EMADOC-1700519818-2335536
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lynparza

International non-proprietary name: Olaparib

Procedure No. EMA/VR/0000287658

Note

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

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Status of this report and steps taken for the assessment				
Current step	**Description**	**Planned date**	**Actual Date**	**Need for discussion**
☐	Submission deadline	25 Jul 2025	23 Jul 2025	☐
☐	Validation	10 Aug 2025	1 Aug 2025	☐
☐	Start date	11 Aug 2025	11 Aug 2025	☐
☐	CHMP Rapporteur AR	15 Sept 2025	18 Sept 2025	☐
☐	CHMP Comments	29 Sept 2025	29 Sept 2025	☐
☐	Updated CHMP Rapporteur AR	2 Oct 2025	2 Oct 2025	☐
☐	Start of CHMP written procedure	7 Oct 2025	7 Oct 2025	☐
☒	CHMP Outcome	9 Oct 2025	9 Oct 2025	☐

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AstraZeneca AB submitted to the European Medicines Agency on 23 July 2025 an application for a variation.

The following changes were proposed:

Variation(s) requested		Type
C.I.4	C.I.4 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data	Variation type II

Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC in order to add paediatric information based on final results from study D0816C00025. This is a Phase I, Open-label, Parallel Group Study to Investigate Olaparib Safety and Tolerability, Efficacy and Pharmacokinetics in Paediatric Patients with Solid Tumours. In addition, the MAH is taking the opportunity to correct errors in CSR Addendum 1 for Lynparza study D081CC00006 (OlympiA).

The requested variation proposed amendments to the Summary of Product Characteristics.

Information on paediatric requirements

AstraZeneca AB submitted the final Clinical Study Report (CSR) for Lynparza Study D0816C00025, titled 'A Phase I, Open-label, Parallel Group Study to Investigate Olaparib Safety and Tolerability, Efficacy and Pharmacokinetics in Paediatric Patients with Solid Tumours' as a Type II Variation (category C.I.4) to fulfil Article 46 of Regulation (EC) No 1901/2006.

Study D0816C00025 is listed in the Olaparib EU PIP (EMEA-002269-PIP01-17-M03) as Study 2. The study evaluated olaparib as monotherapy in 16 paediatric participants from 6 to < 18 years of age with relapsed or refractory solid or primary CNS tumours (excluding lymphoid malignancies) for whom there are no standard treatment options.

This submission of the paediatric study results is performed in compliance with the paediatric investigation plan (PIP) which does not support a paediatric indication.

2. Overall conclusion and impact on the benefit/risk balance

The safety and efficacy of Lynparza in children and adolescents is not established based on the final results of Study D0816C00025, a Phase I, Open-label, multicentre study to investigate the safety, tolerability, pharmacokinetic, pharmacodynamics and preliminary efficacy of Lynparza monotherapy in paediatric patients from ≥ 6 months to < 18 years with relapsed or refractory solid or primary central nervous system (CNS) tumours (excluding lymphoid malignancies) for whom there were no standard treatment options.

The study enrolled 16 patients aged ≥ 6 years to < 18 years with a homologous recombination repair (HRR) deficiency or HRR gene mutation via local test or gBRCA mutation via central test. Lynparza was administered as a single dose on day 1, followed by twice daily in a continuous schedule. Of the 16 patients enrolled, 13 patients aged ≥ 12 years to < 18 years received 300 mg of olaparib tablet twice daily and 3 patients aged ≥ 6 years to < 12 years received 200 mg of olaparib tablet twice daily until disease progression or unacceptable toxicity.

A total of 12 of 16 patients had measurable disease at baseline. Overall, none of the patients had an objective response (primary endpoint) and no patients had stable disease.

The safety and tolerability profile of olaparib at the doses studied in this peadiatric population is generally consistent with the established safety profile in adults.

These results are included in section 4.2, 4.8, 5.1 and 5.2 of the SmPC.

The benefit-risk balance of Lynparza remains positive in the already approved adult populations only.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation(s) requested		**Type**
C.I.4	C.I.4 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data	Variation type II

Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC in order to add paediatric information based on final results from study D0816C00025, a PIP study and submitted in accordance with Article 46 of Regulation (EC) No 1901/2006. This is a Phase I, Open-label, Parallel Group Study to Investigate Olaparib Safety and Tolerability, Efficacy and Pharmacokinetics in Paediatric Patients with Solid Tumours. In addition, the MAH is taking the opportunity to correct errors in CSR Addendum 1 for Lynparza study D081CC00006 (OlympiA).

☒is recommended for approval.

Paediatric data

The CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan (EMEA-002269-PIP01-17-M03) and the results of these studies are reflected in the Summary of Product Characteristics (SmPC).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex I are recommended.

Annex: Rapporteur’s assessment comments on the type II variation

4. Clinical aspects

4.1. Clinical Efficacy

Methods – analysis of data submitted

Study D0816C00025

This was a Phase I open-label, multicentre study to determine the recommended Phase II dose (RP2D) of olaparib monotherapy in the paediatric population, and to evaluate the safety, tolerability, pharmacokinetic (PK), pharmacodynamics (PDx) and preliminary efficacy of olaparib monotherapy in paediatric patients from ≥6 months to <18 years of age at consent, with relapsed or refractory solid or primary central nervous system (CNS) tumours (excluding lymphoid malignancies) for whom there were no standard treatment options.

The study was planned to involve 2 phases: a dose-finding phase and a signal identification phase.

• In the dose-finding phase, patients with a homologous recombination repair (HRR) deficiency based on a local test were to be recruited. For patients without access to local genetic testing, a sponsor-designated central germline breast cancer susceptibility gene (BRCA) test was to be made available. Each phase comprised 3 cohorts: A (≥12 years to <18 years), B (≥3 years to <12 years) and C (≥6 months to <6 years) with consecutive recruitment.

• The signal identification phase was to include patients with documented evidence of a deleterious or suspected deleterious HRR gene mutation as defined by a local test in one of 14 prespecified genes, or by the central germline BRCA test. Variants of uncertain significance or unknown pathogenicity were not eligible during the signal identification phase. The signal identification phase was to include each age cohort once the RP2D had been established and the dose-finding phase for that age cohort was recruited.

Eligible patients were to have pathologically confirmed relapsed or refractory solid or primary CNS tumours (excluding lymphoid malignancies), a HRR deficiency/gene mutation, and no standard treatment options. Eligible patients were to include but not be limited to those with osteosarcoma, rhabdomyosarcoma, non-rhabdomyosarcoma soft tissue sarcoma, Ewing Sarcoma, neuroblastoma, medulloblastoma, and glioma.

A minimum of 4 patients up to approximately 48 patients were to be enrolled in the study.

Patients were to be split into 3 cohorts and dosed throughout the study depending on their age at consent (A: patients aged ≥12 years to <18 years; B: patients aged ≥3 years to <12 years; and C: age-appropriate formulation [AAF] cohort in patients ≥6 months to <6 years) with a maximum of 12 patients per cohort in the dose-finding phase, and up to approximately 12 patients across all cohorts (minimum of 10 patients) evaluable for response analysis (HRR gene mutation confirmed via a central test and measurable disease at baseline) in the signal identification phase. Additional patients were to be recruited if there were insufficient safety or PK data across the ages.

The decision was made to terminate the study on 29 January 2025 due to operational futility in accordance with the end of study definition in the CSP. The last patient last visit (LPLV) took place on 04 February 2025; all data were included in the analysis for CSR using a data cut-off (DCO) date of 28 February 2025.

A total of 16 patients were enrolled and received treatment in the study: 10 patients in Cohort A (patients aged ≥ 12 years to < 18 years) and 3 patients in Cohort B (patients aged ≥ 3 years to < 12 years) of the dose-finding group; for the analysis of efficacy, 5 patients were included in the signal

identification group (consisting of 2 patients specifically enrolled into the signal identification group; plus 3 patients from the dose-finding groups [2 patients from Cohort A and one from Cohort B] who had qualifying HRR/gBRCA mutations. In addition, one patient who was enrolled during the signal identification phase was included in the overall analysis but not for signal identification analysis as did they not have a centrally confirmed HRR gene mutation. As of the DCO date of the CSR (DCO: 28 February 2025), all patients had discontinued study treatment.

Olaparib was administered as a single dose on Day 1, followed by twice daily (bd) in a continuous schedule. For Cohorts A and B, the tablet formulation was used, available in dose strengths of 25 mg and 100 mg. Dosing was started in Cohort A. Dosing in Cohort B was started only when tolerability was established in Cohort A. Note, dosing in Cohort B commenced in patients aged ≥6 years to <12 years (as an age-appropriate formulation (AAF) was available for patients aged 3, 4 and 5 years). For Cohort C, an AAF was developed. The AAF is a sprinkle capsule formulation, available in dose strengths of 15 mg and 19.5 mg. The sprinkle capsules contain 1.5 mg granules which were to be dispersed onto a food vehicle prior to dosing in accordance with the handling instructions. Dosing in Cohort C was planned to commence only when tolerability had been established in Cohort B. However, Cohort C was not started due to study termination.

The dose limiting toxicity (DLT) evaluation period for the dose-finding phase was 1 cycle of 28 days of therapy. Patients enrolled during the dose-finding phase who were not evaluable for toxicity during the cycle of DLT evaluation at the assigned dose level were to be replaced. Olaparib therapy was to be continued until disease progression (determined by Response Evaluation Criteria in Solid Tumours [RECIST] v1.1, International Neuroblastoma Response Criteria [INRC] or Response Assessment in Neuro-oncology [RANO]), unacceptable toxicity, withdrawal of consent, or another discontinuation criteria were met.

There was no formal statistical analysis of safety and tolerability data or efficacy data in this study. Demographic and other baseline disease characteristics, concomitant medication, dosing, exposure, safety, tolerability, dose limiting toxicities, efficacy data, and protocol deviations were listed and summarised by cohort and overall in the dose-finding phase, overall in the signal identification phase and in the total study, as appropriate. The RP2D was defined as the dose level recommended for future trials based on safety, tolerability, and achieving adequate exposure to olaparib based on PK monitoring. The olaparib plasma and saliva concentration data were analysed by non-compartmental analysis to determine olaparib PK in paediatric patients. Objective response rate (ORR), duration of response (DoR), disease control rate (DCR), and best objective response (BOR) were derived for this study.

• Objective response rate was defined as the percentage of patients with an investigator-assessed response of complete response (CR) or partial response (PR) as per RECIST v1.1, INRC or RANO and was based on a subset of all treated patients with measurable disease at baseline per the site investigator.

• ORR^: In order to account for patients with neuroblastoma who had a minor response (MR), a second variable, ORR^ was assessed. ORR^ was defined as the percentage of patients with an investigator-assessed response of CR or PR as per RECIST v1.1, or RANO, or CR, PR, or MR per INRC and was based on a subset of all treated patients with measurable disease at baseline per the site investigator.

• Duration of response was defined as the time from the date of first documented response until date of documented progression or death in the absence of disease progression. The time of the initial response will be defined as the date of the first visit response that was CR or PR.

• Disease control rate was defined as the percentage of patients who have a BOR of CR, PR, MR (if applicable) or who have stable disease (without subsequent cancer therapy) for at least 7 weeks after start of treatment (to allow for an early assessment within the assessment window).

• Best objective response was the best response a patient had following first dose, but prior to starting any subsequent cancer therapy and up to and including RECIST, INRC, or RANO progression or the last evaluable assessment in the absence of RECIST, INRC, or RANO progression.

Only ORR results are described in this assessment report.

Results

A total of 12 of 16 patients had measurable disease at baseline. Overall, none of the patients had an objective response and no patients had stable disease. In total, 11/12 patients had a BOR of progressive disease and 1 patient was not evaluable. Hence, the ORR and disease control rate were both 0%.

The most common reason for study treatment discontinuation was objective disease progression, in 14 of 15 patients (87.5%), with one patient each discontinuting due to 'patient decision' and 'other reasons".

Discussion on clinical Efficacy

Across the entire cohort of 16 enrolled patients, no objective responses were observed. Among the twelve patients who had measurable disease at baseline, eleven experienced disease progression and one was not evaluable. Even in patients without measurable disease at entry, disease stabilisations were short lived and did not extend beyond one hundred and eleven days. Taken together, these findings demonstrate that olaparib monotherapy failed to produce any evidence of clinical benefit in this paediatric population.

Interpretation of the data is further complicated by the small sample size and the considerable heterogeneity of tumour types included, ranging from osteosarcoma and malignant peripheral nerve sheath tumours to central nervous system tumours and adrenal carcinoma. Such diversity inevitably reduces the ability to detect signals of efficacy within a specific subgroup. However, the absence of any objective response across this wide range of histology is nevertheless striking and suggests a fundamental limitation of this therapeutic approach in children and adolescents.

4.2. Clinical Safety

Methods – analysis of data submitted

Safety data have been collected from 16 patients with relapsed or refractory solid or primary CNS tumors (excluding lymphoid malignancies) and with homologous recombination repair (HRR) deficiency according to a local test, for whom there were no standard treatment options.

Of the 16 patients receiving treatment; 13 patients were part of the dose-finding group (including 10 patients aged ≥12 years to <18 years (Cohort A) receiving 300 mg of olaparib bd and 3 patients aged ≥6 years to <12 years (Cohort B) receiving 200 mg of olaparib bd), 5 patients were part of the signal identification group (including 3 patients from the dose-finding group: 2 patients from Cohort A and 1 patient from Cohort B), and 1 patient was recruited for the signal identification group but did not have a centrally confirmed HRR gene mutation and so was not evaluable for analysis in this group (and was therefore only included in the overall total).

Results

Overall, most patients (15/16 patients [93.8%]) experienced at least 1 treatment-emergent adverse event (TEAE). The most frequently observed TEAEs (≥25.0%) were anemia (9/16 patients [56.3%]), vomiting (7/16 patients [43.8%]), decreased appetite and nausea (each in 5/16 patients [31.3%]), and thrombocytopenia, hypernatremia, and pyrexia (each in 4/16 patients [25.0%]).

Among the 16 patients, 11 (68.8%) experienced a TEAE of CTCAE Grade 3 or higher, with the most common TEAE of anemia in 7/16 patients (43.8%).

The following 5 SAEs were experienced by 4/16 patients (25.0%): thrombocytopenia, optic neuropathy, abdominal pain, myalgia, and pyrexia during the study. The events of thrombocytopenia, abdominal pain, and myalgia were considered possibly related to the study treatment by investigator; and the events of optic neuropathy and pyrexia were considered not related to the study treatment by investigator. No patients had an SAE with outcome of death.

No adverse events of special interest (including MDS/AML, new primary malignancy and pneumonitis) were reported in the study.

Overall, dose interruptions were noted in a total of 6/16 patients (37.5%) and dose reductions were noted in 4/16 patients (25.0%). The most common reason for dose interruptions or dose reductions was hematological adverse events. No discontinuations of IP due to an AE were reported in this study.

A total of 9/16 patients died (all from Cohort A of the dose-finding group, including 2 patients also included in the signal identification group). No AEs with fatal outcome were reported in this study. The primary cause of death for 5/9 patients was disease progression; other causes were malignant peritoneal neoplasm, osteosarcoma, neurofibrosarcoma, and adenocarcinoma of colon. All deaths were considered by the investigators to be due to the disease under investigation.

Mean changes from baseline for some hematology and clinical chemistry variables showed greater variability at a few visits; this may be explained by a low number of patients at these visits. There were no apparent clinically meaningful trends in the mean or mean changes from baseline hematology and clinical chemistry parameters over time.

In Cohort A, 1 DLT (Grade 4 platelet count decreased) was observed among the initial 3 patients. Additional 3 patients were subsequently dosed without a DLT. Therefore, the RP2D was established as 300 mg bd for Cohort A. No DLT was observed in the first 3 evaluable patients in Cohort B so the RP2D was established as 200 mg bd for Cohort B.

The safety findings in this study are consistent with the established safety profile of Olaparib in adults.

4.3. Discussion

The safety and efficacy of Lynparza in children and adolescents is considered not established based on the provided data.

There was no objective response observed in the 12 participants enrolled with measurable disease at baseline.

The safety and tolerability profile of olaparib at the doses studied in this peadiatric population is generally consistent with the established safety profile in adults.

5. Changes to the Product Information

As a result of this variation, sections 4.2, 4.8, 5.1 and 5.2, of the SmPC are being updated to add information regarding paediatric data and information.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.