Regulatory Perspective on Developing Long Acting ARVs for HIV Treatment/Prevention

FDA

Division of Antiviral Products

Financial Disclosures

- None

FDA Disclaimer

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Outline

- Treatment
  - New formulation of an approved product
  - New formulation of an investigational product
- Prevention
  - New formulation of an approved product for treatment
  - New formulation of an investigational product
- Need for oral/immediate release formulation

Types of Data to Support Approval

- **PK Comparison**
  - Evaluate PK profile between reference and test product to determine if safety and efficacy extrapolation is possible
    - Ratio AUC, Cmax and Cmin [90% CI 0.8-1.25 (80-125%)]
- **Exposure-Response (E-R)**
  - Target exposures are different
    - E-R data may make it possible to determine if differences are not meaningful
- **Clinical Data**
  - E-R not understood and/or PK significantly differs and E-R not supportive
    - Single clinical trial may be sufficient to change formulations

Scenarios For Treatment

- Reformulating an Approved Oral ARV to Long Acting Injectable (or other delivery system)

- New Investigational Long Acting ARV

Approved Oral ARV to New Long Acting Formulation (eg Liposomal or Nano formulation)

- PK data alone may not be sufficient to support approval
- A full safety evaluation is likely needed unless scientific rationale to support why additional safety data are not needed
  - At least 300 patients depending on what is observed during phase 1/2 trials and what is known about the parent drug
  - Eg liposomal compounds have a variety of host reactions and safety trials are needed
- Efficacy data could be needed if PK data are not supportive

Investigational Long Acting ARV For Treatment

- Typical drug development pathway
  - Single and multiple ascending dose trials
    - Can be developed in absence of immediate release formulation
    - May dose one subject at a time for safety reasons
  - Dose-finding trials
  - Phase 3 trials

Trial Design Considerations

- Conventional noninferiority designs
- Role of switch trials
- Subject retention imperative to overall safety and efficacy evaluation
  - Pre-trial feasibility assessments (# of injections, frequency, volume of injections)
  - Engagement of community, subject and trial site support

PK/PD Considerations

- Residual Drug Exposure (PK tail)
  - Safety
  - Potential development of viral resistance once dosing of LA product is discontinued
- Drug interactions (DDI)
  - Relevant DDI trials as needed based on metabolism profile
  - Also consider DDIs between LA ARV and oral ARVs during PK tail period

LA ARV for PrEP Considerations

- Clinical trials are needed for HIV prevention indications
  - Approved formulation, new formulation of approved drug or new investigational agent
  - Exposure response for prevention not known and no validated biomarkers
- Trial design considerations:
  - Choice of comparator
  - placebo vs active control
  - non-inferiority challenges: MSM vs high risk women
- Oral lead-in is not absolute; can be developed in absence of immediate release formulation
- Other PK/ PD considerations
  - Role of drug concentrations in plasma vs other biologic matrices
  - Window of protection
  - PK tail
  - Tissue exposure

Is there a need for oral/IR formulation in addition to Long-Acting Injectable?

It Depends

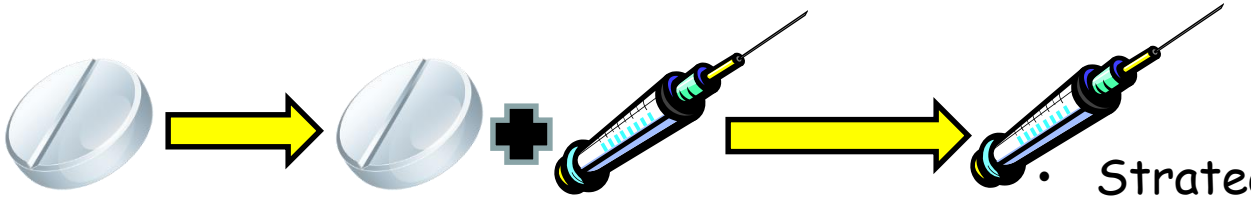
Need for Oral/Immediate-release formulation in addition to Long-Acting Injectable

- Not absolute
- Considerations
  - PK
    - Need for lead-in oral dosing to achieve “target” exposures
  - Safety
    - Early in development program to establish safety profile

IR Oral and LA Injectable Scinarios

Dose oral to steady state

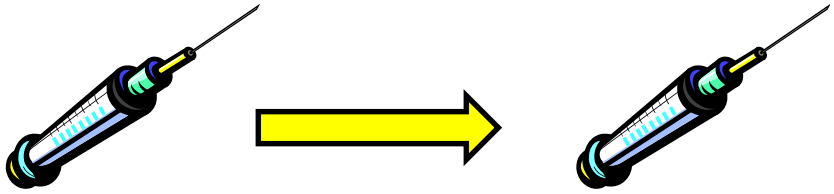
- Rule out safety concerns (eg hypersensitivity)
- Ensure "target" exposures are met



Dose oral

Overlap oral and injection dosing

- Strategy depends on ability to achieve "target" exposures



Initial (Loading) injection dose

Subsequent (Maintenance) injection dose

- Can be used in absence of oral lead-in and may be ideal if adequate exposures are achieved with initial (loading) dose

Risk Mitigation Strategies for No Oral Lead-In

- Stringent enrollment criteria
- Start with small number of subjects
  - Dose 1-2 subjects
  - Stagger dosing between subjects for specified interval
- Stringent stopping rules for individual subjects, cohorts and the study
- Consideration for an independent unblinded medical monitor or data monitoring committee to oversee safety

Curr Opin HIV AIDS 2015, 10:278–281

Regulatory challenges in developing long-acting antiretrovirals for treatment and prevention of HIV infection

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Purpose of review
To outline some of the regulatory challenges inherent to the development of long-acting antiretrovirals (ARVs) for the treatment or prevention of HIV infection.

Recent findings
Despite advances in drug development that have reduced ARV dosing to once daily, suboptimal drug adherence remains an obstacle to successful HIV treatment. Further, large randomized trials of once daily oral ARVs for preexposure prophylaxis (PrEP) have shown that drug adherence correlates strongly with prophylactic effect and study outcomes. Thus, the prospect of developing long-acting ARVs, which may mitigate drug adherence issues, has attracted considerable attention lately.

Summary
Because of their pharmacokinetic properties, the development of long-acting ARVs can present novel regulatory challenges. Chief among them is determining the appropriate dosing regimen, the need for an oral lead-in, and whether existing data with an approved oral agent, if available, can be leveraged for a treatment or prevention indication. For PrEP, because validated biomarkers are lacking, additional nonclinical studies and evaluation of tissue concentrations in multiple compartments may be necessary to identify optimal dosages. Study design and choice of controls for registrational trials of new long-acting PrEP agents might also prove challenging following the availability of an oral PrEP drug.

Keywords
antiretroviral therapy, HIV preexposure prophylaxis, HIV/AIDS, long-acting

Summary

- Long acting systemic formulation of an approved ARV
  - In most situations not possible to match AUC or Cmax
  - Maintaining same or higher trough or predose concentration compared to oral formulation is important
  - Can use E-R data but likely clinical trial data needed
- New Investigational LA ARV for treatment
  - Clinical trial data (safety and efficacy) needed
- Oral lead-in is not absolute
- Other PK/ PD considerations
  - Residual drug exposures (PK tail)
  - Drug Interactions