homologous recombination pathway, this leads to the accumulation of un-repaired double strand breaks that eventually cause the death of the target cell. Although normal cells are expected to repair the double strand breaks induced by inhibiting PARP, there is a risk of increased breaks in all dividing cells which may contribute to development of new primary malignancies.
Evidence source(s) and strength of evidence: Secondary malignancy is consistent with the known outcomes of immunosuppression resulting from chemotherapy. During clinical development, some events of new primary malignancy were reported. However, these events were either deemed not related to rucaparib or there were confounding factors such as other chemotherapy agents. New primary malignancy is serious, potentially life-threatening and would require medical intervention and hence it is an important potential risk.

Important Potential Risk 1: New primary malignancy

Characterisation of the risk:

Clinical (cumulative up to DLP of 30 May 2023)

Cumulatively up to 30 May 2023, there have been 26 serious cases of new primary malignancies in approximately 3,025 patients (approximately 0.8%) who received oral rucaparib in clinical trials, including 4 blinded cases.

PT	Number of events
Acute leukaemia	1
Acute lymphocytic leukaemia	1
Adenocarcinoma of colon	1
Adenocarcinoma of pancreas	1
Basal cell carcinoma	2
B-cell type acute leukaemia	1
B-cell unclassifiable lymphoma high grade	1
Chronic lymphocytic leukaemia	2
Chronic myeloid leukaemia	1
Clear cell renal cell carcinoma	1
Intraductal proliferative breast lesion	1
Lung neoplasm malignant	1
Malignant melanoma	3
Malignant neoplasm of eyelid	1
Nodular melanoma	1
Pancreatic neuroendocrine tumour	1
Papillary thyroid cancer	1
Second primary malignancy	2
Squamous cell carcinoma of skin	2
T-cell lymphoma	1
Total	**26**

Serious adverse event (SAE) Outcomes

	SAE Outcome					
PT	**Fatal**	**Not Recovered/ Not Resolved**	**Recovered/ Resolved**	**Recovered / Resolved with Sequelae**	**Recovering/ Resolving**	**Total**
Acute leukaemia	1					**1**
Acute lymphocytic leukaemia	0	1	0	0	0	**1**
Adenocarcinoma of colon	0	1	0	0	0	**1**
Adenocarcinoma pancreas	0	0	1	0	0	**1**
Basal cell carcinoma	0	1	1	0	0	**2**
B-cell type acute leukaemia	1	0	0	0	0	**1**
B-cell unclassifiable lymphoma high grade	1	0	0	0	0	**1**
Chronic lymphocytic leukaemia	0	1	1	0	0	**2**

Important Potential Risk 1: New primary malignancy

Chronic myeloid leukaemia	0	1	0	0	0	**1**
Clear cell renal cell carcinoma	0	0	1	0	0	**1**
Intraductal proliferative breast lesion	0	0	1	0	0	**1**
Lung neoplasm malignant	0	1	0	0	0	**1**
Malignant melanoma	0	1	1	1	0	**3**
Malignant neoplasm of eyelid	0	0	1	0	0	**1**
Nodular melanoma	0	0	1	0	0	**1**
Pancreatic neuroendocrine tumour	0	0	1	0	0	**1**
Papillary thyroid cancer	0	0	0	0	1	**1**
SPM	1	0	1	0	0	**2**
Squamous cell carcinoma of skin	0	1	0	1	0	**2**
T-cell lymphoma	0	0	1	0	0	**1**
Total	**3**	**7**	**11**	**2**	**1**	**26**

Post-marketing experience (cumulative up to DLP of 30 May 2023)

From the time of first launch of Rubraca in the US on 19 December 2016 to the DLP of 30 May 2023, there were 40 cases that reported events of possible new malignancies including Neoplasm malignant (N=4), Leukaemia (N=4), Breast cancer (N=3), Brain neoplasm (N = 3) Hepatic neoplasm (N=2), Neoplasm (N=2), Malignant melanoma (N=2), Bladder cancer (N = 2) and Basal cell carcinoma (N=2). The following events were reported once: Adenocarcinoma of colon, Brain neoplasm, Pelvic neoplasm, Squamous cell carcinoma of lung, Breast neoplasm, Colon cancer , GI neoplasm, Squamous cell carcinoma, Vaginal neoplasm, Squamous cell carcinoma of skin, Abdominal neoplasm, Lymphoma, Lung neoplasm malignant, Lip and/or oral cavity cancer, Thyroid cancer and Papillary thyroid cancer. A paucity of data makes it difficult to determine in some of the cases whether a secondary malignancy or progression of underlying malignancy was being described.

Risk factors and risk groups:
Prior DNA-damaging chemotherapeutic drugs represents a risk factor for development of new malignancies.[55]

Preventability:
None proposed

Impact on the risk-benefit balance of the product:
Routine pharmacovigilance activities will further characterise the risk of new primary malignancy with respect to number of reports, seriousness, outcome, and risk factors and whether experience in the post marketing setting is consistent with the information already known for this risk from clinical trial data. Routine risk minimisation will be used to communicate information regarding this potential risk.

Public health impact:
Minimal impact due to the rarity of the risk.

Important Potential Risk 2: QTc interval prolongation

MedDRA Terms: Standardised MedDRA Queries (SMQ) was Torsade de Points/QT prolongation

Potential mechanisms:
HERG potassium channels allow the rapid component of myocardial repolarisation; when a drug interferes with their function, the potassium inflow decreases leading to prolongation of repolarisation. In the hERG assay, rucaparib had an IC_{50} value that was approximately 13-fold higher than the unbound C_{max} of 1.79 µM in patients treated with 600 mg BID rucaparib.

Important Potential Risk 2: QTc interval prolongation

Evidence source(s) and strength of evidence:
In vitro studies showed that rucaparib at high concentrations may interfere with the activity of the hERG potassium channels and thus has the potential to induce QTc interval prolongation. An open-label single-arm study in 56 patients showed that a clinically significant QTcF increase (ie > 20 msec) over baseline is unlikely following administration of 600 mg BID rucaparib. During clinical development, there were a few events that were associated with the QT prolongation but all were confounded by other factors. QTc interval prolongation is serious, potentially life-threatening event and hence it is an important potential risk.

Characterisation of the risk:
Frequency

Clinical (cumulative up to DLP of 30 May 2023)

Cumulatively up to 30 May 2023, there have been 28 serious cases of QT prolongation, of which 12 were fatal in approximately 3,025 patients (approximately 0.4%) who received oral rucaparib in clinical trials. The event terms are presented below. Electrocardiogram (ECG) confirmation of QT prolongation was not necessarily available in these cases.

PT	Number of events
Cardiac arrest	7
Cardio-respiratory arrest	2
Long QT syndrome congenital	1
Sudden death	1
Syncope	13
Torsade de pointes	1
Ventricular fibrillation	1
Ventricular tachycardia	2
Total	**28**

SAE Outcomes

	SAE Outcome			
PT SAEs	**Fatal**	**Recovered/ Resolved**	**Recovered/ Resolved with Sequelae**	**Total**
Cardiac arrest	7	0	0	**7**
Cardio-respiratory arrest	2	0	0	**2**
Long QT syndrome congenital	0	0	1	**1**
Sudden death	1	0	0	**1**
Syncope	0	10	3	**13**
Torsade de pointes	1	0	0	**1**
Ventricular fibrillation	1	0	0	**1**
Ventricular tachycardia	0	2	0	**2**
Total	**12**	**12**	**3**	**28**

Post-marketing experience (cumulative up to DLP of 30 May 2023)

From the time of first launch of Rubraca in the US on 19 December 2016 to the DLP of 30 May 2023, there were 35 (33 serious and two non-serious) cases that reported 37 events of interest including Loss of consciousness (N=19), Syncope (N=12), Electrocardiogram QT prolonged (N=3), Cardiac arrest

Important Potential Risk 2: QTc interval prolongation
(N=1), Ventricular tachycardia (N=1) and Cardio-respiratory arrest (N=1). Events of Loss of consciousness, Syncope, Cardiac arrest, Ventricular tachycardia, and Cardio-respiratory arrest had numerous alternative causes and there was no evidence for an association with QTc prolongation. The review of post marketing safety data has not raised any additional safety concerns.
Risk factors and risk groups: Patients with certain congenital and or acquired cardiac abnormalities may be at risk of QTc prolongation. Additionally, factors that predispose to QT prolongation and higher risk of torsades de pointes include older age, female sex, low left ventricular ejection fraction, left ventricular hypertrophy, ischemia, slow hear rate, and electrolyte abnormalities including hypokalaemia and hypomagnesemia. Certain drugs also predispose to QT prolongation.[56]
Preventability: None
Impact on the risk-benefit balance of the product: Routine pharmacovigilance activities will further characterise the risk of QTc interval prolongation with respect to number of reports, seriousness, outcome, and risk factors and whether experience in the post marketing setting is consistent with the information already known for this risk from clinical trial data. Routine risk minimisation will be used to communicate information regarding this potential risk.
Public health impact: Minimal impact due to the rarity of the risk.

Important Potential Risk 3: Embryotoxicity and teratogenicity
MedDRA Terms: SOC Pregnancy, Puerperium and Perinatal
Potential mechanisms: PARPs promote the repair of DNA single-strand breaks and coordinate cellular responses to stress. Mice deficient for PARP1 or PARP2 are hypersensitive to γ-irradiation and alkylating agents, and demonstrate increased genomic instability with elevated sister chromatid exchanges. $Parp1^{-/-}$ and $Parp2^{-/-}$ mice are viable, however, $Parp1^{-/-}$ $Parp2^{-/-}$ double mutant mice die early in embryogenesis, demonstrating the essential requirement for nuclear poly- ADP-ribosylation during embryogenesis.[58] Effective PARP inhibition with olaparib and veliparib induce genomic instability in all human cells examined, resulting in a marked increase of sister chromatid exchanges frequencies and chromatid-type aberrations.[59]
Evidence source(s) and strength of evidence: There were no reports of embryotoxicity or teratogenicity during clinical development.
Characterisation of the risk: **Clinical (cumulative up to DLP of 30 May 2023)** None **Post-marketing experience (cumulative up to DLP of 30 May 2023)** None
Risk factors and risk groups: Not applicable
Preventability: Rubraca can cause foetal harm when administered to a pregnant woman based on its mechanism of action and findings from animal studies. In an animal reproduction study, administration of rucaparib to pregnant rats during the period of organogenesis resulted in embryo-foetal toxicity at exposures below those in patients receiving the recommended human dose of 600 mg BID (SmPC; Section 4.4). Pregnancy/contraception Pregnant women should be informed of the potential risk to a foetus. Women of reproductive potential should be advised to use effective contraception during treatment and for 6 months following the last dose of Rubraca. A pregnancy test before initiating treatment is recommended in women of reproductive potential (SmPC; Section 4.4).

Important Potential Risk 3: Embryotoxicity and teratogenicity
Women of childbearing potential should be advised to avoid becoming pregnant while receiving rucaparib. Patients should be advised to use effective contraception during treatment and for 6 months following the last dose of rucaparib. A pregnancy test before initiating treatment is recommended in women of reproductive potential (SmPC; Section 4.6). Pregnancy There are no or limited data from the use of rucaparib in pregnant women. Studies in animals have shown reproductive toxicity. Based on its mechanism of action and preclinical data, rucaparib may cause foetal harm when administered to a pregnant woman. Rubraca should not be used during pregnancy unless the clinical condition of the woman requires treatment with rucaparib (SmPC; Section 4.6).
Impact on the risk-benefit balance of the product: Routine pharmacovigilance activities will further characterise the risk of embryotoxicity and teratogenicity with respect to number of reports, seriousness, outcome, and risk factors. Routine risk minimisation will be used to communicate information regarding this potential risk.
Public health impact: There are limited data on the effects of rucaparib on pregnancy outcomes and embryofoetal toxicity and hence limited ability to assess public health impact.

SVII.3.2 Presentation of the missing information

Missing information 1: Safety in patients with severe renal impairment
Evidence source: Rucaparib has not been evaluated in patients with severe renal impairment or patients on dialysis. **Clinical (cumulative up to DLP of 30 May 2023)** Cumulatively, there were three serious case that could be identified as use in patients with medical history of severe renal impairment, which was retrieved from clinical trials sponsored by zr pharma&. **Post-marketing experience (cumulative up to DLP of 30 May 2023)** Cumulatively, there were six cases that could be identified as use in patients with medical history of severe renal impairment retrieved from post-marketing data. Examination of the cumulative information does not modify the current knowledge regarding this missing information and examination of future data is still required.
Population in need of further characterisation: The risk of use in patients with severe renal impairment or patients on dialysis cannot be defined based on available evidence and thus the safety profile in this population will be derived from routine pharmacovigilance activities.

Missing information 2: Safety in patients with moderate hepatic impairment
Evidence source: **Clinical (cumulative up to DLP of 30 May 2023)** Patients with moderate hepatic impairment enrolled in Study CO-338-078 (Part 1) reported a higher incidence of TEAEs and a higher incidence of events with higher toxicity grades compared to those patients with normal hepatic function. Due to the small sample size and as the safety data were collected following a single dose of rucaparib, the interpretation of the results as related to the safety profile of rucaparib in patients with moderate hepatic impairment is limited. **Post-marketing experience (cumulative up to DLP of 30 May 2023)** Cumulatively, there were no cases that could be identified as use of Rubraca in patients with medical history of moderate hepatic impairment (defined as $7 \leq$ Child-Pugh score ≥ 9).
Population in need of further characterisation:

The risk of use in patients with moderate hepatic impairment cannot be defined based on available evidence and thus the safety profile in this population will be derived from routine pharmacovigilance activities.

Part II: Module SVIII - Summary of the safety concerns

Table 13. Summary of safety concerns

Summary of safety concerns	
Important identified risks	Myelodysplastic syndrome (MDS)/Acute myeloid leukaemia (AML)
Important potential risks	New primary malignancy QTc interval prolongation Embryotoxicity and teratogenicity
Missing information	Safety in patients with severe renal impairment Safety in patients with moderate hepatic impairment

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

The post-authorisation safety profile of rucaparib is evaluated through the routine pharmacovigilance system of the Applicant. Pharmacovigilance activities are fully described in the Pharmacovigilance System Master File.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Description	Purpose
Targeted AE data collection form for MDS/AML	To determine relatedness to rucaparib treatment

III.2 Additional pharmacovigilance activities

None

III.3 Summary Table of additional Pharmacovigilance activities

Table 14. 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				
None				
Category 3 – Required additional pharmacovigilance activities				
None				

Part IV: Plans for post-authorisation efficacy studies

Table 15: Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorisation				
CO-338-087 (ATHENA) Ongoing	Primary: To compare Investigator assessed PFS per RECIST (invPFS) of oral rucaparib as single agent or in combination with intravenous [IV] nivolumab given as maintenance treatment in patients with high-grade epithelial ovarian, primary peritoneal, or fallopian tube cancer who achieved a response to their first platinum-based regimen. Secondary: To evaluate the safety and tolerability, survival benefit and objective response rate (ORR) and duration of response of oral rucaparib as single agent or in combination with IV nivolumab as maintenance treatment in patients with high-grade epithelial ovarian, primary peritoneal, or fallopian tube cancer who achieved a response to their first platinum-based regimen	Investigate the long-term efficacy of rucaparib maintenance treatment in patients with patients with advanced (FIGO Stages III and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy	Final analysis of overall survival when the data is sufficiently mature at approximately 70% of all death events.	Q2 2027
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

V.1 Routine Risk Minimisation Measures

Table 16. Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risk 1: Myelodysplastic syndrome (MDS)/Acute myeloid leukaemia (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*
Important potential risk 1: 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*
Important potential risk 2: QTc interval prolongation	**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*
Important potential risk 3: 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*
Missing information 1: 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*
Missing information 2: Safety in patients with moderate 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*

V.2 Additional Risk Minimisation Measures

None

V.3 Summary of risk minimisation measures

Table 17. Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation activities	Pharmacovigilance activities
Important identified risk 1: Myelodysplastic syndrome (MDS)/Acute myeloid leukaemia (AML)	**Routine risk minimisation measures:** *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**: *None*
Important potential risk 1: New primary malignancy	**Routine risk minimisation measures:** *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**: *None*
Important potential risk 2: QTc interval prolongation	**Routine risk minimisation measures:** *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**: *None*

Safety concern	Risk minimisation activities	Pharmacovigilance activities
Important potential risk 3: Embryotoxicity and teratogenicity	**Routine risk minimisation measures:** *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*
Missing information 1: Safety in patients with severe renal impairment	**Routine risk minimisation measures:** *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 2: Safety in patients with moderate hepatic impairment	**Routine risk minimisation measures:** *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*

Part VI: Summary of the risk management plan

Summary of risk management plan for Rubraca (Rucaparib)

This is a summary of the risk management plan (RMP) for Rubraca. The RMP details important risks of Rubraca, how these risks can be minimised, and how more information will be obtained about Rubraca's risks and uncertainties (missing information).

Rubraca's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Rubraca should be used.

This summary of the RMP for Rubraca should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Rubraca's RMP.

I. The medicine and what it is used for

Rubraca is indicated as:

- monotherapy for the maintenance treatment of adult patients with advanced (FIGO Stages III and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to first-line platinum-based chemotherapy.
- 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. It contains rucaparib as the active substance and it is given by oral administration.

Further information about the evaluation of Rubraca's benefits can be found in Rubraca's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage (https://www.ema.europa.eu/medicines/human/EPAR/rubraca).

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Rubraca, together with measures to minimise such risks and the proposed studies for learning more about Rubraca's risks, are outlined below.
Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.
In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.
If important information that may affect the safe use of Rubraca is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Rubraca are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Rubraca. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Summary of important risks and missing information	
Important identified risks	Myelodysplastic syndrome (MDS)/Acute myeloid leukaemia (AML)
Important potential risks	New primary malignancy

Summary of important risks and missing information	
	QTc interval prolongation Embryotoxicity and teratogenicity
Missing information	Safety in patients with severe renal impairment Safety in patients with moderate hepatic impairment

II.B Summary of important risks

Important identified risk 1: Myelodysplastic syndrome (MDS)/Acute myeloid leukaemia (AML)	
Evidence for linking the risk to the medicine	During clinical development, some events of MDS/AML were reported. However, there is insufficient scientific evidence to conclude that the cases of MDS and AML were causally related to rucaparib. MDS/AML is serious, potentially life-threatening and would require medical intervention and hence it is an important potential risk.
Risk factors and risk groups	Therapy-related myeloid leukaemia and MDS are recognised clinical syndromes, which are complications of cytotoxic therapy.[27] Therapy-related leukaemia is a complication of chemoradiotherapy used to treat a variety of primary malignancies including ovarian cancer.[50] Travis et al reported a case-control study of secondary leukaemia in a population-based cohort in North America and Europe. Between 1980 and 1993, 28,971 patients with invasive ovarian cancer were followed.[28] It was concluded that platinum-based treatment increases the risk of secondary leukaemia in patients with ovarian cancer. Among the patients who received platinum-based combination chemotherapy, the RR of leukaemia was 4.0 (95% CI, 1.4-11.4). In a Danish study of newly diagnosed ovarian cancer cases between 2000 and 2011, any other concomitant cancer was the most prevalent co-morbidity, registered in 7.9% (121) of the ovarian cancer patients.[22] Recently, in the placebo arm of a randomised, Phase 3 maintenance study of niraparib in patients who had received two or more previous lines of cytotoxic chemotherapy, MDS/AML occurred in 1.2% of patients.[51,52] The majority of patients with AML and MDS are elderly. Based on data from the Haematological Malignancy Research Network, in a cohort of patients with a newly diagnosed haematological malignancy, between 2004 and 2009, the median age at diagnosis for AML and MDS was 68.7 and 76.1 years, respectively. These diseases are more common in men. The sex-rate ratio (male/female) for AML and MDS was 1.25 (95% CI, 1.07–1.45) and 2.09 (95% CI, 1.78–2.48), respectively.[53] Obesity is a risk factor for AML. In a meta-analysis of prospective cohort studies, seven studies reported on the correlation between AML and BMI. Obesity was associated with a significantly increased incidence of AML (RR = 1.53; 95% CI, 1.26–1.85; p < 0.001).[54] There were 5 TEAEs leading to death in the tBRCA population treated with rucaparib. Of these, 4 occurred in the gBRCA group and 1 occurred in a patient for whom the germline/somatic status was unknown. Three of these TEAEs were assessed as not related to rucaparib, including 2 of the TEAEs within the germline subgroup (malignant neoplasm progression [n=1] and cardiac arrest [n=1]) and 1 within the germline/somatic unknown group (histiocytosis haematophagic). Within the gBRCA group, there were TEAEs of AML and MDS that led to death (n=1 each). Both patients had received multiple regimens

	and cycles of prior chemotherapy, including platinum- and/or taxane-containing regimens. While there appeared to be a difference within the gBRCA population as compared to those with somatic or unknown germline/somatic BRCA status, the TEAEs leading to death were either assessed as unrelated to rucaparib or, for the TEAEs of MDS and AML, the causality was confounded by the exposure to prior chemotherapy. Despite the very small number of patients involved, it remains possible/plausible that patients with gBRCA mutations are more likely to develop (fatal) haematological malignancies.
Risk minimisation measures	**Routine risk minimisation measures**: *SmPC section: 4.4, 4.8* *PL section: 2* *Prescription only medicine* **Additional risk minimisation measures**: *None*
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: *None*

Important potential risk 1: New primary malignancy	
Evidence for linking the risk to the medicine	Secondary malignancy is consistent with the known outcomes of immunosuppression resulting from chemotherapy. During clinical development, some events of new primary malignancy were reported. However, these events were either deemed not related to rucaparib or there were confounding factors such as other chemotherapy agents. New primary malignancy is serious, potentially life-threatening and would require medical intervention and hence it is an important potential risk.
Risk factors and risk groups	Prior DNA-damaging chemotherapeutic drugs represents a risk factor for development of new malignancies. [55]
Risk minimisation measures	**Routine risk minimisation measures**: *Prescription only medicine* **Additional risk minimisation measures**: *None*
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: *None*

Important potential risk 2: QTc interval prolongation	
Evidence for linking the risk to the medicine	In vitro studies showed that rucaparib at high concentrations may interfere with the activity of the hERG potassium channels and thus has the potential to induce QTc interval prolongation. An open-label single-arm study in 56 patients showed that a clinically significant QTcF increase (ie > 20 msec) over baseline is unlikely following administration of 600 mg BID rucaparib. During clinical development, there were a few events that were associated with the QT prolongation but all were confounded by other factors. QTc interval prolongation is serious, potentially life-threatening event and hence it is an important potential risk.
Risk factors and risk groups	Patients with certain congenital and or acquired cardiac abnormalities may be at risk of QTc prolongation. Additionally, factors that predispose to QT prolongation and higher risk of torsades de pointes include older age, female sex, low left ventricular ejection fraction, left ventricular hypertrophy, ischaemia, slow hear rate, and electrolyte abnormalities including hypokalaemia and hypomagnesemia. Certain drugs also predispose to QT prolongation. [56]
Risk minimisation measures	**Routine risk minimisation measures**: *Prescription only medicine*

	Additional risk minimisation measures: *None*
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: *None*

Important potential risk 3: Embryotoxicity and Teratogenicity	
Evidence for linking the risk to the medicine	There were no reports of embryotoxicity or teratogenicity during clinical development.
Risk factors and risk groups	Not applicable
Risk minimisation measures	**Routine risk minimisation measures**: *SmPC section: 4.4, 5.3* *PL section: 2* *Prescription only medicine* **Additional risk minimisation measures**: *None*
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: *None*

Missing information 1: Safety in patients with severe renal impairment	
Risk minimisation measures	**Routine risk minimisation measures**: *SmPC section: 4.2, 5.2* *Prescription only medicine* **Additional risk minimisation measures**: *None*
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: *None*

Missing information 2: Safety in patients with moderate hepatic impairment	
Risk minimisation measures	**Routine risk minimisation measures**: *SmPC section: 4.2, 5.2* *Prescription only medicine* **Additional risk minimisation measures**: *None*
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: *None*

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

The following studies are conditions of the marketing authorisation:

Study name	Rationale and study objectives
CO-338-087 (ATHENA)	Primary: To compare the anti tumour efficacy of oral rucaparib as single agent or in combination with intravenous [IV] nivolumab, measured by PFS as assessed by Response Evaluation Criteria in Solid Tumors (RECIST), as assessed by the investigator (invPFS), as maintenance treatment in patients with high-grade epithelial ovarian, primary peritoneal, or fallopian tube cancer who achieved a response to their first platinum-based regimen. Secondary: To evaluate the safety and tolerability, survival benefit and objective response rate (ORR) and duration of response of oral rucaparib as

Study name	Rationale and study objectives
	single agent or in combination with IV nivolumab as maintenance treatment in patients with high-grade epithelial ovarian, primary peritoneal, or fallopian tube cancer who achieved a response to their first platinum-based regimen

II.C.2 Other studies in post-authorisation development plan

None

Annex 4 - Specific adverse drug reaction follow-up forms

Target Follow-up Questionnaire: Myelodysplastic syndrome / Acute myeloid leukaemia

Instructions: If a patient develops MDS/AML while on Rubraca®(rucaparib), zr pharma& would like to gather additional medical information as part of ongoing post-marketing pharmacovigilance.

MedInfo AE Ref #: Vendor Ref #:			AE Report #:		Date:	
Health Care Professional (HCP) Name & Address			HCP Signature (if sent via fax):		Telephone #: Email:	
Patient Information	Patients initials		Age:	Sex: ☐M ☐F	Race:	Weight: kg Height: Inches
Drug	Rubraca® (Rucaparib)	Lot number/ control number:	Dose: Frequency:		Indication for use:	Duration: Start Date: End Date:
Discontinued: ☐ Yes Date: ☐ No If YES: Please specify reason:			Was drug restarted:? ☐ Yes ☐ No If YES: Please provide restart date:		If drug was restarted, what was the patient's response?	

Event description including signs/symptoms (continue under "Additional Comments" below if necessary) include diagnosis where available (e.g., MDS, AML, Refractory Anemia with excess blasts, MDS-del5q)

Please provide all treatment details:

Please provide outcome for the event:

Treating HCP assessment:

Adverse event(s) related to Rubraca®? ☐ YES ☐ NO ☐ UNK

Please provide alternate etiology if Not Related to Rubraca®:

Past/Current Medical History	Yes	No	if yes, onset date	Comments Regarding Question
1. Family history of leukemia/lymphoma	☐	☐	N/A	If yes, how related, age of diagnosis & cancer type:
2. Hematological disorder	☐	☐		If yes, describe:
3. Autoimmune disorder	☐	☐		If yes, describe:
4. Chemo/alkylating agents or Radiotherapy exposure or other toxic occupational exposure	☐	☐		If yes, describe:

5. Recent infection (HIV, malaria, viral hepatitis, etc.)	☐	☐		Please specify infection:
6. Other pertinent history that may contribute to the MDS/AML	☐	☐		Please specify:
7. Smoking history	☐	☐		Please specify:
8. Alcohol use	☐	☐		Please specify:

Concomitant medication (include OTC, herbal, etc.)	Indication for Use	Dose/Route	Start Date	End Date

Fill in appropriate laboratory values with DATE, UNITS, and NORMAL LABORATORY VALUES for your institution when applicable:

Lab Data	Date	Normal Range	Baseline at start of Rucaparib use	Nadir (or peak if applicable)	Upon recovery (or current)
Hemoglobin/HCT					
ANC					
Platelets					
Leukocytes					
Neutrophils (%)					
Lymphocytes (%)					
Monocytes (%)					
Hemoglobin/HCT					
Reticulocytes					
Antineutrophil antibodies					
Blood culture:	☐ Not performed ☐ Date performed: ☐ Negative ☐ Positive for:				
Peripheral Blood Smear:	☐ Not performed ☐ Date performed: ☐ Normal ☐ Abnormal (specify):				
Bone marrow aspiration or biopsy: (check all applicable)	☐ Not performed ☐ Aspirate Date: Special stains (if available): _____ ☐ Biopsy Date: Special stains (if available): _____ % blasts: % myeloid cells: Other cell types: Findings:				
Cytogenetic Abnormalities:	☐ Not performed ☐ Date of test: Results (please describe):				

Lab Data	Date	Normal Range	Baseline at start of Rucaparib use	Nadir (or peak if applicable)	Upon recovery (or current)
Coomb's Test (Direct Antiglobulin Test):	☐Not performed ☐Negative ☐Positive (specify):				

Additional Comments and Patient Details

Instructions: Please provide a brief summary on the clinical course of the event of MDS/AML from development of signs/symptoms to diagnosis.

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable