Long-acting injectable, biodegradable in-situ forming implant of EP055 for reversible non-hormonal male contraception

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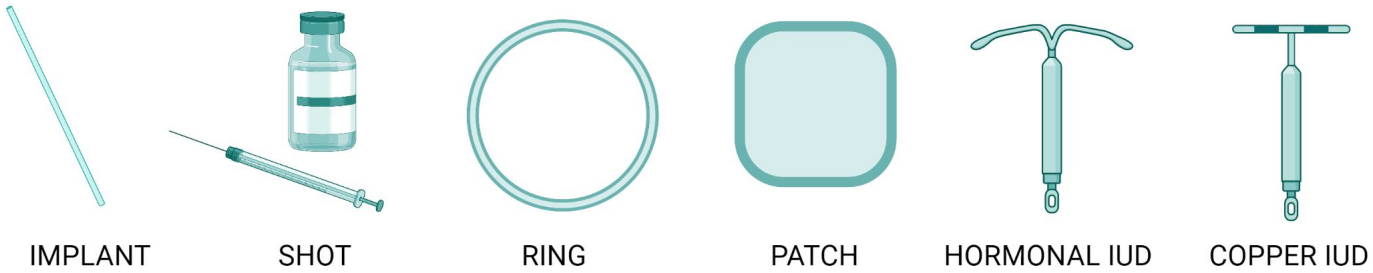
THE FUTURE OF DELIVERY SCIENCE

Need for Novel Male Contraceptives

Over 120M Unintended Pregnancies Each Year[1]

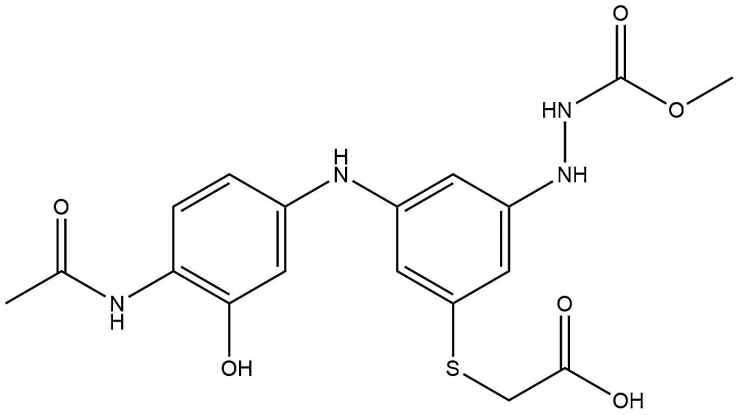
Long-Acting Reversible Contraceptives (LARCs) are the most effective and reliable forms of birth control[2].



1: State of World Population 2022 (UNFPA); 2: Long-Acting Reversible Contraceptive (LARCs) methods (Bahamondes 2020)

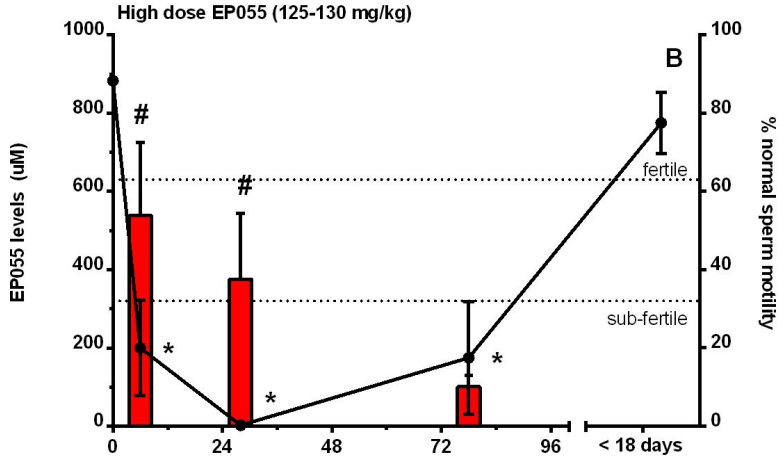
Background

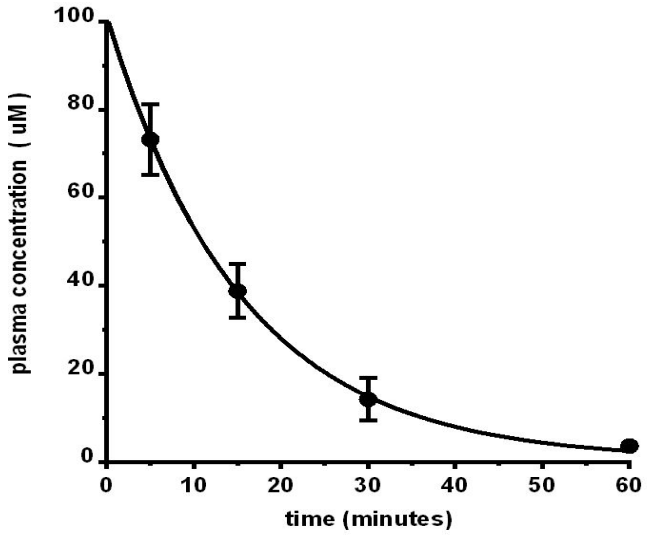
EP



Non-Hormonal contraceptive drug developed by Eppin Pharma[3]

- Irreversibly binds to C-terminal of epididymal protease inhibitor (EPPIN) on sperm surface
- Short plasma half-life of 10.6 mins
- Retained in testes for approx. 3 days



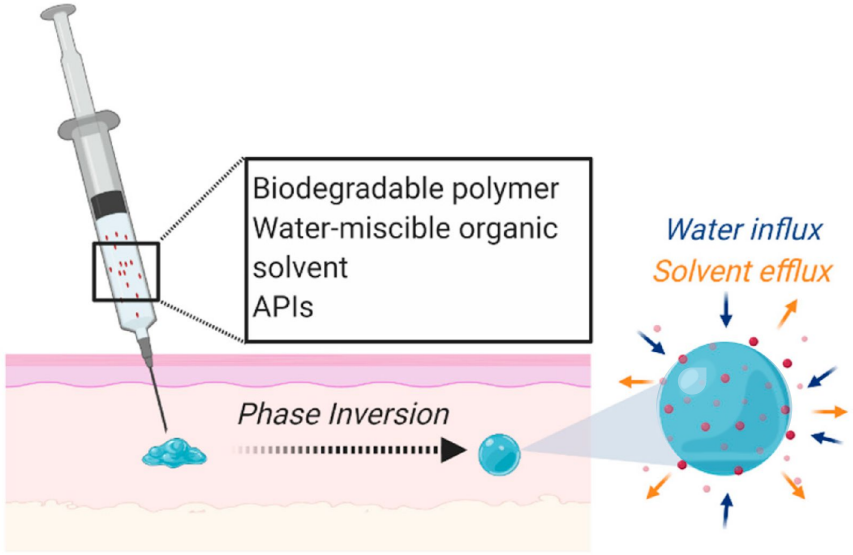


IV EP055 inhibits sperm motility temporarily in macaques

But has high plasma clearance, requiring extremely frequent dosing.

3: Inhibition of sperm motility in male macaques with EP055, a potential non-hormonal male contraceptive (O'Rand 2018)

In-Situ Forming Implants (ISFIs)



Mechanisms of Drug Release

Long-Acting[4]

30+ Day Delivery Possible

Sustained, Tunable Release

- Fine-tuning concentrations and properties of polymer, solvent, and drug

Biodegradable and Removable[4]

Non-invasive injectable administration

- Controlled polymer biodegradation over time
- Solid depot allows for removal if necessary

ISFIs can overcome frequent dosing of EP055 required for long-term efficacy and promote adherence to become the first LARC for men.

4: Ultra-long-acting tunable biodegradable and removable controlled release implants for drug delivery (Benhabbour 2019)

Project Aims

Aim 1: Optimize ISFI Formulation *In-Vitro*

a) Tune ISFI components to achieve 30+ days of sustained release in vitro

b) Validate drug activity post-release from ISFI system

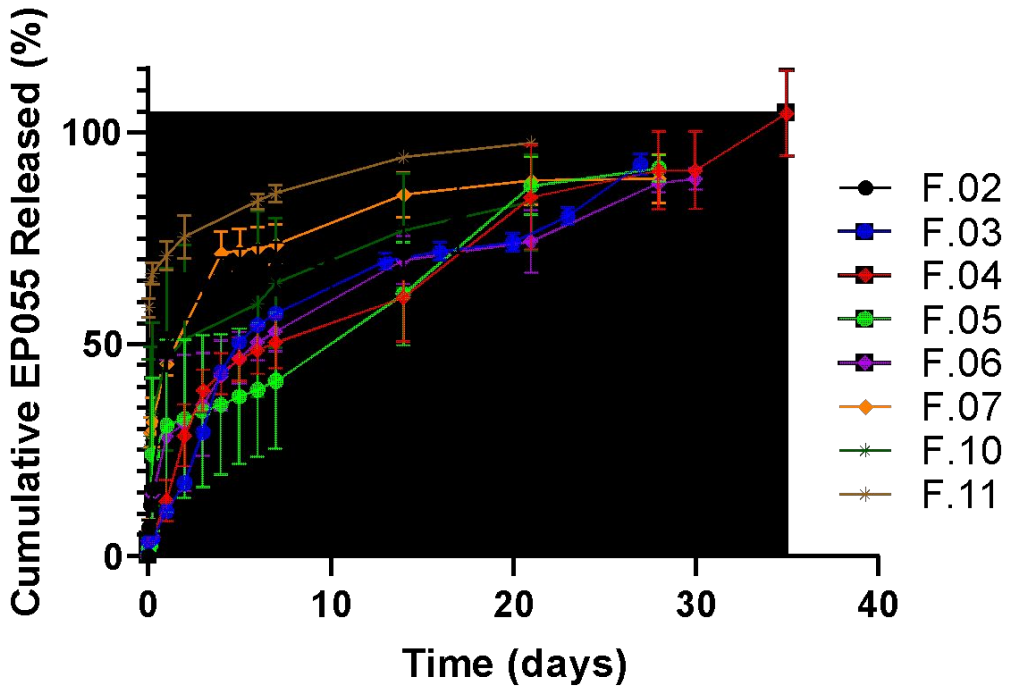
Aim 2: Investigate Pharmacokinetics of Optimized Formulation *In-Vivo*

a) Sustain EP055 in Plasma and Target Tissues for 30+ days

b) Assess reversibility following implant removal

c) Quantify residual EP055 in extracted depots

Aim 1a: Tune ISFI components to achieve 30+ days of sustained release in vitro

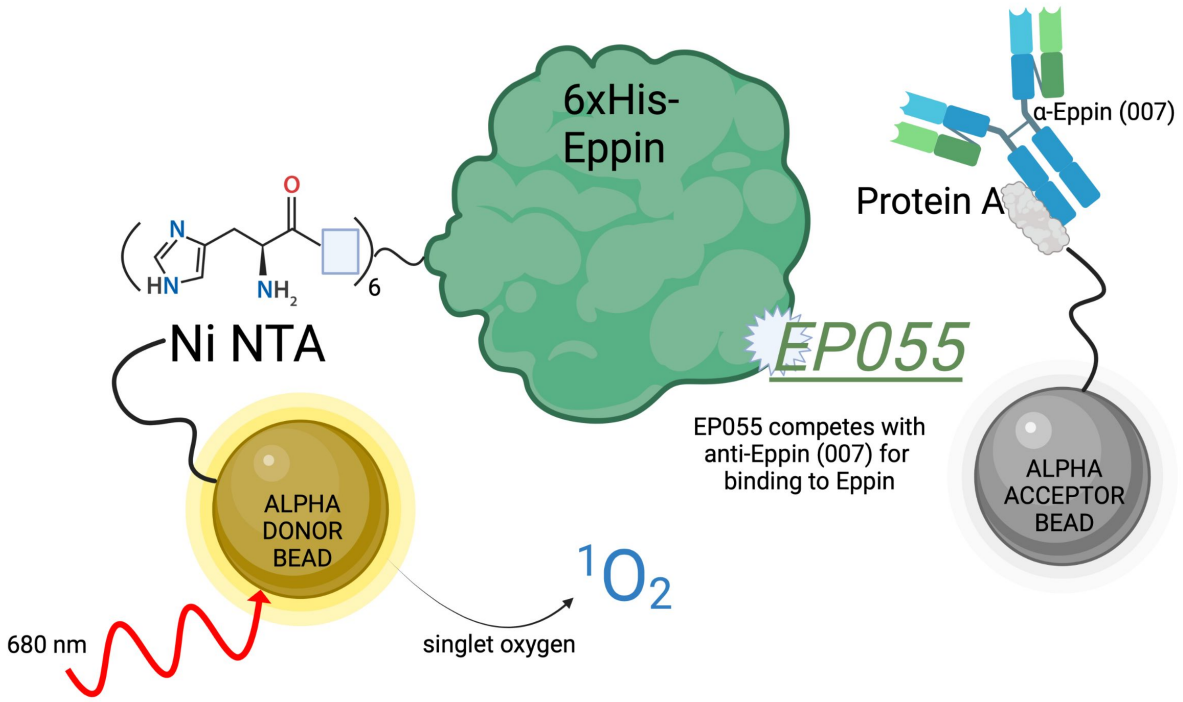


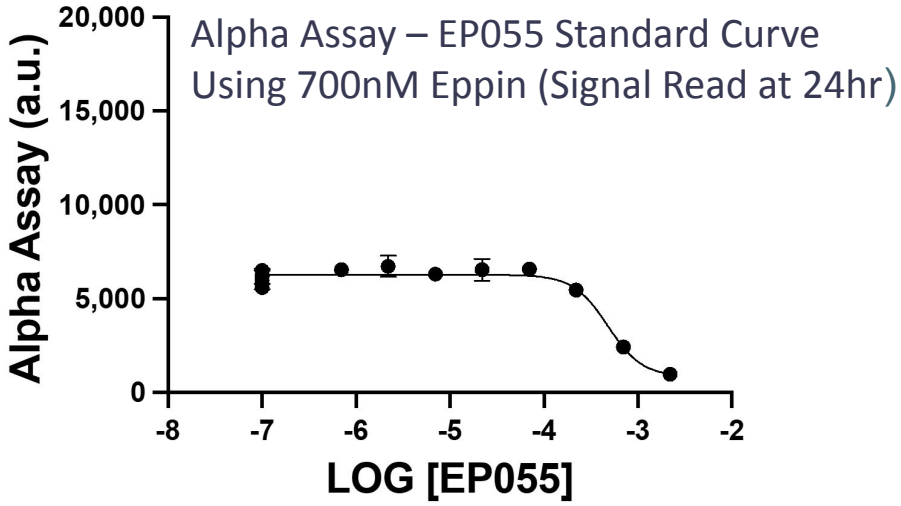
Formulation	Drug (mg/mL)	PLGA:Sol	PLGA MW	Solv % NMP	Solv % BB	Burst %	Time to Completion
F.02	100	1:2	27kDa	100	0	48.2±4.5	17 days
F.03	100	1:1.5	27kDa	90	10	10.5±1.5	27 days
F.04	150	1:1.5	27kDa	90	10	13.0±4.8	35 days
F.05	100	1:1.5	27kDa	80	20	30.7 ±20.3	28 days
F.06	150	1:1.5	27kDa	80	20	28.3 ±18.0	30 days
F.07	150	1:2	27kDa	80	20	65.6±2.4	16 days
F.10	175	1:2	27kDa	90	10	46.4 ±21.5	21 days
F.11	166	1:2	10kDa	90	10	70.9±3.4	21 days

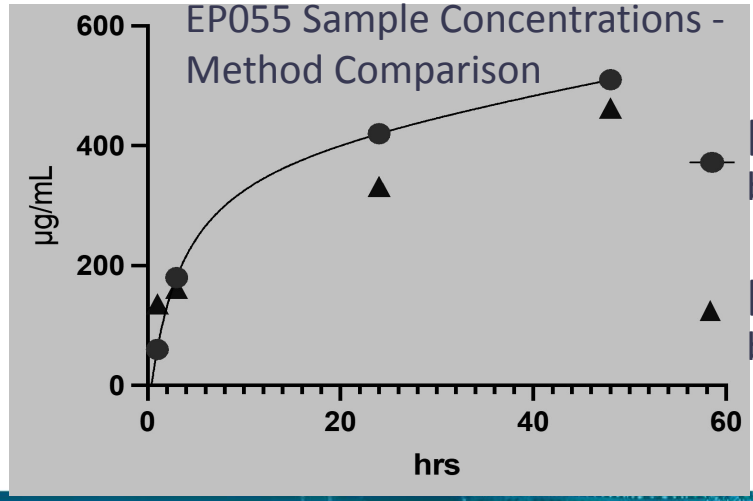
PLGA: Poly(lactic-co-glycolic) acid; MW: Molecular Weight; NMP: N-methyl pyrrolidone; BB: Benzyl Benzoate

F.04 [150mg EP055/mL 1:1.5 27kDa PLGA:(9:1 NMP:BB)] achieved 35 days of sustained release *in vitro.*

Aim 1b: Validate drug activity post-release from ISFI system





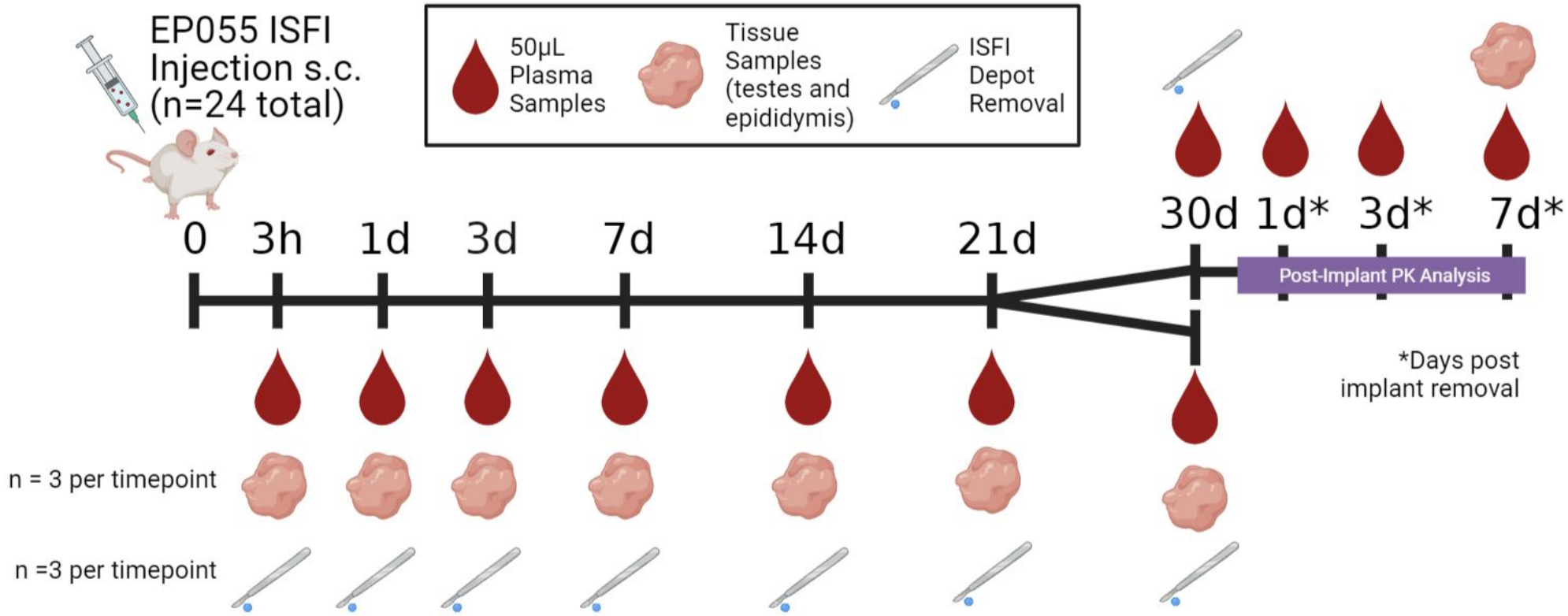


['active' EP055] by Alpha

[EP055] by HPLC

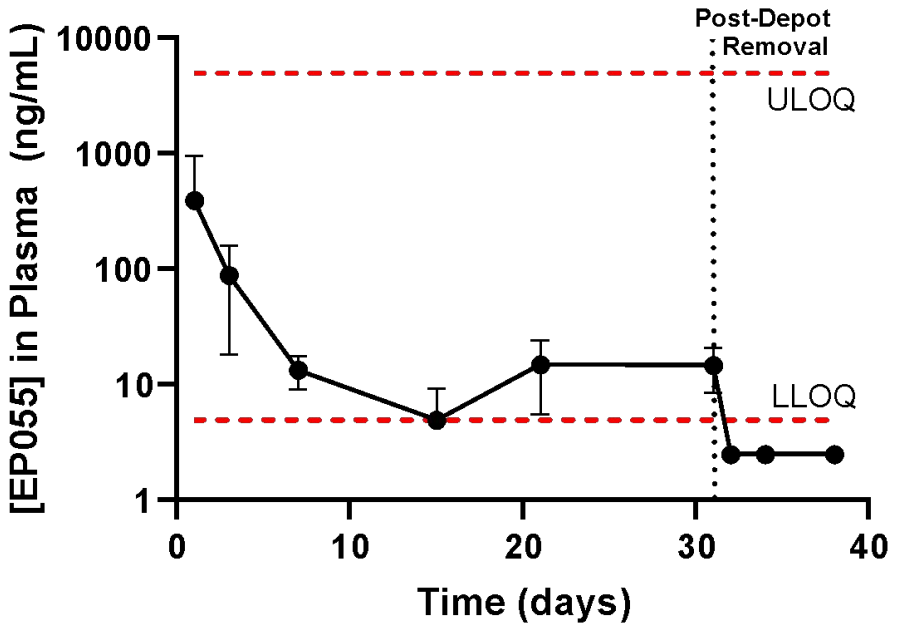
EP055 biological activity is sustained following release from ISFI.

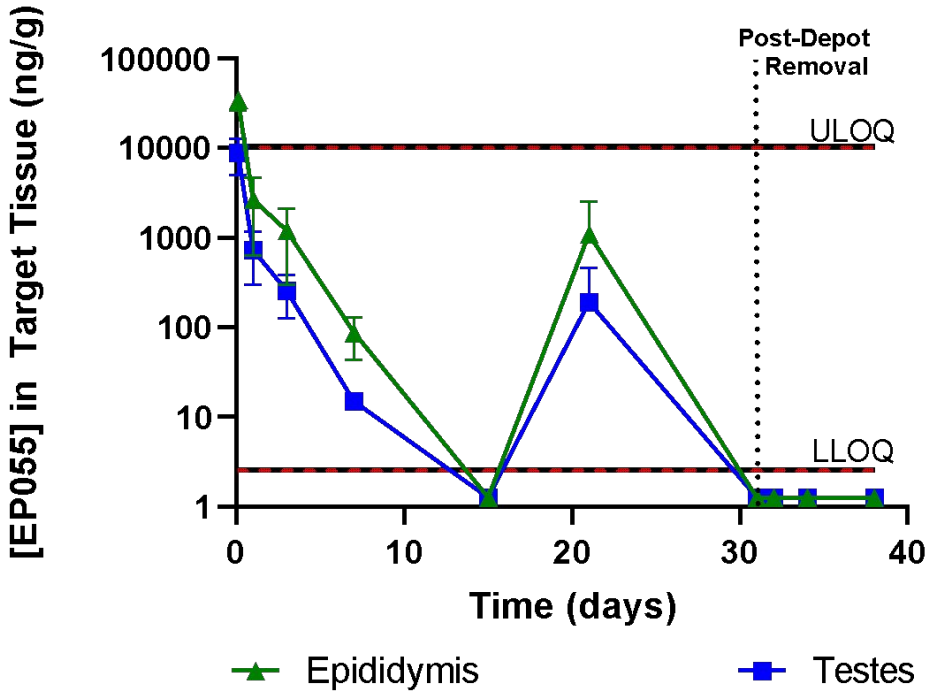
Aim 2:



Aim 2a: Sustain EP055 in Plasma and Target Tissues for 30+ days

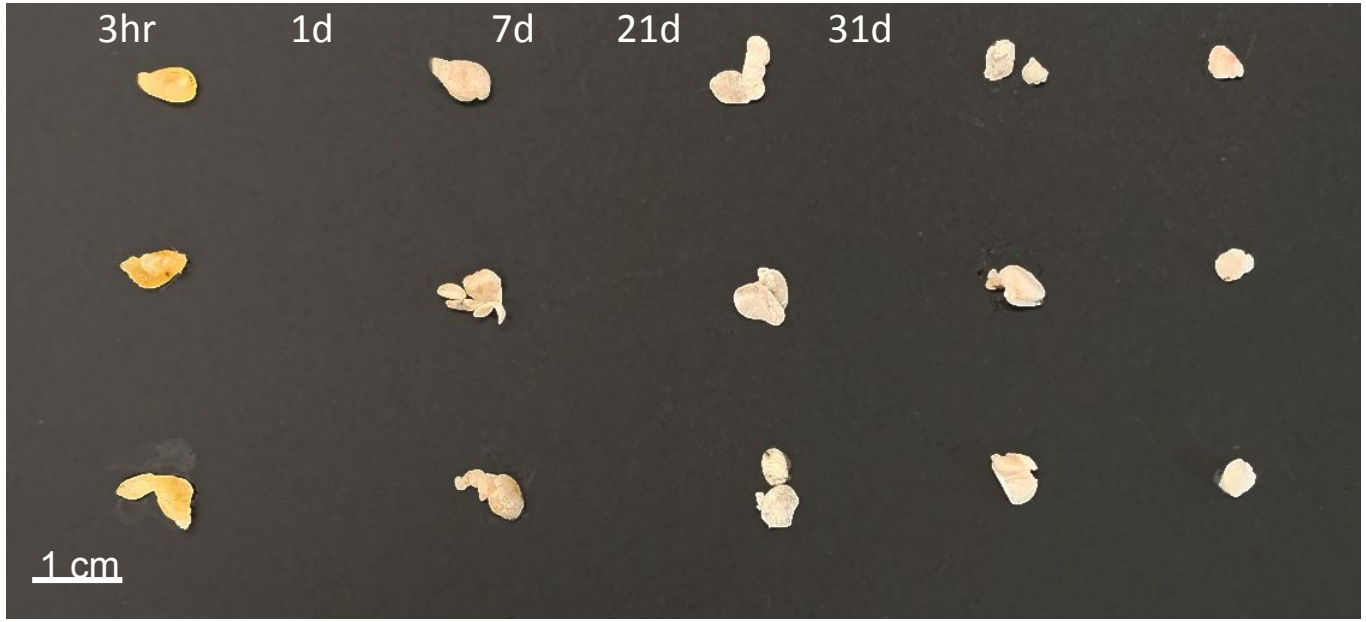
Aim 2b: Assess reversibility following implant removal

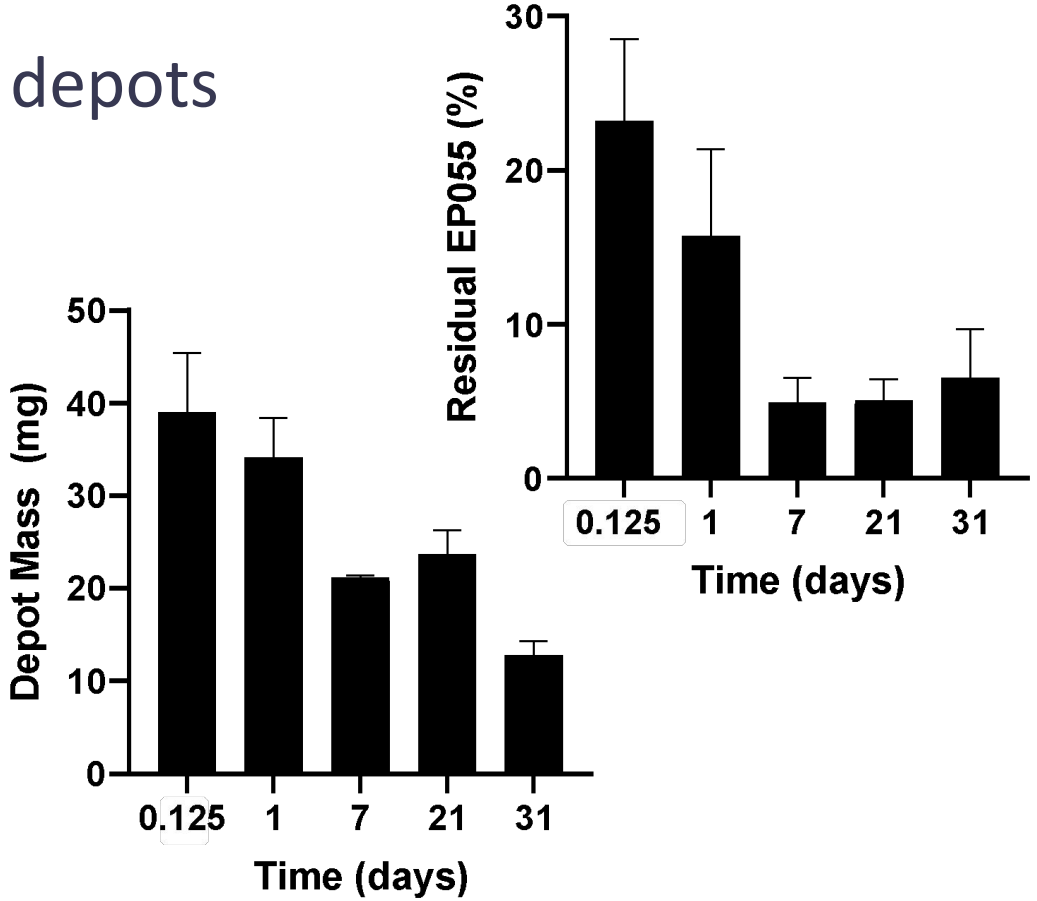




EP055 sustained in plasma for 31 days and tissue for 21 days.
Drug undetectable following implant removal for reversibility.

Aim 2c: Quantify residual EP055 in extracted depots





Depot mass loss observed over time.

Residual EP055 quantified in depots retrieved at day 31 post administration.

Conclusions and Future Directions

In Summary

- Optimized EP055-loaded ISFI for 35 days release *in vitro*
- Sustained drug in plasma/tissue with potential for longer release
- Demonstrated treatment reversibility following depot removal

Next Steps for EP055 ISFI

- Examine additional tissues for drug reservoir
- Efficacy of EP055 levels observed *in vivo*
- Characterization of optimized formulation long-term stability

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Male Contraceptive Initiative

NSF

bioRender

Questions?

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Citations

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2. Bahamondes L, Fernandes A, Monteiro I, Bahamondes MV. Long-acting reversible contraceptive (LARCs) methods. *Best Pract Res Clin Obstet Gynaecol*. 2020;66:28-40. https://doi:10.1016/j.bpobgyn.2019.12.002

3. O'Rand, M. G., Hamil, K. G., Adevai, T., & Zelinski, M. (2018). Inhibition of sperm motility in male macaques with EP055, a potential non-hormonal male contraceptive. *PloS one*, *13*(4), e0195953. https://doi.org/10.1371/journal.pone.0195953

4. Benhabbour, S.R., Kovarova, M., Jones, C. *et al.* Ultra-long-acting tunable biodegradable and removable controlled release implants for drug delivery. *Nat Commun* **10**, 4324 (2019). https://doi.org/10.1038/s41467-019-12141-5

Characterization

EP055 is highly soluble in NMP and DMSO

- Approx. 490mg/mL in both

EP055 has no/very low solubility in BB

- Below HPLC LLOQ of 17ng/mL

EP055 is light sensitive

- 20-30% degradation after a week

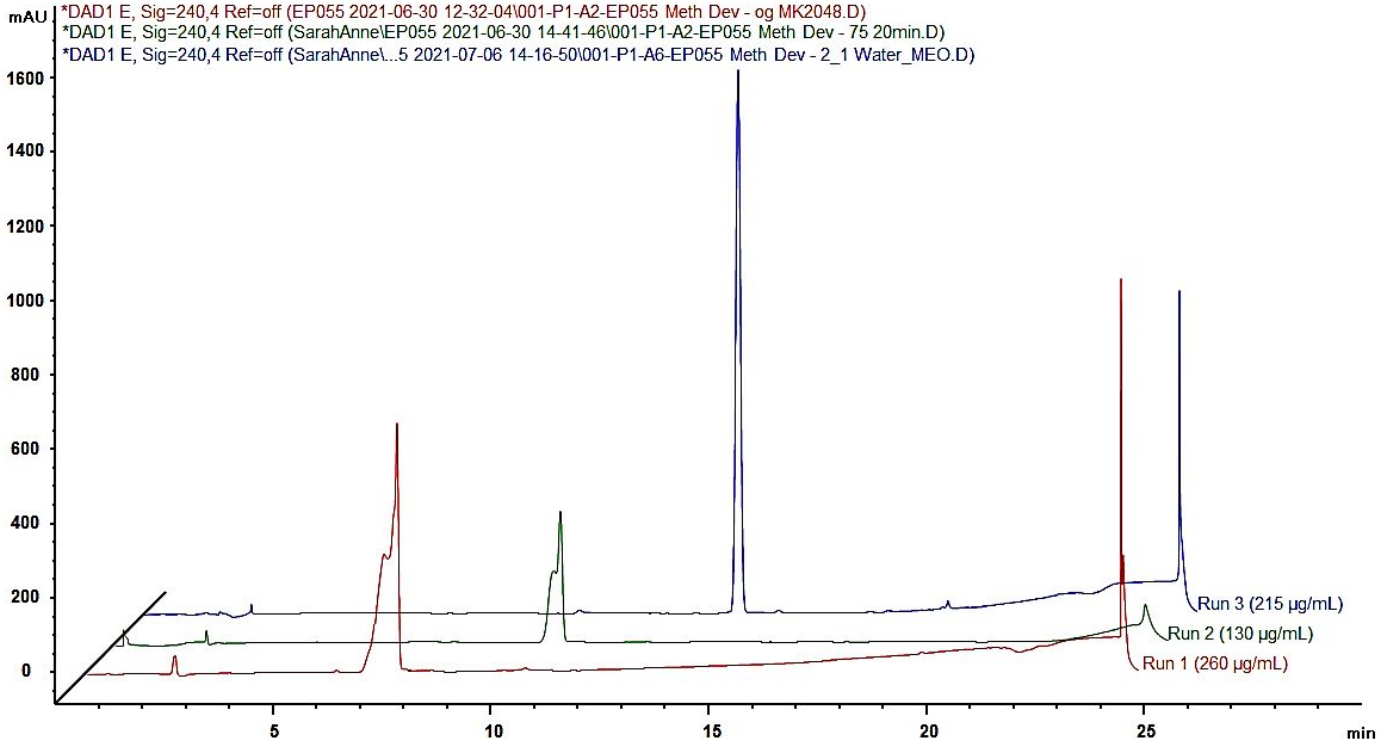
EP055 is very hydrophilic

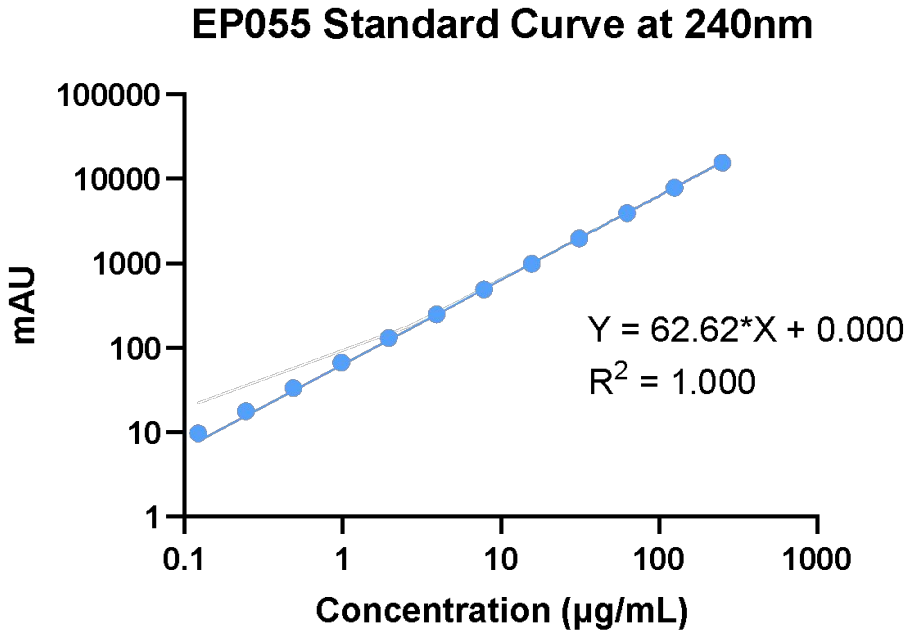
- LogP -2.67

Supplemental

Method Development

EP055 Quantification by HPLC





LLOD: 4ng/mL

LLOQ: 15.7ng/mL