Disclosures

- Trial funded by Vical, Inc.
- MPM employed by Vical, Inc.
Genital Herpes

- Recurrent sexually-transmitted infection; mainly due to HSV-2
- 16% of U.S. population 14 to 49 years of age are infected
- Initial outbreak followed by intermittent viral shedding with or without genital lesion recurrences in “boxer shorts” distribution

Vical’s Therapeutic HSV-2 DNA Vaccine

- **T-cell responses are the strength of DNA technology**
  - Simulates live attenuated approach without safety issues
  - CMV DNA vaccine showed reduced viremia in transplant patients in Phase 2 trial*

- **Collaboration with Fred Hutchinson Cancer Research Center and University of Washington (UW)**
  - Antigen discovery by Corey and Koelle
  - Top candidates: glycoprotein D (gD) and tegument proteins UL46, UL47

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**Preclinical studies show immunogenicity and efficacy against HSV-2**

- Mice – Immunogenicity *(Muller et al, JGV 2009)*
- Mice – Vaxfectin® adjuvant effect and full-length gD *(Shlapobersky et al, JGV 2012)*
- Guinea pigs – Therapeutic proof of concept *(Veselenak et al, Vaccine 2012)*

HSV-2 Vaccine Candidates

**Bivalent**

- UL46
- US6
- Codon-optimized genes
- Tegument Protein VP11/12
- Glycoprotein D
- Full-length HSV-2 proteins

**Monovalent**

- US6
- Codon-optimized genes
- Glycoprotein D

**Vaxfectin® Liposomes**

(±)-N-(3-aminopropyl)-N,N-dimethyl-2,3-bis(cis-9-tetradeceneyloxy)-1-propanaminium bromide

1,2-diphytanoyl-sn-glycero-3-phosphoethanolamine

Vical
Phase 1/2 Trial Design

- Randomized, double-blind, placebo-controlled trial
- Bivalent and monovalent vaccines
  - for safety and efficacy
- Placebo*
  - primarily for blinded safety comparisons

* Phosphate buffered saline

<table>
<thead>
<tr>
<th>Cohort (N)</th>
<th>Treatment (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (7)</td>
<td>1 mg Bivalent or Placebo (5:2)</td>
</tr>
<tr>
<td>B (7)</td>
<td>2 mg Bivalent or Placebo (5:2)</td>
</tr>
<tr>
<td>C1 (14)</td>
<td>4 mg Bivalent or 4 mg Monovalent or Placebo (5:5:2)</td>
</tr>
<tr>
<td>C2 (137)</td>
<td>4 mg Bivalent or 4 mg Monovalent or Placebo (5:5:2)</td>
</tr>
</tbody>
</table>
Cohort C Design and Endpoints

Comparing swabbing periods – participant serves as own control

- **Primary endpoints**
  - Safety and tolerability
  - Change in shedding rate by UW PCR assay

- **Secondary endpoints**
  - Change in viral load (shedding)
  - Change in lesion rate
  - Recurrence rate post-vaccination
  - Immunogenicity
Key Eligibility Criteria

- Healthy men and women 18-50 years of age
- HSV-2 positive by Western blot
- ≥ 1-year duration of HSV-2
- 2-9 recurrences per year (self-reported)
- Willing to refrain from
  - Suppressive antivirals throughout the trial
  - Episodic antivirals during swabbing periods
- Body Mass Index (BMI) < 35
- Antinuclear antibody (ANA) ≤ 1:80
## Demographics Per Protocol Efficacy Analysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Bivalent (56)</th>
<th>Monovalent (54)</th>
<th>Placebo (21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – median year (range)</td>
<td>37.2 (20-50)</td>
<td>34.7 (21-50)</td>
<td>37.5 (23-50)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>36 (64.3%)</td>
<td>34 (63.0%)</td>
<td>12 (57.1%)</td>
</tr>
<tr>
<td>White race (%)</td>
<td>36 (64.3%)</td>
<td>37 (68.5%)</td>
<td>18 (85.7%)</td>
</tr>
<tr>
<td>Median years from 1\textsuperscript{st} HSV episode (range)</td>
<td>8 (1-27)</td>
<td>10 (1-31)</td>
<td>10 (1-32)</td>
</tr>
<tr>
<td>Median # of prior HSV episodes/year (range)</td>
<td>4.8 (2-12)</td>
<td>5.1 (2-10)</td>
<td>4.5 (2-8)</td>
</tr>
<tr>
<td>HSV-1 seropositivity (%)</td>
<td>46.4%</td>
<td>42.6%</td>
<td>71.4%</td>
</tr>
<tr>
<td>Previously used suppressive antivirals (%)</td>
<td>14 (25.0%)</td>
<td>14 (25.9%)</td>
<td>4 (19.0%)</td>
</tr>
<tr>
<td>Mean # prevaccine swabs/ Mean # 1\textsuperscript{st} postvaccine swabs</td>
<td>62/58</td>
<td>61/57</td>
<td>63/61</td>
</tr>
</tbody>
</table>
Significant Adverse Events (AEs) Related to Study Product in All Cohorts

- Summary
  - No serious adverse events / No AEs of special interest
  - No Grade 4 AEs
  - Grade 3 AEs: 21 (13%) of participants (20 in Cohort C)
    - 10 bivalent, 11 monovalent

- Independent Safety Monitoring Board reviewed all AEs
  - Deemed vaccines to be safe and tolerable in this trial

<table>
<thead>
<tr>
<th>Grade 3 AEs</th>
<th>Fatigue</th>
<th>Headache</th>
<th>Myalgia</th>
<th>Nausea</th>
<th>Vomiting</th>
<th>Injection Site Pain or Tenderness</th>
<th>Fever</th>
</tr>
</thead>
<tbody>
<tr>
<td># of AEs</td>
<td>12</td>
<td>4</td>
<td>8</td>
<td>1</td>
<td>1</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td># of Participants</td>
<td>11</td>
<td>4</td>
<td>7</td>
<td>1</td>
<td>1</td>
<td>7</td>
<td>2</td>
</tr>
</tbody>
</table>
Primary Endpoint: Shedding Rate at 3mo Compared to Baseline*

(150 copies/mL assay cut-off)

<table>
<thead>
<tr>
<th>Change</th>
<th>Bivalent (56)</th>
<th>Monovalent (54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-20%</td>
<td>p = 0.17</td>
<td>p = 0.52</td>
</tr>
</tbody>
</table>

Placebo (21): -45%, p = 0.002

Shedding rate: HSV DNA PCR+ swab per total # swabs per participant

Baseline shedding rates: Bivalent 14.7%, Monovalent 15.0%, Placebo 18.4%

Secondary Endpoint: Viral Load in Positive Swabs at 3mo Compared to Baseline

**Viral load**: HSV DNA copies, $\log_{10}$

**Placebo (21)**: Change of +0.28, $p = 0.127$
Secondary Endpoint: Lesion Rate Compared to Baseline*

Placebo (21): 3mo: -47%, p = 0.135 and 9mo: -62%, p = 0.062

Lesion rate: # days with lesions relative to number of days evaluated

Baseline lesion rates: Bivalent 6.0%, Monovalent 6.0%, Placebo 6.4%

Secondary Endpoint: Post-Vaccine Recurrence Rate - Bivalent versus Placebo

3 months

-50% -25% 0% 25% 50%

Change

p = 0.75

Bivalent (56)

9 months

p = 0.62

Monovalent (54): 3mo: +52%, p = 0.29 and 9mo: +30%, p = 0.39
Exploratory Endpoint: Median Time to First Recurrence Until 9 Months

Placebo (21): 111 days

Bivalent vs monovalent $p = 0.003$  Bivalent vs placebo $p = 0.396$
gD-Specific T-cell Responses: Vaccine Shows Biological Activity

N = 125 participants
* p < 0.05

IFN-γ ex vivo ELISPOT assay using 15-mer gD peptides overlapping by 11 amino acids
UL46-Specific T-cell Responses: Vaccine Shows Biological Activity

IFN-γ ex vivo ELISPOT assay using 15-mer UL46 peptides overlapping by 11 amino acids

N = 125 participants
* p < 0.02
Trial Conclusions: Bivalent Vaccine

- **Virologic endpoints**
  - Nonsignificant reduction in shedding rate <150 copies/mL (primary endpoint)
  - Significant reduction in viral load among PCR+ swabs (secondary endpoint)

- **Lesion rate (secondary endpoint)**
  - Significant reduction of 49% (p = 0.031) at 3 months
  - Significant reduction of 57% (p = 0.009) at 9 months - suggests a durable effect
  - Nonsignificant reductions for monovalent and placebo groups

- **Additional clinical endpoints**
  - Favorable impact on recurrence rate, time to first recurrence and recurrence-free

- **Immunological endpoint**
  - Significant increase in UL46-specific IFN- producing T cells after 2nd & 3rd doses

- **Safety**
  - Independent SMB deemed trial vaccinations to be safe and tolerable

➢ **Trial results support further clinical investigation in Phase 2**
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Special thanks to our trial participants as well as site & support staff and Vicalites who contributed to this collaboration!
Backup Slides
**Why the discordance between impact of bivalent vaccine on shedding and lesion rates?**

<table>
<thead>
<tr>
<th>Viral Load (copies/mL)</th>
<th>% of Shedding Episodes</th>
<th>% Associated with Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low ((10^2 - 10^4))</td>
<td>41</td>
<td>9</td>
</tr>
<tr>
<td>Medium ((&gt;10^4-10^6))</td>
<td>24</td>
<td>27</td>
</tr>
<tr>
<td>High ((&gt;10^6))</td>
<td>35</td>
<td>67</td>
</tr>
</tbody>
</table>

**Schiffer et al, PNAS, 2010**
1,000 shedding episodes among 386 participants

**Tronstein et al, JAMA, 2011**
\(\log_{10} \) copies/mL 5.6 in lesions vs 4.3
Exploratory Endpoint: Shedding Rate Compared to Baseline at 3mo

(10,000 copies/mL cut-off)

Placebo (21): -38% p = 0.08

Shedding rate: HSV DNA PCR positive swab per total # swabs collected for each participant

Baseline shedding rates: Bivalent 14.7%, Monovalent 15.0%, Placebo 18.4%
Exploratory Endpoint: Proportion of Subjects Recurrence-Free

Placebo (21): 62% at 3mo; 33% at 9mo