Targeted therapeutics at the forefront of oncology

CORPORATE PRESENTATION

September 2021
Note on the presentation and forward looking statements

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Ryvu at a glance

Clinical Pipeline Across Heme and Solid Tumors

RVU120
- Wholly owned, first-in-class, selective, oral CDK8/19 inhibitor
- Phase Ib study in AML/MDS: Early signs of efficacy reported at EHA 2021; further enrollment ongoing
- Phase Ib study in solid tumors: FPI August 2021

SEL24
- First-in-class dual PIM/FLT3 kinase inhibitor for AML in Phase II
- Single agent efficacy and acceptable safety profile demonstrated in r/r AML, enrollment in IDH+ patients ongoing
- Partnered with Menarini

Small Molecule Platform with Differentiated Synthetic Lethality Targets

Developing small molecule therapies which address high value emerging targets and pathways in oncology

- Synthetic Lethality: WRN, PRMT5, Novel SL targets
- Immuno-Oncology: HPK1, STING

Robust internal drug discovery engine (130 FTEs)
Partnerships including Galapagos and Merck

Listed on Warsaw Stock Exchange, market cap of $285m
- One of the largest drug discovery companies in the region, headquartered in Kraków, Poland
- ~$25.3m cash position and significant non-dilutive grant funding (>$25m secured for the period 2021-2023)
### Broad pipeline addressing emerging targets in oncology

#### CLINICAL PROJECTS

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<thead>
<tr>
<th>PROGRAM / TARGET NAME</th>
<th>INDICATION</th>
<th>DISCOVERY</th>
<th>PRECLINICAL</th>
<th>PHASE I</th>
<th>PHASE II</th>
<th>PARTNER</th>
<th>ANTICIPATED MILESTONES</th>
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<td>SEL24 (MEN1703)</td>
<td>AML</td>
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<td>Phase II data 2022</td>
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<td>RVU120 CDK8/19</td>
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<td>Additional Phase Ib data 4Q 2021</td>
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<td></td>
<td>SOLID TUMORS</td>
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<td>Initial Phase I data H1 2022</td>
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#### DISCOVERY & PRECLINICAL PROJECTS

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<thead>
<tr>
<th>PROGRAM / TARGET NAME</th>
<th>INDICATION</th>
<th>DISCOVERY</th>
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<th>PHASE I</th>
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<td>NOVEL TARGETS</td>
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<td>HPK1</td>
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<td>Pre-clinical candidate 2022</td>
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<td>STING</td>
<td>SOLID TUMORS</td>
<td></td>
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<td>IND filing 2022</td>
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#### DISCOVERY COLLABORATIONS

Galápagos  
Merck
Strong momentum since the focusing of Ryvu Therapeutics as a standalone oncology biotech

- **10.2019**
  - Corporate spin-out of Selvita (CRO) from Ryvu Therapeutics completed, >$100m incremental value created for Ryvu shareholders

- **03.2020**
  - SEL24 – successfully completed Phase I in acute myeloid leukemia
  - RVU120 – orphan drug designation in AML by FDA

- **04.2020**
  - Collaboration with Galapagos in inflammatory disorders

- **07.2020**
  - Completed construction and move into a new fully-owned $20m research center in Krakow
  - $38m (PLN143m) raised in a follow-on public offering
  - First patient dosed with SEL24 in Phase II study

- **01.2021**
  - Clinical Trial Application approved for RVU120 AML/MDS Phase Ib sites in Europe

- **02.2021**
  - Secured $5.5m non-dilutive grant funding for RVU120 in solid tumors

- **06.2021**
  - Preliminary positive RVU120 Phase I clinical and preclinical data presented at EHA2021
  - Positive SEL24(MEN1703) Phase II clinical data presented at EHA2021

- **08.2021**
  - First patient dosed with RVU120 in Phase I/II solid tumor study
Clinical Candidates in Hematology and Solid Tumors
RVU120: Highly selective first-in-class CDK8/CDK19 inhibitor with broad potential in hematological malignancies and solid tumors

**RVU120**

<table>
<thead>
<tr>
<th>BLOOD CANKERS</th>
<th>SOLID TUMORS</th>
<th>BLOOD DISORDERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML</td>
<td>Breast</td>
<td>Diamond-Blackfan Anemia (DBA)</td>
</tr>
<tr>
<td>JAK2 mut</td>
<td>Prostate</td>
<td></td>
</tr>
<tr>
<td>AML/MPN</td>
<td>Other</td>
<td></td>
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<tr>
<td>MDS</td>
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<tr>
<td>ALL, NHL</td>
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**RVU120 Rationale/ Opportunity**

- Direct cytotoxicity (induction of apoptosis)
- Eradication of Leukemic Stem Cells (LSC), responsible for tumor relapse in AML
- Preclinical data indicate safe and synergistic combination with chemo and targeted therapies
- Targeted MOA by transcriptional regulation of cancer-dependent genes
- Preclinical data to support broad potential in multiple solid tumors
- Modulation of immune cell activity (NK cells)
- Translational data to support erythroid differentiation, reversing anemia
- High unmet need in an orphan indication

**Orphan drug designation in AML in 2020**

**Therapy Acceleration Program (TAP) grant support**

**Total funding: $3.25m**
Targeting CDK8/19 with RVU120 has rationale as an effective and safe oncology therapeutic

**CDK8/19 is a differentiated anti-cancer target**

CDK8 is a kinase subunit of the Mediator complex involved in
- regulation of Pol II mediated transcription including expression of pro/anti-apoptotic genes
- regulation of super enhancers (SE)
- regulation of cellular differentiation processes

Unique MoA differentiates CDK8/CDK19 from other CDK family members
- Does not interfere with cell cycle progression (like CDK1, CDK2, CDK4/6)
- Unique across mediators of transcriptional reprogramming (induction of silent genes, not physiological transcription) preventing metastasis and drug-resistance
- Different stratification of responders and biomarkers of response

**CDK8/19 inhibitors designed to provide targeted and safer treatment options**
- Selective targeting of cancer cells while sparing healthy ones unlike other CDK Inhibitors (e.g. CDK4/6, CDK9 affect both normal and cancer cells – possible cytopenias, no bone marrow recovery)
- Selective regulation of transcription in a cancer gene specific context

**RVU120 is a potent and selective CDK8/CDK19 inhibitor**

Low nM activity on CDK8/CDK19 and excellent kinase selectivity (broad kinome)

- Internally discovered by Ryvu
- Spares CDK2, CDK4, CDK6, CDK7, CDK9, etc.
- Type I, ATP-competitive mechanism of binding and inhibition of CDK8/19 activity
- Lack of binding to off-targets potentially associated with toxicity of pre-clinical EMD Serono CDK8/19 inhibitors (such as JNK1 or GSK3b)¹
- Higher selectivity based on comparison of gene expression effects²
- Composition of matter patents valid until 2033

¹Chen et al. 2019
²Rzymski et al. 2017

CDK8 is a kinase subunit of the Mediator complex involved in
- regulation of Pol II mediated transcription including expression of pro/anti-apoptotic genes
- regulation of super enhancers (SE)
- regulation of cellular differentiation processes

CDK8/19 inhibitors designed to provide targeted and safer treatment options
- Selective targeting of cancer cells while sparing healthy ones unlike other CDK Inhibitors (e.g. CDK4/6, CDK9 affect both normal and cancer cells – possible cytopenias, no bone marrow recovery)
- Selective regulation of transcription in a cancer gene specific context
Unmet needs in acute myeloid leukemia may be addressed with RVU120 and SEL24

Most common, highly aggressive type of acute leukemia in adults with poor outcomes in most patients

~20,000 new cases diagnosed and >11,000 deaths in the US in 2018

AML makes up 1% of all cancers and 34% of all adult leukemia cases

Occurs in a predominantly elderly, frail patient population; 75% of patients diagnosed with AML were aged >60 years

Lowest survival among all blood cancers; only 26% of patients survive 5 years after diagnosis

30% AML patients with an ITD mutation in the FLT3 gene have a less favorable prognosis; 70% of patients are refractory to current inhibitors targeting FLT3 mutation

2020 AML Market

$1.2 billion

46% CAGR

2025 AML Market

$8.0 billion

References:
1 Mayo Clinic
2 Cancer.net
3 Leukemia & Lymphoma Society
4 Walter, R; Leukemia 2015
5 Evaluate Pharma
**Clinical landscape: targeted small molecule therapies for AML**

<table>
<thead>
<tr>
<th>FIRST-IN-CLASS</th>
<th>CDK8/CDK19</th>
<th>FLT3</th>
<th>Dual PIM/FLT3</th>
<th>PIM</th>
<th>IDH1 or IDH2</th>
<th>Others</th>
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<tr>
<td><strong>RYVU CLINICAL PROGRAMS</strong></td>
<td><strong>DESIGNED TO FULFILL UNMET NEEDS IN AML</strong></td>
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<tr>
<td>RVU120 IS THE ONLY CDK8/CDK19 INHIBITOR IN CLINICAL DEVELOPMENT</td>
<td>SEL24 (MEN1703) IS A UNIQUE, CLINICAL-STAGE DUAL PIM/FLT3 INHIBITOR</td>
<td></td>
<td>RYVU CLINICAL PROGRAMS DESIGNED TO FULFILL UNMET NEEDS IN AML</td>
<td>OVERCOMING RESISTANCE TO SINGLE-TARGET MUTATION-SPECIFIC INHIBITORS</td>
<td>EFFICACY IN BROADER PATIENT POPULATIONS</td>
<td>REDUCING CHEMOTHERAPY-BASED TREATMENT REGIMENS</td>
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<tr>
<td>Phase 1/2</td>
<td>Phase 3</td>
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- RYVU THERAPEUTICS
- RVU120
- SEL24 (MEN1703)
- Hanmi
- arog
- XOSPATA
- RYDAPT
- Nexavar
- MEI Pharma
- MEI
- SYROS
- GlycoMimetics, Inc.
- Venetoclax
- DAURISMO
- BerGenBio
- Aptose
- Oryzon
- Apellis
- Rafael
- Forma Therapeutics
- Novartis
- IMmunoGeneTics
- IDH1
- IDH2
- SFDP Pharma
- RYVU
- MZNARINI
- Incyte
- TIBSOVO
- IDH1RA
- IDHI2A
- RYVU
- MEI
- SYROS
- GlycoMimetics, Inc.
Transcriptional deregulation is a hallmark of AML.

CDK8 is a kinase subunit of the Mediator complex, serving as a bridge between basal transcription and regulatory elements involved in:
- Deregulation of super enhancers (SE)
- Affected differentiation and pro/anti-apoptotic genes

**RATIONALE FOR CDK8/CDK19 INHIBITORS IN AML**

- Transcriptional deregulation is a hallmark of AML
- CDK8 is a kinase subunit of the Mediator complex serving as a bridge between basal transcription and regulatory elements involved in:
  - Deregulation of super enhancers (SE)
  - Affected differentiation and pro/anti-apoptotic genes

**EFFICACY OF RVU120 - CDK8/CDK19 INHIBITOR - IN AML**

- Selectively targets leukemic cells, sparing normal blood cells (unaffected normal hematopoiesis)
- Promotes cell death (differential cytotoxicity on STAT5+ AML)
- Represses increased levels of anti-apoptotic proteins and induces lineage commitment genes in undifferentiated AML cells
RVU120: Preclinical data support key clinical features

- Excellent on-target activity of RVU120 in pSTAT positive AML cell models
- RVU120 is a potent and selective CDK8/CDK19 inhibitor
- pSTAT1/pSTAT5 levels and stemness markers discriminate responders/non-responders in vitro
- RVU120 induces complete regression and bone marrow recovery in AML PDX models in vivo

Experiments performed in CD34+ AML patient-derived xenografts:

- Complete regression (peripheral blood)
- Hematologic recovery (bone marrow)

RVU120 strongly synergizes with venetoclax in vitro and in vivo
- RVU120 potentially addresses treatment resistant disease through safe, indirect MCL-1 downregulation in cancer cells
- Compelling potential for RVU120 in combination with venetoclax
RVU120: Phase Ib AML/MDS study – initial data presented at EHA 2021

Patients with Acute Myeloid Leukemia or Myelodysplastic Syndrome

> STUDY POPULATION:
- Patients with relapsed/refractory AML or high risk MDS
- No upfront patient stratification

> PRIMARY OBJECTIVE:
- To assess safety and tolerability
- To determine the recommended dose

> SECONDARY OBJECTIVE:
- To evaluate pharmacokinetics
- To evaluate the preliminary anti-leukemic activity

> EXPLORATORY OBJECTIVE:
- To evaluate pharmacodynamics

PROJECT MILESTONES

2Q 2021
INITIAL RESULTS FROM PHASE Ib at EHA

H2 2021
ADDITIONAL RESULTS FROM PHASE Ib

H1 2022
PHASE Ib COMPLETION

H2 2022
PHASE II IN AML/MDS

STATUS AND PLANS

5 SITES IN US

SITE EXPANSION in EUROPE
2 sites in Poland to be activated in September 2021
RVU120 Phase I AML/MDS study design

**PART 1: ESTABLISHING RECOMMENDED PHASE 2 DOSE (RP2D)**

- **COHORT 1**
- **COHORT 2**
- **COHORT 3**
- **UP to 8 COHORTS**

**RP2D MTD**

**SAFETY, EFFICACY, PK, PD**

**PART 2: SAFETY EXPANSION**

- **SAFEY EXPANSION**
  - Average of 24 PATIENTS
  - 6 PATIENTS

**EXPANSION FROM THE SINGLE PATIENT COHORT TO A 3+3 DESIGN**

- DLTs evaluated at completion of cycle 1 in each cohort

**ORAL DOSE**

- Three week cycle: Single dose every other day for a total of 7 doses/cycle followed by one week off

**H2 2019-2021**

**Q1-Q2 2022**

**2022 START**

**PHASE II**

- **AML SINGLE AGENT**
  - Front line: Triplet with venetoclax

- **AML COMBINATION**
  - Front line: Triplet with venetoclax

- **MDS SINGLE AGENT**

- **MDS COMBINATION**
  - Front Line with SOC HMAs
RVU120 Phase I data show acceptable safety and PK characteristics

RVU120/SEL120 PRELIMINARY RESULTS FROM INITIAL DOSE ESCALATION COHORTS of CLI120-001 TRIAL: A PHASE1b STUDY OF SEL120/RVU120, SELECTIVE CDK 8/19 INHIBITOR, IN PATIENTS WITH AML OR HIGH RISK MDS

N. Angelosanto,1 C. Abboud,2 G. Borthakur,3 S. Solomon,4 W. Donnellan,5 J. Bendell,6 A. Nazha,7 A. Gerds,8 T. Bradley,9 J. M. Zaucha,9 E. Lech,8 M. Zara,9 K. Brzózka,1 T. Rzymski,1 J. Dow,1 E. Mouhayar,4 S. Shamsi1

SAFETY

• No DLTs were observed, 4 SAEs were reported/assessed by the investigator as unlikely or not related to study drug

PK ANALYSIS

• PK analysis performed using plasma samples collected at C1D1 and C1D13
• Relatively rapid absorption, linear exposure with doses between 10-75 mg, plasma half-life from 22 to 40 hr
• Low accumulation, based on half-life or the ratio of AUC D13/D1;
• Low within patient variability of plasma concentrations of RVU 120, over at least 6 cycles
RVU120 Phase I data show early signs of efficacy in AML and MDS

Of the first five patients enrolled (across the first four dose cohorts), clinically relevant responses were seen in patients in the two higher dose cohorts:

- **Cohort 3 patient** (50mg, escalated to 75mg): HRMDS, demonstrated an **erythroid response**
- **Cohort 4 patient** (75mg): R/R AML, response in C2 improved to **Complete Remission (CR)** in C7

**INITIAL EFFICACY**

<table>
<thead>
<tr>
<th>MDS</th>
<th>AML</th>
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<tbody>
<tr>
<td>SD</td>
<td>SD</td>
<td>PD</td>
<td>SD</td>
<td>SD</td>
<td>PD</td>
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</table>

**Cycles completed/Response/Reason for discontinuation**

Data cutoff: 20 May 2021

- **SD** = Stable Disease, **PD** = Progressive Disease, **CR** = Complete Remission, **ER** = Erythroid Response, **R** = Relapsed Disease.
Case Focus: Cohort 4 AML patient achieved CR despite poor prognostics

**COHORT 4 AML PATIENT:**

- FLT3+ and NPM1+ AML
- Failed 3 prior lines of therapy, including 2 FLT3 inhibitors and venetoclax+decitabine – known to be associated with poor prognosis (median OS 2.4 months\(^1\))
- Received 75mg dose
- Showed fast clearance of bone marrow blasts at C1D17, and recovery in platelets and absolute neutrophil count (ANC) from C2, but due to skin leukemia lesions, no CR was reportable at that time
- Skin leukemia gradually improved under RVU120 treatment up to complete resolution in C7, achieving a CR
- Patient progressed at the end of C8.


Case Focus: Cohort 3 HRMDS patient achieved erythroid response, and remains on study after one year of treatment with RVU120

- Failed 3 prior lines of therapy, including previous HMA, associated with median OS of 4.5 months
- Received 50mg dose and escalated to 75mg from C7
- Achieved an erythroid response according to Cheson Criteria from C5 and maintained the difference in the number of Red Blood Cells (RBC) units of at least 4 units in 8-week interval period vs baseline requirement up to C7, with a new increase (but lower than baseline) in transfusion requirement after D15 of C7
- Patient was first dosed on August 26, 2020 and remains on treatment after more than 12 months (C16) with SD


Translational data support erythroid differentiation potential of RVU120

Anemia in Chronic Hematological Diseases

- Anemia in chronic hematological diseases may occur due to ineffective erythropoiesis, causing an imbalance in various progenitor and precursor cells that proliferate, differentiate and mature into red blood cells.
- Anemia is a hallmark of several diseases such as myelodysplastic syndrome and Diamond-Blackfan anemia.

RVU120 Induces Erythroid Differentiation

- RVU120 induces erythroid differentiation in (Lin-) CD34+, that acquired genetic abnormalities characteristic for MDS/AML and DBA.

RVU120 INDUCES COMMITMENT INTO ERYTHROID LINEAGE IN LEUKEMIC CELL MODEL

- TEX: primary model for POC studies showing erythroid commitment potential of RVU120.
- Model is based on CD34+ hematopoietic progenitor cells transformed with TLS-ERG - a fusion gene of (16;21)(p11;q22) translocation, associated with primary AML and secondary MDS/AML.
- Transformed cells displayed increased capacity for self-renewal, proliferation and altered erythroid differentiation.

RVU120 induces erythroid differentiation measured by increasing number of CD47+/CD71+ erythroid lineage cells and gradual decrease of CD34+/CD38- undifferentiated hematopoietic progenitor cells.

Erythroid master regulators such as GATA1 are transcriptionally induced by RVU120 by the mechanism involving displacement of CDK8 from TSS, which can be occupied by Pol2.

Rzymski et al, EHA 2021, S164, Oral Session

RVU120 beyond blood cancers: potential role of CDK8/CDK19 in solid tumors

RVU120: expansion plan in multiple solid tumors and other heme malignancies

Phase I ongoing, preliminary results: 2022

CDK8/CDK19 inhibitors have potential in multiple solid tumors

- Confirmed *in vitro* or *in vivo* potential in breast, colorectal and prostate cancer

Chart inspired by Pharmaceuticals 2019, 12,92 + Ryvu data
RVU120: development in solid tumors and other heme malignancies
First patient dosed in August 2021. Enrollment ongoing; preliminary results in 2022

PART 1: ESTABLISHING RECOMMENDED DOSE

A 3+3 STUDY DESIGN
18 PATIENTS
DLTs evaluated at completion of cycle 1 in each cohort

PART 2: EFFICACY & SAFETY EXPANSION SIMON 2-STAGE

STAGE 1
14 PATIENTS
R/R mTNBC
+ 10 PATIENTS
UP TO 3 OTHER SOLID TUMORS
SAFETY, EFFICACY, PK, PD

STAGE 2
UP TO 20 PATIENTS
+ 10 PATIENTS

RP2D determined

SINGLE ORAL DOSE EOD
7 DOSES/CYCLE
3 WEEK CYCLE

Go/no-go decision to enroll next 10 patients based on RECIST ORR after cycle 3

PFS at 9 months
Overall survival follow-up: 2 years
SEL24 (MEN1703) is a differentiated, first-in-class PIM/FLT3 dual kinase inhibitor

1. PIM and FLT3 are oncogenes involved in AML.
2. Dual targeting creates potential for broader activity, more durable responses than selective FLT3 inhibitors such as gilteritinib.
3. Potential for treating patients that have relapsed on selective FLT3 inhibitors – PIM kinases are largely responsible for the development of resistance to FLT3 inhibitors.

VALUE THROUGH GLOBAL DEAL WITH

- Partnered globally with Menarini in 2017
- Menarini is fully responsible for clinical development and funds translational research at Ryvu
- Ryvu eligible to receive >$100M in milestones and double-digit royalties

PHASE I/II CLINICAL STUDY

Study title: A Phase I/II Study of SEL24 in Patients With Acute Myeloid Leukemia

INITIAL RESULTS OF THE PHASE I STUDY:
- Determined the recommended Phase II dose (RP2D), the PK profile and the single agent activity in R/R or newly diagnosed AML patients; study results published at EHA 2020 Conference in June 2020
- Ryvu has received $1.9m milestone payment for successful completion of Phase I studies

INITIAL RESULTS OF THE PHASE I/II STUDY (ASH 2020, EHA 2021)
- As of January 21, 2021 (cut-off date), n=48 pts were treated across the dose escalation (DE, n=25) and Phase II cohort expansion (CE, n=23).
- Confirmed pS6 biomarker inhibition
- Across DE and CE, 4 CR/CRi occurred, three of which in pts with IDH mutations.
- A total of 3 out of 5 pts with IDH mutations treated at doses ≥75 mg achieved CR/CRi, including a CR in a patient with IDH2 mutant AML relapsed on Enasidenib.

FOLLOW-UP PHASE II STUDY IN PATIENTS WITH IDH MUTATION INITIATED IN JULY 2021
**SEL24 (MEN1703) Phase II data confirm manageable safety profile**

**RESULTS FROM DIAMOND-01 (CLI24-001) TRIAL: FIRST IN HUMAN STUDY OF SEL24/MEN1703, A DUAL PIM/FLT3 KINASE INHIBITOR, IN PATIENTS WITH ACUTE MYELOID LEUKEMIA**

Scott Solomon,1 Pau Montesinos,2 Joz Naiha,3 Stephen Strickland,4 Giovanni Martinelli5 Armando Santoro,6 Roland Walter,7 Rachel Cook,8 Maria Calbado,9 Susan Vives,10 Salimani Faizal,11 Krzysztof Brzózka,12 Setareh Parvaz,12 Simone Baldini,13 Andrea Pellecan,13 Farhad Ravanani,14

**RESULTS**

- 48 patients were treated: in DE (n = 25) and in CE (n = 23) part
- Data cut-off date: April 19, 2021

**SAFETY**

- At RD, SEL24/MEN1703 showed a manageable safety profile with most Grade ≥3 treatment-emergent AEs (TEAEs) being hematologic or infectious

<table>
<thead>
<tr>
<th>Grade ≥3 TEAEs (incidence &gt;10%) at RD (125 mg, N=30)</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile neutropenia</td>
<td>9 (30.0%)</td>
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<tr>
<td>Pneumonia</td>
<td>9 (30.0%)</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>6 (20.0%)</td>
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<tr>
<td>Sepsis</td>
<td>4 (13.3%)</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>4 (13.3%)</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>4 (13.3%)</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>4 (13.3%)</td>
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</table>

**DEMOGRAPHICS AND BASELINE PATIENT CHARACTERISTICS**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Median (range)</th>
<th>All (n=48)</th>
<th>125 mg (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>69 (25-84)</td>
<td>69.5 (38-83)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reason for inclusion, n (%)</th>
<th>Newly diagnosed AML</th>
<th>3 (6.3%)</th>
<th>2 (6.7%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary refractory AML</td>
<td>16 (33.3%)</td>
<td>7 (23.3%)</td>
<td></td>
</tr>
<tr>
<td>Relapsed AML</td>
<td>29 (60.4%)</td>
<td>21 (70.0%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AML status, n (%)</th>
<th>De novo AML</th>
<th>27 (56.3%)</th>
<th>16 (53.3%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non De novo AML</td>
<td>21 (43.7%)</td>
<td>14 (46.7%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cytogenetics, n (%)</th>
<th>Favorable</th>
<th>7 (14.6%)</th>
<th>3 (10.0%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate</td>
<td>6 (12.5%)</td>
<td>4 (13.3%)</td>
<td></td>
</tr>
<tr>
<td>Unfavorable</td>
<td>22 (45.8%)</td>
<td>15 (50.0%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>11 (22.9%)</td>
<td>8 (26.7%)</td>
<td></td>
</tr>
</tbody>
</table>

**Most frequent mutations, n (%)**

| FLT3/ITD | 12 (25.0%) | 8 (26.7%) |
| FLT3/TKD | 1 (2.1%)   | 1 (3.3%)  |
| DNMT3A   | 7 (14.6%)  | 3 (10.0%) |
| IDH1     | 6 (12.5%)  | 2 (6.7%)  |
| IDH2     | 2 (4.2%)   | 0 (0.0%)  |
| NPM1     | 7 (14.6%)  | 5 (16.7%) |
SEL24 (MEN1703) showed single agent efficacy in R/R AML patients, in particular in IDH+ population

- Objective responses have been reported in 4 out of 48 patients (8%) across DE and CE phases, with 3 out of 4 responders harboring IDH mutations
- Median number of cycles in responding patients was 7 (Range 7-8)
- 3 out of 5 patients with IDH mutations treated at doses 75-125 mg achieved CR/CRi, including a CR in a patient relapsed on enasidenib
- 1 patient with IDH1 mutation achieved CRi and underwent allogeneic-HSCT

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Age</th>
<th>Dose Level</th>
<th>AML Status</th>
<th>Reason for inclusion</th>
<th>Cytophysiology</th>
<th>Mutations</th>
<th>No of cycles</th>
<th>Response by cycle #</th>
</tr>
</thead>
<tbody>
<tr>
<td>004-012</td>
<td>81</td>
<td>75 mg</td>
<td>de novo AML</td>
<td>Relapsed AML</td>
<td>Intermediate</td>
<td>DNMT3, IDH2</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>004-022</td>
<td>75</td>
<td>125 mg</td>
<td>AML post MDS</td>
<td>Relapsed AML</td>
<td>Unfavourable</td>
<td>ASXL1, CUX1, DDX41 (C.3G&gt;A, R525H), EZH2, PRPF8</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>401-031</td>
<td>63</td>
<td>125 mg</td>
<td>AML post MDS</td>
<td>Relapsed AML</td>
<td>Unfavourable</td>
<td>IDH1</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>401-034</td>
<td>55</td>
<td>125 mg</td>
<td>de novo AML</td>
<td>Relapsed AML</td>
<td>Unfavourable</td>
<td>IDH1</td>
<td>7</td>
<td>3</td>
</tr>
</tbody>
</table>

- SEL24 (MEN1703) as single agent showed preliminary efficacy in R/R AML, particularly clustering in patients with IDH mutant disease
- FOLLOW-UP PHASE II STUDY IN PATIENTS WITH IDH MUTATION STARTED IN JULY 2021
- BROADER CLINICAL DEVELOPMENT PLAN in AML AND OTHER INDICATIONS AGREED WITH MENARINI
Small Molecule Platform with Focus on Synthetic Lethality
✓ **MultiDEP**: proprietary bioinformatic engine
  - Discovery of novel synthetic lethal target pairs
  - Enables multicomponent and multigene analysis to provide comprehensive, large-scale analysis, unprecedented among competitors

✓ Integrated, multidisciplinary processes: rapid lead identification/optimization with deep translational biology support

✓ Platform has delivered 2 projects in clinical development; multiple projects in discovery/research

✓ Team of ~150 scientists (with ~80 PhDs) with international expertise in drug discovery and track record in delivering new clinical candidates

✓ Broad portfolio of synthetic lethal and immuno-oncology targets at various stages of the cycle – clinical candidate selection to target validation and hit finding

**Synthetic Lethality**
- WRN, PRMT5, Novel SL targets

**Immuono-Oncology**
- HPK1, STING
Ryvu strategically utilizes synthetic lethality phenomenon to access new treatment modalities

- Neomorphic activity
- Hyperactivity
- Aberrant expression

**LACK OF RATIONAL OPTIONS FOR CANCERS DRIVEN BY:**
- Undear dominant oncogenic event
- Non-druggable oncogenes
- Mutations in tumor suppressors/loss of function mutations

**PREDOMINANTLY ONCOGENES**

- ~40K PROTEINS IN HUMAN GENOME (Gencode/NCBI)
- ~20K PROTEIN-CODING GENES
- ~2K DRUGGABLE GENOME
- ~60 DRUG TARGETS
- ~293 CANCER DRIVER GENES
  (Bailey, Cell 2018)
- >99% SNVs PASSENGER MUTATIONS

**LOSS-OF-FUNCTION MUTATION IN GENE X LEADS TO GENE Y ADDICTION IN CANCER CELLS**

Synthetic lethal compounds selectively kill cancer cells by targeting tumor cell-essential processes, but leave healthy cells unharmed.
Small molecule inhibitors of WRN

**WRN INHIBITORS PROGRAM IN RYVU**

<table>
<thead>
<tr>
<th>KEY RATIONALE</th>
<th>Synthetic lethality of WRN with microsatellite instability (MSI-high)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MoA</td>
<td>WRN inhibitors of ATPase activity selectively targeting tumors with microsatellite instability (MSI)</td>
</tr>
<tr>
<td>NOVELTY</td>
<td>First or best-in-class potential Focus on anti-targets selectivity (RecQ)</td>
</tr>
<tr>
<td>TOP TUMOR INDICATIONS</td>
<td>Tumor agnostic with MSI-high vulnerability (~10-30% of colorectal, endometrial, gastric, ovarian cancers)</td>
</tr>
<tr>
<td>BIOMARKERS</td>
<td>Distal biomarker developed</td>
</tr>
<tr>
<td>DEVELOPABILITY</td>
<td>Target druggable with small molecules Multiple hits identified from HTS</td>
</tr>
<tr>
<td>STATUS</td>
<td>Hit to lead generation ongoing</td>
</tr>
</tbody>
</table>

**WRN INHIBITORS OF ATPase ACTIVITY SELECTIVELY TARGETING TUMORS WITH MICROSATellite INSTABILITY**

**Helicase function validated in vitro as critical requirement**

1. Ryvu identified several preliminary small molecule hits – first-in-class inhibitors of WRN ATPase activity
2. Distal PD biomarker developed, battery of in vitro assays being developed
3. Discovery engine: Rational med.-chem hit-to-lead expansion

WRN confirmed as specific vulnerability of MSI-H cell lines in several genome-wide screens

*Chan 2019*
MTAPdel cancers – PRMT5 MTA-cooperative inhibitors

**KEY RATIONALE**
PRMT5 MTA-cooperative inhibitors exert synthetic lethal phenotype in MTAP deleted cells

**MoA**
MTA-cooperative inhibitors

**NOVELTY**
Best-in-class potential (vs Mirati, Tango)

**TOP TUMOR INDICATIONS**
MTAP deletions, up to 15% of all cancers, one of the largest genetically defined population: pancreatic, lung, DLBCL, bladder, oesophageal (by %: mesothelioma, GBM)

**BIOMARKERS**
MTAP and p16 status
SAM (plasma), SDMA (tissue) levels

**DEVELOPABILITY**
Target druggable with small molecules
Ryvu SL PRMT5 inhibitors identified

**VALUE INFLECTION POINTS**
2021: Hit-to-lead
2022: Lead, in vivo PoC
2023: Preclinical candidate

**RYVU HAS SL PRMT5 INHIBITORS WITH BEST-IN-CLASS POTENTIAL**
Ryvu HIT cmpd exhibits synthetic lethal phenotype: differential PD biomarker inhibition in isogenic pair in HCT116 (3D)

**DATA FROM COMPETITORS**
- Patentable chemical series, confirmed biomarker inhibition
- Immediate program kick-off: full in vitro pharmacology cascade in place, PRMT5 crystallography and in vivo pharmacology up and running
- Fast progress possible due to fully developed cascade and chemical properties of hit series.
Ryvu has selective, potent HPK1 inhibitors with anti-tumor efficacy in mice

**RYVU APPROACH**

**STATUS**

**APPROACH**

- Small molecule, selective, orally bioavailable inhibitors of HPK1 kinase activity

**CURRENT DIFFERENTIAL FACTORS**

- High selectivity against kinases from TCR pathway
- Immunostimulatory activity in immunosuppressed, resistant hPBMC and T cells across species

**MILESTONES FOR HPK1 INHIBITOR**

- 2021: LEAD OPTIMIZATION
- 2022: DEVELOPMENT CANDIDATE
- 2023: IND

**EFFICACY IN CT26 (MOUSE MODEL OF COLON CANCER)**

**COMBINATION WITH ANTI-mPD1**

- 75 mg/kg BID, 21 days + anti-mPD1 5 mg/kg: TGI = 60.9%
- 100 mg/kg BID, 21 days + anti-mPD1 5 mg/kg: TGI = 69.8%

*currently Treadwell Therapeutics, in phase I clinical trials

**RYVU SMALL MOLECULE HPK1 INHIBITORS SHOW EFFICACY IN MOUSE SYNGENEIC MODEL COMPARABLE TO CLINICAL REFERENCE COMPOUND**

<table>
<thead>
<tr>
<th>hHPK1</th>
<th>RVU-918</th>
<th>RVU-293</th>
<th>UHN</th>
<th>TAKEDA/ARIAD</th>
<th>GENENTECH</th>
<th>INCYTE</th>
<th>BAYER</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC50 (nM)</td>
<td>1.0</td>
<td>1.4</td>
<td>2.7</td>
<td>0.55</td>
<td>4.5</td>
<td>33</td>
<td>2.9</td>
</tr>
<tr>
<td>Ki (nM)</td>
<td>0.1</td>
<td>0.3</td>
<td>0.7</td>
<td>0.1</td>
<td>1.6</td>
<td>20.7</td>
<td>0.4</td>
</tr>
</tbody>
</table>

**UHN REFERENCE***

- RVU-293

---

* 30
Small molecule, direct, systemic STING agonists with strong anti-tumor efficacy

**RYVU APPROACH**

<table>
<thead>
<tr>
<th>STATUS</th>
<th>APPROACH</th>
<th>CURRENT DIFFERENTIAL FACTORS</th>
<th>IP RIGHTS STATUS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Small molecule, systemic, direct STING agonists amenable to ADC technology</td>
<td>Superior \textit{in vitro} activity and anti-tumor efficacy</td>
<td>Several patent applications covering broad chemical estate filed, initial FTO confirmed</td>
</tr>
</tbody>
</table>

**KEY DIFFERENTIATION**

Small molecule, direct, systemic STING agonists with multiple routes of administration (IV, SC, IT) allowing two tracks of development:

- standalone systemic treatment
- using targeted delivery as \textit{payload} for antibodies (antibody-drug conjugates ADC approach)

Systemic efficacy in mouse models on par with GSK reference (IV) and outperforming Aduro/Novartis agonist (IT) accompanied with favorable safety profile

Active across multiple STING haplotypes to target broad patient population

Well protected IP and confirmed initial FTO space

**Selected properties of Ryvu STING agonists**

<table>
<thead>
<tr>
<th>Generation</th>
<th>Example compounds</th>
<th>II generation</th>
<th>III generation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RyVU-24024</td>
<td>Several candidates</td>
<td></td>
</tr>
<tr>
<td>Chemotype</td>
<td>Non-CIN small molecule</td>
<td>Non-CIN small molecule</td>
<td></td>
</tr>
<tr>
<td>Development approach</td>
<td>SINGLE AGENT</td>
<td>SINGLE AGENT / WITH FUNCTIONAL HANDLE ADC AMENABLE</td>
<td></td>
</tr>
<tr>
<td>Molecular Weight clogP/clogD</td>
<td>&lt;3.00 / &lt;6.00</td>
<td>2.9-4.0 / 2.4-2.5</td>
<td></td>
</tr>
<tr>
<td>FD5 Attenuation [°C] 50µM human/mouse STING</td>
<td>11 / 17</td>
<td>28-30 / 16-21°</td>
<td></td>
</tr>
<tr>
<td>BMDC IFN EC50 [µM]</td>
<td>0.055</td>
<td>0.24-0.31</td>
<td></td>
</tr>
<tr>
<td>THP 1 IFN EC50 [µM]</td>
<td>0.39</td>
<td>0.017-0.027</td>
<td></td>
</tr>
<tr>
<td>HMDC IFN EC50 [µM]</td>
<td>0.24</td>
<td>0.030*</td>
<td></td>
</tr>
<tr>
<td>In vitro antitumor efficacy</td>
<td>confirmed</td>
<td>confirmed</td>
<td></td>
</tr>
<tr>
<td>General characteristic</td>
<td>Highly potent mouse STING agonists; lower potency on human STING</td>
<td>Potent human STING agonists; lower potency on murine STING protein</td>
<td></td>
</tr>
</tbody>
</table>

* Data currently available for selected compounds
### Financial results & employment

#### Cash position
- **August 31, 2021**
- **$25.3M**

#### Available grant funding
- **>$25M**

#### Financing secured until
- **Q1 2023**

#### $ million

<table>
<thead>
<tr>
<th></th>
<th>H1 2020</th>
<th>H1 2021</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revenues</td>
<td>6.1</td>
<td>3.2</td>
</tr>
<tr>
<td><em>Partnering</em></td>
<td>3.7</td>
<td>0.1</td>
</tr>
<tr>
<td><em>Grants</em></td>
<td>2.4</td>
<td>3.0</td>
</tr>
<tr>
<td>Costs*</td>
<td>9.1</td>
<td>11.5</td>
</tr>
<tr>
<td>EBIT*</td>
<td>-3.0</td>
<td>-8.3</td>
</tr>
<tr>
<td>EBITDA*</td>
<td>-1.7</td>
<td>-6.7</td>
</tr>
<tr>
<td>CAPEX</td>
<td>-4.8</td>
<td>-2.3</td>
</tr>
</tbody>
</table>

*without the impact of Incentive Scheme (of $1.8m)
## Ryvu drives value creation from its multiple data readouts

<table>
<thead>
<tr>
<th>Program/target name</th>
<th>Indication</th>
<th>Discovery and preclinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Partners / Collaborators</th>
<th>2021</th>
<th>2022+</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEL24 (MEN1703) PIM / FLT3</td>
<td>AML</td>
<td></td>
<td></td>
<td></td>
<td>• Ph. II interim data</td>
<td>• Ph. II complete</td>
<td></td>
</tr>
<tr>
<td>RVU120 CDK8</td>
<td>AML / MDS</td>
<td>Solid tumors</td>
<td></td>
<td></td>
<td>• Initial Ph. Ib data</td>
<td>• Ph. II initiation</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Ph. I Initiation</td>
<td>• Ph. I Interim data</td>
<td>• Ph. II initiation</td>
</tr>
<tr>
<td>MTAP</td>
<td>Solid tumors</td>
<td></td>
<td></td>
<td></td>
<td>• Hit-to-lead</td>
<td>• Lead optimization</td>
<td>• Non-GLP tox</td>
</tr>
<tr>
<td>WRN</td>
<td>Solid tumors</td>
<td></td>
<td></td>
<td></td>
<td>• Hit-to-lead</td>
<td>• Lead optimization</td>
<td>• Non-GLP tox</td>
</tr>
<tr>
<td>HPK1</td>
<td>Solid tumors</td>
<td></td>
<td></td>
<td></td>
<td>• Lead optimization</td>
<td></td>
<td>• Non-GLP tox</td>
</tr>
<tr>
<td>STING</td>
<td>Solid tumors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• IND-enabling studies</td>
</tr>
</tbody>
</table>

### Anticipated Milestones

**2021**
- 2 Clinical stage assets
- 2 Human PoCs
- 7+ Early pipeline programs

**2022+**
- 3+ Clinical stage assets
- 3+ Human PoCs
- 10+ Early pipeline programs
Ryvu investment highlights

- Developing small molecule therapies which **address high value emerging targets and pathways in oncology**

- Diverse pipeline targeting **kinases, synthetic lethality and immuno-oncology**

- First-in-class selective **CDK8 inhibitor (RVU120)** with potential across **multiple indications**

- Validation from strategic **collaborations** including partnership with Menarini on **SEL24(MEN1703)**

- Extensive early stage pipeline **delivering near term clinical candidates**

- Robust internal drug discovery engine and **partnership options** for early-stage candidates

- **Limited cash burn** thanks to non-dilutive grants and cost-efficient discovery platform, significant resources located in Poland

**Near term milestones**

- **RVU120**
  - Additional Phase I data in AML at ASH2021
  - Initial solid tumor data in H1 2022

- **SEL24(MEN1703)**
  - Phase II – new data at ASH2021

- New programs expected to enter the clinic in 2022

- Additional near-term PC and late discovery targets

- Partnering deals in the early pipeline
Excellent on-target activity of RVU120 in pSTAT positive AML cell models

RVU120 is a potent and selective CDK8/CDK19 inhibitor

Low nM activity on CDK8/CDK19 and excellent kinase selectivity (broad kinome)

- Spares CDK2, CDK4, CDK6, CDK7, CDK9, etc.
- Type I, ATP-competitive mechanism of binding and inhibition of CDK8/19 activity
- Lack of binding to off-targets potentially associated with toxicity of pre-clinical EMD Serono CDK8/19 inhibitors (such as JNK1 or GSK3b)¹
- Higher selectivity based on comparison of gene expression effects²
- Composition of matter patents granted in 2017

¹Chen et al. 2019
²Rzymski et al. 2017
RVU120 induces complete regression and bone marrow recovery in AML

In CD34+ AML patient-derived xenografts

Research performed at:

**RVU120**

**PDX cells**

**NSG mice**

**Vehicle / RVU120**

Dose: 45mg/kg

**Leukemia burden analysis**

**COMPLETE REGRESSION** (PERIPHERAL BLOOD)

**HEMATOLOGIC RECOVERY** (BONE MARROW)

**REDUCED SPLENOMEGALY**

---

**TUMOR GROWTH KINETICS**

**PERIPHERAL BLOOD**

**BODY WEIGHT CHANGE**

**BONE MARROW**

**SPLEEN**

---

Research performed at:

[Research Institution Logo]
RVU120 strongly synergizes with Venetoclax

RVU120 potentially addresses treatment resistant disease through safe, indirect MCL-1 downregulation in cancer cells

Compelling potential for RVU120 in combination with Venetoclax

MV-4-11 cells IV NSG mice RVU120+Venetoclax Daily, PO, 21 days Leukemia burden analysis

COMPLETE REGRESSION HEMATOLOGIC RECOVERY (BONE MARROW)
Contact data

Ryvu Therapeutics S.A.

www.ryvu.com
ryvu@ryvu.com