LAPaL
THE LONG-ACTING THERAPEUTICS PATENTS AND LICENCES DATABASE

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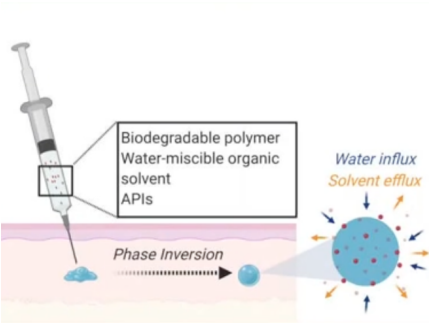



# Ultra-Long-Acting Multi-Purpose In-situ Forming Implant (ISFI)

Verified by the innovator, on Apr 2022

## Developer(s)


University of North Carolina at Chapel Hill
https://benhabbour.web.unc.edu/

US

Harnessing engineering, chemistry, and pharmacology tools to design and engineer innovative drug delivery platform technologies for disease treatment and prevention.

## Sponsor(s)


NIH-NIAID

https://www.niaid.nih.gov/

## Partnerships

No partner indicated

# Technology information

## Type of technology

In-situ forming gel/implant

## Administration route

Subcutaneous

## Development state and regulatory approval

**Active Pharmaceutical Ingredient (API)**

Cabotegravir (CAB), Medroxyprogesterone acetate (MPA)

**Development Stage**

Pre-clinical

**Regulatory Approval**

Not provided

## Description

The in-situ forming implant (ISFI) consists of a liquid co-formulation utilizing excipients that form a biodegradable depot after subcutaneous injection for a controlled sustained release of active ingredients. It is based on a biodegradable polymer such as PLGA, a water miscible organic solvent such as NMP and the API or combination APIs of interest.

## Technology highlight

First-in-line, ultra-long-acting injectable MPT that offers durable and sustained protection from HIV transmission, high efficacy of contraception, increased user compliance, and the ability to be removed if required. The ISFI offers at least 3 months sustained release after a single subcutaneous administration. It is biodegradable yet removable in case of adverse events or need for treatment reversibility.

## Technology main components

poly(DL-lactide-co-glycolide) (PLGA), N-methyl-2-pyrrolidone (NMP), dimethyl sulfoxide (DMSO)

### Information on the raw materials sourcing, availability and anticipated price

Polymers readily available on the market

## Delivery device(s)

No delivery device

# APIs compatibility profile

## API desired features

### Water-soluble molecules

### Water-insoluble molecules

### Small molecules

Dolutegravir (DTG), Cabotegravir (CAB), Rilpivirine (RPV)

### Nucleic acids

Confidential

### Proteins

Confidential

### Additional solubility data

Not provided

### Additional stability data

Not provided

### API loading: Maximum drug quantity to be loaded

To be provided

## API co-administration

2 different APIs : at least 2 different APIs

## LogP

Not provided

# Scale-up and manufacturing prospects

## Scale-up prospects

To be determined

## Tentative equipment list for manufacturing

To be determined

## Manufacturing

To be determined

## Specific analytical instrument required for characterization of formulation

To be determined

# Clinical trials

Not provided

# Excipients

## Proprietary excipients used

No proprietary excipient used

## Novel excipients or existing excipients at a concentration above Inactive Ingredients Database (IID) for the specified route of administration

No novel excipient or existing excipient used

## Residual solvents used

No residual solvent used

# Additional features

## Other features of the technology

- Biodegradable
- Drug-eluting
- Monolithic
- Removable
- Single-use
- Room temperature storage
- At least 1 year shelf life
- Needs insertion kit

## Release properties

Zero order release

## Injectability

26-16 gauge needles

## Safety

Absence of adverse local or systemic inflammation when administered to mice or non-human primates

## Stability

To be determined

## Storage conditions and cold-chain related features

To be determined

# Potential application(s)

## Therapeutic area(s)

Contraception

Multipurpose technology : "HIV PrEP and contraception"

Diabetes

HBV

TB

COVID 19

HIV

Pain management

Oncology

### Use case(s)

Pre-Exposure Prophylaxis (PrEP)

Treatment

## Use of technology

### Ease of administration

- Administered by a nurse
- Administered by a specialty health worker
- To be determined

### Frequency of administration

To be determined

## User acceptance

To be determined

## Targeted user groups

### Age Cohort

- Adults

### Genders

- All
- Male
- Female
- Cisgender female
- Cisgender male
- Transgender female
- Transgender male
- Intersex
- Gender non-binary

### Pregnant individuals

Yes

### Lactating individuals

Yes

### Healthy individuals

Unspecified

### Comment

Not provided

# Potential associated API(s)

## Cabotegravir (CAB), Medroxyprogesterone acetate (MPA)

### Class(es)

Not provided

### Development stage

Pre-clinical

### Clinical trial number(s)

Not provided

### Foreseen/approved indication(s)

Not provided

### Foreseen user group

Not provided

### Foreseen duration between application(s)

Not provided

### Applications to Stringent Regulatory Authorities (SRA) / regulatory approvals

Not provided

## Cabotegravir (CAB), Etonogestrel (ENG)

### Class(es)

Not provided

### Development stage

Pre-clinical

### Clinical trial number(s)

Not provided

### Foreseen/approved indication(s)

Not provided

### Foreseen user group

Not provided

### Foreseen duration between application(s)

Not provided

### Applications to Stringent Regulatory Authorities (SRA) / regulatory approvals

Not provided

## Dolutegravir (DTG), Medroxyprogesterone acetate (MPA)

### Class(es)

Not provided

### Development stage

Pre-clinical

### Clinical trial number(s)

Not provided

### Foreseen/approved indication(s)

Not provided

### Foreseen user group

Not provided

### Foreseen duration between application(s)

Not provided

### Applications to Stringent Regulatory Authorities (SRA) / regulatory approvals

Not provided

## Dolutegravir (DTG), Etonogestrel (ENG)

### Class(es)

Not provided

### Development stage

Pre-clinical

### Clinical trial number(s)

Not provided

### Foreseen/approved indication(s)

Not provided

### Foreseen user group

Not provided

### Foreseen duration between application(s)

Not provided

### Applications to Stringent Regulatory Authorities (SRA) / regulatory approvals

Not provided

# Patent info

# Technology patent families

## Patent informations

| Patent description | Representative patent | Categories | Patent holder | Licence with MPP | Patent source |
|---|---|---|---|---|---|
| Injectable, biodegradable and removable polymer based drug suspension for ultra-long-acting drug delivery<br>Expiry date: 2042-06-30<br>Injectable, biodegradable and removable polymer based drug suspension for ultra-long-acting drug delivery are disclosed. Ultra-long-acting in-situ forming implant (ISFI) drug suspension delivery systems as multipurpose prevention technologies for a multitude of applications are also provided. Methods of use, including treatment of subjects, using the disclosed compositions and ISFIs are also provided. | WO2023278695 | | The University Of North Carolina At Chapel Hill | No | Company |

## Patent status

| Patent status/countries | Low, Low- middle and upper-middle | High income |
|---|---|---|
| Granted | | |
| Filed | Albania, North Macedonia, Serbia, Türkiye | Canada, Austria, Belgium, Switzerland, Cyprus, Czechia, Germany, Denmark, Estonia, Spain, Finland, France, United Kingdom, Greece, Croatia, Hungary, Ireland, Iceland, Italy, Liechtenstein, Lithuania, Luxembourg, Latvia, Monaco, Malta, Netherlands, Norway, Poland, Portugal, Sweden, Slovenia, Slovakia, San Marino, Japan, United States of America, Bulgaria, Romania |

| Patent status/countries | Low, Low- middle and upper-middle | High income |
| --- | --- | --- |
| Not in force | World Intellectual Property Organization (WIPO) | World Intellectual Property Organization (WIPO) |

## MPP Licence(s)

# Supporting material

## Publications

** <a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8948873/" rel="noopener noreferrer" target="_blank" style="color: rgb(48, 48, 48);">Effects of Injection Volume and Route of Administration on Dolutegravir In Situ Forming Implant Pharmacokinetics. </a> <br> Joiner, J. B., King, J. L., Shrivastava, R., Howard, S. A., Cottrell, M. L., Kashuba, A., Dayton, P. A., & Benhabbour, S. R. (2022). <br> ?Pharmaceutics, 14(3), 615. https://doi.org/10.3390/pharmaceutics14030615 **

Due to the versatility of the in situ forming implant (ISFI) drug delivery system, it is crucial to understand the effects of formulation parameters for clinical translation. We utilized ultrasound imaging and pharmacokinetics (PK) in mice to understand the impact of administration route, injection volume, and drug loading on ISFI formation, degradation, and drug release in mice. Placebo ISFIs injected subcutaneously (SQ) with smaller volumes (40 µL) exhibited complete degradation within 30–45 days, compared to larger volumes (80 µL), which completely degraded within 45–60 days. However, all dolutegravir (DTG)-loaded ISFIs along the range of injection volumes tested (20–80 µL) were present at 90 days post-injection, suggesting that DTG can prolong ISFI degradation. Ultrasound imaging showed that intramuscular (IM) ISFIs flattened rapidly post administration compared to SQ, which coincides with the earlier Tmax for drug-loaded IM ISFIs. All mice exhibited DTG plasma concentrations above four times the protein-adjusted 90% inhibitory concentration (PA-IC90) throughout the entire 90 days of the study. ISFI release kinetics best fit to zero order or diffusion-controlled models. When total administered dose was held constant, there was no statistical difference in drug exposure regardless of the route of administration or number of injections.

**Keywords:** long-acting, in situ, injectable, biodegradable, implants, PLGA, controlled release, drug delivery, ultrasound, pharmacokinetics

** <a href="https://www.mdpi.com/2073-4360/13/15/2450/htm" rel="noopener noreferrer" target="_blank" style="color: rgb(34, 34, 34);">Multipurpose Prevention Technologies: Oral, Parenteral, and Vaginal Dosage Forms for Prevention of HIV/STIs and Unplanned Pregnancy. </a> Young IC, Benhabbour SR. ?Polymers. 2021; 13(15):2450. https://doi.org/10.3390/polym13152450 **

There is a high global prevalence of HIV, sexually transmitted infections (STIs), and unplanned pregnancies. Current preventative daily oral dosing regimens can be ineffective due to low patient adherence. Sustained release delivery systems in conjunction with multipurpose prevention technologies (MPTs) can reduce high rates of HIV/STIs and unplanned pregnancies in an all-in-one efficacious, acceptable, and easily accessible technology to allow for prolonged release of antivirals and contraceptives. The concept and development of MPTs have greatly progressed over the past decade and demonstrate efficacious technologies that are user-accepted with potentially high adherence. This review gives a comprehensive overview of the latest oral, parenteral, and vaginally delivered MPTs in development as well as drug delivery formulations with the potential to advance as an MPT, and implementation studies regarding MPT user acceptability and adherence. Furthermore, there is a focus on MPT intravaginal rings emphasizing injection molding and hot-melt extrusion manufacturing limitations and emerging fabrication advancements. Lastly, formulation development considerations and limitations are discussed, such as nonhormonal contraceptive considerations, challenges with achieving a stable coformulation of multiple drugs, achieving sustained and controlled drug release, limiting drug–drug interactions, and advancing past preclinical development stages. Despite the challenges in the MPT landscape, these technologies demonstrate the potential to bridge gaps in preventative sexual and reproductive health care.

## Additional documents

No documents were uploaded

## Useful links

- LAI for prevention of HIV and unplanned pregnancy, I. Young, CROI2022

# Access principles

## Collaborate for development

Consider on a case by case basis, collaborating on developing long acting products with potential significant public health impact, especially for low- and middle-income countries (LMICs), utilising the referred to long-acting technology

Not provided

## Share technical information for match-making assessment

Provide necessary technical information to a potential partner, under confidentiality agreement, to enable preliminary assessment of whether specific medicines of public health importance in LMICs might be compatible with the referred to long-acting technology to achieve a public health benefit

Not provided

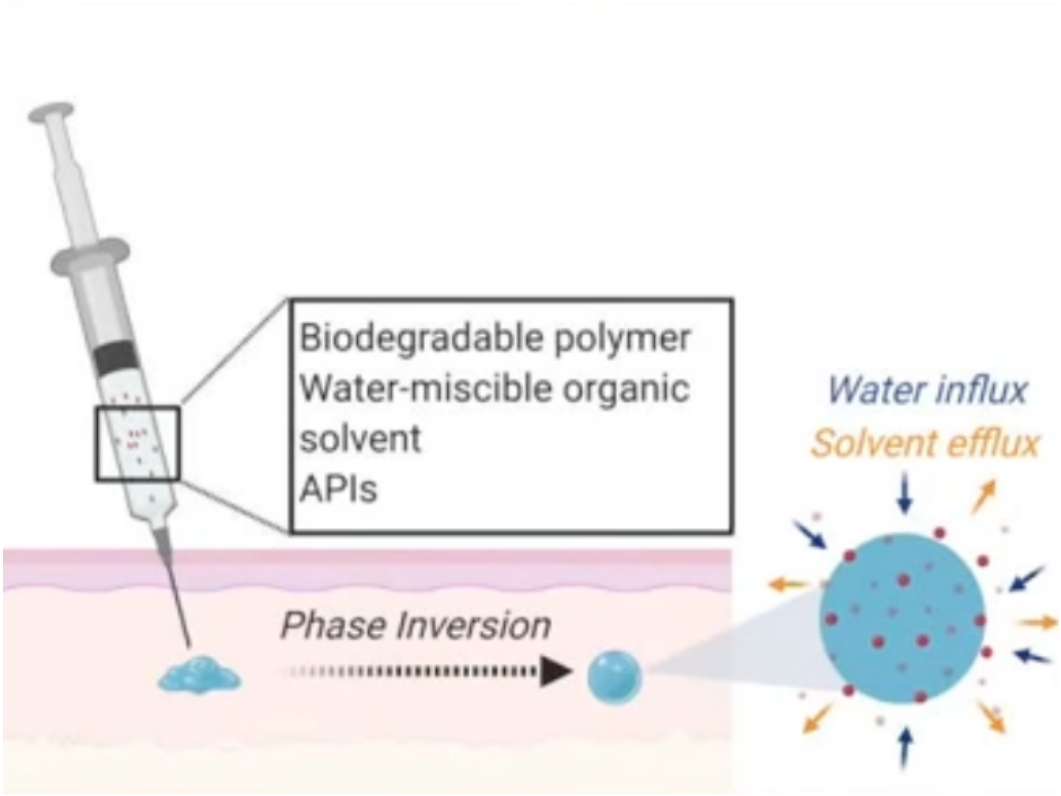
## Work with MPP to expand access in LMICs

In the event that a product using the referred to long-acting technology is successfully developed, the technology IP holder(s) will work with the Medicines Patent Pool towards putting in place the most appropriate strategy for timely and affordable access in low and middle-income countries, including through licensing

Not provided

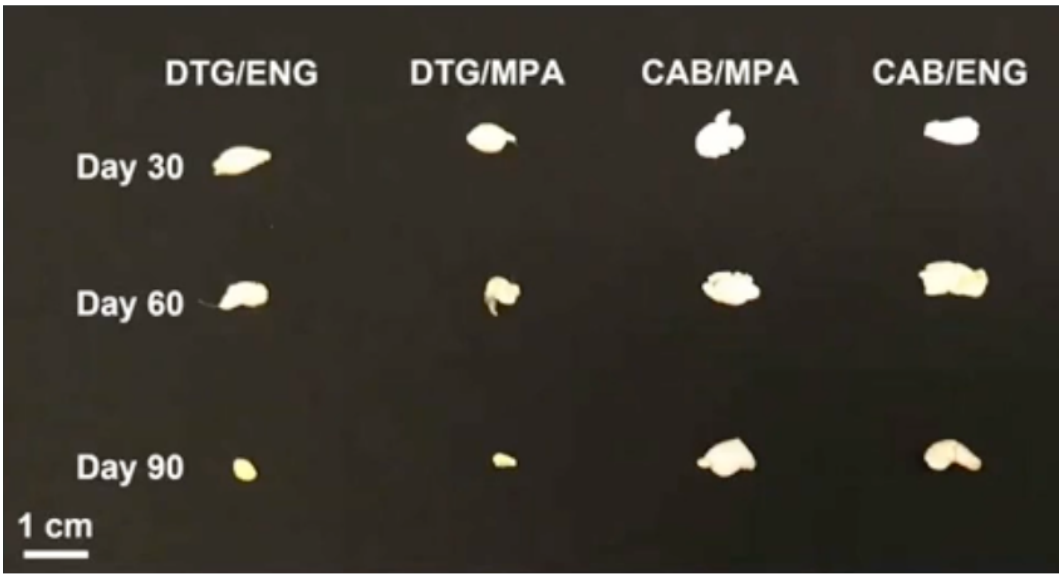
# Comment & Information

# Illustrations




ISFI mechanism and drug release. A liquid solution incorporating a biodegradable polymer, water-miscible organic solvent, and APIs is subcutaneously administered and undergoes a phase inversion

Young I, Benhabbour SR et al. CROI, 2022




Depots retrieved 90 days post subcutaneous administration in mice model to quantify residual drug and polymer degradation

Young I, Benhabbour SR et al. CROI 2022