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Ryvu presents updated clinical Phase I/II data of RVU120 in patients with relapsed/refractory metastatic or advanced solid tumors at the ESMO Congress 2023 together with the RVU120 Development Plan update

The Management Board of Ryvu Therapeutics S.A. with its registered office in Krakow, Poland ("Company", "Ryvu") informs that today, on October 23, 2023, the Company presented updated clinical Phase I data from RVU120 Phase I/II study in patients with relapsed/refractory metastatic or advanced solid tumors, presented at the European Society for Medical Oncology (ESMO) Congress 2023, taking place October 20-24, 2023, in Madrid, Spain. The Company has also provided an update on the progress of the ongoing Phase Ib study in patients with acute myeloid leukemia (AML) and high-risk myelodysplastic syndromes (HR-MDS) and presented the updated development plan for RVU120 program.

With a data cutoff of September 26, 2023, the results presented at the ESMO 2023 conference are featured in a poster presentation entitled “Phase I/II trial of RVU120, a CDK8/CDK19 inhibitor, in patients with relapsed/refractory metastatic or advanced solid tumors”.

- RVU120 achieved 12 disease stabilizations with a good safety profile in unselected and heavily pretreated patients.
- The dose of 250 mg is safe and tolerated, results in exposure in the pharmacologically active range, and is expected to result in robust efficacy in selected patients. Further dose optimization is ongoing, and the final results may be used in future additional solid tumor clinical studies, depending on translational data in different indications.

Results as of the Data Cut-Off Date of September 26, 2023:

- 39 patients with metastatic or locally advanced solid tumors received treatment distributed across 8 cohorts, with doses ranging from 75 to 400 mg of RVU120.
- Median patient age is 58 years, and median prior lines of therapy is 5 (heavily pre-treated).
- 12 patients achieved stable disease (SD), and 8 out of 12 patients had a duration of therapy on RVU120 longer than the prior line of therapy. A trend of a longer treatment duration was observed in patients with adenoid cystic carcinoma (AdCC).
- RVU120 was generally well tolerated. Most common adverse events (AEs) were GI-related (nausea/vomiting) and occurred shortly after initial RVU120 dosing (average time to onset of slightly over 1 hour).
  A robust relationship between exposure to RVU120 and inhibition of PD marker was observed:
  - Analysis of cells exposed to patient plasma samples after treatment with RVU120 revealed that inhibition of pSTAT5 closely correlated with achieved exposures (Cmax, AUC), reaching a biologically significant range of more than 50% at doses 250 mg and above.

Moreover, Ryvu's Management Board presented an update of the development plan for RVU120, which was first announced by the Company in the current report 16/2022 on August 19, 2022:

- Both Phase I studies of RVU120 in patients with solid tumors (AMNYS-51) and AML/HR-MDS (RIVER-51) have provided convincing RVU120 safety data, effectively reducing the risk associated with both the target and the molecule as a first-in-class CDK8/19 inhibitor.
- Both studies have demonstrated relevant levels of target inhibition at safe doses.
- Meaningful signs of clinical activity have been reported in patients with AML and HR-MDS, including a complete remission in a patient with NPM1 and DNMT3 mutations, in line with the preclinical data first published by Ryvu in 2019. The Phase II development in AML/HR-MDS study is planned to be initiated in Q4 2023 with two cohorts of genetically defined patients with AML or HR-MDS as a single agent (RIVER-52) and in combination with venetoclax (RIVER-81).
- Induction of erythropoiesis in multiple patients in RIVER-51, consistent with RVU120's mechanism of action, encouraged Ryvu to financially support a dedicated Phase II clinical trial in patients with low-risk myelodysplastic syndromes (LR-MDS) – the REMARK study. REMARK will be conducted as an investigator-initiated study through the EMSCO network, with Prof. Uwe Platzbecker, a globally renowned expert in the field of LR-MDS, taking on the role of Coordinating Principal Investigator. Start-up activities for the study are scheduled to commence later this year, and patient enrollment is planned to start in H1 2024.
- RVU120's effect on bone marrow and hematopoietic cells observed in RIVER-51, supported by the translational data generated with Prof. Rajit Rampal as part of a scientific collaboration established in 2021, encouraged Ryvu to initiate a new, previously unplanned study in patients with myelofibrosis (MF) – the POTAMI-61 study. Start-up activities for the study are scheduled to commence this year, with patient enrollment planned to begin in Q2 2024.
- Even though AMNYS-51 study has provided signs of RVU120 single-agent activity in solid tumors, including long-term disease stabilizations in patients with adenoid cystic carcinomas (AdCC) and evidence of on-target activity in a patient with pancreatic cancer, Ryvu will not immediately open any tumor type-specific cohorts in AMNYS-51 study. However, considering the attractive development opportunities in hematologic malignancies, Ryvu will focus its efforts on the aforementioned RIVER-52, RIVER-81, REMARK and POTAMI-61 clinical studies.
- Translational research in solid tumors will be ongoing, including combination studies in multiple solid tumor types, as well as academic collaborations on medulloblastoma and sarcoma.
- The updated RVU120 clinical development plan includes studies that may, in the opinion of Ryvu's Management Board, lead to three approvals in 2026-2027.
- The total budget for Phase II clinical development of RVU120, aimed at enrollment of over 270 patients across four Phase II clinical studies (RIVER-52, RIVER-81, REMARK and POTAMI-61), is approximately €68M. This budget also includes necessary drug manufacturing activities required for the approval pathway, translational research, and internal costs related to RVU120 clinical development. The total budget for the Phase II clinical development of RVU120 aligns with the estimates initially announced in the Ryvu Development Plans for 2022-2024.
- The budget for the three-year period from 2023 to 2025 assumes total Ryvu costs (Clinical Development, Early Pipeline and G&A) of approximately €145M. The current Ryvu cash runway extends through Q1 2026.

Further decisions on prioritizations within RVU120 development plan are planned to be made in Q1 2025, after the initial data from the four Phase II studies described above (RIVER-52, RIVER-81, REMARK and POTAMI-61) become available.

Company informs that it will host a webinar on Monday, October 23, 2023, at 9:00 am CEST to discuss the RVU120 development plan. The webinar can be accessed by following this link: https://ryvu.clickmeeting.com/ryvu-esmo-2023-results-rvu120-development-plans/register.

Disclaimer: This English language translation has been prepared solely for the convenience of English-speaking readers. Despite all the efforts devoted to this translation, certain discrepancies, omissions or approximations may exist. In case of any differences between the Polish and the English versions, the Polish version shall prevail. Ryvu Therapeutics S.A., its representatives and employees decline all responsibility in this regard.

Legal basis: Article 17.1 of MAR

Representatives of the Issuer:

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- Hendrik Nogai – Member of the Management Board