Expanding Inclusion for Long-Acting HIV Treatment Trials Workshop

FDA Perspective

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Disclaimer Slide

- This presentation reflects the view of the author and should not be construed to represent FDA's views or policies

- Defer to the relevant sponsor/applicant for any specific drug development rationale

Agenda

- Background
- Regulatory Considerations in HIV-1 Drug Development
- Recent Examples
- Enhancing Diversity in Clinical Trials
- Summary

Background

- FDA acknowledges:
  - Desire of investigators to expand the use of LA ARVs (or other ARVs) in populations not evaluated in clinical trials
  - Registration trials are typically not powered for various subgroups
- FDA can encourage clinical trials for specific indications and patient populations (but not mandate)
- FDA works with IND sponsors to include a diverse population

ARVs, antiretrovirals; IND, investigational new drug; LA, long-acting

Background

- Not every premarket or postmarket trial is included in labeling
  - Practice of medicine and guidelines
- FDA does not consider price or cost-effectiveness when evaluating drug products
- FDA is not involved in the policies that state formularies or insurance require for coverage

Regulatory Considerations in HIV-1 Drug Development

- FDA encourages IND sponsors to evaluate ARVs in a wide range of patients by enrolling a diverse patient population at all stages of drug development
- FDA can not mandate IND sponsors to evaluate a product in all populations or subgroups (with some exceptions):
  - Safety concern identified in early development
  - Safety concern identified during review
  - Pediatric studies

ARVs, antiretrovirals; IND, investigational new drug

Regulatory Considerations in HIV-1 Drug Development

- Changing an indication/patient population
  - A randomized controlled trial is needed in most situations
    - Exception: HTE population (FDA guidance)
  - Adding labeling in other populations
- Only the commercial sponsor can request changes to the specific indication and patient population

HTE, heavily treatment-experienced

GUIDANCE DOCUMENT

Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment

NOVEMBER 2015

https://www.fda.gov/media/86284/download

Regulatory Considerations in HIV-1 Drug Development

- Inclusion of various subgroups during drug development is dependent on the characteristics of the drug
- As the safety, efficacy and general benefit-risk assessment is better understood, additional populations may be included in later stages of drug development, including post-approval
- Final indication is reflective of the overall benefit-risk assessment for various populations studied

Efficacy and Safety Determination Time Points

Table 1: Recommendations for Efficacy and Safety Determination Time Points According to HIV Patient Population[6]

Patient Population	Efficacy Determination Time Point	Safety Determination Time Point
Group 1: Fully susceptible to all approved drugs, treatment-naïve, or previous treatment with a well-documented treatment history demonstrating no virologic failure.	Virologic response at 48 weeks	Safety outcomes through 48 weeks
Group 2: Drug resistance to multiple drugs and multiple drug classes. Not able to construct a treatment regimen that can suppress HIV-RNA to levels below assay quantification limits.	Virologic response at 2 weeks (or less) plus virologic follow-up at 24 weeks	Safety outcomes through 24 weeks
Group 3: Drug resistance present and able to construct a treatment regimen that can suppress HIV-RNA to levels below assay quantification limits.	Virologic response at 24-48 weeks*	Safety outcomes through 24-48 weeks

* Twenty-four weeks of data is appropriate for drugs that have some benefit over existing options (e.g., better efficacy, tolerability, ease of administration), while 48 weeks is recommended for drugs with comparable characteristics to existing options.

GUIDANCE DOCUMENT

Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment

NOVEMBER 2015

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Recent Examples

- Studies conducted in other populations that are not included in labeling (published and cited by other groups)
  - Women
- Studies conducted by third parties that are included in labeling
  - Elvitegravir/cobicistat
- Drug development in TN and TE patients
  - Doravirine and doravirine/lamivudine/tenofovir disoproxil fumarate
  - Dolutegravir/lamivudine
- Cabotegravir/rilpivirine development

TE, treatment-experienced; TN, treatment-naïve

Studies Conducted in Other Populations Not Included in Labeling

- Gender, Race And Clinical Experience (GRACE) study was conducted to evaluate sex- and race-based differences in outcomes after treatment with a darunavir/ritonavir-based ARV regimen[1]
- Efficacy and safety of switching to bictegravir/emtricitabine/ tenofovir alafenamide in women[2]

[1] Currier J, Averitt Bridge D, Hagins D, et al. *Sex-based outcomes of darunavir-ritonavir therapy: a single-group trial*. Ann Intern Med. 2010;153:349-57.
[2] Kityo C, Hagins D, Koenig E, et al. *Switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide (B/F/TAF) in virologically suppressed HIV-1 infected women: a randomized, open-label, multicenter, active-controlled, phase 3, noninferiority trial*. J Acquir Immune Defic Syndr. 2019;82:321-328.

Elvitegravir/Cobicistat and Pregnancy

- Elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide is not recommended for use during pregnancy[1]

Human Data

A prospective study, reported in the literature, enrolled 30 pregnant women living with HIV who were receiving elvitegravir and cobicistat-based regimens in the second or third trimesters of pregnancy and through 6 to 12 weeks postpartum to evaluate the pharmacokinetics (PK) of antiretrovirals during pregnancy. Twenty-eight women completed the study through the postpartum period. Paired pregnancy/postpartum PK data were available from 14 and 24 women for the second and third trimesters, respectively. Exposures of elvitegravir and cobicistat were substantially lower during the second and third trimesters compared to postpartum. The proportion of pregnant women who were virologically suppressed was 77% in the second trimester, 92% in the third trimester, and 76% postpartum. No correlation was observed between viral suppression and elvitegravir exposure. HIV status was also assessed for infants: 25 were uninfected, 2 had indeterminate status, and no information was available for 3 infants.

Overall support: International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) was provided by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH)

[1]Genvoya Prescribing Information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/207561s029lbl.pdf. Accessed 11/9/22
Momper, J. D., Best, B. M., Wang, J.,et al., & IMPAACT P1026s Protocol Team (2018). Elvitegravir/cobicistat pharmacokinetics in pregnant and postpartum women with HIV. *AIDS (London, England)*, *32*(17), 2507–2516.

Doravirine

- 2018: initial approval in TN adults
  - Phase 3 trials: DRIVE-AHEAD and DRIVE-FORWARD
- 2019: indication extended to VS adults
  - Phase 3 trial: DRIVE-SHIFT
    - Open-label, randomized, active-controlled, noninferiority switch trial
    - Switch from a stable ARV regimen to the once-daily, single-tablet, three-drug regimen DOR/3TC/TDF

ARV, antiretroviral; DOR, doravirine; TDF, tenofovir disoproxil fumarate; TN, treatment-naïve; VS, virologically suppressed; 3TC, lamivudine

DRIVE-AHEAD (NCT02403674), DRIVE-FORWARD (NCT02275780), DRIVE-SHIFT (NCT02397096)

Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate

DRIVE-SHIFT

- Participants (VS adults) randomly assigned (2:1) to switch to:
  - Immediate Switch Group
    - DOR/3TC/TDF on day 1
  - Delayed Switch Group
    - Continue baseline regimen until week 24; switch to DOR/3TC/TDF
- Immediate vs. delayed approach has also been used in HCV treatment trial design

DOR, doravirine; HCV, hepatitis C virus; TDF, tenofovir disoproxil fumarate; VS, virologically suppressed; 3TC, lamivudine
DRIVE-SHIFT (NCT02397096)

Dolutegravir/Lamivudine

- Once-daily, single-tablet, two-drug regimen
- 2019: initial approval in TN adults
  - Phase 3 trials: GEMINI-1 and GEMINI-2
- 2020: indication extended to VS adults
  - Phase 3 trial: TANGO

TN, treatment-naïve; VS, virologically suppressed
GEMINI-1 (NCT02831673), GEMINI-2 (NCT02831764), TANGO (NCT03446573)

Dolutegravir/Lamivudine

- Review team had concerns initiating DTG/3TC phase 3 trials in TN adults
  - Absence of additional supporting data
  - Durability and development of resistance of a 2-drug regimen in TN adults with high baseline HIV-1 RNA
- Two pilot studies in TN adults: PADDLE and ACTG 5353
  - Data in participants with baseline HIV-1 RNA >100,000 c/mL
- GEMINI-1 and GEMINI-2
  - Initial protocols excluded participants w/ screening HIV-1 RNA >100,000 c/mL
  - Amended protocols: screening HIV-1 RNA ≤500,000 c/mL (set by Applicant)

DTG, dolutegravir; TN, treatment-naïve; VS, virologically; 3TC, lamivudine
GEMINI-1 (NCT02831673), GEMINI-2 (NCT02831764); PADDLE (NCT02211482); ACTG 5353 (NCT02582684)

Cabotegravir/Rilpivirine Development

- Only approved in VS adolescents and adults
- Stepwise approach prior to initiation of phase 3 trials (VS)
  - Phase 2b trial: LATTE, induction period with oral CAB + 2 NRTIs
  - Phase 2b trial: LATTE-2, induction/maintenance with oral followed by IM
  - Phase 3 trials (VS): FLAIR, ATLAS, ATLAS-2M
- Expand the population in labeling (example)
  - Detectable HIV-1 RNA: Group 3 (FDA Guidance)
    - Durability of dual regimen
    - Efficacy/Safety: 24 - 48 weeks
    - Limited to those with baseline HIV-1 RNA <100,000 copies/mL (RPV)

CAB, cabotegravir; IM, intramuscular; NRTI, nucleoside reverse transcriptase inhibitor; RPV, rilpivirine; VS, virologically suppressed

FDA Guidance:
Enhancing the Diversity of Clinical Trial Populations

- Guidance for Industry: November 2020
- Certain groups continue to be underrepresented in many clinical trials
- Guidance recommends approaches that sponsors can take to increase enrollment of underrepresented populations in their clinical trials


GUIDANCE DOCUMENT

Enhancing the Diversity of Clinical Trial Populations – Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry

NOVEMBER 2020

https://www.fda.gov/media/127712/download

FDA Draft Guidance: Diversity Plans

- Draft guidance: April 2022
- Purpose

*Provides recommendations to sponsors developing medical products on the approach for developing a **Race and Ethnicity Diversity Plan** to enroll representative numbers of participants in clinical trials from underrepresented racial and ethnic populations in the U.S.*


GUIDANCE DOCUMENT

Diversity Plans to Improve Enrollment of Participants From Underrepresented Racial and Ethnic Populations in Clinical Trials; Draft Guidance for Industry; Availability

Draft Guidance for Industry

APRIL 2022

https://www.fda.gov/media/157635/download

- Recommended elements
  - Overview of the disease
  - Scope of development program
  - Define enrollment goals
  - Specific plan of action to enroll and retain diverse participants
  - Status
- Plans should be discussed with the FDA as soon as practicable

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