ATACs®: a Unique New Mode of Action to Fight Cancer

Inv€$tival Showcase - 14th November 2022
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Such factors include, among others, the following: uncertainties related to results of our clinical trials, the uncertainty of regulatory approval and commercial uncertainty, reimbursement and drug price uncertainty, the absence of sales and marketing experience and limited manufacturing capabilities, attraction and retention of technologically skilled employees, dependence on licenses, patents and proprietary technology, dependence upon collaborators, future capital needs and the uncertainty of additional funding, risks of product liability and limitations of insurance, limitations of supplies, competition from other biopharmaceutical, chemical and pharmaceutical companies, environmental, health and safety matters, availability of licensing arrangements, currency fluctuations, adverse changes in governmental rules and fiscal policies, civil unrest, acts of God, acts of war, and other factors referenced in this communication.

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Heidelberg Pharma – a Clinical Stage Company

Our Company

~ 110 employees

Headquarters in **Heidelberg** area, Germany

**Listed** on Frankfurt Stock Exchange: HPHA

**Clinical stage** biotech

Complete **in-house research** capabilities

Cash reach until mid-2025
(as of November 2022)

Our Approach

Inhibition of RNA Polymerase II
Targeted delivery via antibodies (**ADC technology**) Use Amanitin as toxic payload (**ATAC® technology**)

Our Mission

Provide new options in cancer therapy

Overcome resistance mechanisms

Kill dormant tumor cells

**Develop biomarker** for patient stratification
## 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>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Partner</th>
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<tbody>
<tr>
<td>HDP-101</td>
<td>BCMA</td>
<td>Multiple Myeloma (DBCL/CLL)</td>
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<td>Huadong (Asia)</td>
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<td>HDP-102</td>
<td>CD37</td>
<td>NHL</td>
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<td>Huadong (Asia, option)</td>
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<tr>
<td>HDP-103</td>
<td>PSMA</td>
<td>Prostate cancer</td>
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<td>HDP-104</td>
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<td>Gastrointestinal (e.g. CRC)</td>
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<td>Huadong (Asia, option)</td>
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<td>Solid &amp; hematological malignancies</td>
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<td>Proprietary</td>
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**ATAC® pipeline**

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>MGTA-ATACs</td>
<td>CD117, CD45</td>
<td>HSCs, conditioning programs for blood cancers and genetic diseases</td>
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<td>TAK-ATAC</td>
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<tr>
<td>CHIOMÉ-ATAC</td>
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<td>Chiome</td>
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**ATAC® partners**

<table>
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<th>Product</th>
<th>Target</th>
<th>Indication</th>
<th>Research</th>
<th>Preclinic</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Partner</th>
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<tbody>
<tr>
<td>TLX250-CDx</td>
<td>CA-IX</td>
<td>Renal and urothelial carcinoma, TNBC</td>
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<td>Telix</td>
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<tr>
<td>TLX250</td>
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<td>Telix</td>
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<tr>
<td>RHB-107</td>
<td>CA-IX</td>
<td>Oncology/GI, Covid-19</td>
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<td>LH011</td>
<td>Pancreatic</td>
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<td>Link Health</td>
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ATAC® Technology & Proprietary Projects
ATACs: ADCs with Amanitin as a Payload

Amanitin as Warhead
- Differentiated mechanism of action: inhibition of RNA Polymerase
  - Kills dormant tumor cells
  - Overcomes resistance
  - Predictive biomarker
- Synthetic amanitin derivatives with improved properties
- GMP manufacturing through fully synthetic process

Antibody
- Targeting tumor antigen

Site-specific Conjugation
- Proprietary conjugation sites
- Improved therapeutic index (TI)
- Excellent stability in circulation
Amatoxins – a novel mode of action in oncology

Group of toxins from the poisonous green death cap mushroom (Amanita phalloides)

Amanita phalloides

Amanitins is a specific inhibitor of RNA polymerase II activity:
• The only currently known inhibitor of RNA polymerase II:
  • A new mode of action in oncology
  • All tumors are naïve to it
  • Cell-cycle independent mechanism of action
  • Low intracellular target copies, 1:1 binding

Murine breast cancer xenograft model

• Same antibody (Trastuzumab), different payload (topoisomerase inhibitor vs. amanitin)
• Complete remission after single-dose application of HER2-ATAC.

PBS (Control) (10mL/kg) i.v.
Enhertu, 20 mg/kg, i.v.
Trastuzumab-ATAC, 2.5mg/kg, i.v.

Drawing: Tamara Clark; tamaracleark.com
ATACs promise higher efficacy in certain aggressive tumors

**del(17p) as a potential biomarker for higher ATAC sensitivity**

- Chromosomal deletion that eliminates *p53* (higher-risk tumor) and frequently *POL2RA* gene: lower RNA polymerase II level
- Less amanitin is required to kill these cells: larger therapeutic window

**Clinical relevance:**
- Broad prevalence (ca. 25-60%) across most tumors
- Increased prevalence in advanced and metastatic disease
- Associated with aggressive disease, poor outcomes

**Significance:**
- Higher ATAC efficacy in aggressive tumors with del(17p)
- Use as clinical biomarker in development for patient stratification

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**Collaboration with MD Anderson:**

Higher ATAC® sensitivity of del(17p) myeloma cells

- *p53 WT*
- *p53-KO/ POLR2A-KD*

Orlowski et al. MD Anderson ASH 2019
First-in-Human Clinical Trial with an ATAC
HDP-101: anti-BCMA-ATAC for multiple myeloma

Clinical trial designed to determine safe dose and assess preliminary efficacy

Two-part, Open-label, Multicenter Phase I/IIa Study

- **2022**: FPI
  - Dose escalation in MM patients: up to 36 patients

- **2023**: RP2D
  - First clinical safety data

- **2024**: Assess accelerated approval option
  - BCMA naïve MM
    - Del(17p) stratified
  - Post BCMA Tx MM
    - Del(17p) stratified

- **2025**: AA
  - Registrational cohort
  - BLA
  - Additional indications / Combinations

Trial sites active and enrolling*:
- MD Anderson, Houston
- Emory University, Atlanta
- Mount Sinai Hospital, New York
- University Hospital Heidelberg
- University Hospital Mainz
- University Hospital Kiel

*Further US and European sites currently being opened
**ATACs Promise Significant Clinical Benefits**

<table>
<thead>
<tr>
<th>Unique preclinical features of HDP-101</th>
<th>Potential clinical benefit</th>
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<tbody>
<tr>
<td>Efficacious against dormant tumor cells</td>
<td>Longer PFS and MRD negativity</td>
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<tr>
<td>Efficacious in ultra-low target-expressing tumor cells</td>
<td>Deeper responses and higher ORR</td>
</tr>
<tr>
<td>Novel MoA to which all patients will be naïve</td>
<td>Overcome resistance</td>
</tr>
<tr>
<td>Ocular toxicity not seen for Amanitin or HDP-101</td>
<td>Superior safety profile</td>
</tr>
<tr>
<td>Enhanced efficacy in high-risk del(17p) tumors</td>
<td>Breakthrough designation and accelerated approval</td>
</tr>
</tbody>
</table>

**ATACs® have best-in-class potential**
Strategic partnership with Huadong
Strategic Partnership With Huadong Medicine

Building a robust ADC product pipeline with best-in-class potential

Investment 80 m EUR
Shareholding 35%
2 seats in Supervisory Board

Commercial Agreements

- Exclusive development and commercialization rights for HDP-101 and HDP-103,
  - Deal value: up to 469 m USD + royalties
- Exclusive option for HDP-102 and HDP-104;
  - Deal value: up to 461 m USD + royalties
- Next 2 ATAC® candidates: Right of first negotiation (ROFN)
- Territory: Asia*

* People’s Republic of China, Hong Kong, Macao, Taiwan, South Korea, Indonesia, Singapore, The Philippines, Thailand, Bangladesh, Bhutan, Brunei, Myanmar, Cambodia, Laos, Malaysia, Maldives, Mongolia, Nepal and Vietnam; excludes Japan, India, Pakistan, Sri Lanka
A Transformative Deal with a Strong Partner: Supporting our Strategy to Become a Global ADC Player

- Immediate strengthening of cash position
- Dedicated, long-term investor
- Accelerated development and broadening of pipeline
- Potential expansion of the collaboration

Success-based milestones and royalties offer long-term cash infusion
Efficient resource sharing via co-development
Secures market access in large parts of Asia
Partner Projects & Next steps
Targeted conditioning programs with ATACs®:
selectively eliminate stem cells and/or immune cells from a patient prior to transplant or gene therapy.

MGTA-117: Depletion of hematopoietic stem and progenitor cells
• Phase I/II trial in AML or MDS started in Q1 2022

Next steps: Initial clinical data expected at ASH 2022, further data in Q1 2023

CD45-ATAC: Immune reset in various transplant and autoimmune disease models
• IND-enabling activities ongoing

License agreement for an ATAC®:
Worldwide exclusive license for an ATAC targeting a previously selected target molecule (not disclosed)

Research and option agreement for an ATAC®:
Couple amanitin to an antibody that targets CDCP1, expressed on many solid tumors

HDP is entitled to clinical development, regulatory and sales-related milestone payments for each ATAC candidate
Partner Telix: Progressing towards Filing for Market Approval

Pivotal Phase III ZIRCON reported Positive topline results with imaging agent TLX250-CDx in November 2022

Accurate diagnosis of clear cell renal cell carcinoma (ccRCC) with TLX250-CDx (89Zr-DFO-girentuximab)

- Global multicenter Ph III trial with 284 evaluable patients with renal cancer
- Imaging compared to histology of surgically obtained tissue (standard of truth)
- All endpoints met:
  86% sensitivity, 87% specificity and 93% positive predictive value

- Next steps:
  Filing for regulatory approval with the FDA and other agencies

- Indication expansion:
  Ongoing Ph I and II studies in bladder cancer and in triple-negative breast cancer
## Next Steps Proprietary ATAC Pipeline

<table>
<thead>
<tr>
<th>HDP-101</th>
<th>HDP-102</th>
<th>HDP-103</th>
<th>HDP-104</th>
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</thead>
</table>
| **Phase I/IIa study in RRMM**  
• Dose escalation ongoing  
• First safety data expected 2022  
• Phase I completion in 2023 | **CD37-ATAC for NHL**  
• On track to IND 2024 | **PSMA-ATAC for prostate cancer**  
• On track to IND 2023 | **Guanylyl cyclase C (GCC)-ATAC for colorectal cancer**  
• Preclinical development ongoing |
Investment Summary

A clinical-stage company with the goal of becoming a global ADC player

**Disruptive first-in-humans mode of action provides high efficacy and potential for unique clinical advantages**

**Clinical lead program with best-in-class potential for indication with high medical need**

**Increased efficacy against certain aggressive tumors based on biomarker**

**Validated by international high-quality partnerships**

**Strategic partnership for Asia, fastest growing pharmaceutical market**

**High value potential with growing ATAC® pipeline and attractive ADC environment**
Thank you for your attention and please get in touch with us!

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LLD from the University of Mannheim

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