# MPT Long Acting Injectable Target Product Profile

Product Name: ARV + HC Long Acting Injectable/Systemic MPT

**Please note:** This dosage form TPP is designed to serve as a guiding document and tool for the general category of MPT Long Acting Injectables of the type combining ARVs with HCs. The development of a particular MPT LAI TPP will require expertise and development planning that is product specific with regard to target parameters and supporting data requirements.

Each section of the TPP contains three areas: (1) Target: Labeling language intended for product; (2) Annotations: Summary information for planned/necessary studies in support of target; and (3) Comments: Additional information to provide clarity on content in above two sections.

## 1) Indications & Usage

| Target | Annotations |
|---|---|
| Prevention of unintended pregnancy and prevention of HIV infection through vaginal (contraception and HIV prevention) or rectal (HIV prevention) sexual exposure. | Demonstrated via cGCP phase 3 efficacy study(s) with statistical power adequate to satisfy regulatory agency requirements for safety and efficacy for each indication. |

| Comments: |
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## 2) Dosage & Administration

| Target | Annotations |
|---|---|
| i. Route of Administration: Intramuscular or subcutaneous injection<br>ii. Drug Load/Dose: Drug specific- adequate for achieving targeted efficacies and duration of effect targets; must be safe and well tolerated<br>iii. Dosing regimen: Injection volume and number and frequency of injections adequate for target efficacy and consistent with established acceptability.<br>a. *Minimally acceptable:* Co-administration of two, 1.0 mL injections- one for contraception and one for HIV prevention, administered no less than every two months.<br>b. *Optimal*: a co-formulated dose of ≤ 1.0mL administered no less than once every 3 months | i. Standard P1-P2 safety, tolerability and acceptability<br>ii. In vitro, ex vivo, in vivo animal and human pharmackinetic and pharmacodynamic studies<br>iii. Dose escalation studies in animals with associated PK and safety; possible animal model efficacy studies (hu-mouse; NHP; rabbit pregnancy); expanded P1 trials with PK and PD assessments; P3 trials conducted with targeted label claim for dose and dosing regimen |

**Comments:**

i. Initial administration at launch by health care professional with appropriate training
ii. Determining drug load or exposure dose will require appropriate safety and model system efficacy studies involving escalating dose evaluations. Once the safe and effective in vivo target exposure is defined, it will be necessary to determine what drug load and dose are necessary
iii. The dosing volume and interval will need to have well demonstrated acceptability in the target population, which extends beyond the trial settings that involve incentives for retention. Injection Site Reactions (ISR) will likely be the most common AE, and therefore must occur at an acceptable frequency and intensity

## 3) Dosage Forms & Strengths

| Target | Annotations |
|---|---|
| TBD Per Product | |

**Comments:**

## 4) Contraindications

| Target | Annotations |
|---|---|
| i. HIV positive women, pregnant women, girls under age 15<br>ii. Possible HC related contraindications: active venous thrombosis disorder, history of severe hepatic disorder, liver tumors, hormone related malignancies, undiagnosed vaginal bleeding, cerebral vascular or coronary artery disease, severe hypertension, acute cervicitis, vaginitis, or BV, known or suspected carcinoma of the breast<br>iii. ARV drug contraindications: Will be API specific<br>iv. Testing requirements: Recommended HIV and pregnancy testing requirements for continued product use must be defined | ii. HC related contraindications should be established using existing guidelines such as the WHO MEC, or established via appropriate studies or the status of the API. However, an LAI with an ARV only and demonstrated safety in pregnant women would be preferable for this population.<br>iii. Pending ARV status, contraindications may already be defined and would be incorporated into the TPP<br>iv. Use of existing, accepted guidelines for pregnancy testing. HIV testing algorithms TBD |

**Comments:**

i. Acceptability for use by pregnant women could be established via appropriate studies or the status of the API incorporated into the IVR

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| ii. HC related contraindications will be product specific and will be determined by particular hormone inclusion strategy (e.g. progestin only, etc.)<br>iii. Possible ARV contraindications are likely to be drug type specific (e.g., NNRTI, NRTI, etc.) and are known from treatment indications.<br>iv. Pregnancy testing will potentially be required depending upon the ARV used in the LAI, Implemented testing algorithms will require end-user acceptability |

## 5) Warnings & Precautions

| Target | Annotations |
|---|---|
| TBD Per Product | |

| Comments: |
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## 6) Adverse Reactions

| Target | Annotations |
|---|---|
| TBD per product: See "Comments, Clinical Safety" in section 14, below | |

| Comments: |
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## 7) Drug Interactions

| Target | Annotations |
|---|---|
| i. Combination API compatibility; compatible with other drugs TBD by SRA and other local regulatory authorities | i. DDI clinical trials as per FDA or other regulatory guidance; assessment of API PK effects; etc. |

| Comments: |
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| i. Examples: co-use of drugs that induce CYP3A4, increasing progestin metabolism (e.g. NNRTI effect). Further, it may be necessary to evaluate product compatibility with other commonly used drugs (e.g., TB treatment, etc.) regionally |

## 8) Use in Specific Populations

| Target | Annotations |
|---|---|
| i. Non-pregnant women seeking protection from or at risk for HIV and unintended pregnancy<br>ii. Other populations: adolescent reproductive age women, obese women, breast feeding women | i. Adequate clinical safety data in global populations targeted for commercialization and product introduction and use; includes adolescent girls of reproductive age<br>ii. Adequate safety studies in the specific populations |

**Comments:** Minimally, these products will target women at risk for HIV and unintended pregnancy in resource constrained parts of the world. An expanded target population could include: younger adolescent women (<18 yrs); breastfeeding women seeking protection against HIV and unintended pregnancy.

## 9) Description

| Target | Annotations |
|---|---|
| i. Parenteral long acting formulation for the prevention of HIV and unintended pregnancy. Could exist as a single co-formulated product or as a co-packaged entity of two distinct dosing elements.<br>ii. Formulation provided as a pre-existing suspension in a glass vial or appropriate syringe, as a lyophilized entity requiring suspension prior to administration, or some alternative acceptable format.<br>iii. Appearance: As per above where described.<br>iv. Packaging: Individual primary packaging, or as a kit complete with syringes, needles and solubilizing reagent if needed<br>v. Drug concentration and volume per vial or syringe appropriate for achieving the safe and effective drug exposure and acceptable to end user | ii. Appropriate packaging required, i.e. physically/chemically stable.<br>iii. Appearance assay specification for release and stability<br>iv. Evaluated via GMP stability studies and leachable packaging studies.<br>v. In vitro drug dissolution assay and specification (as per USP); in vivo release as per P1/P2 PK studies; other specifications and tests- uniformity of dose; purity; residual solvents; heavy metals; water content; potency; sterility; preservative challenge and assay; others as needed per dosage form |

**Comments:**

i. Qualified vendors supplying appropriate grade raw materials including APIs; established supply chain for all raw materials. NOTE: the product could exist as a co-formulated or co-packaged entity (e.g., 2 injectable formulations in a single product entity)
ii. Based on currently available commercial long acting parenteral formulations or vaccines used in target populations
iv. As per ISO and ICH guidance
v. As per ICH, ISO, GMP, FDA, USP or other requirements. The specifications listed will be per final product as well as per API, as needed.

## 10) Clinical Pharmacology

| Target | Annotations |
|---|---|
| i. Appropriate systemic distribution and bioavailability for targeted duration of effect period<br>ii. Demonstration of efficacy via surrogate and/or sufficient model studies (e.g., ex vivo, animal model, human pharmacodynamics models, etc) | i. Phase 1 PK studies targeting plasma, and for ARVs, genital tract fluid and tissue levels.<br>ii. Human PK/PD studies targeting plasma and other appropriate compartments; appropriate animal model evaluations |

**Comments:**

i. LA injectable products will typically be characterized by long half life (both ARV and HC). Therefore, the full PK profile to drug elimination will need to be defined for both drugs in both formulations

ii. Limitations with available models are acknowledged, however justification for P3 trial investment as well as the need to present a dose/drug delivery level rationale for regulatory purposes dictates the need for meaningful surrogate of efficacy data and PK/PD data

***12.1 Mechanism of Action:*** For regulatory purposes it will be necessary to establish the mechanisms of action for prevention of HIV infection by the ARV as well as the hormonal contraceptive mechanism of action. This could rely on pre-existing data for each API, or may require demonstration during clinical evaluation of the combination in the MPT product.

## 11) Nonclinical Toxicology

| Target | Annotations |
|---|---|
| i. Non-genotoxic/non-mutagenic<br>ii. Non-teratogenic<br>iii. Non-carcinogenic<br>iv. No systems toxicity including uterus, ovaries, bladder, spleen, liver, etc.<br>v. No chronic toxicity findings<br>vi. Anmal models for contraceptive reversibility<br>vii. Other in vivo toxicity studies as needed (e.g., immune effects in the genital tract; effects on the GT microbiome, etc) | i. Ames test, chromosome aberrations test, micronucleus testing, etc.<br>ii. Segs 1,2,3 reprotoxicity testing<br>iii. FDA approved carcinogenicity protocol<br>iv. Acute tox, repeat dose tox, dose escalation; Toxicokinetic studies<br>v. Two species, 6-9 month dosing study<br>vi. TBD<br>vii. TBD |

**Comments:**

i-iv. The need for these studies will be dependent upon what is available from the component APIs in the MPT product. Exacerbating or other toxicity effects of the combination of drugs will need to be ruled out via appropriate tox studies and DDI studies in animals prior to human trials. Studies may require test formulations that differ from final formulation in order to achieve the necessary dose interval. Conversion of oral API to LA API may be achievable with safety bridging studies. Safety studies to assess topical effects are not anticipated to be needed for LAI systemic delivery.

## 12) Clinical Studies

| Target | Annotations |
|---|---|
| ***Efficacy:***<br>i. Minimally acceptable efficacy: >75% for prevention of HIV infection; >95% for prevention of unintended pregnancy<br>ii. Reversibility: For HIV susceptibility-drug/formulation specific; return to fertility optimally within ~6 months (longer may be acceptable)<br>iii. Special efficacy: Active against relevant resistant isolates of HIV; depending on mechanism of action and GT secretion, active in the presence of seminal and cervico-vaginal fluids; efficacy unaffected by sexual intercourse<br>iv. In vitro/in vivo mechanism of action studies<br><br>***Clinical Safety:***<br>i. no systemic toxicity; no meaningful effects on the FGT/RT transcriptome, or proteome; no significant induction of inflammatory response markers; no unacceptable effects on daily life style or schedule; no social harm effects/AEs<br>ii. AE's: Minimally acceptable- No grade 3 AEs or higher observed during trials; No higher than grade 2 AE that are product related and acceptable to target population; AE frequency consistent with systemic use of similar ARV or HC products<br>iii. Side Effects: Optimally, the side effects profile should target fewer side effects and lesser intensity than that seen with related API products, and should occur at or below the frequency observed with single indication products with similar drugs. No irreversible effects on ability to conceive. No systemic toxicity findings. | ***Efficacy:***<br>i. Appropriately powered, statistically significant cGCP phase 3 trial(s) per indication<br>ii. Appropriate fertility studies (as part of planned trials or with independent clinical studies)<br>iii. In vitro/ex vivo infection models for resistant isolate potency, and activity in the presence of GT fluids/semen. Clinical evaluation of effects of intercourse on drug levels and efficacy will probably not be required<br>iv. Full in vitro/ex vivo characterization for new API's cross reference for approved API<br><br>***Clinical Safety:***<br>i. Appropriate Phase 1 thru Phase 3 clinical trials with appropriate pharmacovigilence studies post approval.<br>ii. Phase 1 safety and PK studies in women; Expanded safety phase 2 trials with necessary sub-studies in the target or other specific populations<br>iii. Effects on menses/bleeding patterns will be a potential acceptability issue and will need to be appropriately evaluated for acceptability and relevance to adherence and product uptake |

**Comments:**
***Efficacy:***
i. Stated efficacies are minimally acceptable and based on the efficacy findings obtained with systemic use of oral truvada in the Partners PrEP study (HIV prevention) and long acting injectable HC product (e.g. DepoProvera) (contraception). Pre-phase 3 studies evaluating surrogates for efficacy

will be required (animal, PK/PD models, ex vivo, etc.).

ii. Return to HIV susceptibility will depend on the potency of the drug, and systemic and compartments of exposure drug half-life. Resulting tail concentrations will require quantification via PK studies, and potentially require clinical management strategies

iii. Typical in vitro assessments of activity for the drugs will be required. ARV API should be active against HIV isolates resistant to alternative mechanisms of action.

iv. Will depend on available information from the individual drugs

***Clinical Safety:***

i. The minimally acceptable general safety profile should be equivalent to current comparable products (e.g. Injectable HC products, and currently available ARV treatment products). LA Injectable products cannot be removed once administered; therefore, safety must be well characterized. Importantly, it may be necessary for oral run in dosing with the ARV API prior to administration of an injectable version. This will need to be determined in a product specific manner with regulatory authorities.

ii. Vaginal bleeding or spotting profile and general cycle effects are particularly relevant to the end-user and must be acceptable to the target population. An acceptable AE profile must be developed in the context of end-user data.

iii. The following possible side effects should not exceed frequency or intensity observed with related single indication products. *HC related*: Injection Site Reactions, mild nausea, vomiting, bloating, stomach cramps, changes in weight or appetite; breast pain, tenderness, or swelling; headache, nervousness, dizziness, tired feeling; freckles or darkening of facial skin, increased hair growth, loss of scalp hair; problems with contact lenses; vaginal itching or discharge, changes in menstrual periods, decreased sex drive. *Possible ARV related*: Rash, headache, depression, mild dizziness, mild nausea, diarrhea, dark urine, tiredness and fatigue, muscle or joint pain, reduction in bone mineral density, stomach pain, sleep problems and insomnia, elevations in liver functions, elevations in serum creatinine, upper respiratory tract infections, some kidney function anomalies, inflammatory syndromes, etc. Note: the AE/side effect profile for the ARV will be drug- and drug class-specific

## 13) Useful References

Gilead. (2013). Truvada [package insert]. Foster City, CA.

Pfizer. (2006). Depo-Provera [package insert]. New York, NY.

Spreen, W.R., Margolis, D.A., & Pottage Jr., J.C. (2013). Long-acting injectable antiretrovirals for HIV treatment and prevention. *Current Opinion in HIV and AIDS*, 8(6), 565-71.

U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for Industry and Review Staff: Target Product Profile – A Strategic Development Process Tool. (2007).

## 14) How Supplied/Storage & Handling

| Target | Annotations |
|---|---|
| ***Stability & Storage:***<br>i. Shelf Life: Minimum 36 months; preferred 60 months<br>ii. Storage conditions: Minimum: 30$^{o}$C, 65% RH; Preferred: zone 4b conditions; light stable | ***Stability & Storage:***<br>i. Appropriate ICH stability studies with finalized specifications and validated test methods<br>ii. Appropriate ICH stability studies with finalized specifications and validated test methods |

**Comments:**
***Stability & Storage:*** Temperature cycling, freeze thaw and appropriate excursion studies will also be required.

NOTE: It will be critical for products in development to be compliant with all CMC related requirements from the FDA and other SRAs. This will involve all aspects of the product development history, through finalization of scalable GMP manufacture of material for commercial supplies. The details for the CMC regulatory package will need to be addressed on a product specific basis with the FDA.

## 15) Patient Counseling Information

| Target | Annotations |
|---|---|
| i. This product should be used in the context of safe sex practices (e.g., condom use)<br>ii. Correct and consistent product use is necessary for efficacy and safety<br>iii. End users will be counseled on the need for follow up testing for HIV infection (and possibly pregnancy) | The P3 efficacy and safety trails will be conducted in the context of safe sex counseling and the provision of condoms. Further, all clinical studies will be conducted with meaningful counseling on correct and consistent product use in an adherent fashion. The effects of interruption or inconsistent use of product, if any will need to be determined on a product specific basis. HIV and pregnancy testing will be required to avoid risk of resistance selection in sero-convertors using these products, or possible fetal exposure to ARV drugs |

**Comments:**