VOICE OF THE PATIENT

CLINICAL POST COITAL STUDY
HUMAN CONTRACEPTIVE ANTIBODY FILM (ZB-06)

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Non Hormonal Contraceptive Options for Women

**Copper IUD**
- **PROS:** failure rate <1%, lasts up to 10 years, cost effective, reversible
- **CONS:** menorrhagia, dysmenorrhea, lack of non-contraceptive benefits

**Barrier Devices (Condoms, Diaphragms)**
- **PROS:** On demand, nonhormonal, protect against some STIs
- **CONS:** Only 85% effective in actual use (high user failure rate), male condoms not woman controlled.
Non Hormonal Contraceptive Options for Women

- **Tubal Ligation**
  - **PROS**: highly effective, tubal cancer reduction (?)
  - **CONS**: irreversible, requires laparoscopic surgery

- **Spermicides**
  - **PROS**: on demand, OTC, reversible
  - **CONS**: > 15% failure rate, may cause vaginal irritation, enhance HIV risk
Immuocontraception

Use of the immune system for contraception
- Active immunization (vaccines)
- Passive immunization (transfer of antibodies)

Infertility patients often have antisperm antibodies that agglutinate and immobilize sperm.

We have selected an antisperm antibody from an infertility patient for development as a Human Contraceptive Antibody (HCA).
Goals of the HCA Program

• Transiently express IgG1 human contraceptive antibody (HC4, drug substance), in *Nicotiana benthamiana*; purify to GMP standards.

• Incorporate HC4 into ZB-06 film (drug product) for use as an on-demand vaginal contraceptive.

Properties of ZB-06 film

<table>
<thead>
<tr>
<th>Component</th>
<th>% (wt/wt)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HC4 Antibody</td>
<td>10</td>
</tr>
<tr>
<td>PVA 8-88</td>
<td>60</td>
</tr>
<tr>
<td>Maltitol</td>
<td>25</td>
</tr>
<tr>
<td>Histidine</td>
<td>0.1</td>
</tr>
<tr>
<td>Polysorbate 20</td>
<td>0.01</td>
</tr>
<tr>
<td>Water</td>
<td>5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>
• **The target**: GPI-anchored 34 kD glycoprotein made by epithelial cells in the caput epididymis and transferred to sperm membrane. Abundant on the sperm surface.

• **The epitope**: o-glycosylated carbohydrate structure on CD52 peptide backbone. Only present in the human male reproductive tract and is a common target for antisperm antibodies from infertility patients.
# ZB-06 Film Development

## Contraceptive Commercial Profile

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Phexxi</th>
<th>Annovera</th>
<th>ZB-06</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-prescription</td>
<td>X</td>
<td>X</td>
<td>✓</td>
</tr>
<tr>
<td>MPT</td>
<td>?</td>
<td>X</td>
<td>✓</td>
</tr>
<tr>
<td>Non-hormonal</td>
<td>✓</td>
<td>X</td>
<td>✓</td>
</tr>
<tr>
<td>Efficacy</td>
<td>~86%</td>
<td>~97%</td>
<td>≥ 97%</td>
</tr>
<tr>
<td>Safety</td>
<td>Moderate irritation, UTIs</td>
<td>Potential clotting</td>
<td>Minimal irritation</td>
</tr>
<tr>
<td>Stability / Shelf Life</td>
<td>RT for up to 2 years</td>
<td>RT for up to 1 year</td>
<td>RT for up to 2 years</td>
</tr>
<tr>
<td>Cost to Consumer</td>
<td>~$260 with insurance (12 units)</td>
<td>$60-$200 with insurance</td>
<td>$0.50 / film $5.00 / ring</td>
</tr>
</tbody>
</table>
Pre IND

• Multiple Animal Safety Studies were Completed to Support the First-in-Human HC4 Study
  – Rat Repeat-Dose Toxicology (Intravaginal)
    • No indication of mAb-related or film-related toxicity at a dose 75x the clinical dose
  – Rabbit Vaginal Irritation
    • No indication of mAb-related or film-related toxicity at a dose 16x the clinical dose
  – Tissue Cross Reactivity
    • No indication of off-target reactivity that would be problematic for a topical product
Pre IND

- ZB-06 program builds on a precursor product: MB66, a vaginal film that contains human monoclonal antibodies against HIV and HSV-2; also produced in the *Nicotiana* platform.

- A Phase 1 single and repeat-dose study of MB66 was completed in 2015. MB66 had a high safety profile; effective levels of antibodies were detected in vaginal secretions up to 24 hours post dosage.

- An Exploratory IND was filed by ZabBio in December 2020 to assess feasibility of the contraceptive film product ZB-06.
  - Under the Exploratory IND, Phase 1a clinical trial ZB-06-01 was allowed to proceed in January 2021 to evaluate ZB-06 film efficacy in the post-coital test (PCT).
Phase I Contraceptive Efficacy “Surrogates”

- Ultimate Efficacy Biomarker = Pregnancy
- Hormonal Contraception:
  - Anovulation (Serum P4, Ovarian follicular development on TVUS)
- Non-Hormonal/Barrier Contraceptives:
  - For barrier contraceptives: Vaginal PSA (≤ 48 hrs), Y chromosomal DNA (≤ 7 days)
  - Post Coital Test – functional, *in vivo*, PD surrogate of cervical mucus/sperm interaction
Timed Visits to Peak Fertility

Changes in the Ovary & Endometrium during the menstrual cycle

- Menstruation
- Proliferative phase
- Ovulation
- Secretory phase

**Progesterone**

- Peaks at around day 14
- Levels decrease to baseline

**Oestrogen**

- Peaks earlier in the cycle
- Levels decrease to baseline

**Gonadotrophins**

- LH (Luteinizing Hormone)
- FSH (Follicle-Stimulating Hormone)

- LH peaks at ovulation, around day 14
- FSH levels are relatively flat throughout the cycle
PCT Study Population

- Healthy, women aged 18 – 50 yo
- OVULATORY
- Tubal Sterilization (Investigational Product)
- Not on exogenous hormones
- Heterosexually active
- Male partner has no history of infertility, vasectomy or sperm dysfunction
- Female participant and male partner are consented
# PCT Study Visits

<table>
<thead>
<tr>
<th>V1</th>
<th>V2</th>
<th>V3</th>
<th>V4</th>
<th>V6</th>
<th>V7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screen</td>
<td>Enroll</td>
<td>BASELINE NO PRODUCT CMC/PCT (5+ PMS/HPF)</td>
<td>PRODUCT CMC/PCT (1°ENDPOINT) (&lt;5 PMS/HPF)</td>
<td>Pre HC4 Film Use CMC</td>
<td>HC4 Film Use PCT</td>
</tr>
<tr>
<td></td>
<td>ENROLL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Enroll – Give LH Kit, start ovulation testing on day 10</td>
<td>Baseline Cervical Mucus Check (CMC)</td>
<td>Baseline PCT No Product</td>
<td></td>
<td></td>
</tr>
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<td></td>
</tr>
</tbody>
</table>
# Insler Score

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Volume</strong></td>
<td>None</td>
<td>0.01 - 0.10 ml or approximately 0.1 ml</td>
<td>0.11 - 0.29 ml or approximately 0.2 ml</td>
<td>&gt; 0.3 ml or approximately 0.3 ml or more</td>
</tr>
<tr>
<td><strong>Viscosity</strong></td>
<td>Thick, highly viscous, premenstrual mucus</td>
<td>Mucus of intermediate viscosity</td>
<td>Mildly viscous mucus</td>
<td>Watery, minimally viscous, mid-cycle (preovulatory) mucus</td>
</tr>
<tr>
<td><strong>Spinnbarkeit</strong></td>
<td>&lt; 1 cm</td>
<td>1 - 4 cm</td>
<td>5 - 8 cm</td>
<td>9 cm +</td>
</tr>
<tr>
<td><strong>Fern Pattern</strong></td>
<td>No crystallization</td>
<td>Atypical fern formation</td>
<td>Primary and secondary stem ferning</td>
<td>Tertiary and quaternary stem ferning</td>
</tr>
<tr>
<td><strong>Cellularity (using leukocytes and other cells)</strong></td>
<td>&gt; 20 cells per HPF or &gt;1000 cells per µL</td>
<td>11-20 cells per HPF or 501-1000 cells per µL</td>
<td>1-10 cells per HPF or 1-500 cells per µL</td>
<td>0 cells</td>
</tr>
</tbody>
</table>
Spinnbarkeit

https://youtu.be/mAG7I7Jp-7o
Viscosity, Volume
Ferning

https://youtu.be/cvXoX6t-1do
Cellularity
Examining CM for Motile Sperm

For each of the 9 hpfs, count:
# Progressively motile sperm
# Non-progressively motile sperm
# Immotile sperm
# Total sperm

Take average of 9 hpfs for each

Evaluating lab is blinded to
Baseline versus product use cycle

Laboratory personnel available on the weekend
PCTs in Previous and Current Non Hormonal Contraceptives

- **SILCS/CAYA Diaphragm**

- **Lea’s Shield**

- **Fem Cap**

- **Acidform (Amphora) and N9**

- **Ovaprene IVR (Dare Biosciences)**
  - ClinicalTrials.gov #NCT03598088
PCT Correlates with Contraceptive Efficacy

- SILCS/CAYA Diaphragm (with Buffergel versus N9)
- Lea’s Shield (w and w/o spermicide)
- Fem Cap (vs Ortho All Flex Diaphragm)
- Acidform and N9 Gels alone
  - Burke et al Obstet Gynecol 2010;116(6):1265-1273
- Amphora Clinical Efficacy Trials
  - Evofem Phase 3 Contraceptive Efficacy Trials
Recent PCT Studies

• **CONRAD 126 (NCT02309554, 9 visits):** Phase I PCT study of CAYA Used with 2% N9 gel, Contragel or No gel (12/2014 – 10/2015)
  - 27 enrolled (EVMS 11, Profamilia 16) → 18 Discontinued (Poor Baseline CMC, anovulation) → 9 completers (EVMS 4, Profamilia 5)

• **Dare Ovaprene Safety/PCT (NCT03598088, 21 visits):** 6 US Sites (5 are CCTN sites), 5/2018 – 11/2020 (2.5 years)
  - 135 screenings, 38 enrolled, 26 completed at 6 sites
  - EVMS: Screen 55 (~ 1 – 2 per month), 10 successful Baseline PCTs, 8 completers at EVMS
Recruitment Initiatives:
- Contacted previous BTL participants
- Referral from faculty practice
- EVMS CRC Facebook Page
- Craigslist
- Telephone screens from other studies

53 Screenings Scheduled

23 SCREENINGS (1 – 2 per month)

3 Screen Fails:
Menses > 35 d prior to BL (1)
Abnormal Pap (2) HGSIL, WNL +HRHPV

30 No Shows, Unsuccessful attempts at re-scheduling

20 ENROLLMENTS

11 Discontinuations:
Failed baseline PCT < 5 PMS/hpf (3)
Male Health Issue (1)
Couple Discord/Social (4)
LTFU (1)
Anovulation (2)

8 COMPLETERS
Safety and Acceptability Assessments

• No Product or Procedure Related Adverse Events
  – Amendment for 2 Film insertions for one participant

• Female and Male Acceptability Assessed
  – Female – Fairly easy insertion (some stickiness to finger), no change in lubrication, no change in sexual pleasure. Some didn’t like that insertion 30 minutes pre-intercourse
  – Male – Did not feel film, did not change pleasure, some noted more or less lubrication with film
CONCLUSIONS

- ZB-06 Film met PCT benchmark for excluding PMS from ovulatory cervical mucus

- Single dose (one participant 2 exposures) was safe and well tolerated among women and their male partners
EVMS Team

- Annie Thurman, MD, PI
- DeDe Raney, CNM Sub-I
- Jamie Evans RN, Study Coordinator
- Estella Jones, PhD Andrologist, Back-Up Coordinator
Acknowledgements
Let’s Meet Our Participant!
Questions

- Tell us about yourself
- Job at EVMS
- Previous Experience with Family Planning Methods
- Previous Experience with Clinical Studies
- What did your husband think about being in the study?
- Good things/Bad things about the film