Ultra-Long-Acting MPT Injectable with Dolutegravir and Levonorgestrel for HIV PrEP and Contraception

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BACKGROUND

HIV prevention and unplanned pregnancy remain major global issues, with over **1.3 million new HIV infections** and **121 million unintended pregnancies each year**.

- Compared to daily oral pills, long-acting injectables (LAIs) reduce stigma and enhance acceptability, adherence, and efficacy.
- Current LAIs are not removable and elicit a long pharmacokinetic (PK) tail.
- Contraceptive long-acting implants require surgical insertion and removal.

To overcome these limitations, we developed a subcutaneous (SC) ultra-long-acting (ULA) injectable in-situ forming implant (ISFI) with dolutegravir (DTG) alone and in combination with levonorgestrel (LNG) as once-yearly injectables for HIV PrEP and as an MPT for HIV PrEP and contraception.

METHODS

Figure 1. ISFI formation and mechanism of drug release

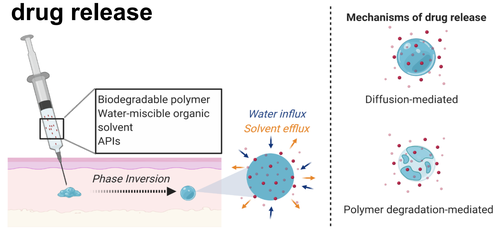


Figure 2. Macaque study design

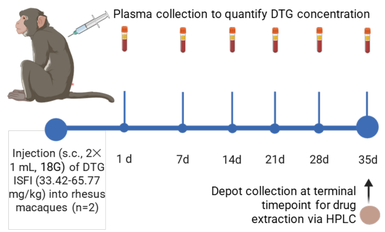
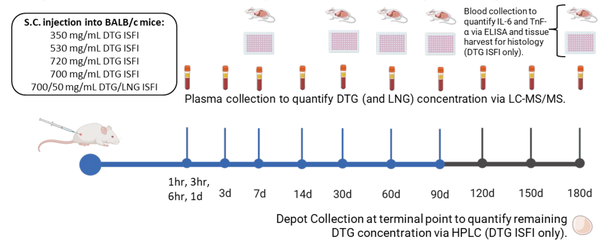


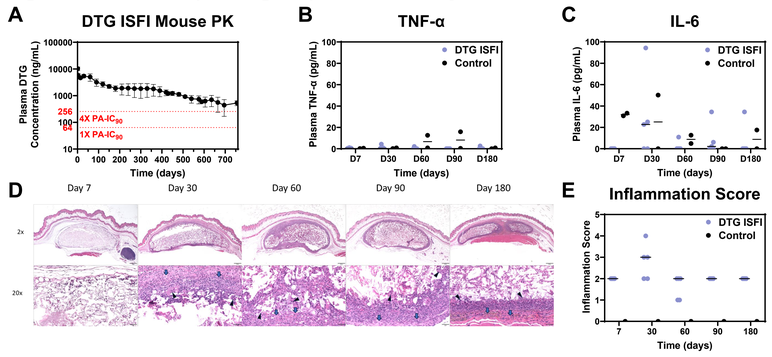
Figure 3. Mouse Safety and PK study design



DTG & DTG/LNG ISFIs are potential once-yearly injectables for HIV PrEP (and contraception).

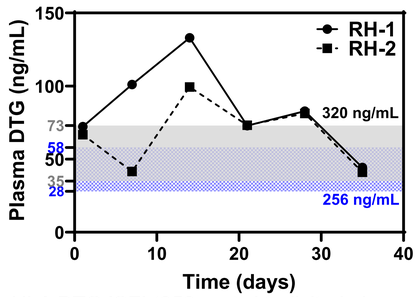
RESULTS

Figure 4. DTG ISFI (350 mg/mL) PK and safety in mice.



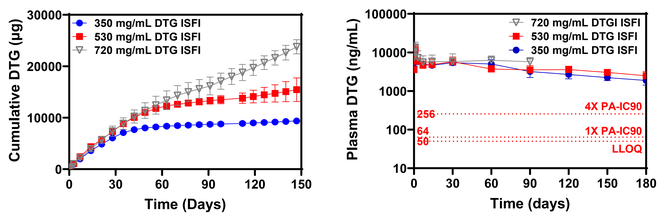
- ULA DTG ISFI (350 mg/mL) elicited plasma concentrations above the 4× PA-IC90 for 756 days (**Fig 4A**).
- Low plasma concentrations of IL-6 and TNF-α at day 7-180, indicating minimal systemic inflammatory response (**Fig. 4B-C**).
- Infiltrates of neutrophils (blue arrows) and macrophages (black arrows) were present at the injection site SC tissue and slightly increased over time (**Fig.4D**). There was an initial moderate local inflammation response by day 30, which declined to mild at later timepoints (**Fig. 4E**).

Figure 5. DTG ISFI Pilot Macaque PK.



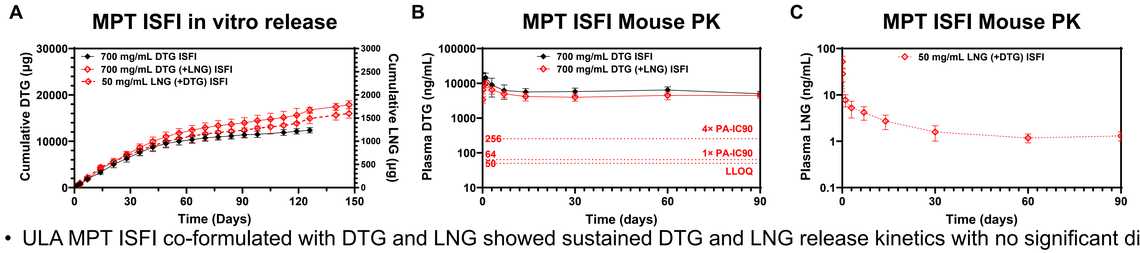
- ULA DTG ISFI (350 mg/mL) elicited plasma concentrations above the human $Ctrough$ (grey region) and 4×PA-IC90 (blue) target windows translated to macaques for 35 days (**Fig 5**).
- Using published DTG clearance values from cynomolgus monkeys to deconvolute plasma PK data, estimated DTG absorption rates ranged from 2337-6270 µg/day. Assuming each implant contains 350 mg and releases drug at a constant (zero-order) rate, this implant is projected to last for 116-350 days.

Figure 6. Optimized DTG ISFI in vitro release and PK in mice.



- To extend release duration, optimized formulations of ULA DTG ISFI were investigated. ISFIs were optimized to achieve DTG concentrations up to 720 mg/mL (**Fig. 6A**).
- All formulations elicited plasma concentrations above the 4× PA-IC90 for up to 180 days in mice (**Fig 6B**). ISFIs collected at d180 post administration had ~62% DTG remaining demonstrating the potential to achieve DTG release beyond 180 days.

Figure 7. DTG/LNG MPT ISFI in vitro release and PK in mice.



- ULA MPT ISFI co-formulated with DTG and LNG showed sustained DTG and LNG release kinetics with no significant difference in DTG release when formulated alone or in combination with LNG (**Fig. 7A**).
- The MPT ISFI elicited sustained plasma DTG and LNG concentrations for 90 days (last timepoint analyzed, ongoing study) in mice (**Fig 7B-C**).

CONCLUSIONS

- First-in-line ULA DTG and MPT (DTG/LNG) ISFIs as once-yearly SC injectables for HIV PrEP (and contraception) that are biodegradable and removeable (only if needed).
- DTG ISFIs were well tolerated with minimal systemic inflammation response and mild-moderate local inflammation response.
- Optimized ULA DTG and MPT ISFI formulations show the potential for extended duration in mice and macaques.
  - ULA DTG ISFI elicited plasma concentrations above 4× PA-IC90 for over two years after a single injection in mice.
  - ULA DTG ISFI elicited plasma concentrations within the C_{trough} and 4× PA-IC90 for 30 days after #2 1 mL injections in macaques.
  - ULA optimized DTG ISFI and MPT ISFI elicited plasma concentrations above 4× PA-IC90 for up to 180 days after a single injection in mice.

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PLAIN LANGUAGE SUMMARY

We are developing once-yearly injectables for HIV PrEP, including one that also provides contraceptive coverage. In animal studies, target drug levels have the potential to be maintained for >3-11 months in macaques after two 1 mL injections and >90 days in mice after a single injection, supporting their potential as long-acting prevention options.