"It was the best of times, it was the worst of times,
it was the age of wisdom, it was the age of foolishness,
it was the epoch of belief, it was the epoch of incredulity,
it was the season of Light, it was the season of Darkness,
it was the spring of hope, it was the winter of despair,
we had everything before us, we had nothing before us,
we were all going direct to Heaven, we were all going direct the other way
—in short, the period was so far like the present period…."
A Tale of Two Cities, Charles Dickens

Dear Ryvu Investors, Business Partners, and Friends,

It has become a tradition for me to share a few words of a summary of the scientific, business, and corporate developments at Ryvu in the past year and offer a few thoughts on our plans for 2023.

This time this letter will not be focused on Ryvu only, and that is because 2022 was a special year for everyone in Europe. We experienced something our grandparents were telling us about and something we will definitely be telling our grandchildren about: a brutal invasion and war waged by barbarian Russia on freedom- and peace-loving Ukrainians.

I am extremely proud of the necessary actions that multiple liberal democracies have undertaken to support Ukraine, preserving the country's independence, indirectly protecting Central and Eastern Europe, as well as hopefully discouraging other totalitarian regimes worldwide from invading their neighbors. Ukrainians are paying their price in blood, the West (with some help from Japan, Australia, South Korea, etc.) mostly in money, which has naturally impacted the global macroeconomic outlook pushing the world just recovered from COVID-19 to the brink of a recession.

We, working in the biomedical community, are especially sensitive to the disgraceful lack of respect for human life the Russians have shown in Ukraine, as well as a huge waste of energy, money and human talent that should be utilized to fight the major problems the world is facing: climate change, access to high-quality healthcare and poverty, rather than to satisfy someone's imperial ambitions.

The war in Europe has increased the pressure on the most innovative businesses operating in long-term investment cycles, especially biotechnology companies. We already observed this trend in the US in 2021, triggered by the increased cost of capital post-COVID, growth in inflation, reconstruction of supply chains, drug pricing problems, and operating issues at clinical sites, causing trial delays. As a result, development-stage biotech companies have faced significant challenges worldwide, resulting in a >50% fall in the BBC index in the first half of 2022 with limited recovery in H2.

Paradoxically, this was also probably the best year in Ryvu's history (*).

Our most important value driver, the selective CDK8/19 inhibitor RVU120, is progressing well in the early studies. In the solid tumor AMNYS-51 study, we have continued dose-escalation of RVU120 as a single agent, without any dose-limiting toxicities, which is very important for a first-in-class therapeutic, and could observe several promising disease stabilizations in patients who had been progressing on previous treatments. At the EORTC-NCI-AACR Symposium in October 2022, we presented biomarker inhibition of >70% in a patient dosed at the 135mg cohort. Based on preclinical assumptions, this threshold is sufficient for high efficacy in selected patient groups with hematologic malignancies. As of March 3, 2023, enrollment was ongoing at the dose of 375 mg EOD.

In the AML/MDS study RIVER-51, somewhat impacted by longer alignments with the FDA and intrinsic issues in the AML patient population, we advanced to a dose of 110 mg EOD and observed multiple patients with hematologic improvement and one complete response. As of March 3, 2023, the enrollment was ongoing at the dose of 135 mg EOD. At this stage of development, individual patient stories mean more than just statistics. We are exceptionally motivated by hearing about a patient suffering from secondary leukemia who had failed two lines of therapy and was transfusion-dependent at the start of RVU120 treatment but was still alive and transfusion-independent almost one year from the study entry.

The most important findings of 2022 are that RVU120 can be dosed safely at the current doses, results in clinical benefits for some patients in different cancer indications, and that we have room for improvement by further dose escalation, identifying the best responders and combining with other drugs both in heme and solid tumor development tracks. We will explore all of these development directions in the coming years.

SEL24, our PIM/ FLT3 inhibitor developed in collaboration with Menarini, was progressing in a Phase II study in IDH-mutated AML patients. The initial results, disclosed at EHA 2022, are guiding Menarini to the development in combinations, and we hope that additional studies with the drug will be initiated in 2023.

In the early pipeline, this was a year of fantastic dealmaking. In July, we licensed our STING agonist as a payload for antibody-drug conjugates to Exelixis, and in November, we struck the transformational collaboration with the German immunotherapy powerhouse BioNTech. The partnership, anchored by a license to our STING agonists to be used as naked small molecules, will comprise multiple collaboration tracks on other targets, hopefully resulting in multiple clinical-stage candidates over the coming years. BioNTech has not only paid a record €20M upfront to Ryvu but is already funding research FTEs at our company. In both Exelixis and BioNTech collaborations, Ryvu is eligible to receive significant downstream economics. BioNTech has also decided to engage in Ryvu as an investor and participated in our last fundraising.

In our synthetic lethality pipeline, we reported the first *in vivo* data for MTA-cooperative PRMT5 inhibitor and progressed a few other programs in the life cycle.

We have also been busy on the corporate development side. In August, we secured a €22 M venture loan from the European Investment Bank at very favorable terms. In December, we raised €53M in a secondary offering on the Warsaw Stock Exchange, mostly subscribed to by Polish institutional investors and BioNTech which became an 8% shareholder in Ryvu. I am also pleased to mention that me and Tadeusz

Wesołowski, the Deputy Chairman of Ryvu's Supervisory Board and our investor since 2011, participated in the round with a total of €5M investment.

We are very positive about the year ahead of us. We certainly hope for a decisive victory by Ukraine, relieving macro pressure on the region and its financial markets and biotech market recovery in the US and in other countries. But having little influence on the external issues, we will focus on what's in our control:

- Smart and resolute development of RVU120 in different oncology settings where we plan to start clinical trials involving ~300 patients in the coming years;
- Support Menarini in the development of SEL24 (MEN1703);
- Deliver to our strategic partner BioNTech across the multiple collaboration streams and hope for good outcomes from Exelixis and Galapagos partnerships;
- Move our PRMT5 inhibitor program quickly to the best-in-class clinical candidate, resulting in a potential IND filing in 2024 and replenishing the synthetic lethality pipeline with new projects at H2L and L2C stage;
- Cost-consciously allocate more than €100 M funds at our disposal and supplement it with additional non-dilutive funding from partnership and grants;

We have multiple paths toward creating significant value for our shareholders. Apart from the weakness of the financial markets, all other determinants of Ryvu's future success seem favorable.

Good collaboration with clinical sites on drugs that have already demonstrated initial safety and signs of efficacy, Ryvu management and scientific teams strengthened with top talent over the last two years, cutting edge research infrastructure in Krakow, cultural changes since the spin-out of Selvita CRO, and cost advantages resulting from a favorable HQ location in Poland have created favorable conditions for a good performance of the company over the coming years. And if the capital markets are in better shape, it should also be very visible in our share price performance.

I would like to thank our patients, clinicians, investors, scientific collaborators and all employees for your trust and support for Ryvu.

With kind regards,

Pawel Przewiezlikowski

(*) all price-sensitive information on Ryvu's progress is based on the last publicly available data cut-offs at major conferences and periodic reports.