ATACs: a Unique New Mode of Action to Fight Cancer

September 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.

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 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: 34.17 million
Market cap: ~€230 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)
ATAC Technology

Business model: develop proprietary ATAC pipeline, partner ATAC technology platform and generate upside potential from legacy clinical portfolio
Highlights of ADC Deals and Approvals

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

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ATACs Fill the Gap
Missing MoA of Cancer Chemotherapeutics

Amanitin – novel mode of action for cancer therapy

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 \textit{in vivo} and \textit{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

[Diagram showing RNA, DNA, Proteins, and their interactions with drugs like 6-Mercaptopurine, Hydroxyurea, 5-Fluorouracil, Cytarabine, Doxorubicin, L-Asparaginase, Paclitaxel, Cisplatin, Ribonucleotides, Deoxyribonucleotides, Purines and pyrimidines]

Missing: Inhibition of mRNA synthesis

Adapted from http://chemistry.elmhurst.edu/vchembook/655cancer2.html

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Antibody Targeted Amanitin Conjugates (ATACs)
Combining the Best of Two Therapeutic Modalities

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

**Highly effective payload**
- Death cap mushroom

**From nature to the lab**
- Chemical synthesis

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

**ATAC technology**
- Chemical synthesis of toxins, optimal linker attachment sites, portfolio of different linkers, site-specific conjugation technology

Source: pilz-ratgeber.de
ATACs Overcome Resistance
Early and Explorative Model for Breast Cancer

Complete remission of a breast cancer xenograft model after single-dose application of HER2-ATAC

Clinical dose of FDA-approved Kadcyla®, a HER2-DM1-ADC, is ineffective

Equivalent dose of HER2-ATAC shows complete remission

→ ATACs are highly potent & superior to existing payloads

→ ATACs can overcome resistance in *in vivo* models
ATACs Kill Dormant Tumor Cells
Lead Candidate HDP-101 ex-vivo Model

Anti-BCMA-ATAC (HDP-101) 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

Antibody-Drug Conjugates (ADCs) can kill non-dividing primary tumor cells and may eliminate dormant tumor stem cells

**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
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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**17p deletion is a potential biomarker to increase therapeutic window and identify high-risk patients**
Corporate Overview

Technology & Validation

Business model

Proprietary ATAC projects

Financials & Outlook
## 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

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

### GMP supply with Amanitin

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# 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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<tr>
<td>Proprietary ATAC pipeline</td>
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## Licensed legacy assets (non ATACs)

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<td>Renal Ca</td>
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<td>Link Health</td>
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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

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)

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.

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**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.

\([^1\) 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)**
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

- 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
HDP-101: Clinical Development Plan for Multiple Myeloma

2021
- IND
- FPI
- Dose escalation in MM patients
- First clinical safety data

2022
- Expansion cohorts
- Del(17p) stratified
- Non-stratified MM patients
- Additional indications / Combinations

2023
- RP2D
- Assess accelerated approval option
- Registrational cohort
- BLA

2024
- HDP-101 has best-in-class potential in all RRMM patients.

2025
- HDP-101 has potential for accelerated approval in high-risk myeloma patients with del(17p).

Status
- Contract with MD Anderson Cancer Center signed; further US and German sites to follow
- MD Anderson site initiation planned for second half of September
- Treatment of the first patient this year
## Financials

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<th>H1 2021</th>
<th>Guidance FY 2021</th>
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<td>1.1</td>
<td>5.5 – 7.5</td>
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<td><strong>Operating expenses</strong></td>
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<td>36.0 – 40.0</td>
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<tr>
<td>Cost of sales</td>
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<td>R&amp;D costs</td>
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<td>Other expenses</td>
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<td><strong>Operating result (EBIT)</strong></td>
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<td>12.9</td>
<td>30.0 – 34.0</td>
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<tr>
<td><strong>Net loss for the period</strong></td>
<td>18.4</td>
<td>13.1</td>
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### Financing
- Cash as of 31 May 2021: €0.9 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 + €17.5 m
- Cash reach is secured until mid-2022 based on current budget planning

### Shares
- Shares outstanding: 34,173,009
- Shareholders:
  - 75% Dietmar Hopp and affiliated companies*
  - 3% UCB
  - 22% Freefloat and Corporate Bodies

### Analysts
- Stifel 07/21: target € 8.94
- Pareto 07/21: target € 9.30
- Bryan, Garnier 07/21: 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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<td>H.C. Wainwright 23rd Annual Global Investment Conference</td>
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<td>Q3 – Interim Results on the first nine months of 2021</td>
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<td>World ADC</td>
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<td>PEGS Europe</td>
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<tr>
<td>German Equity Forum</td>
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<td>22 – 24 November 2021</td>
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## Ticker data

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