

# NICHD CONTRACEPTIVE RESEARCH CENTERS

P50 HD096957

ANTIBODY-BASED MPTS:  
PRECLINICAL AND CLINICAL RESEARCH

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## VOICE OF THE PATIENT

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

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*Annie Thurman, MD*

*Professor of OBGYN, Director of Eastern Virginia Medical  
School/CONRAD Clinical Research Center*



# Non Hormonal Contraceptive Options for Women

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- **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.

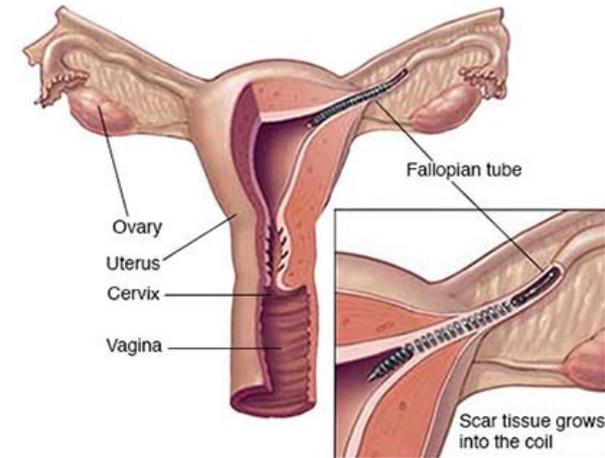


# Non Hormonal Contraceptive Options for Women

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- **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



# Immunocontraception

Use of the immune system for contraception

- Active immunization (vaccines)
- Passive immunization (transfer of antibodies)

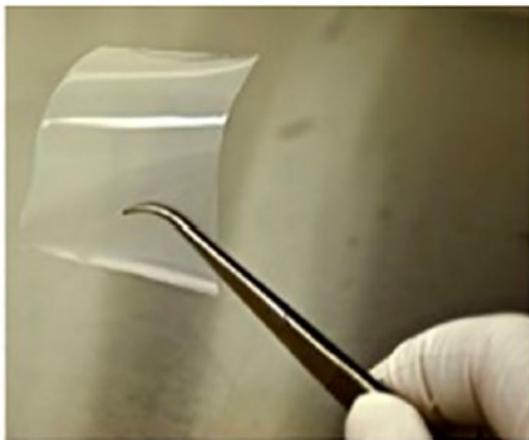
Infertility patients often have antisperm antibodies that agglutinate and immobilize sperm.

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

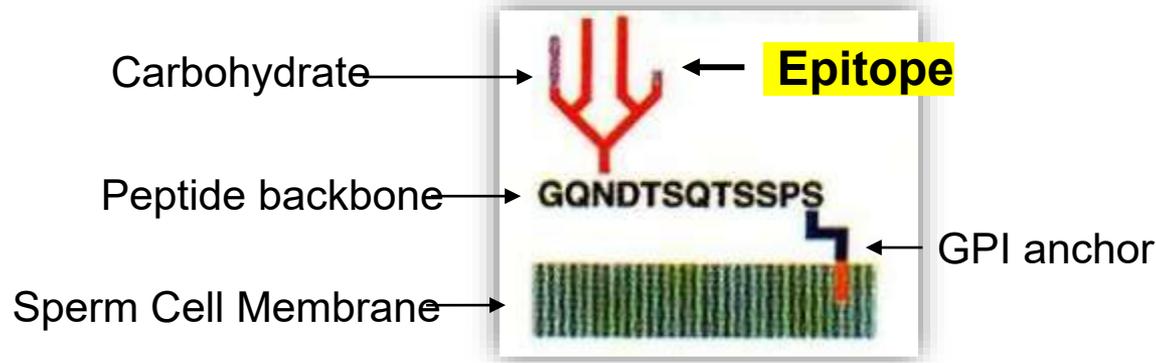


Component	% (wt/wt)
HC4 Antibody	10
PVA 8-88	60
Maltitol	25
Histidine	0.1
Polysorbate 20	0.01
Water	5
<b>Total</b>	<b>100</b>

# ZB-06 Film Development

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## CD52g Sperm Antigen – HC4 Target



- **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

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## Contraceptive Commercial Profile

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

# Pre IND

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- 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

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- 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)

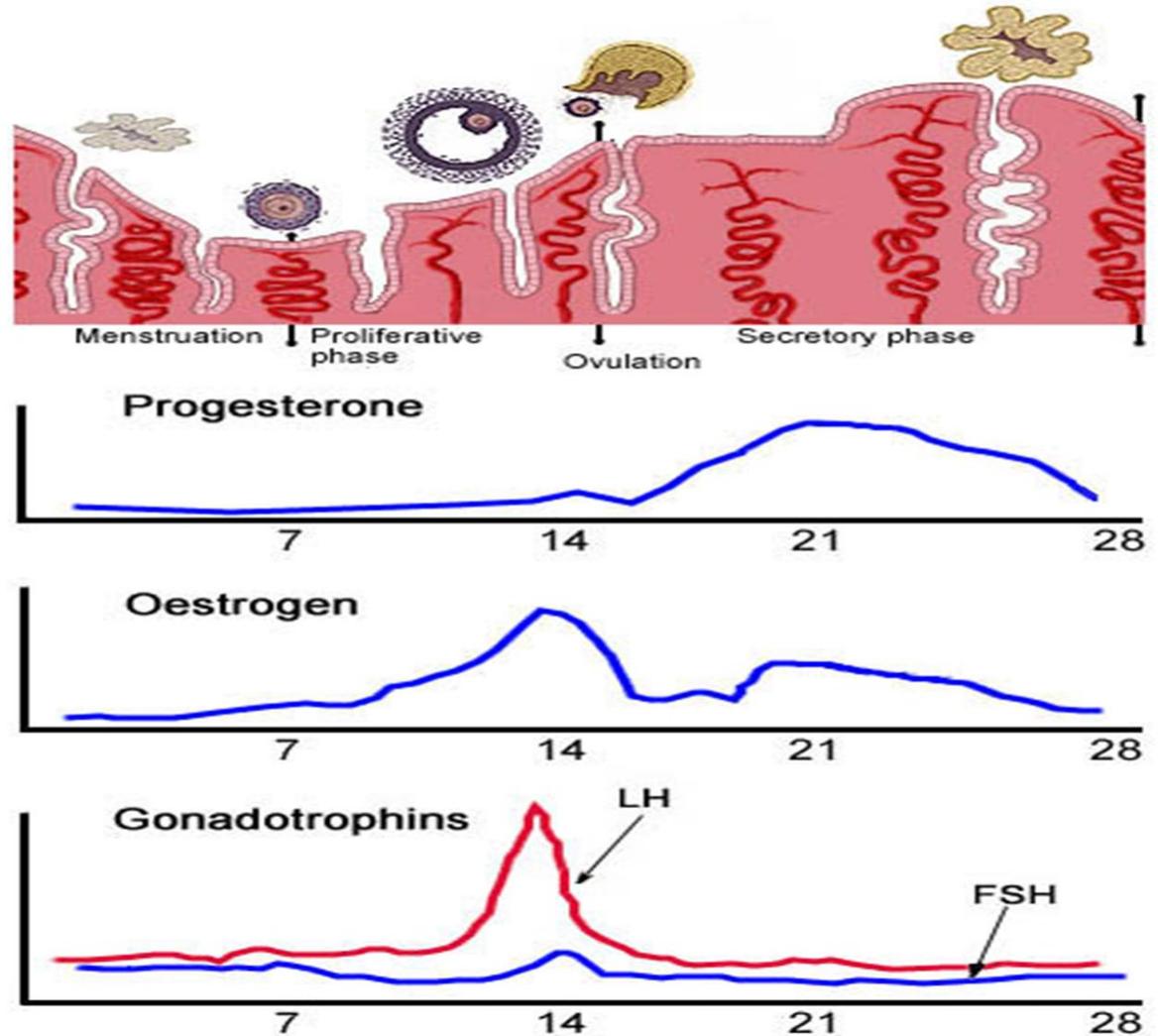
# Phase I Contraceptive Efficacy “Surrogates”

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- Ultimate Efficacy Biomarker = Pregnancy
- Hormonal Contraception:
  - Anovulation (Serum P4, Ovarian follicular development on TVUS)
- Non-Hormonal/Barrier Contraceptives:
  - For barrier contraceptives: Vaginal PSA ( $\leq 48$  hrs), Y chromosomal DNA ( $\leq 7$  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



# PCT Study Population

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- 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

V1		V2	V3	V4	V6	V7
		ENROLL	BASELINE NO PRODUCT CMC/PCT (5+ PMS/HPF)		PRODUCT CMC/PCT (1°ENDPOINT) (<5 PMS/HPF)	
Screen	Enroll – Give LH Kit, start ovulation testing on day 10	Baseline Cervical Mucus Check (CMC)	Baseline PCT No Product	Pre HC4 Film Use CMC	HC4 Film Use PCT	

# Insler Score

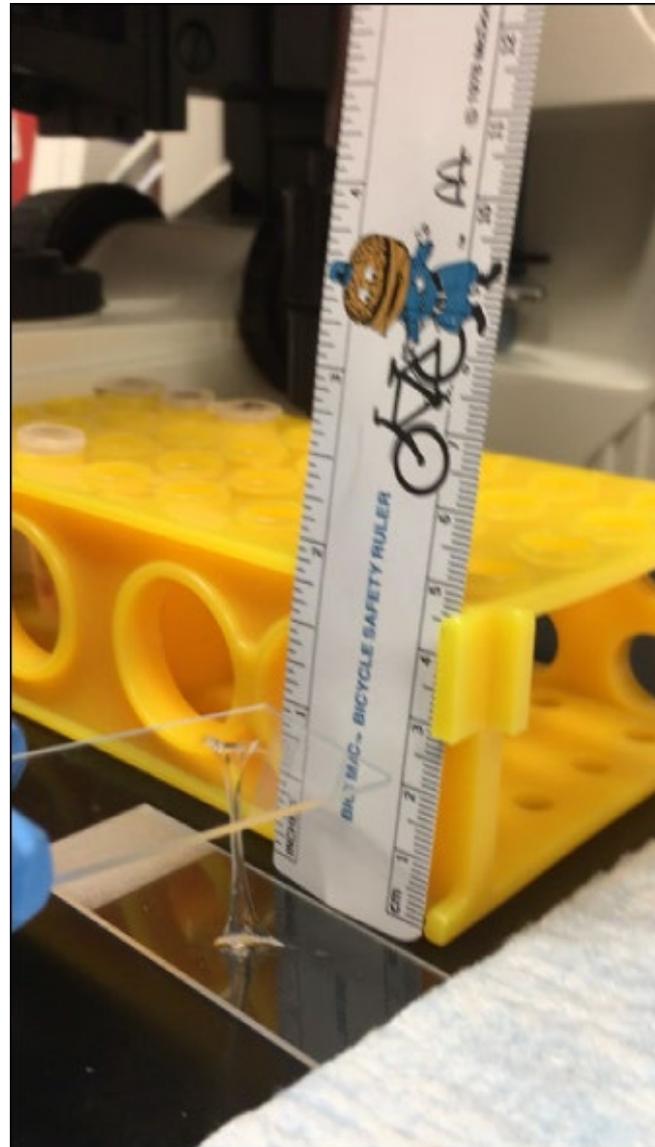
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Score	0	1	2	3
<b>Volume</b>	None	0.01 - 0.10 ml or approximately 0.1 ml	0.11 - 0.29 ml or approximately 0.2 ml	> 0.3 ml or approximately 0.3 ml or more
<b>Viscosity</b>	Thick, highly viscous, premenstrual mucus	Mucus of intermediate viscosity	Mildly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

CERVICAL MUCUS CHECKS: INSLER 10+, NO SPERM

# Spinnbarkeit

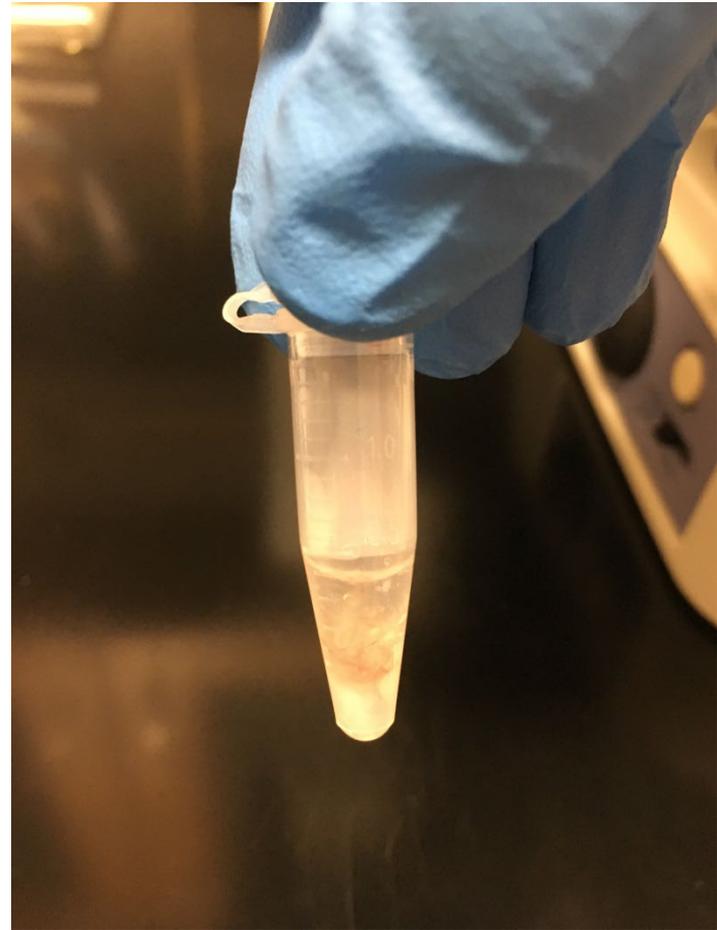
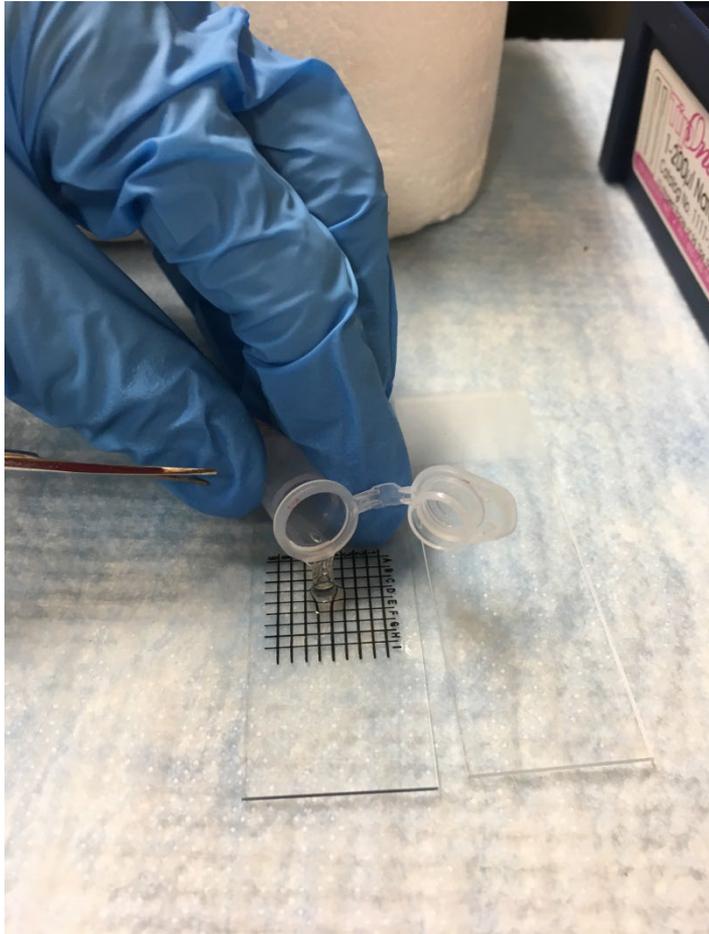
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<https://youtu.be/mAG7I7Jp-7o>

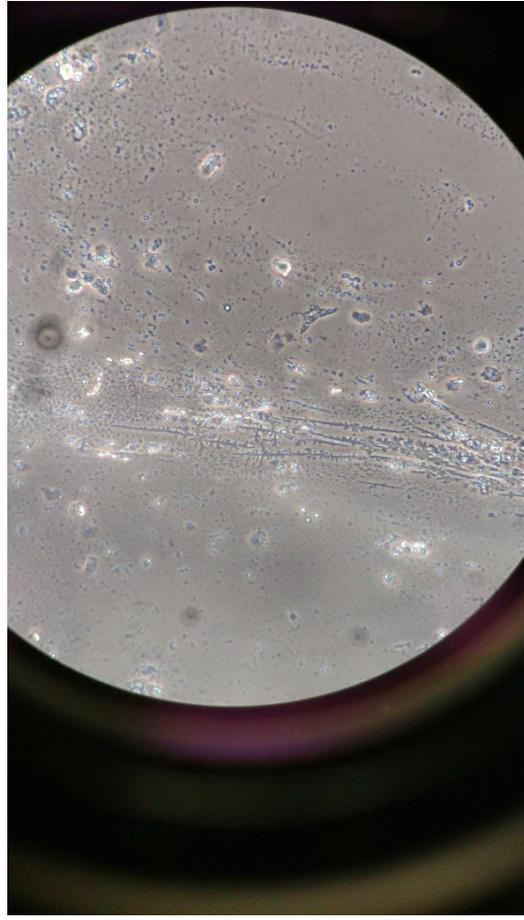
# Viscosity, Volume

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# Ferning

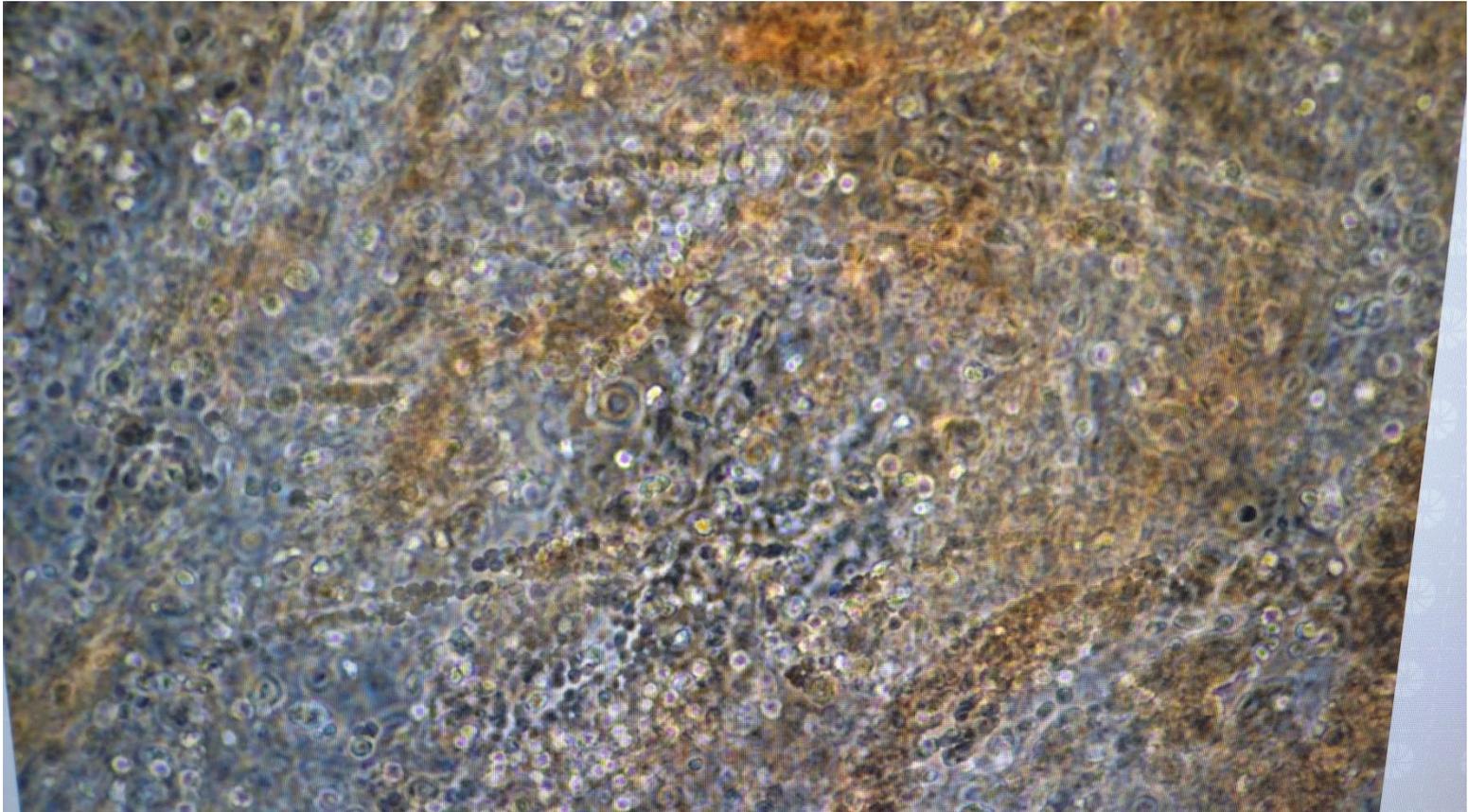
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<https://youtu.be/cvXoX6t-1do>

# Cellularity

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# Examining CM for Motile Sperm

For each of the 9 hpfs, count:

# Progressively motile sperm

# Non-progressively motile sperm

# Immotile sperm

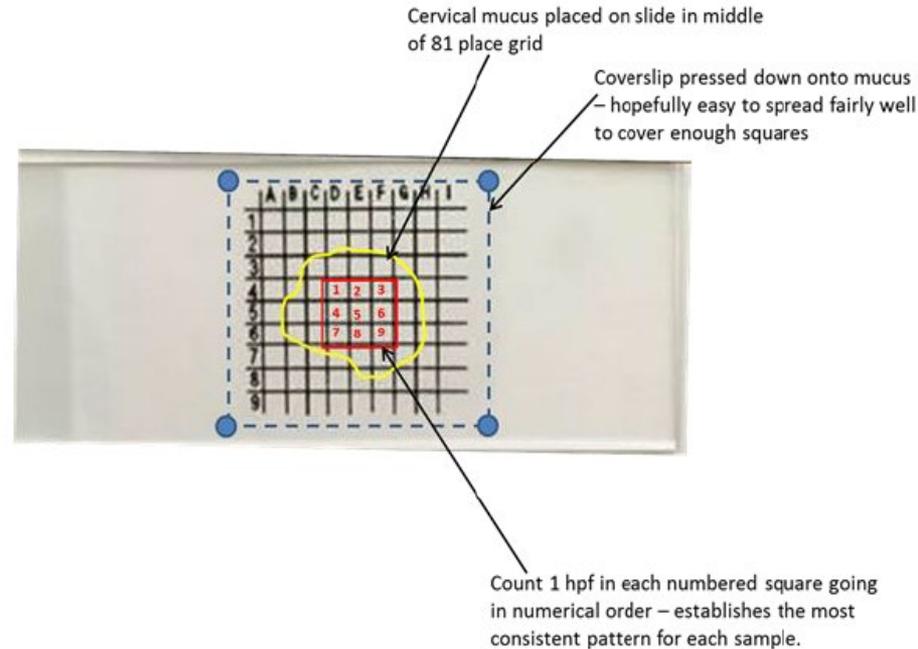
# Total sperm

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
  - *Schwartz et al. Contraception 2008;78(3):237-44.*
  - *Mauck et al. Contraception 2017;96:124-130.*
- Lea's Shield
  - *Archer et al. Contraception 1995;52(3):167-73.*
- Fem Cap
  - *Mauck et al. Contraception 1997;56(2):111-5.*
- Acidform (Amphora) and N9
  - *Amaral, Mauck et al. Contraception 2004;70:492-7.*
- Ovaprene IVR (Dare Biosciences)
  - *ClinicalTrials.gov #NCT03598088*



# PCT Correlates with Contraceptive Efficacy

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- SILCS/CAYA Diaphragm (with Buffergel versus N9)
  - *Schwartz et al. Obstet Gynecol 2015;125(4):895-903*
- Lea's Shield (w and w/o spermicide)
  - *Mauck et al. Contraception 1995;52(3):167-73.*
- Fem Cap (vs Ortho All Flex Diaphragm)
  - *Mauck et al. Contraception 1999;60(2):71-80.*
- Acidform and N9 Gels alone
  - *Barnhart et al. Obstet Gynecol 2016;127:118S-125S*
  - *Burke et al Obstet Gynecol 2010;116(6):1265-1273*
- Amphora Clinical Efficacy Trials
  - *Evoform Phase 3 Contraceptive Efficacy Trials*



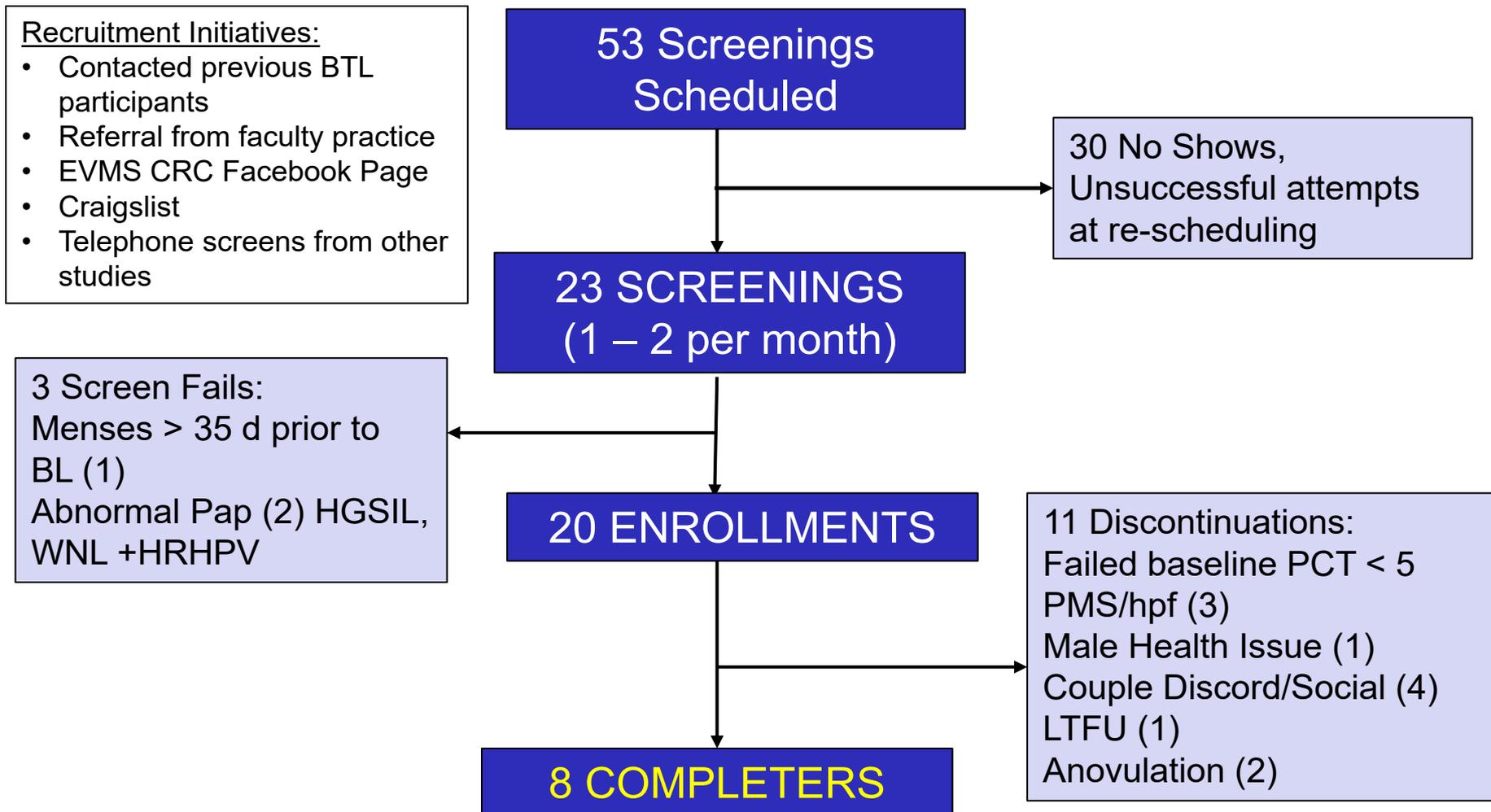
# Recent PCT Studies

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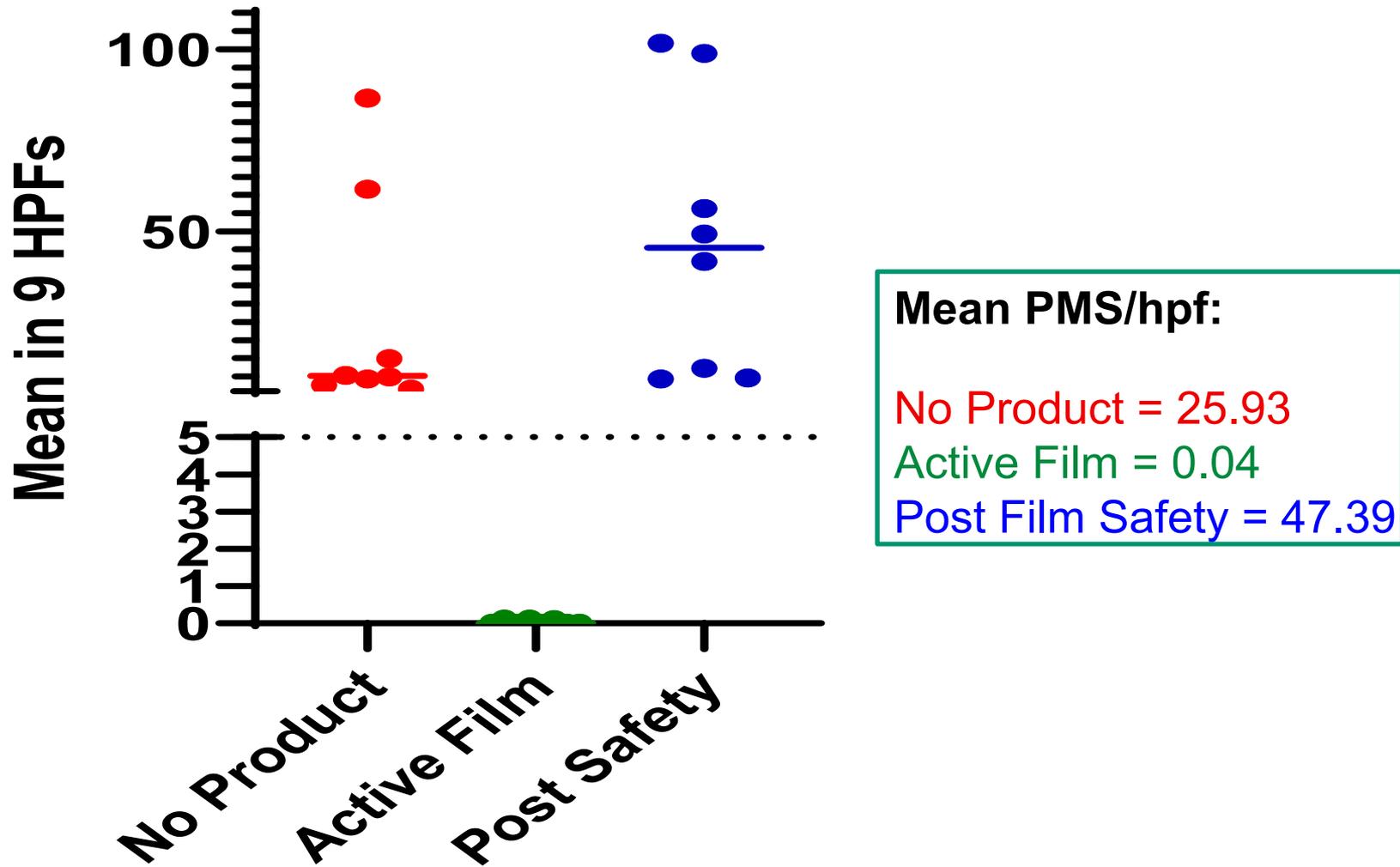
- **CONRAD 126 (NCT02309554, 9 visits):** Phase I PCT study of CAYA Used with 2% N9 gel, Contragel or No gel (12/2014 – 10/2015)
- 27 enrolled (EVMS 11, Profamilia 16) → 18 Discontinued (Poor Baseline CMC, anovulation) → **9 completers (EVMS 4, Profamilia 5)**
  - *Mauck CK, Brache V, Kimble T, Thurman A, et al. Contraception. 2017;96(2):124-30.*
- **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**
  - *Mauck C, Thurman AT, Baker J, Jensen J, Schreiber C, et al. Successful PCT Results of Ovaprene, a Monthly Hormone-Free Vaginal Contraceptive. ACOG Annual clinical Meeting Abstract.*

# Status Update NCT04731818

1/26/2021 Site Activation, 2/8/2021 First Screen, LPLV 2/24/2022



# Progressively Motile Sperm



# Safety and Acceptability Assessments

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- 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

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- 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

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- Annie Thurman, MD, PI
- DeDe Raney, CNM Sub-I
- Jamie Evans RN, Study Coordinator
- Estella Jones, PhD Andrologist,  
Back-Up Coordinator



# Acknowledgements

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**Boston University**  
School of Medicine



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**NICHD**

National Institute of Child Health  
& Human Development

**EVMS**  
Eastern Virginia Medical School



# Let's Meet Our Participant!

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# Questions

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- **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**