EDISON

Ryvu Therapeutics

Rebalancing R&D pipeline towards clinical stage

Company outlook

Pharma & biotech

2020 has been a memorable year for Ryvu. Menarini, the partner sponsoring SEL24/MEN1703 development, completed the Phase I part of the Phase I/II trial in acute myeloid leukaemia (AML) and presented the first ever data with an in-house developed asset. In April 2020, Ryvu signed a discovery agreement in inflammatory diseases with Galapagos. Ryvu could receive up to €53.5m (€1.5m paid upfront). On the internal R&D front, the company has terminated two preclinical stage projects for strategic reasons (A2A/A2B antagonist and SMARCA2 inhibitor) and submitted a clinical trial application to start a new Phase I/II trial with SEL120 in solid tumours. Notably, the FDA granted an orphan drug designation for SEL120 in AML in March 2020. The share issue in July 2020 will support existing plans for the next two years. Our updated valuation of Ryvu is PLN1.17bn or PLN63.6/share vs PLN68.9/share previously.

Year end	Revenue (PLNm)	PBT* (PLNm)	EPS* (PLN)	DPS (PLN)	P/E (x)	Yield (%)
12/18*	51.7	(23.0)	(1.49)	0.0	N/A	N/A
12/19	33.7	(45.0)	(2.83)	0.0	N/A	N/A
12/20e	34.5	(36.7)	(2.14)	0.0	N/A	N/A
12/21e	19.3	(65.5)	(3.58)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding amortisation of acquired intangibles and exceptional items. 2018 results relate to Selvita before the corporate split and are not reconciled. 2019 restated after accounting standard changed to IFRS.

Active management of preclinical assets

As indicated by the company, Ryvu's decision to terminate the two preclinical projects was based on a comprehensive assessment of their viability. As a drug discovery and development company, Ryvu has a broad preclinical candidate pipeline, so the termination of two projects will not diminish its strategy to bring new candidates from discovery through to the clinic, in our view. While it is not uncommon to stop preclinical stage projects, we were particularly intrigued by Ryvu's determination to initiate a new clinical Phase I trial with SEL120 in solid tumours. This will rebalance the R&D pipeline toward the clinical stage.

Lead asset SEL120 has broad potential

Ryvu's strategy with SEL120 indicates the company's belief in its broad utility. Initially, Ryvu is targeting the third-line monotherapy setting in AML and HR-MDS, which is the fastest way to market. The preclinical data, however, allows it to expand the label to second- and potentially first-line settings in combination with standard of care. Furthermore, Ryvu has showed preclinical proof-of-concept in a number of solid tumours, including in breast and colorectal cancer. The company has decided to start a new Phase I/II trial in solid tumours this year. In the first instance, this will include triple-negative breast cancer (TNBC), which we add to our valuation.

Valuation: PLN1.17bn or PLN63.6/share

Our valuation of Ryvu is PLN1.17bn or PLN63.6/share, vs PLN1.10bn or PLN68.9/share previously. The R&D assumption changes had a slight net negative effect, which was partially offset by higher net cash after the recent share issue. The main changes include the removal of the A2A/A2B antagonist and SMARCA2 inhibitor projects, while we have added a new indication – TNBC – for SEL120.

24 February 2021

Price	**PLN49.80**
Market cap	**PLN914m**

Net cash (PLNm) at end-Q320	161
Shares in issue	18.4m
Free float	40%
Code	RVU
Primary exchange	WSE

Share price performance

%	1m	3m	12m
Abs	(6.0)	(4.2)	3.3
Rel (local)	(4.6)	(8.7)	12.2

52-week high/low	PLN75.00	PLN30.10

Business description

Ryvu Therapeutics is a drug discovery and development company focusing on novel small molecule therapies in oncology. The lead asset is wholly owned SEL120, a selective CDK8/19 inhibitor being studied in a Phase Ib clinical trial for AML and myelodysplastic syndrome that also has potential in solid tumours. SEL24/MEN1703 is a dual PIM/FLT3 kinase inhibitor licensed to the Menarini Group in a Phase I/II trial for AML. The preclinical-stage pipeline includes assets in immunoncology and synthetic lethality.

Next events

SEL24/MEN1703 Phase I/II Part 1 data presentation (depends on partner)	2021
SEL120 Phase I preliminary study results	H121
Initiation of the Phase I trial with SEL120 in solid tumour	2021

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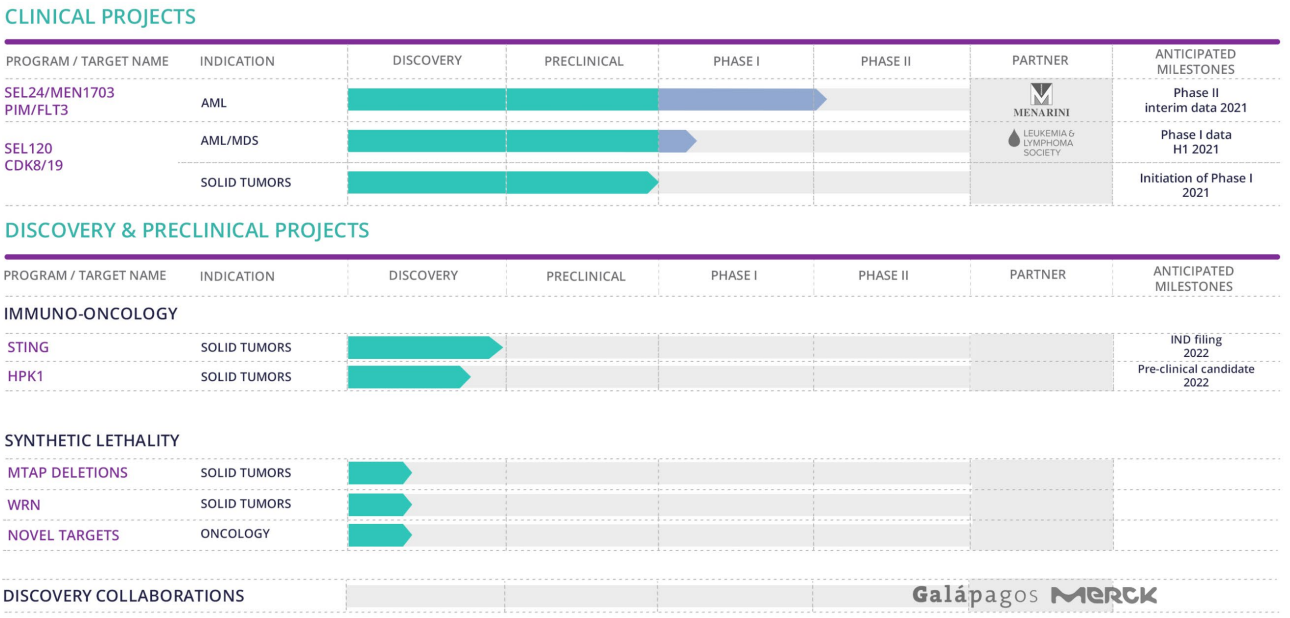
R&D pipeline shifting towards clinical-stage projects

As previously, Ryvu's clinical stage pipeline (Exhibit 1) includes **SEL24/MEN1703**, a dual PIM/FLT3 kinase inhibitor, and **SEL120**, a selective CDK8/19 inhibitor. The revised preclinical pipeline now includes immunoncology projects (a small molecule **STING agonist** for systemic administration and an **HPK1 inhibitor**) and synthetic lethality projects (**WRN ATPase inhibitors** and cancers with a deletion of the metabolic **MTAP** gene). Ryvu also has several undisclosed projects at earlier stages and we expect these to feed into the preclinical and clinical pipelines.

Exhibit 1: Ryvu's R&D pipeline



Source: Ryvu

Clinical projects

SEL120: Lead wholly owned asset in Phase Ib

SEL120 is a first-in-class selective CDK8/19 inhibitor. Depending on subtypes, cyclin-dependent kinases (CDKs) play varied roles in the control of the cell cycle, proliferation and mRNA transcription. Specifically, CDK8 is uniquely differentiated and is part of a multi-protein complex that regulates gene expression. Preclinical studies point to potential efficacy in haematological malignancies, but also in solid tumours, such as TNBC and colorectal cancer, and in combination therapies with immunoncology products.

The first Phase Ib trial started recruiting patients with relapsed or refractory AML or high-risk myelodysplastic syndrome (HR-MDS) in September 2019. In June 2020, Ryvu presented a poster with the trial details at the European Hematology Association (EHA) Congress. The open-label, multi-centre trial is a dose escalation/small safety expansion Phase I study, which should enrol about 50 patients. As usual, the **primary endpoint** is safety/tolerability and to establish the recommended Phase II dose. **Secondary endpoints** include pharmacokinetic/pharmacodynamic (PK/PD) evaluation, but also preliminary anti-leukaemic activity.

The ongoing COVID-19 pandemic has affected enrolment speed, but the expected delay to full enrolment is around six months, which is manageable, in our view, and preferable to data loss. The

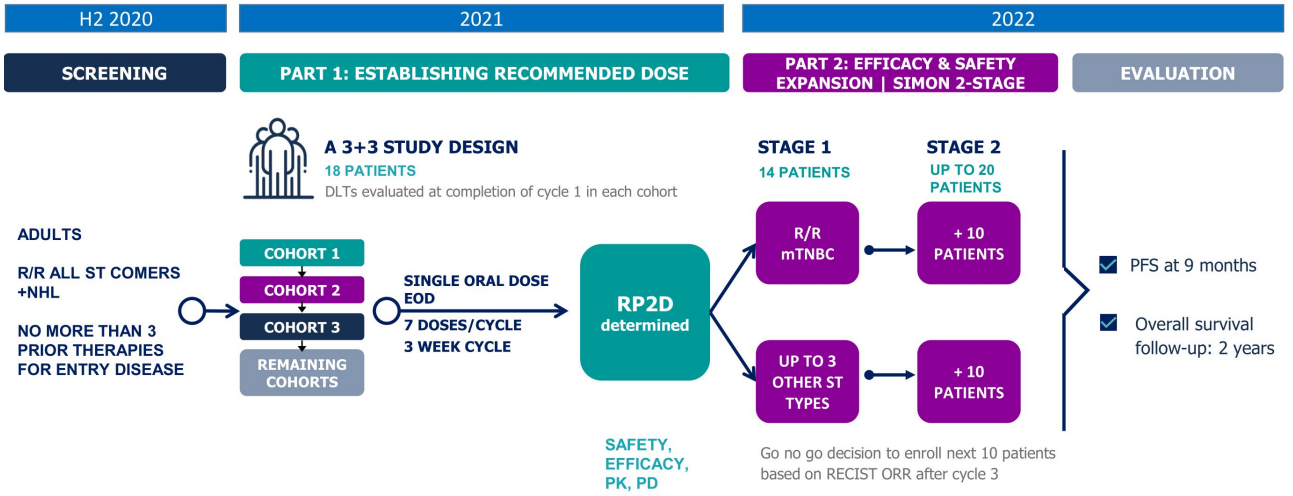
initial results from the Phase Ib part of the study, therefore, are now **expected in H121, with final results to follow in H221**. To address the delay, Ryvu has initiated the European arm of the study earlier than planned, so that more centres would be active.

SEL120 positioning

Ryvu's R&D strategy with SEL120 reveals management's belief in its high potential. Initially, Ryvu is targeting the third-line setting with SEL120 as monotherapy in AML and HR-MDS, which is the fastest way to market. The preclinical data, however, allows Ryvu to plan to expand the label to second- and potentially even first-line settings as a combination with standard of care.

Ryvu has also demonstrated preclinical proof of concept in a number of solid tumours, including in breast and colorectal cancer. Based on this evidence, the company has decided to initiate a new Phase I/II trial in solid tumours. Initially, this will include TNBC, and also several other types. More details and the initiation of the trial are expected in 2021.

Exhibit 2: Preliminary design of Phase I study in solid tumours



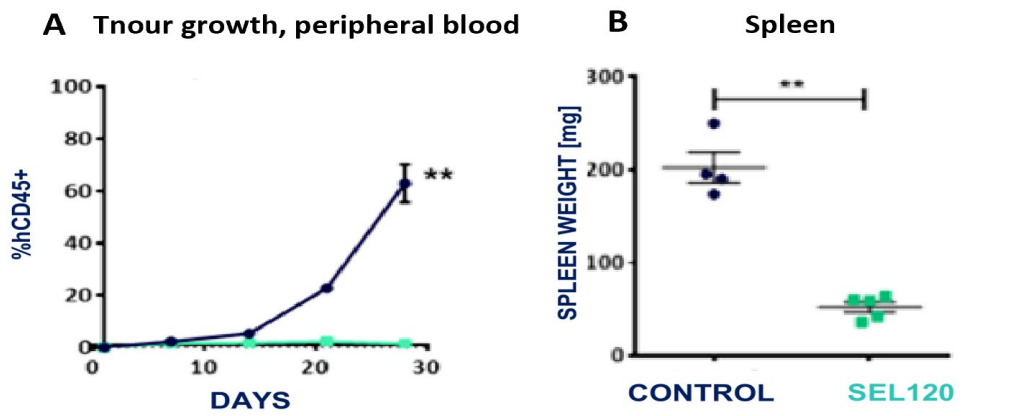
Source: Ryvu

Comprehensive preclinical data package

Ryvu has accumulated a substantial data package in the preclinical studies with SEL120. The AML in vivo models chosen for SEL120 preclinical studies are known to have high translational potential. We have covered Ryvu's key data presentations at scientific conferences in our previous reports (outlook reports in particular), but some of the highlights include:

- SEL120 was effective with nanomolar activity in cell lines with activated STAT signalling and CD34 expression, which, among others, are features of leukaemia stem cells (LSCs). LSCs contribute to AML relapse through treatment-resistant clones. SEL120 induced cell differentiation primarily towards myeloid and erythroid lineages.
- In a murine AML model, the treatment of leukaemic mice with SEL120 resulted in a reduced leukaemia burden in bone marrow and blood.
- In an orthotopic AML model, SEL120 completely eliminated circulating primitive CD45+/CD34+ leukaemic cells in comparison to control animals (Exhibit 3A). Fewer hCD45+/CD34+CD38- cells were observed in bone marrow in the SEL120 treated group than control and spleen weight was also significantly lower in the SEL120 group (spleen is enlarged in AML) (Exhibit 3B).

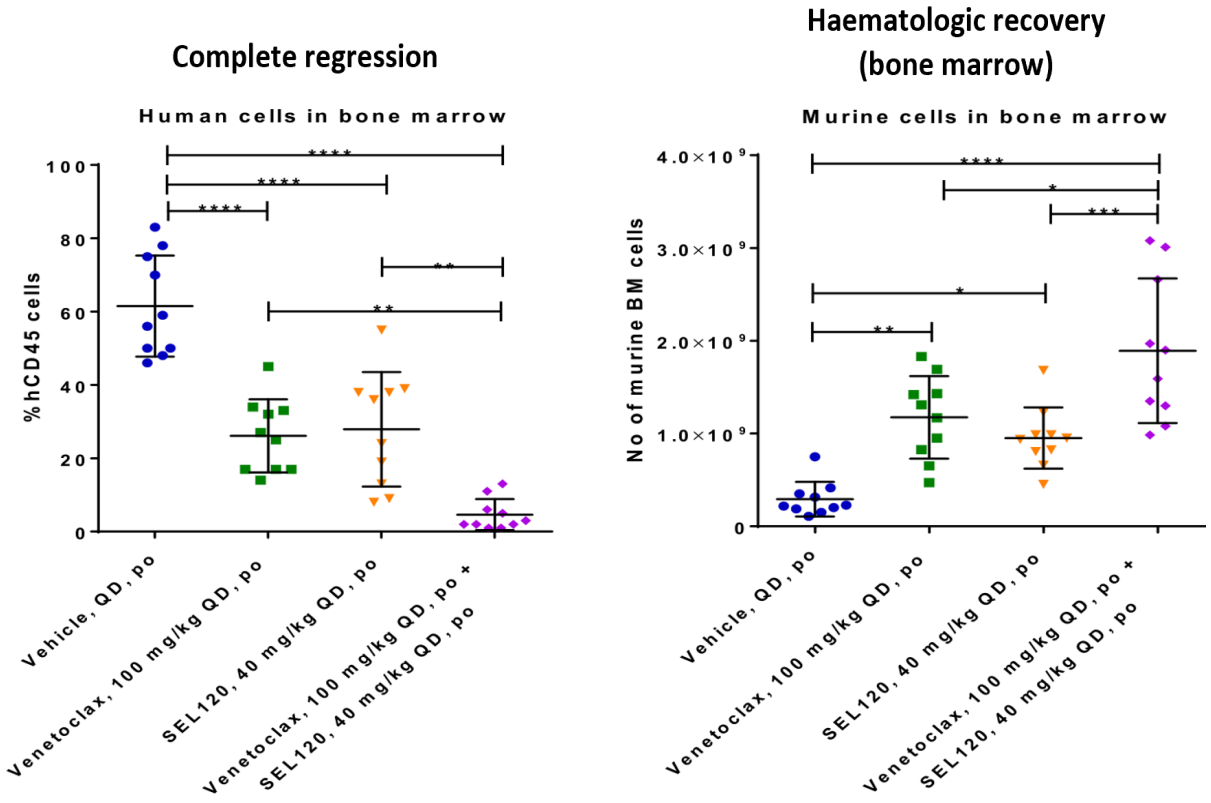
Exhibit 3: SEL120 demonstrated an anti-leukaemic effect in an AML PDX mouse model



Source: Ryvu

- In an orthotopic AML *in vivo* of model where immunodeficient mice were injected with AML cell lines, a significant synergistic therapeutic effect has been observed in animals that received both SEL120 and venetoclax (Exhibit 4). Venetoclax (a BCL-2 inhibitor, Venclexta, AbbVie) is approved as frontline therapy for frail, elderly AML patients and is forecast to reach sales of $1.5bn by 2026 (EvaluatePharma).

Exhibit 4: SEL120 is active in combination therapy with recently approved for AML venetoclax



Source: Ryvu. Note: Cell line-derived mouse model (MV-4-11 cells).

SEL24/MEN1703: Phase I/II trial dose-escalation results

SEL24/MEN1703 is **a dual PIM/FLT3 kinase inhibitor** in a Phase I/II trial for AML. In March 2020, Ryvu reported that its partner Menarini Group (via subsidiary Berlin-Chemie) had successfully completed the dose-escalation part (Phase I) of the ongoing Phase I/II study with SEL24/MEN1703,

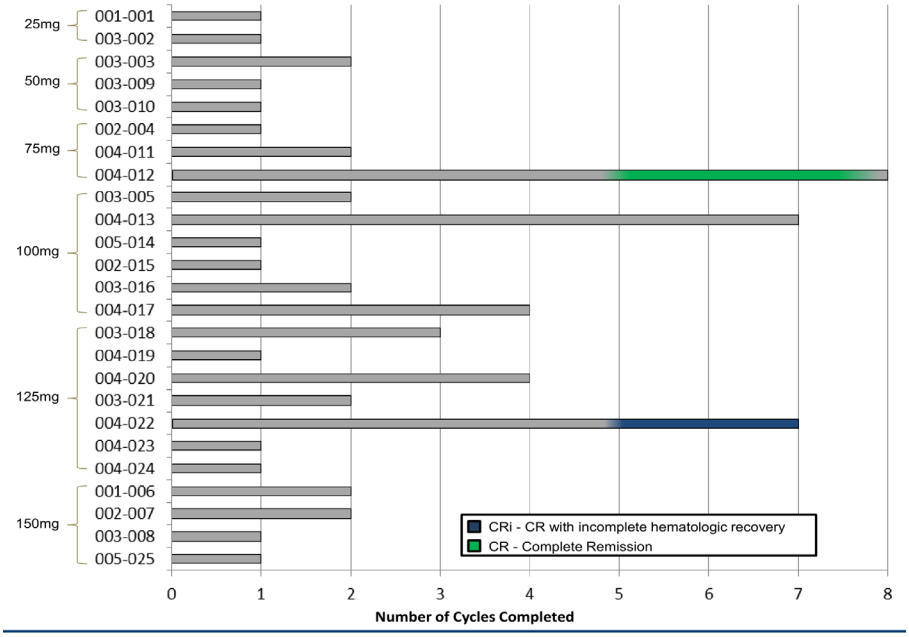
triggering a €1.75m milestone payment to Ryvu. The recommended dose for the Phase II part of the study (cohort expansion) has been established.

The Phase I results were presented at the 25th EHA Congress on 11–14 June 2020. The Phase I part of the study followed 3+3 design, which in total recruited 25 elderly (22 evaluable), advanced AML patients in five US centres. SEL24/MEN1703 was given 14 days on, followed by seven days off over 21-day cycles until disease progression or unacceptable toxicity.

The **primary endpoint** was to determine the maximum tolerated dose (MTD) and the recommended Phase II dose (RP2D), while the **secondary endpoints** were the assessment of the PK profile and preliminary single agent activity. The highlights from the EHA Congress presentation include:

- SEL24/MEN1703 showed an acceptable safety profile up to the recommended dose established at 125mg/day. Most grade ≥3 treatment-related adverse events were predictably hematologic or infectious.
- Initial evidence of single agent efficacy was observed with two objective responses: one complete response (CR) and one complete response with incomplete hematologic recovery (CRi). Notably, these patients were elderly patients and had exhausted standard therapeutic options.
  - One patient with DNMT3A/IDH2 mutation, who progressed on enasidenib (IDH2 inhibitor), demonstrated a rapid clearance of disease burden and achieved CR at 75mg;
  - One patient with ASXL1/EZH2 mutation, who relapsed after chemotherapy and decitabine, achieved CRi at 125mg.

Exhibit 5: Individual patient treatment duration in Phase I/II trial dose-escalation part



Source: Solomon et al. Note: Results of the dose escalation part of DIAMOND trial (CLI24-001): First-in-human study of SEL24/MEN1703, a dual PIM/FLT3 kinase inhibitor, in patients with acute myeloid leukaemia. EHA, June 2020.

Next steps

The trial is progressing into the Phase II cohort expansion part (DIAMOND-01), which will further investigate the single agent activity and the safety profile of SEL24/MEN1703 in relapsed/refractory AML patients. Recruitment has already started in the US and European centres (first patient

recruited in July 2020 in the US and in September 2020 in Europe) and the **trial is anticipated to complete in H221**, a potential key catalyst for Ryvu in the near term.

SEL24/MEN1703: Dual mechanism of action

SEL24/MEN1703 specifically inhibits PIM- and FLT3-related pathways and exhibits broader anti-tumour activity in AML compared to selective FLT3-ITD or PIM inhibitors. FMS-like tyrosine kinase receptor-3 gene internal tandem duplication (FLT3-ITD mutation) is one of the most common genetic mutations in AML (around 25% of newly diagnosed AML cases) and, although its inhibition has been shown to be effective in clinical trials, resistance to treatment develops rapidly. PIM kinases are major oncogenes and downstream targets with expression triggered by FLT3-induced STAT5 activity. The expression of PIM kinases amplifies FLT3's oncogenic potential in addition to other pro-oncogenic signalling, thus presenting a rationale for a dual FLT3/PIM inhibition. Previously, third-party data have shown PIM expression increases cancer resistance to FLT3-ITD inhibitors, while PIM inhibition would restore cancer sensitivity to FLT3 inhibitors. SEL24/MEN1703, a first-in-class dual inhibitor of PIM and FLT3 kinases, can simultaneously inhibit both kinases and provides a novel treatment strategy.

Before SEL24/MEN1703 was out-licensed to Menarini, Ryvu tested it in various in vitro and in vivo studies comparing it to control or active treatment with standalone PIM (AZD1208, AstraZeneca) or FLT3-ITD (AC220/quizartinib, Daiichi Sankyo) inhibitors. These preclinical studies demonstrated a synergistic effect of dual inhibition of PIM and FLT3 kinases, which had broader anti-proliferative activity in AML cell lines than that of selective PIM inhibitors or FLT3 inhibitors. In vivo efficacy has also been demonstrated in AML models. Of particular note is that SEL24 had a largely similar effect in both the FLT3 wild type and FLT3-ITD models. The Phase I trial therefore recruited patients regardless of FLT3 mutation status. The overview of the preclinical data was published in an article in Oncotarget.

AML still an unmet need; changing treatment paradigm

AML normally originates in the bone marrow (where new blood cells are made), but often quickly moves into the blood, resulting in uncontrolled growth and accumulation of malignant white blood cells, which fail to function normally and interfere with the production of normal blood cells. AML is the most common type of acute leukaemia in adults and affects nearly 40,000 patients in the EU and US (new cases per year). The five-year survival rate for all AML patients, irrespective of age or genetic status, is around 23%.

Until recently, the standard-of-care treatment for AML was primarily based on chemotherapy (cytarabine with anthracycline or mitoxantrone), followed by a stem cell transplant where appropriate. The goal of treatment is to reduce the blasts in the bone marrow to below 5% and return the blood cell counts to normal levels. A bone marrow transplant is generally recognised as the only curative treatment option, but is not always appropriate.

Rydapt (midostaurin, Novartis) was the first novel drug, approved in April 2017, that specifically targets FLT3 for the treatment of adults with newly diagnosed FLT3-ITD AML in combination with standard-of-care chemotherapy. This was the first large Phase III trial (RATIFY) to confirm a therapeutic benefit of FLT-ITD inhibition in AML patients. Overall survival was increased from approximately two years to just over six years and there was a 23% reduction in risk of death compared to the placebo arm (hazard ratio 0.77, p=0.0074). EvaluatePharma's consensus forecast is for Rydapt sales of $240m in 2026.

In November 2018, the FDA approved gilteritinib (Xospata, Astellas) as monotherapy for adults with FLT3-positive AML in a relapsed or refractory setting. Approval was based on the results of the Phase III ADMIRAL trial. Treatment with gilteritinib resulted in CRs, or CRs with partial haematologic recovery in 21% of patients (95% CI 14.5–28.8%). The consensus forecast for Xospata sales in 2026 is $770m (EvaluatePharma).

Outside the FLT3 inhibitor space, the FDA has approved other novel drugs for AML:

- Glasdegib in November 2018 (a hedgehog pathway inhibitor, Daurismo, Pfizer; consensus AML sales forecast of $490m in 2026),
- Venetoclax in November 2018 (BCL-2 inhibitor, Venclexta, AbbVie/Roche; consensus AML sales forecast of $1.5bn in 2026),
- IDH1/IDH2 inhibitors ivosidenib in July 2018 (Tibsovo, Agios Pharmaceuticals; consensus AML sales forecast of $400m in 2026) and enasidenib in August 2017 (Idhifa, BMS/Celgene; consensus AML sales forecast of $270m in 2026).

Despite these advances, the novel drugs have extended survival by just several months, so survival rates remain poor. In addition, these new drugs rely on combinations with chemotherapy, which causes significant toxicity and poor quality of life, so the unmet need in AML remains high. EvaluatePharma calculates the total market value of AML drugs at $1.2bn in 2020, which is forecasted to grow to $9.4bn in 2026.

TNBC: Ryvu's first attempt to tackle solid tumours

By pathological definition, TNBC lacks an expression of oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2). TNBC accounts for around 10–20% of the total of new breast cancer cases each year, which would imply c 110k patients in the US and Europe. This type of cancer is typically more aggressive when compared to other types of breast cancer and is unresponsive to hormonal and monoclonal antibody therapies (eg trastuzumab).

If the cancer is still localised, surgery is the mainstay treatment. In advanced cases, the standard initial chemotherapy treatment includes classic chemotherapy agents, such as anthracyclines, taxanes, capecitabine and gemcitabine, but patients have a poorer prognosis and overall survival than in other types of breast cancer.

A variety of new targeted therapies are in investigation and during the last couple of years several novel treatment options have been approved:

- The combination of checkpoint inhibitor atezolizumab (Tecentriq) plus nab-paclitaxel (Abraxane) was approved in 2019 as the first-line treatment for unresectable or locally advanced or metastatic TNBC, but only for patients expressing PD-L1, as in the general population the benefit was not observed.
- Another checkpoint inhibitor pembrolizumab (Keytruda) was approved in November 2020 also as a first-line treatment for unresectable locally advanced or metastatic TNBC expressing PD-L1, in combination with chemotherapy. The approval was based on progression-free survival only benefit.
- PARP inhibitors olaparib (Lynparza) and talazoparib (Talzenna) were approved in 2018 and 2019 for advanced TNBC patients with BRCA1/2 mutation. Phase III trials confirmed a progression-free survival benefit, but not overall survival.
- Antibody-drug conjugate sacituzumab govitecan (Trodelvy, Gilead Sciences; consensus sales of $1.9bn expected by 2026 according to EvaluatePharma) was approved in April 2020 for the treatment of patients with metastatic TNBC who have received at least two prior therapies. Trodelvy is comprised of a chemotherapy metabolite (topoisomerase inhibitor class) and an antibody against ubiquitously expressed Trop-2 protein on TNBC cells. The approval was based on OS benefit of 5.4 months (12.1 vs 6.7 months; HR, 0.48). Trodelvy is currently being evaluated in early-stage breast cancer in patients undergoing neoadjuvant chemotherapy (before surgery, potentially curative setting).

Despite the recent progress in the treatment of TNBC, the clinical benefit in most cases is marginal. Demonstration of an overall survival benefit is as challenging as ever; therefore, we believe the industry's interest in novel drugs in this indication will not subside any time soon.

Preclinical-stage projects

Following the revision of its preclinical R&D pipeline in October 2020, Ryvu now classifies its projects into **immunoncology** and **synthetic lethality**. The immunoncology platform aims to provide novel immunotherapies mobilising the immune system to attack tumours. This approach transforms 'cold' or resistant tumours into 'hot'. The disclosed programmes in this platform are STING pathway agonists and HPK1 inhibitors.

Immunoncology: STING agonists

The most advanced immunoncology project in this platform is small molecule STING (stimulator of interferon genes) pathway agonists. A STING receptor is a known mediator of the immune system, which when activated induces expression of type I interferon and other T-cell recruitment factors. This results in the activation of dendritic cells, which act as antigen presenting cells. The ultimate outcome is the specific immune response with 'trained' CD8+ T-cells attacking the cancer. The strategic opportunity for STING agonists could be patients not responding to checkpoint inhibitors (CPIs), but there is also potential for use in combination with CPIs.

Ryvu's STING molecules are a potentially best-in-class, non-nucleotide, non-macrocyclic, small molecule, direct STING agonist, a direct protein binder to multiple STING haplotypes. This unique structure and optimised absorption, distribution, metabolism and excretion (ADME) properties together with a possibility of systemic delivery as antibody-drug conjugate payloads distinguish Ryvu's compounds from competitors that develop derivatives of nucleic acid, which, due to their chemical nature, are mainly used for inconvenient intratumoural injections. Activity across STING haplotypes potentially broadens the patient populations that could respond to treatment.

Ryvu is **optimising the lead series of molecules** and **has conducted initial in vivo proof-of-concept studies** and will select a drug candidate for further preclinical development.

Immunoncology: HPK1 inhibitors

A more recently introduced project involves hematopoietic progenitor kinase 1 (HPK1), one of the major proteins in the T-cell receptor (TCR) signalling cascade. Inhibition of HPK1 could potentially have synergies with established immunotherapies like checkpoint inhibitors by addressing immune suppression in the tumour microenvironment and cancer immune response evasion. The main strength of HPK1 inhibitors lies in their ability to simultaneously activate dendritic cells and T cells, which potentially makes them a unique immunotherapy for cancer with potential to treat both 'cold' and 'hot' tumours. Optimisation of the chemical series is currently underway to identify a lead candidate for in vivo proof-of-concept studies. Ryvu is **optimising the lead series of molecules.**

Synthetic lethality

The lead projects in this area are in the discovery stages and focus on **WRN (Werner syndrome helicase) inhibitors** and **cancers with a deletion of the metabolic MTAP gene**. Due to competition, little information has been disclosed about the latter. WRN is a DNA unwinding helicase playing a role in DNA repair and genome integrity maintenance. Inhibition of WRN helicase activity impairs viability of tumour cells with so called microsatellite instability (MSI). MSI is a feature in a number of major cancer indications, where checkpoint inhibitors are widely used, however, the efficacy is usually less than 50%. The strategic opportunity for WRN inhibitors, therefore, is attractive in these indications (whether single agent or in combination with checkpoint inhibitors will be decided as the project progresses). Ryvu has **started the hit expansion phase**.

Nodthera

A project in the inflammation field, NLRP3 inflammasome inhibitors, was spun out to NodThera and seeded together with Epidarex Capital in 2016 (see our report for a detailed overview). Ryvu's last reported ownership is 6.07% on a fully diluted basis, which should fall to 4.8% after all tranches from the B series are issued. During the latest funding round NodThera raised £44.5m from a syndicate of new investors including Novo Holdings, Cowen Healthcare Investments and Sanofi Ventures, as well as the existing shareholders 5AM Ventures, F-Prime Capital Partners, Sofinnova Partners and Epidarex Capital. The funds raised by NodThera now total to £80.8m since 2016.

NLRP3 inflammasome inhibitors, a first-in-class technology, are based on the scientific programme originated and developed at Ryvu since 2012. Inflammasomes have been identified as the molecular mechanism behind the activation cascade of interleukin (IL)-1. IL-1 is a family of pro-inflammatory cytokines that have been widely implicated in pain, inflammation and autoimmune conditions and more recently in cancer. The fact that NodThera is attracting such well-known investors in the industry shows that Ryvu is capable of discovering cutting-edge technology.

Financials

Ryvu has changed reporting standards to IFRS in 2020 and restated its 2019 results, which we now use for our estimates. Following the corporate split in 2019, Ryvu has been the beneficiary of most of the grant funding, as it is tied to R&D projects. The company booked PLN14.5m in grant funding in the first nine months of 2020 (9M20) (vs PLN22.3m in 9M19). Licensing income was PLN15.2m in 9M20 (vs PLN3.1m in 9M19), which included a €1.75m grant from Menarini after the completion of the Phase I trial with SEL24/MEN1703 and an upfront of €1.5m from Galapagos after the two companies signed a research and development cooperation agreement.

Ryvu reported a significantly improved cash position of PLN164m (net cash of PLN161m) at the end of Q320 after the share issue in July 2020. The company raised in total PLN135m net by issuing c 2.4m new shares (15% of the total number of shares outstanding prior to the issue) at PLN60 per share.

As a pure-play biotech, Ryvu reports operating losses, partially offset by the stable grant income. The 9M20 operating loss of PLN24.2m was lower than PLN34.3m in 9M19 mainly because of licensing and grant income, both of which can fluctuate on a quarterly basis. Total 9M20 operating expenses were largely similar year-on-year (PLN54.2m in 9M20 vs PLN60.1m in 9M19). Ryvu has also completed the building of its new R&D centre, which is the main reason for capex of PLN28.2m in 9M20 and PLN24.0m in 2019.

Valuation

Our valuation of Ryvu is PLN1.17bn or PLN63.6 per share, compared to PLN1.10bn or PLN68.9 per share previously. The R&D assumption changes had a slight net negative effect, which was partially offset by the improved cash position after the recent share issue. We have made changes to our rNPV valuation in line with Ryvu's revision of its R&D pipeline. Namely:

- We have removed A2A/A2B antagonist and SMARCA2 inhibitor projects.
- We have added a new indication – TNBC – for SEL120 with the assumptions listed in Exhibit 7. We note that so far, we have included only one solid tumour indication, but Ryvu has clearly stated that it is evaluating other cancers, which will be evaluated in the upcoming trial.
- We have delayed the SEL24/MEN1703 and SEL120 in AML projects by roughly one year and delayed the licensing deal in the STING project from 2021 to 2023 due to the prolonged effect of the COVID-19 pandemic.

Our updated analysis indicates that Ryvu has largely maintained the overall value of its pipeline despite the discontinuation of the two preclinical projects. This is mainly because the pipeline has shifted toward clinical-stage trials, as although they require larger investments, the value creation is much more rapid. Some of the catalysts for the share price expected over the next 12–18 months include:

- Final readout from a Phase II trial with SEL24/MEN1703 is planned in 2022, although this ultimately depends on the decision of Joint Steering Committee of Menarini and Ryvu.
- SEL120 interim data from the Phase Ib AML-HR-MDS study (2021).
- Initiation of the Phase I trial with SEL120 in solid tumours.
- New data publications from preclinical projects.
- Potential licensing deal for one or more of the earlier projects.

Exhibit 6: Sum-of-the-parts Ryvu valuation

Product		Peak sales ($m)	NPV (PLNm)	NPV/share (PLN)	Probability	rNPV (PLNm)	rNPV/share (PLN)
SEL24/MEN1703	Relapsed/refractory AML	750	895.9	48.8	15%	174.1	9.5
SEL120	AML or high-risk myelodysplastic syndrome	1,500	2,082.1	113.4	15%	329.3	17.9
SEL120	Triple negative breast cancer	2,000	1,695.4	92.4	10%	328.1	17.9
STING agonist	Solid tumours	1,000	1,027.7	56.0	2%	162.0	8.8
Merck collaborations		2,000	64.9	3.5	5%	12.8	0.7
Net cash (last reported)					100%	161.1	8.8
Valuation			**5,766.0**	**314.1**		**1,167.3**	**63.6**

Source: Edison Investment Research. Note: WACC = 12.5% for product valuations.

Exhibit 7: Assumptions for R&D projects and services business

Product/stage/ indication	Comments
SEL24/MEN1703 – Phase I/II – r/r AML	Market potential: $750m indicative peak sales. R&D costs and timelines: Menarini is sponsoring the clinical trials and Ryvu will not incur any R&D costs. We assume launch in 2024 with peak sales reached in six years. Licensing terms: Menarini deal terms include an upfront payment of €4.8m, a total of €89.1m in potential milestone payments and non-specified single- to low-double-digit royalties (we assume up to 10%). Market protection: until mid-to-late 2030.
SEL120 – Phase Ib – AML or HR-MDS – TNBC	Market potential: $1.5bn indicative peak sales for AML and TNBC, mainly to reflect blockbuster potential of SEL120 (top-down approach; due to early stage of the projects, bottom-up modelling is premature). R&D costs and timelines: ■ AML: $13m in R&D costs for Ryvu to develop the drug through the reminder of Phase Ib to end of Phase II. Then out-licensing in 2023. The partner continues the development and launches in 2027–28 with peak sales reached in six years. ■ TNBC: same assumptions as with AML, out-licensing in 2024. Licensing terms: As previously, in Phase II we assume a licensing deal with terms similar to the Novartis/Astex deal, which involved CDK4/6 inhibitor Kisqali (ribociclib) in Phase I (mechanism of action different although same class). Novartis paid $520m in total. Upfront was undisclosed; we use 5% of the milestone value $26m. We assume up to 15% royalty rates. Market protection: until mid-to-late 2030.
STING agonist	Market potential: $1bn indicative peak sales (top-down approach; due to early stage of the projects, bottom-up modelling is premature). STING agonists have broad potential to be used in combinations with other chemotherapeutic agents and immunoncology drugs. R&D costs and timelines: We assume that a clinical candidate will be partnered in 2023. We assume the R&D cost for Ryvu to develop the asset to a partnership deal is $5m (through the remaining preclinical studies and Phase I). Phase II will start in 2024, and the partner continues the development and launches in 2031 with peak sales reached in six years. Licensing terms: We use the terms of the deal between Aduro and Eli Lilly involving the preclinical-stage STING asset. Lilly paid $12m upfront and $620m in milestone payments. We assume 10% royalty rates. An earlier deal between Aduro and Novartis was even more impressive, where Novartis paid $200m upfront, invested $25m in Aduro, while up to $500m are due in milestones. We use the deal with Lilly to err on the conservative side and due to the fact that it is the most recent one. Market protection: until late 2030
Cancer metabolism and immunometabolism platform	
Merck deals #1 and #2 – preclinical – cancer	Technology remains undisclosed. We assume two projects with launch in 2028 and peak sales of $1bn in each project in 2034. Licensing fee €0.2m; total milestone payments could add up to €16.5m in each deal. Royalties have not been disclosed; we assume up to 2%.

Source: Edison Investment Research

Exhibit 8: Financial summary

PLN'000s	2019	2020e	2021e
Year end 31 December	IFRS	IFRS	IFRS
PROFIT & LOSS			
Revenue	33,720	34,501	19,337
EBITDA	(37,397)	(28,862)	(57,748)
Operating Profit	(45,385)	(37,001)	(65,888)
Net Interest	347	347	347
Other	0	0	0
Profit Before Tax (norm)	(45,038)	(36,654)	(65,540)
Profit Before Tax (reported)	(45,038)	(36,654)	(65,540)
Tax	(161)	(161)	(161)
Profit After Tax (norm)	(45,199)	(36,815)	(65,701)
Profit After Tax (reported)	(45,199)	(36,815)	(65,701)
Average Number of Shares Outstanding (m)	16.0	17.2	18.4
EPS - normalised (PLN)	(2.83)	(2.14)	(3.58)
EPS - reported (PLN)	(2.83)	(2.14)	(3.58)
Dividend per share (PLN)	0.0	0.0	0.0
BALANCE SHEET			
Fixed Assets	97,929	122,353	124,213
Intangible Assets	2,924	2,924	2,924
Tangible Assets	62,249	82,312	84,172
Other	32,756	37,117	37,117
Current Assets	89,976	154,718	87,157
Stocks	1,586	1,586	1,586
Debtors	14,681	9,681	9,681
Cash	72,107	141,849	74,287
Other	1,603	1,603	1,603
Current Liabilities	(31,364)	(18,141)	(18,141)
Creditors	(22,636)	(10,636)	(10,636)
Deferred income	(2,299)	(2,299)	(2,299)
Short term borrowings	(824)	(824)	(824)
Other	(5,605)	(4,383)	(4,383)
Long Term Liabilities	(35,961)	(35,961)	(35,961)
Long term borrowings	(2,362)	(2,362)	(2,362)
Deferred revenues	(21,184)	(21,184)	(21,184)
Other long-term liabilities	(12,415)	(12,415)	(12,415)
Net Assets	120,580	222,969	157,268
CASH FLOW			
Operating Cash Flow	(17,401)	(36,898)	(57,562)
Capex	(23,995)	(28,202)	(10,000)
Acquisitions/disposals	(2,989)	0	0
Financing	0	134,842	0
Other	22,457	0	0
Net Cash Flow	(21,927)	69,742	(67,562)
Opening net debt/(cash)	(90,805)	(68,921)	(138,663)
Other	44	(0)	0
Closing net debt/(cash)	(68,921)	(138,663)	(71,101)

Source: Edison Investment Research, Ryvu accounts. Note: Ryvu changed reporting standards to IFRS in 2020 and restated the 2019 results.

Contact details	Revenue by geography
R&D Center for Innovative Drugs Leona Henryka Sternbacha 2 30-394 Kraków, Poland +48 12 314 02 00 www.ryvu.com	N/A

Management team

Chief executive officer (co-founder): Paweł Przewięźlikowski	Chief scientific officer: Krzysztof Brzózka
Paweł Przewięźlikowski co-founded Ryvu in 2007. From 1994 to 2007 he worked at Comarch, a Polish information technology company, becoming VP on the management board in 1996. While at Comarch, he was also the co-founder and the first CEO of Interia, the third largest online portal in Poland. He holds an MBA and MSc in information technology.	Krzysztof Brzózka joined Ryvu in 2007, became project manager (oncology compound) in 2009 and was appointed CSO in 2012. From 2003 to 2007 Krzysztof worked on a broad immunology research programme at Ludwig Maximillian University (Munich). He holds a PhD (molecular biology), an MSc and an MBA.
Chief Medical Officer: Setareh Shamsili	**Chief operating officer: Kamil Sitarz**
Dr Shamsili joined Ryvu in 2019 as the CMO. She brings more than 20 years of clinical oncology and drug development experience. Dr Shamsili was the first CMO of Merus NV, where she brought two initial candidates to the clinic for development in acute myeloid leukemia and the treatment of solid tumours. From 2006–12, she served as global medical leader oncology at Astellas Pharma Global Development. Dr Shamsili hold an MD degree a PhD in oncology.	Dr Sitarz joined Ryvu in 2013 as a senior scientist and biology leader and, after several promotions, in November 2020 he became the COO. He holds an MSc degree in biophysics and a PhD degree in human/medical genetics. Dr Sitarz is the co-author of a number of scientific publications in peer-reviewed journals.

Principal shareholders	(%)
Paweł Przewięźlikowski	27.19
Bogusław Sieczkowski	5.04
Augebit Investment Fund	6.17
Nationale-Nederlanden Open-End Pension Fund and Nationale–Nederlanden Voluntary Pension Fund	8.68

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