Debio 0123 is a potent, oral, brain-penetrant, and highly selective small-molecule inhibitor of the WEE1 kinase

- Good efficacy in multiple preclinical in vivo models
- No targeting of the PLK1/2 axis

Currently in Phase 1 clinical development as single agent, and in combination with SOC in patients with solid tumors

- Better safety/tolerability profile to date vs. other clinical-stage WEE1 inhibitors, either as monotherapy or in combination with carboplatin
- Signals of antitumor activity and consistent WEE1 target engagement observed in patients
- Further clinical development plan is ongoing

Excellent opportunity to combine it with a wide array of cancer therapeutic regimens allowing to address multiple indications and maximize clinical development options

Expected time to market 2030, with current market exclusivity up to 2043
### Well-Differentiated, Clinical-Stage WEE1 Inhibitor

<table>
<thead>
<tr>
<th></th>
<th>adavosertib (AZD-1775) (AstraZeneca)</th>
<th>azenosertib (Zn-c3) (Zentalis Pharma)</th>
<th>Debio 0123</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Status</strong></td>
<td>Discontinued (Ph 2) due to safety concerns</td>
<td>Phase 2</td>
<td>Phase 1</td>
</tr>
<tr>
<td><strong>Structure similarity to adavosertib</strong></td>
<td>–</td>
<td>adavosertib-like§</td>
<td>DIFFERENT CHEMOTYPE</td>
</tr>
<tr>
<td><strong>Brain Penetration</strong></td>
<td>No / Low¶</td>
<td>No / Low†</td>
<td>YES¶</td>
</tr>
<tr>
<td><strong>PLK1/2 inhibition</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>NO</td>
</tr>
<tr>
<td><strong>Clinical safety profile</strong></td>
<td>High rate of hematological &amp; GI toxicity</td>
<td>Significant rate of hematological toxicity</td>
<td>LOW RATE of hematological &amp; GI toxicity</td>
</tr>
<tr>
<td><strong>Clinical efficacy profile</strong></td>
<td>31-43% ORR#</td>
<td>In same range as adavosertib</td>
<td>In same range as adavosertib</td>
</tr>
<tr>
<td><strong>Addressed indications</strong></td>
<td>Mainly gynecological</td>
<td>Gynecological, osteosarcoma, CRC, AML</td>
<td>SCLC, GBM*</td>
</tr>
</tbody>
</table>

§ Huang et al., J. Med. Chem. 2021
¶ Shwetal et al., AACR 2023 abstract # 2796
† Piggott et al, AACR 2023 abstract #6185
# Moore et al., CCR 2021, Leijen et al., JCO 2016, Embaby et al., ASCO 2022
The Target
WEE1
Blocking DNA repair pathways in cancer cells through inhibition of checkpoint kinases renders cells more vulnerable to DNA damaging therapies

Failed DNA repair will lead to anti-proliferative efficacy

In cancer cells, DDR pathways are often upregulated due to genomic instability

This leads to resistance to DNA damaging therapies

Hanahan D, Weinberg RA. Cell. 2011;144(5):646-74
Debio 0123, a WEE1 Inhibitor

**Inhibition of WEE1 Leaves Cancer Cells Vulnerable to Failed DNA Damage Repair, Leading to Cell Death**

- **WEE1 inhibition** leads to cell-cycle progression despite unrepaired DNA damage
- Accumulation of damages and continued cell cycle induces *cell death*
- Expected synergies with deficiencies in other DDR pathways
WEE1 is an Attractive & Promising Target for Future Anticancer Therapy

- WEE1 is a hot target in oncology pursued in the clinics
- Debio 0123 is a potential best-in-class, first-choice WEE1 inhibitor
- WEE1 inhibition has demonstrated antitumoral efficacy in the clinics#
- WEE1 targeting by Debio 0123 offers multiple opportunities for development

# Moore et al., ACR 2021, Liu et al., JCO 2021, Leijen et al., JCO 2016
Our Compound

A potent and selective WEE1 inhibitor to exploit DDR dependency of cancer cells
Debio 0123 is a Selective WEE1 Inhibitor with High Potency

**In vitro profile**

### High potency and selectivity

<table>
<thead>
<tr>
<th>Target</th>
<th>Debio 0123 IC₅₀ (nM)</th>
<th>Adavosertib IC₅₀ (nM)</th>
<th>Zn-C3 IC₅₀ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WEE1</td>
<td>0.8</td>
<td>3.9*</td>
<td>3.8*</td>
</tr>
</tbody>
</table>

IC₅₀ on WEE1 (ADP-competitive binding assay)

### More selective than competition on PLK1/2

<table>
<thead>
<tr>
<th>Target</th>
<th>Debio 0123 IC₅₀ (nM)</th>
<th>Adavosertib IC₅₀ (nM)</th>
<th>Zn-C3 IC₅₀ (nM)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLK1</td>
<td>&gt; 10 000</td>
<td>79</td>
<td>227</td>
</tr>
<tr>
<td>PLK2</td>
<td>&gt; 10 000</td>
<td>79</td>
<td>40</td>
</tr>
</tbody>
</table>

IC₅₀ on PLK1 and PLK2 (kinome screen)

Source: unpublished data

* Huang et al., *J. Med. Chem.* 2021, 64, 17, 13004-13024

Studies conducted using versions of adavosertib synthesized by third-party contract research chemists, using publicly available information
Debio 0123 Demonstrates Strong & Sustained Target Engagement

**Target engagement in vitro**

**IC$_{50}$ on pCDC2: 142nM**

pCDC2 by ELISA in HT29 cells treated with Debio 0123

Unpublished data

- Complete & sustained reduction of pCDC2 up to 24h with Debio 0123 at 30mpk, p.o.

**Strong & sustained target engagement in vivo**

Debio 0123 (30mg/kg, p.o.)

- Strong & sustained γ-H2AX induction observed with Debio 0123 over 48h
Debio 0123 Shows Favorable Brain Penetration in Different Species

Shows similar penetration across brain tumor and healthy brain

- In the mouse, the brain to plasma ratio is similar to that of Temozolomide (TMZ)\(^1\)
- AZD1775 penetrates poorly into brain

1 TMZ= GBM SoC; Source: De Gooijer M.C et al., Neoplasia Vol. 20, No. 7, 2018

Studies conducted using versions of AZD1775 synthesized by third-party contract research chemists, using publicly available information
Debio 0123 Shows a Broad Range of Activity \textit{in vitro}

- Broad sensitivity to Debio 0123 monotherapy across multiple indications
- Median $IC_{50}$ value 1.23 µM (range: 0.109 to 7.08 µM) ➤ Good response across various histotypes
- To support further development in monotherapy, efforts are ongoing to identify predictive biomarkers

Source: O’Dowd et al., AACR 2019 #4423.
Debio 0123 Outperforms adavosertib \textit{in vivo}

NSCLC model (A427)

![Graph showing tumor volume over days for different treatment groups]

Source: O'Dowd et al., AACR 2019 #4423.
Debio 0123 Shows Strong Activity in Combination with Carboplatin and Etoposide in Lung Cancer Models

**NCI-H446 (SCLC)**
- Vehicle
- Carboplatin
- Debio 0123
- Carboplatin + Debio 0123

Carboplatin: iv once a week, 50 mg/kg
Debio 0123: po, 30 mg/kg, 3 consecutive days a week, starting on the day of Carboplatin
N = 5 per group, mean ± SEM

**NCI-H1048 (SCLC)**
- Vehicle
- Debio 0123
- Etoposide
- Etoposide + Debio 0123
- Etoposide + Carboplatin + Etoposide

Etoposide: iv 12.5mg/kg QW
Carboplatin: ip 50mg/kg QW
Debio 0123: po 30mg/kg QD

- Strong anti-tumor efficacy observed in combination with carboplatin or etoposide
- Triple combination significantly improves tumor response over SOC carboplatin/etoposide
- All treatments were well tolerated, including triplet combination

Sources:
Gelderblom et al, ESMO 2020 abstract #3893
Piggott et al, AACR 2022 abstract #4894
Debio 0123 + Temozolomide Leads to Sustained Regressions

*In vivo*

- Sustained complete regressions observed in 75% of animals treated with Debio 0123 + TMZ

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**Source**
Piggott et al, AACR 2023 abstract #6185
Our Development Path
Ongoing Studies

Debio 0123-101 / Phase 1 / Combination with carboplatin / NCT03968653
- Dose escalation exploring 2 schedules of Debio 0123 (D1-D3 arm A and D1-D3, D8-D10 arm B), in advanced solid tumors that recurred or progressed following prior cisplatin or carboplatin-containing therapy

Debio 0123-102 / Phase 1b / Single agent / NCT05109975
- **Part A**: dose escalation in advanced solid tumors
- **Part B**: expansion in specific advanced tumor types in case of efficacy signal

Debio 0123-SCLC-104 / Phase 1 / Combination with carboplatin / etoposide / NCT05815160
- **Part A**: dose escalation in relapsed SCLC (CTFI ≥ 45d)
- **Part B**: expansion in relapsed SCLC (CTFI ≥ 90d)

Debio 0123-GBM-105 / Phase 1/2 / Combination with temozolomide or temozolomide + radiotherapy / NCT05765812
- **Phase 1**: dose escalation in combination with (A) TMZ in recurrent GBM or anaplastic astrocytoma, and (B) TMZ + RT in newly diagnosed GBM or anaplastic astrocytoma
- **Phase 2**: combination with TMZ in recurrent GBM / Controlled with a Synthetic Control Arm approach (non-randomized trial)
Debio 0123-101 & -102 Phase 1 Trials
Design of Dose Escalation Parts

DEBIO 0123-101 Phase 1 Trial / Combination with carboplatin

STUDY LOCATIONS
The Netherlands, Spain

ADMINISTRATIONS & DLT ASSESSMENT
Arm A
- Cycle 1 (24d)
  - Debio 0123 (p.o.)
- From Cycle 2 onwards (21d)
  - Debio 0123 (p.o.)
  - Carboplatin (i.v.)

DLT ASSESSMENT PERIOD
Covers Cycles 1 & 2 (45d)

ENDPOINTS
- SAFETY (RP2D, AEs, DLTs) / EFFICACY (ORR, PFS, OS, …) / PK, food-effect and effect of high gastric pH / TRANSLATIONAL (PDy, biomarkers, …)

DEBIO 0123-102 Phase 1 Trial / Monotherapy

STUDY LOCATIONS
US, Switzerland

ADMINISTRATIONS & DLT ASSESSMENT
All cycles (21d)
- Debio 0123 (p.o.)

DLT ASSESSMENT PERIOD
Covers Cycle 1 (21d)

ENDPOINTS
- SAFETY (RP2D, AEs, DLTs)
- EFFICACY (ORR, PFS, OS, …)
- TRANSLATIONAL (PDy, biomarkers, …)
Debio 0123-SCLC-104 & -GBM-105 Trials
Design of Dose Escalation Parts

DEBIO 0123-SCLC-104 Phase 1 Trial / Combination with carboplatin / etoposide

STUDY LOCATIONS
US, Spain

ADMINISTRATIONS & DLT ASSESSMENT

All cycles (21d)
- Debio 0123 (p.o.)
- Carboplatin (i.v.)
- Etoposide (i.v.)

DLT ASSESSMENT PERIOD
Covers Cycle 1 (21d)

ENDPOINTS
- RP2D
- SAFETY (AEs, DLTs, …) and EFFICACY (ORR, PFS, OS, …)
- TRANSLATIONAL (PDy, biomarkers, …)

DEBIO 0123-GBM-105 Phase 1/2 Trial / Combination with temozolomide ± RT

STUDY LOCATIONS
US, Switzerland, Spain

ADMINISTRATIONS & DLT ASSESSMENT

Arm A (all cycles) (28d)
- Debio 0123 (p.o.)
- Temozolomide (p.o.)

DLT ASSESSMENT PERIOD
Covers Cycle 1 (21d)

Arm B (6 weeks (42d)
- Debio 0123 (p.o.)
- Temozolomide (p.o.)
- Radiotherapy

DLT ASSESSMENT PERIOD
Covers 6 weeks (42d)

ENDPOINTS
- RP2D
- SAFETY (AEs, DLTs, …) and EFFICACY (ORR, PFS, OS, …)
- TRANSLATIONAL (PDy, biomarkers, …)
Debio 0123-101 Trial
Combination with Carboplatin

Debio 0123 hasShown Lower Hematological & GI Toxicity vs. Competitors when Combined with Carboplatin*

<table>
<thead>
<tr>
<th></th>
<th>Neutropenia</th>
<th>Thrombocytopenia</th>
<th>Anemia</th>
<th>Diarrhoea</th>
<th>Nausea</th>
<th>Vomiting</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>adavosertib</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,2 N= 46 (23 + 23)</td>
<td>35-43%</td>
<td>22-39%</td>
<td>70%</td>
<td>48-52%</td>
<td>61%</td>
<td>9-48%</td>
</tr>
<tr>
<td><strong>azenosertib</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 N=14</td>
<td>50.0%</td>
<td>7.1%</td>
<td>64.3%</td>
<td>35.7%</td>
<td>71.4%</td>
<td>28.6%</td>
</tr>
<tr>
<td><strong>Debio 0123</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 N=38</td>
<td>10.5%</td>
<td>2.6%</td>
<td>31.6%</td>
<td>7.9%</td>
<td>21.1%</td>
<td>2.6%</td>
</tr>
</tbody>
</table>

*No head-to-head comparison has been done and results are coming from different studies, and different patient populations.

References
1. Moore KM et al. *Clin Cancer Res* 2022;28:36-44 Carboplatin, cohort C
3. Liu J. et al., ASCO 2023 Abstract #5513
4. Gelderblom H. et al., ASCO 2023 Abstract #3012
Early Signals of Antitumor Activity in a Heavily Pre-treated Patient Population*

Platinum-Resistant Ovarian Cancer Response | N (%) (total 12 Pts evaluable)
--- | ---
Complete response (CR) | 0 (0%)
Partial Response (PR) | 4 (33.3%)
Overall response rate (ORR) | 33.3%
Stable Disease (SD) | 6 (50%)
Disease control rate (DCR) | 83.3%
- 15 out of 21 skin biopsies show pCDC2 reduction from 150 mg onwards
- Up to 95% reduction in pCDC2 observed in the skin
- up to 64% reduction in pCDC2 also observed in tumor biopsies
Value Proposition
Differentiation Factors

Once-a-Day, Oral WEE1 Inhibitor

Clinical-stage WEE1 inhibitor with best-in-class potential

More attractive profile vs. other WEE1i (adavosertib and azenosertib)

1. Higher selectivity – No inhibition of PLK1/2
   - Better safety / tolerability profile to date
   - More favorable combinability allowing to address multiple indications
   - Preliminary clinical efficacy in line with other WEE1 inhibitors

2. Brain-penetrant drug with favorable tissue distribution profile

3. Oral, QD dosing: convenience for patients

Market-ready formulation
   - Suitable for pediatrics
Maximal Value & Commercial Opportunities Unlocked with Debio 0123

Value Proposition

LARGE MARKET POTENTIAL

Multiple combinations potential across a broad range of indications
Monotherapy in selected patients

CLEAR PATH TO MARKET IDENTIFIED

2030
Expected time to market

EXPECTED PATENT PROTECTION

Composition of matter
Expiration date: 2038 + max 5 years (country-by-country)
Interested?

Find out more!
Contact information

Sandra von Meier, PhD
Head BD&L
Debiopharm International SA
sandra.vonmeier@debiopharm.com

Debiopharm Group™
Headquarters
Lausanne, Switzerland
www.debiopharm.com