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Clinical update on RVU120 Phase II program

The Management Board of Ryvu Therapeutics S.A. with its registered office in Kraków ("Ryvu", the "Company"), provides an update on RVU120 Phase II program.

Ryvu has successfully launched all four RVU120 Phase II clinical studies planned for 2024: RIVER-52, RIVER-81, POTAMI-61 and REMARK, in accordance with RVU120 Development Plans communicated in current report no 45/2023 on October 23, 2023. All studies are progressing on track toward key efficacy analyses in H1 2025.

As of December 11, 2024, Ryvu activated 106 clinical sites in Poland, Italy, Spain, France, Germany, and Canada and 78 patients have been enrolled in all studies. The Management Board estimates that across all four RVU120 Phase II studies, 113 sites will be activated and anticipates dosing approximately 100 patients by the end of the 2024. The pace of recruitment has picked up significantly since September 2024, with nearly three times as many patients expected to be treated in Q4 2024 alone compared to the combined total from Q1 to Q3.

RVU120 demonstrates a favorable safety profile compared to other drugs used to treat acute myeloid leukemia (AML).

In the RIVER-81 study (RVU120 in combination with venetoclax in patients with relapsed/refractory AML, r/r AML, who have failed a previous venetoclax/HMA-based regimen), within eight patients treated with RVU120 at 250 mg (RP2D) that had at least one evaluable post-baseline assessment, one patient achieved a complete remission (CR), and another patient achieved a significant blast reduction. Part 1 of the study (combination dose escalation) was completed, and Part 2 is currently enrolling at the full doses of RVU120 (250 mg) and venetoclax (400 mg). In the RIVER-52 study (RVU120 as a monotherapy in patients with r/r AML and high-risk myelodysplastic syndromes; HR-MDS), one of two evaluable patients in cohort 2 (NPM1 mutation) achieved a 50% blast reduction, while disease stabilizations and reduction of peripheral blasts were observed in patients in cohort 3 (DNMT3A mutation). Key efficacy readouts in both RIVER-52 and RIVER-81 studies and the first efficacy data in the POTAMI-61 and REMARK trials are expected in H1 2025.

All studies align with the originally planned budgets, while Ryvu's cash runway guidance to Q1 2026 remains unchanged.

RIVER-81: Phase II study of RVU120 in combination with venetoclax administered to patients with AML who are relapsed or refractory to prior therapy with venetoclax and a hypomethylating agent (NCT06191263).

The RIVER-81 study is a multicenter, open-label clinical trial that aims to assess the safety, tolerability, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD).

The study is divided into three parts. Part 1 aims to identify safe and tolerated doses of RVU120 and venetoclax when used in combination through dose escalation of both study drugs. In Part 2, the selected doses will be evaluated for safety and efficacy in a larger group of patients. Part 3 is confirmatory. The planned overall enrollment for the study is approximately 35 to 98 patients, depending on the decision on the final scope of the study, driven by the data.

The first patient in the study was dosed on January 31, 2024 as reported by the Company in the current report 5/2024 dated January 31, 2024. Since then, the study has completed Part 1 by progressing through the following dose levels: dose level 1 (125 mg of RVU120 and 200 mg of venetoclax), dose level 2 (200 mg and 200 mg respectively) and dose level 3 (250 mg and 400 mg respectively). RVU120 has demonstrated a consistent safety profile, with no new signals observed when combined with venetoclax at any dose level.

The Company has successfully completed Part 1 of the study and, based on the results, decided to advance it to Part 2, which is currently enrolling. Completion of Stage 1 enrollment for Part 2 (18 patients) is expected in Q1 2025.

The RIVER-81 study was initially launched at the clinical sites in Poland and Italy, followed by the activation of additional sites in Spain and France. As of December 11, 2024, all 33 sites planned for this year had been activated in these countries.

As of December 11, 2024, 28 patients were enrolled, with one patient (within eight patients treated with RVU120 at 250 mg (RP2D) that had at least one evaluable post-baseline assessment) achieving a CR and another achieving a blast reduction to a level below 5%.

RIVER-52: Phase II study of RVU120 as a single agent for the treatment of patients with genetically defined subtypes of AML (including NPM1 and DNMT3A mutations) and HR-MDS who have no alternative treatment options (NCT06268574).

The RIVER-52 study is a multicenter, open-label clinical trial designed to assess the safety, tolerability, anti-tumor activity (efficacy), pharmacokinetics (PK), and pharmacodynamics (PD).

The study is divided into two parts. Part 1 aims to assess the level of anti-tumor activity in patients with genetically defined subtypes of AML, including NPM1 and DNMT3A mutations, as well as in patients with HR-MDS. Based on the outcomes of Part 1, Part 2 will further evaluate the safety, tolerability, and anti-tumor activity in a larger group of patients within the subtypes that exhibit the highest sensitivity to RVU120. The planned overall enrollment is approximately 40 to 140 patients, depending on the decision on the final scope of the study, driven by the data.

The first patient in the study was dosed on February 14, 2024 as reported by the Company in the current report 10/2024 dated February 14, 2024. The RIVER-52 study was initially launched at clinical sites in Poland and Italy. Starting in September 2024, the study expanded to Spain, France and Canada. As of December 11, 2024, 42 out of 44 sites planned for this year had been activated.

As of December 11, 2024, 31 patients were enrolled, including 24 patients in cohorts 2-4 (NPM1-mutated, DNMT3A-mutated, and HR-MDS, respectively). One of two evaluable patients in cohort 2 achieved 50% blast reduction, while disease stabilizations and reductions of peripheral blasts were observed in patients in cohort 3.

Enrollment in the study significantly accelerated in Q4 2024 and is expected to lead to key efficacy readouts in the coming months. Data from at least 10 patients in each cohorts 2-4 are expected in H1 2025.

POTAMI-61: Phase II study of RVU120 as a single agent and in combination with ruxolitinib (RUX) for the treatment of patients with myelofibrosis (MF) (NCT06397313).

The POTAMI-61 study is a multicenter, open-label Phase II study of RVU120, being explored as a single agent for the treatment of patients with primary or secondary MF previously treated with or ineligible for a JAK inhibitor, e.g., ruxolitinib, and in combination with ruxolitinib for patients with suboptimal response to JAK inhibitors. Key endpoints will include spleen volume reduction (SVR), total symptom score (TSS) improvement, and reduction of bone marrow fibrosis.

The study has been initiated based on RVU120's clinical safety and efficacy data observed in the RIVER-51 (Phase Ib in AML/HR-MDS) study, as well as translational data in MF generated in cooperation with Prof. Raajit Rampal from Memorial Sloan Kettering Cancer Center in New York. *In vivo* data demonstrate the beneficial effects of CDK8 inhibition in improving symptoms of MF, i.e., splenomegaly, hepatomegaly, anemia, and thrombopenia. Importantly, disease modification properties of RVU120 were shown by the reduction of mutated allele burden. RVU120 can potentially become a novel therapeutic strategy in myeloproliferative neoplasms (MPNs), including MF.

The POTAMI-61 study consists of two parts. Part A of the study, with a planned enrollment of approximately 20 patients, will comprise two cohorts: 1) single-agent therapy with RVU120 in patients resistant or refractory to prior JAK inhibitor treatment or ineligible for JAK inhibitor treatment and 2) RVU120 in combination with RUX in patients who experience a suboptimal response to prior JAK inhibitor treatment. Depending on results from Part A, cohorts 1 and/or 2 could be expanded in Part B, which will further assess safety, tolerability, and antitumor activity in a larger cohort, totaling up to approximately 230 patients for both Part A and Part B combined. RVU120 could also be investigated in a frontline setting in

cohort 3. Ryvu will initially proceed with the execution of Part A of the study, while the decision on the potential initiation of Part B will be based on the outcomes of Part A.

The first patient in the study was dosed on December 4, 2024 as reported by the Company in the current report 37/2024 dated December 5, 2024, and five more patients were undergoing screening as of December 11, 2024. Part A of the study will initially enroll patients across clinical sites in Poland and Italy. If Ryvu decides to initiate Part B, the study will expand to include additional sites in the EU and non-EU countries, totaling approximately 50 clinical sites worldwide. As of December 11, 2024, 12 out of 17 sites planned for this year had been activated.

Initial efficacy data is expected in Q2 2025, based on a 12-week patient observation period.

REMARK: Phase II study of RVU120 as a single agent for the treatment of patients with lower-risk myelodysplastic syndromes (LR-MDS) (NCT06243458)

The REMARK study is a multicenter, open-label Phase II study of RVU120, conducted as an investigator-initiated trial with the European Myelodysplastic Neoplasms Cooperative Group (EMSCO), with Prof. Uwe Platzbecker serving as the Coordinating Principal Investigator (CPI).

REMARK has been initiated based on the clinical safety and efficacy data gathered so far, and strong preclinical and mechanistic rationale.

MDS pathogenesis is influenced by gene expression alterations that hinder the maturation of hematopoietic cells. RVU120 triggers erythroid gene expression programs orchestrated by STAT5 and GATA1 in aberrant stem cells from MDS patients. Importantly, RVU120's activity does not lead to significant hematopoietic toxicity. As a result, RVU120 is a promising drug candidate for treating transfusion-dependent MDS patients.

In the REMARK study, the planned overall enrollment is approximately 40 patients who receive RVU120 for at least 8 complete cycles (24 weeks). The primary goal is to achieve hematologic improvement in the form of an erythroid response (HI-E), with secondary goals including independence from RBC transfusions, improvement in hemoglobin levels, quality of life, disease progression, and analysis of specific gene mutations.

The first patient in the study was dosed on September 19, 2024 as reported by the Company in the current report 29/2024 dated September 19, 2024, and as of December 11, 2024, 18 patients were treated. Patient enrollment commenced across five countries: Poland, Germany, France, Spain and Italy. As of December 11, 2024, 19 out of a planned total of 24 sites were activated.

Initial efficacy data is expected in Q2 2025, based on a 16-week observation period.

An online conference call covering the RVU120 Phase II studies update will be held on December 12 (Thu), at 10:00 AM (CET). The live stream is available at: https://livingmedia.com.pl/live/ryvu/rvu120update

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:

- Paweł Przewięźlikowski – President of the Management Board
- Hendrik Nogai – Member of the Management Board

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