ATACs fighting Cancer

November 2019
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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Developing new options to address major challenges in cancer therapy

Our Company
Listed as Heidelberg Pharma AG
Frankfurt Stock Exchange: WL6
Shares outstanding: 28.16 million
Market cap: ~€60 million
Headquarters: Ladenburg, Germany
70 employees

Our Mission
Improve efficacy
Overcome resistance mechanisms
Kill dormant tumor cells
Provide new options in cancer therapy

Our Approach
New mode of action in cancer therapy
• Induction of apoptosis by inhibition of RNA Polymerase II
• Application of innovative payload by harnessing ADC therapeutic modality
Antibody Targeted Amanitin Conjugates (ATACs)
Management Team with Strong Pharma and R&D Experience

CEO / CFO
@ Heidelberg Pharma since 2001

20 years’ experience in commercial and financial leadership positions in pharma and chemical companies, including BASF

Managing Director of an Austrian BASF Pharma subsidiary (EBEWE Arzneimittel GmbH) from 1997 to 2001, prior several positions at the BASF Group

LLD from the University of Mannheim

CSO
@ Heidelberg Pharma since 2012

20 years’ experience in research and higher education

Head of Late Pharmacology at Nycomed and Takeda Pharmaceuticals from 2008 to 2012

Professor of Pharmacology and Toxicology at the University of Erlangen-Nuremberg (FAU)

PhD in chemistry from the University of Berlin
Strategic Cornerstones

- Build proprietary ATAC pipeline
- Sign technology licensing collaborations
- Additional upside potential with partnered non-ATAC legacy clinical assets

Proprietary lead candidate HDP-101

Other proprietary ATAC candidates incl. co-research with third-parties

ATAC technology partnering with pharma and biotech

ATAC technology partner

Lead ATAC HDP-101

ATAC platform & pipeline

Partnered clinical assets

TLX250-CDx – imaging agent (REDECTANE®)

MESUPRON® - uPA inhibitor
Link Health, RedHill Biopharma
Early Validation and Cash Through Pharma Collaborations + Future High Value Potential with Proprietary Portfolio

Partnering target by target

Antibodies from partners, license to the partner, development by the partner

ATAC toolbox:
customized and target-optimized toxins and linkers

Defined payload
Linker variations
Amanitin derivatives

In-licensed antibodies, internal development activities

HDP-101

Proprietary
# ATACs – Growing Pipeline of Proprietary and Partnered Programs

<table>
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<tr>
<th>Product</th>
<th>Target</th>
<th>Indication</th>
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<td>BCMA</td>
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Amanitin – Innovative Cell Toxin with High Clinical Potential

• Amanitin kills dividing AND quiescent tumor cells by binding and inhibiting RNA polymerase II

→ Potential clinical benefits by
  o Strong efficacy in *in vivo* and *in vitro* models
  o Ability to overcome resistance
  o Kill dormant tumor cells causing metastasis & tumor relapse, independent of cell proliferation

• ATAC technology applicable to every tumor entity

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**Heidelberg Pharma**

- Death cap mushroom
- Chemical synthesis
- Amanitin
- Linker

**Partner / Licensor**

- Antibodies for different tumor targets
- Targets determine indications
- Tumor specific delivery
- Internalization of target
- Access to antibodies through licensing or partnering

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Antibody Drug Conjugate Technology – Proven & Established Technology

ADC: Combining the best of two therapeutic modalities

Antibody specificity + toxin efficacy → improved therapeutic window and fewer side effects

ATAC:
Antibody-Targeted Amanitin Conjugate

1. ATAC is prepared and released into bloodstream
2. Binding to tumor-associated antigen
3. Internalization
4. Release of Amanitin from the antibody/ATAC
5. Amanitin relocates from the lysosome to the nucleus
6. Amanitin binds to the RNA polymerase II and inhibits mRNA synthesis

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# Amanitin Compared Favorably to Approved ADC Toxins

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<th>PBD</th>
<th>Auristatin</th>
<th>Maytansinoids</th>
<th>Exatecan</th>
<th>Amanitin</th>
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<td><strong>Target</strong></td>
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<td>Tubulin</td>
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<td>Topo I</td>
<td>RNA Pol II</td>
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<td><strong>Target concentration</strong></td>
<td>?</td>
<td>$10^{-5}$ M</td>
<td>$10^{-5}$ M</td>
<td>?</td>
<td>$10^{-8}$ - $10^{-9}$ M</td>
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<td><strong>Structure</strong></td>
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<td>hydrophobic</td>
<td>hydrophobic</td>
<td>hydrophobic</td>
<td>hydrophilic</td>
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<td><strong>Activity on non-dividing cells</strong></td>
<td>medium to high</td>
<td>low</td>
<td>low</td>
<td>?</td>
<td>high</td>
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<tr>
<td><strong>Activity on multi-drug resistant cells</strong></td>
<td>high</td>
<td>low</td>
<td>low</td>
<td>?</td>
<td>high</td>
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<tr>
<td><strong>Aggregation of conjugates</strong></td>
<td>high</td>
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<td>high</td>
<td>high</td>
<td>low</td>
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<td>organic</td>
<td>organic</td>
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<td><strong>Antigen expression</strong></td>
<td>high to low</td>
<td>high</td>
<td>high</td>
<td>high to medium</td>
<td>high to very low</td>
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<td><strong>Clinical data</strong></td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>Yes</td>
<td>no</td>
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</table>

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Complete remissions in JIMT-1 xenograft models after single dose application of 2.9mg/kg Her2-ATAC

Clinical dose of T-DM1 ineffective (FDA approved Kadcyla®)

Equivalent dose of HER2-ATAC shows complete remission

Kadcyla could not achieve remission

Comparison with auristatin-ADC confirmed superiority of Amanitin payload
Heidelberg Pharma is the first company using Amanitin for cancer treatment

**IP protection for ATACs est. 2029 up to 2039**

Approx. 20 patents granted or applied for:
- Chemical synthesis of toxins (different derivatives) established
- Optimal linker attachment sites identified
- Portfolio of different linkers to select optimal linker for each antibody, target & tumor
- Site-specific conjugation technology adapted for Amanitin
- Use of 17p deletion as biomarker
## Multi-Target Research and Option Agreements with Takeda and Magenta

### Research & Option Agreements

- Synthesis of ATACs using antibodies from the Takeda/Magenta portfolio
- Both companies have exclusive target licensing option for global development and marketing rights for development candidates
- Option for several exclusive targets
- If option exercised, partner is responsible for further preclinical and clinical development as well as commercialization

### Financials

- Upfront technology access fees and R&D support
- Option fee for each option exercised
- Clinical development, regulatory and sales-related milestone payments:
  - Takeda: Up to USD 113 million for each product candidate; up to three targets
  - Magenta: Up to USD 85 million per target; up to four targets
- Royalties on sales

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**One of the top 15 pharmaceutical companies worldwide**

**Developing innovative medicines for immune reset through stem cell transplant**
Collaboration enables and accelerates Magenta’s research and development efforts across several targeted conditioning programs for bone marrow transplant with ATACs.
Multiple Myeloma – Major Unmet Medical Need

• Second most prevalent hematopoietic malignancy*

• 70,000 deaths due to MM annually; median age at diagnosis is 65-70 years

• Malignancy characterized by the proliferation of single clone of plasma cells derived from B-cells which produce abnormal antibody proteins

• MM is initially confined to bone marrow, natural progression of disease can result in end organ damage

• Current treatment options: Chemotherapy, immunomodulatory drugs, proteasome inhibitors and autologous stem cell transplantation (ASCT)

• MM is still considered incurable, median survival ~30-60 months

HDP-101 Offers Potential Advantages versus Other BCMA Approaches

BCMA target – Validated but need for better treatment options remains

- CAR-T: Safety concerns, complex CMC, only 1 year PFS
- Bispecifics: Need for continuous infusion, Cytokine storm, no clinical data for half-life extended yet

- **ADCs targeting BCMA – small competitive environment**
  - GSK (GSK2857916): BCMA-MMAF ADC, Pivotal phase II ongoing; @ASH 12/2017: Overall response rate of 60%
  - Medimmune (MEDI-2228): Phase I
  - Celgene / Sutro collaboration (CC-99712): IND approved, undisclosed payload
  - **HDP-101**: IND and CTA in preparation for filing in Q2 2020
HDP-101 – Favorable Results in Head-to-head Comparison Evaluating Efficacy of Toxins

Comparison with MMAF (Auristatin Conjugate as used by GSK) on MM Patient Cells

- Green lines: Non-dividing (quiescent) cells isolated from multiple myeloma patient bone marrow biopsies
- Black lines: Dividing tumor cells from lab cell lines

- Strong cytotoxic effect at very low doses, even in cancer cells with a low concentration of BCMA antigens
- No toxicity on non-BCMA expressing control cells
- First time that the efficacy of Amanitin on cancer cells taken from human patients was demonstrated
- Results from research collaboration with Heidelberg University and the DKFZ presented at ASH

Only HDP-101 is efficacious on non-dividing primary tumor cells isolated from multiple myeloma patients

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PSMA-ATAC – Prostate Cancer – Next Potential ATAC Development Candidate

- PSMA is a clinically validated target, e.g. 177Lu-PSMA-617, a radio-ligand therapy for metastatic castration-resistant prostate cancer (mCRPC)
- PSMA is a commercially attractive target: Novartis acquired Endocyte for that program for USD 2.1 billion
- Strong IP position for the antibody & platform
- Preclinical data package comprises in vitro and in vivo efficacy, tolerability, PK in rodents and monkeys

- Therapeutic window based on mouse efficacy and monkey tolerability (HNSTD > 7.5 mg/kg) \(\Rightarrow\) TI = 15
- Target product profile for metastatic Castration Resistant Prostate Carcinoma (mCRPC)
• TP53 gene on chromosome 17 is frequently mutated (> 50%) in human cancer cells
• POLR2A gene frequently co-deleted with TP53

⇒ higher sensitivity to treatment with ATACs
17p Deletion – Potential Biomarker for ATACS across Various Indications

TP53 loss creates therapeutic vulnerability in colorectal cancer

Yanhua Liu1, Xixia Zhang2,3, Credil Han1, Guoshui Wan1, Xingyu Huang4, Cristina Ivan1,2, Dahai Jiang1,2, Cristian Rodriguez-Aguayo1,5, Gabriel Lopez-Berestein5,6, Pullarthi H. Rao6, Diven M. Maru1, Andreas Pahl7, Xiaoming He8, Anil K. Sood1,8, Lee M. Ellis9, Jan Ander10 & Xionghui Lu11

• 10 x increased susceptibility to Amanitin in the case of loss of POLR2A
• POLR2A potential biomarker to increase therapeutic window

Publication with scientific partner MD Anderson in Nature, April 2015
Literature Confirms Poor Prognosis for MM Patients with 17p Deletion

Overall survival with and without 17p deletion

*Blood 2009, Jul 16;114 (3): 522-525*
Case study: HDP-101 for multiple myeloma

- MM patients with 17p deleted tumors have a very high medical need for new treatment options
- HDP-101 has preferential activity on 17p deleted tumor cells derived from MM patients
- Potential options to speed-up market approval for such a selected patient population if preclinical data translate into clinical benefits
- Potentially broader therapeutic window resulting in lower development risk and new treatment option for patient segment with bad prognosis

Company to apply for Fast Track designation for HDP-101 at time of IND submission

Source: FDA
## Financials and Shares

### Guidance

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<th>Guidance 03/2019</th>
<th>9M 2019</th>
<th>Revised Guidance 10/2019</th>
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<td>Sales revenue and other income</td>
<td>4.4</td>
<td>5.0 to 7.0</td>
<td>6.7</td>
<td>7.5 to 8.5</td>
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<td>Operating expenses</td>
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<td>14.0 to 18.0</td>
<td>12.4</td>
<td>15.5 to 17.5</td>
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<td>Operating result (EBIT)</td>
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<td>-8.0 to -12.0</td>
<td>-5.6</td>
<td>-7.5 to -9.5</td>
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<td>Funds required</td>
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<td>10.0 to 14.0</td>
<td>6.7</td>
<td>8.0 to 10.0</td>
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<td>Funds required per month</td>
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<td>0.9 to 1.2</td>
<td>0.8</td>
<td>0.7 to 0.9</td>
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### Financing

- Mixed non-cash and cash capital increase in November 2017: €34.4 m total transaction volume
- Cash at the end of 9M 2019: €12.7 m
- Cash reach is secured until mid 2020 based on current budget planning

### Shares

- Shares outstanding: ~28M
- Average daily trading volume: ~15,000 shares (all stock exchanges, ytd)
- Majority shareholder: Dietmar Hopp and affiliated companies*

### Analysts

- MainFirst (Stifel) 11/19: target €4.10
- Pareto 10/19: target €4.20
- EQUI.TS 10/19: target €3.85
- Baader Helvea 10/18: target €4.40

*dievini Hopp BioTech holding GmbH & Co. KG + DH Holding Verwaltungs GmbH
Achievements – Last 12 Months

Proprietary lead candidate HDP-101
• Core GMP manufacturing milestones achieved
• Preclinical GLP tox studies – first part completed
• HDP-101 clinical trial preparation
  ✓ Agreement signed with clinical CRO
  ✓ Clinical centers identified (US, GER)
  ✓ Synopsis issued
  ✓ CMC/CDT documentation started

ATAC technology partnering
• Magenta Therapeutics
  ✓ 3 posters presented at ASH 2018
  ✓ 2nd licensing option exercised (11/2019)
  ✓ 3 posters announced at ASH and ACR 2019

ATAC platform & pipeline
• Biomarker 17p deletion validated with MD Anderson, presented at ASH 2018
• Compelling preclinical data on PSMA-ATAC and hematological follow-up candidates
• GMP manufacturing established for different Amanitin-linker derivatives

TLX250-CDx (Telix)
• New production process for Ab; milestone payment for HDP
• Phase III trial in EU and Australia
• Phase I/II trial in Japan

MESUPRON®
• Link Health received IND to conduct clinical trials in China
Next Steps and Potential Milestones

ATAC technology and proprietary pipeline

HDP-101
• Complete GLP toxicity study
• Complete GMP manufacturing of clinical trial material
• Submit Clinical Trial Application in Germany/IND in US
• Initiate clinical development in 2020
• Continue biomarker development

Select next proprietary development candidate

Magenta collaboration
• Present CD117-ADC gene therapy data and
• CD45-ADC immune reset data @ASH 2019 in Dec.

Sign additional license and collaboration agreements

Partnered legacy clinical programs

TLX250-CDx® (Telix) – imaging agent
• ZIRCON Phase III trial: patient recruitment in EU and Australia
• ZIRCON: Add new sites – US and Canada (subject to reg. approval)
• Start Phase I/II study in Japan

TLX250 - 177Lu-girentuximab
• Initiate trials with therapeutic radioimmuno-conjugate &
  checkpoint inhibitor in the US

MESUPRON® (Link Health)
• Revise development plan for China based on new NMPA regulations
Investment Summary

Developing new options to address major challenges in cancer therapy

- Heidelberg Pharma is developing **new treatment options** with Amanitin for **a variety of cancer indications**, also validated by **high quality collaborations**

- The innovative **first-in-humans** mode of action provides **high efficacy** and **potential for unique clinical advantages** including treatment of dormant tumor cells as well as **increased efficacy against 17p deleted** tumor cells

- **Increased valuation expected in 2020** as lead product candidate HDP-101 enters the clinic

- Dual business model – **early validation** and cash through pharma collaborations + future **high value potential** with proprietary portfolio
### Upcoming conferences & events

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<td>18 – 22 November 2019</td>
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<tr>
<td>German Equity Forum</td>
<td>Frankfurt</td>
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<td>ASH 2019 Annual Meeting</td>
<td>Orlando</td>
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<td>JP Morgan Healthcare Conference</td>
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Katja Arnold (CIRO)  
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Email: katja.arnold[at]mc-services.eu

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