ATACs: a Unique New Mode of Action to Fight Cancer

German Equity Forum
22nd November 2021
Safe Harbor

Forward looking statements

This communication contains certain forward-looking statements, relating to the Company's business, which can be identified by the use of forward-looking terminology such as “estimates”, “believes”, “expects”, “may”, “will” “should” “future”, “potential” or similar expressions or by general discussion of strategy, plans or intentions of the Company. Such forward-looking statements involve known and unknown risks, uncertainties and other factors, which may cause our actual results of operations, financial condition, performance, or achievements, or industry results, to be materially different from any future results, performance or achievements expressed or implied by such forward-looking statements.

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Heidelberg Pharma at a Glance

Developing new options to address major challenges in cancer therapy

Our Company

- Listed as Heidelberg Pharma AG
- Frankfurt Stock Exchange: HPHA
- Shares outstanding: 34.18 million
- Market cap: ~€200 million
- Headquarters: Ladenburg, Germany
- ~90 employees

Our Mission

- New option in cancer therapy with a unique mode of action
- Overcome resistance mechanisms
- Kill dormant tumor cells
- Biomarker for patient stratification and expedited development

Our Approach

- Inhibition of RNA Polymerase II
  - Amanitin as toxic payload
  - Targeted delivery via antibodies (ADC technology)

Business model: develop proprietary ATAC® pipeline, partner ATAC® technology platform and generate upside potential from legacy clinical portfolio
ADCs are HOT!

ADCs have become one of the most validated and sought-after therapeutic modalities

- AstraZeneca inks $6bn deal with Daiichi Sankyo for HER2 ADC
- Gilead acquires Immunomedics for $21bn deal with SeaGen
- Merck acquires VelosBio for $2.8bn for ROR1 ADC
- Boehringer acquires NBE-Therapeutics for $1.4bn
- Daiichi Sankyo invests $13.8bn in 3 ADC programs
- BMS acquires anti-FOLR1 ADC for $650m from Elsai
- Gilead acquires Immunomedics for $21bn
- Merck inks $4.5bn deal with SeaGen
- Sep

Highlights of ADC Deals and Approvals
Amanitin specifically binds and inhibits RNA polymerase II – the only currently known inhibitor of RNA polymerase II.

Amanitin kills dividing AND quiescent tumor cells by inhibiting mRNA synthesis.

→ Potential clinical benefits by

- **Strong efficacy** in *in vivo* and *in vitro* models
- **Ability to overcome resistance**
- **Kill dormant tumor cells** causing metastasis & tumor relapse, independent of cell proliferation

Heidelberg Pharma’s technology platform makes highly toxic Amanitin accessible for cancer therapy.

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Adapted from [http://chemistry.elmhurst.edu/vchembook/655cancer2.html](http://chemistry.elmhurst.edu/vchembook/655cancer2.html)
**Antibody Targeted Amanitin Conjugates (ATACs)**
Combining the Best of Two Therapeutic Modalities

**ADCs with Amanitin as toxic payload = ATACs (Antibody Targeted Amanitin Conjugates)**

<table>
<thead>
<tr>
<th>Highly effective payload</th>
<th>ATAC technology</th>
<th>Highly specific antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death cap mushroom</td>
<td></td>
<td>- Antibodies for <strong>different tumor targets</strong></td>
</tr>
<tr>
<td>From nature to the lab</td>
<td></td>
<td>- Targets determine indications</td>
</tr>
<tr>
<td>Chemical synthesis</td>
<td></td>
<td>- Tumor specific delivery</td>
</tr>
<tr>
<td>Amanitin</td>
<td></td>
<td>- Internalization of target</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Access to antibodies through licensing or partnering</td>
</tr>
</tbody>
</table>

Source: pilz-ratgeber.de

* IP protection includes chemical synthesis of toxins, optimal linker attachment sites, portfolio of different linkers, site-specific conjugation technology
**ATACs Overcome Resistance Mechanisms**

Complete remission after single-dose of HER2-ATAC (resistant breast cancer model)

ATACs can overcome resistance in *in vivo* models

ATACs are highly potent & superior to existing payloads

*CHMP assessment report Enhertu: In the JIMT-1 model, DS-8201a at 3 and 10 mg/kg, inhibited tumour growth by 64% and 85% respectively.*
ATACs Kill Dormant Tumor Cells

Anti-BCMA-ATAC (HDP-101 ex-vivo Model) is able to kill non-dividing primary tumor cells

Comparison with MMAF (Auristatin Conjugate as used by GSK) on MM Patient Cells
- Non-dividing (quiescent) cells isolated from multiple myeloma patients bone marrow biopsies
- Dividing tumor cells from lab cell lines

Anti-BCMA-Ab coupled with GSK payload MMAF

HDP-101 (anti-BCMA-Ab coupled with payload Amanitin)

ATACs can kill non-dividing primary tumor cells and may eliminate dormant tumor stem cells
ATACs Exhibit Synergy with Immune Checkpoint Inhibitors

C57BL76-Tg(WapHER2) mice orthotopically implanted with HER2-low EO771 cells with 11B loss

Tumor growth curve

Survival analysis

HER2-ATAC potentiates immune checkpoint blockade therapy in treating HER2-low Breast Cancer.

**Platform Wide Del(17p) Biomarker to Enable Accelerated Approval**

**del(17p) tumors have higher sensitivity to ATACs**

- ATACs delivers Amanitin to tumor cells, where it binds to and inhibits RNA Polymerase II.
- Tumor cells with del(17p) have reduced RNA Polymerase II, leading to higher sensitivity to treatment with ATACs.
- Further, del(17p) identifies **high-risk patients** with unmet medical need.

**Poor prognosis for MM patients with del(17p)**

- Lower survival for **del(17p)** compared to **Standard Risk**: 47.3 vs. 109.8 months


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## Strategic Cornerstones

### Build proprietary ATAC® pipeline
- HDP-101 – ATAC® targeted against BCMA (multiple myeloma)
- ATACs for additional oncology indications (HDP-102 & HDP-103)
- Antibody discovery for further targets

### ATAC® collaborations
- Licensing collaborations with pharma and biotech
- Various research partnerships based on Material Transfer Agreements

### Licensed legacy assets (non-ATACs)
- Additional upside potential from clinical programs
- TLX250-CDx – diagnostic imaging agent
- RHB-107 – serine protease inhibitor (upamostat)

### GMP supply with Amanitin
## Growing Pipeline of Proprietary and Partnered Programs

<table>
<thead>
<tr>
<th>Product</th>
<th>Target</th>
<th>Indication</th>
<th>Research</th>
<th>Preclinic</th>
<th>Clinic</th>
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<td>BCMA</td>
<td>Multiple myeloma (DLBCL/CLL)</td>
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### Proprietary ATAC pipeline

<table>
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<tr>
<th>Product</th>
<th>Target</th>
<th>Indication</th>
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<td>HSCs, Conditioning programs for blood cancers/genetic diseases</td>
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<td>Takeda/Millenium</td>
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### ATAC collaborations

<table>
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<th>Target</th>
<th>Indication</th>
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<th>Clinic</th>
<th>Partner</th>
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<td>TLX250-CDx</td>
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<td>Renal Ca</td>
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<td>Telix</td>
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### Licensed legacy assets (non-ATACs)

<table>
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<th>Product</th>
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<th>Preclinic</th>
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Potential Partner Milestones Legacy Portfolio

Partnered legacy clinical programs

TLX250-CDx® – imaging agent (89Zirconium-girentuximab)
• Ongoing ZIRCON Phase III trial next steps:
  • Completion planned by the end of 2021
  • Rolling submission of the BLA in the US to be completed in 2022, accelerated procedure
• License payments expected from 2022
• Launch of ZiP-UP Phase I study in bladder cancer
• Launch of OPALESCENCE Phase II study in triple-negative breast cancer

TLX250 – therapeutic agent (177Lu-DOTA-girentuximab)
• Two Phase II combination studies (STARLITE 1 and 2) with different checkpoint inhibitor immunotherapies planned in the US
• IND granted in September; Study start planned in 2021

RHB-107 – serine protease inhibitor upamostat
• Ongoing Phase 2/3 study in non-hospitalized patients with symptomatic COVID-19 not requiring supplemental oxygen; site expansion in US and to South Africa
• Development plans in oncology/GI

LH011 – serine protease inhibitor upamostat
• Chinese Phase I trial in patients with locally advanced/metastatic pancreatic cancer expected to be completed end of 2021
## Proprietary ATAC® Candidates: HDP-101, HDP-102 and HDP-103

### HDP-101: anti-BCMA-ATAC
- BCMA (B-cell maturation antigen) overexpression and activation are associated with multiple myeloma
- Multiple myeloma:
  - 70,000 deaths due to MM annually;
  - Characterized by the proliferation of single clone of plasma cells derived from B-cells
  - Median survival ~47-110 months
- MM patients with 17p deletions have a particularly high medical need for new treatment options
- Potential for biomarker-based stratification
- Potential improvement on ocular toxicity risk seen in approved and marketed anti-BCMA ADC Blenrep from GSK
- IND granted, first trial centers initiated

### HDP-102: anti-CD37-ATAC
- CD37 is overexpressed on B-cell lymphoma cells
- Specific indication of non-Hodgkin lymphoma (NHL)
- High prevalence of 17p deletion in NHL

### HDP-103: anti-PSMA-ATAC
- PSMA is overexpressed in nearly all cases of prostate cancer; limited expression in normal tissue
- Target indication is Metastatic Castration-Resistant Prostate Cancer (mCRPC)
- Prevalence of 17p deletion in mCRPC is 60%
- 17p biomarker has been validated preclinically for prostate cancer (Nature Commun. 2018 22:4394)

### Additional Information
- HDP-101 has best-in-class potential for relapsed / refractory multiple myeloma (RRMM)
- Potential IND application for both preclinical candidates 2022/23
HDP-101: Anti-BCMA-ATAC with Unique Properties

Cytotoxicity data in primary tumor cells from multiple myeloma patients

**Efficacious in ultra-low BCMA cells**
- HDP-101 is efficacious in dormant tumor cells that express BCMA at very low levels, e.g. multiple myeloma patient 7.
- No toxicity in control bone marrow stromal cells from healthy donor.

**More efficacious than MMAF-BCMA ADC**
- HDP-101 is highly efficacious in dormant tumor cells from MM patients, while an MMAF-BCMA ADC\(^3\) shows very poor activity in these patient cells.
- GSK’s BLENREP is an MMAF-containing anti-BCMA ADC.

**Overcomes resistance mechanisms**
- HDP-101 is efficacious in tumor cells resistant to daratumumab and elotuzumab / pomalidomide.

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1. BCMA density expressed as antibody binding sites per cell
2. n.d. = not determined
3. MMAF conjugated to HDP’s anti-BCMA Ab (DAR=4) as a surrogate for Blenrep
## HDP-101: Differentiated Profile Predicts Clinical Benefit

### Unique preclinical features of HDP-101

- Efficacious on dormant tumor cells
- Efficacious in ultra-low BCMA tumor cells
- Novel MoA to which all patients will be naïve
- Ocular toxicity not seen for Amanitin or HDP-101
- Enhanced efficacy in high-risk del(17p) tumors

### Potential clinical benefit

- Longer PFS and MRD negativity
- Deeper responses and higher ORR
- Overcome resistance
- Superior safety profile
- Breakthrough designation and accelerated approval

**HDP-101 has best-in-class potential for relapsed / refractory multiple myeloma (RRMM)**
HDP-101-01 Clinical Trial for Multiple Myeloma
Two-part, Open-label, Multicenter Phase I/IIa Study

Clinical trial designed to determine safe dose and assess preliminary efficacy

**Phase I:**
- Up to 36 patients with relapsed / refractory multiple myeloma (RRMM)
- Dose-escalation of HDP-101
- Retrospective biomarker evaluation
- Establish optimal and safe dose for Phase IIa part

**Phase IIa:**
- Up to 30 patients with RRMM
- Biomarker stratification based on 17p deletion status
- Preliminary anti-tumor activity of HDP-101 and clinical relevance of the 17p deletion

**Study scheme**

- Screening
  - RRMM patients with no or limited therapeutic options

- Enrollment

- Cycle 1
  - HDP-101 administered intravenously every 3 weeks
  - Dose-limiting toxicity observation period

- Cycle 2 and any subsequent cycles
  - Tumor assessment at every cycle

- End of treatment
  - Any of these
    - Disease progression
    - Adverse reaction
    - Investigator decision
    - Withdraw consent

- Follow up
  - Subsequent treatments, survival

- Follow up

- • Adaptive study design applied using Bayesian Logistic Regression Model to guide dose escalation and select the best dose for the phase II part
- • Robust safety features to ensure early detection of possible toxicities especially liver and kidney damage

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HDP-101: Clinical Development Plan for Multiple Myeloma

**2021**
- IND
- MD Anderson Cancer Center, Emory University and Heidelberg University trial site initiated, further US and German sites to follow
- Treatment of the first patient this year
- First clinical safety data H1 2022 expected

**2022**
- FPI
- Dose escalation in MM patients
- First clinical safety data

**2023**
- RP2D
- Non-stratified MM patients
- Expansion cohorts
- del(17p) stratified
- Registrational cohort
- Assess accelerated approval option
- BLA

**2024**
- Additional indications / Combinations

**2025**
- HDP-101 has best-in-class potential in all RRMM patients.
- Additionally, HDP-101 has potential for accelerated approval in high-risk myeloma patients with del(17p).
## Financials

<table>
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<tr>
<th>in € m</th>
<th>FY 2020</th>
<th>9M 2021</th>
<th>Guidance FY 2021</th>
<th>Rev. guidance 09/2021</th>
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<td>Sales revenue and other income</td>
<td>9.6</td>
<td>1.6</td>
<td>5.5 – 7.5</td>
<td>2.0 – 2.5</td>
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<td>Operating expenses</td>
<td>27.9</td>
<td>20.1</td>
<td>36.0 – 40.0</td>
<td>26.0 – 28.5</td>
</tr>
<tr>
<td>Cost of sales</td>
<td>5.6</td>
<td>3.0</td>
<td></td>
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<tr>
<td>R&amp;D costs</td>
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<td>14.1</td>
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<tr>
<td>Administrative costs</td>
<td>3.6</td>
<td>2.6</td>
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<tr>
<td>Other expenses</td>
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<td>0.4</td>
<td></td>
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<tr>
<td>Operating result (EBIT)</td>
<td>(18.3)</td>
<td>(18.5)</td>
<td>(30.0 – 34.0)</td>
<td>(23.5 – 26.5)</td>
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<tr>
<td>Net result for the period</td>
<td>(18.4)</td>
<td>(18.9)</td>
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</table>

### Financing
- Cash as of 31 August 2021: €13.6 m
- €20 m gross proceeds from private placement in June 2021 with select institutional investors and dievini, using €12.5 m from dievini financing commitment
- Remaining financing commitment from dievini: €5 m loan + €17 m
- Cash reach is secured until mid-2022 based on current budget planning

### Shares
- Shares outstanding: 34,175,809
- Shareholders:
  - 75% Dietmar Hopp and affiliated companies
  - 3% UCB
  - 22% Freefloat and Corporate Bodies

### Analysts
- Stifel 10/21: target € 8.94
- Pareto 10/21: target € 8.90
- Bryan, Garnier 10/21: target € 12.00
- EQUI.TS 02/21: target € 8.15
Investment Summary

Disruptive first-in-humans mode of action provides high efficacy and potential for unique clinical advantages, including treatment of dormant tumor cells.

Increased efficacy against 17p deleted and aggressive tumor cells based on biomarker.

Validated by high quality collaborations (early validation and cash).

On the verge of becoming a clinical-stage company.

High value potential with growing proprietary portfolio and attractive ADC environment.
### Upcoming conferences & events

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<tr>
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<th>Venue</th>
<th>Date</th>
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<tr>
<td>German Equity Forum</td>
<td>Virtual</td>
<td>22 – 24 November 2021</td>
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<tr>
<td>ASH 2021 Annual Congress</td>
<td>Atlanta</td>
<td>11 – 14 December 2021</td>
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<tr>
<td>JP Morgan Healthcare Conference</td>
<td>San Francisco</td>
<td>10 – 13 January 2022</td>
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</table>

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### Ticker data

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