

NEW FDA INDUSTRY GUIDANCE FOR DEVELOPING ANTIRETROVIRAL DRUGS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS-1 (HIV-1) INFECTION

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This summer (2013), the FDA issued draft guidance for the industry development of antiretroviral drugs for HIV-1 infection. Replacing the 2002 version, it provides the FDA's current thinking on the overall development program and clinical trial designs for antiretroviral drugs. The following summary highlights changes specific to trial design.

SIGNIFICANT CHANGES INCLUDED IN THE UPDATE WERE:

- More details on nonclinical development of antiretroviral drugs
- A greater emphasis on recommended trial designs for HIV-1-infected heavily treatment-experienced patients (those with multiple-drug resistant virus and few remaining therapeutic options)
- Use of a primary endpoint evaluating early virologic changes for studies in heavily treatment-experienced patients
- Use of the traditional approval pathway for initial approval of new antiretrovirals, with primary analysis time points dependent on the indication sought.

REGULATORY HISTORY OF HIV DRUG APPROVALS

Most of the antiretroviral drugs were first marketed under accelerated approval using surrogate endpoints of viral load and CD4 cell count changes at 24 weeks of treatment. Prior to 1997, traditional drug approval was based on confirmatory trials with clinical endpoints of HIV disease progression and death. After 1997, traditional approval was based on longer term HIV- RNA changes at 48 weeks of treatment to show sustained HIV-RNA suppression. Using HIV-RNA for traditional approval was based on a wide range of data that showed HIV-RNA decreases were predictive of clinical benefit. For drugs fulfilling an unmet need, approvals based on 24 week viral load data were later confirmed with 48 week viral load data, typically within the same trial.

NEW REGULATORY APPROACH

Since 1997, all 13 antiretroviral drugs that entered the market via accelerated approval, based on 24 week HIV-RNA changes, later received traditional approval based on 48 week changes in HIV-RNA. Now, using viral load (HIV-RNA) is considered a fully validated surrogate endpoint. Going forward, the duration of trials and primary endpoint assessment will be based on the patient population (Naïve or Treatment experienced) being tested. There will no longer be a need for a two step approval process, with accelerated followed by traditional. The table below summarizes the recommended treatment durations suggested to support approval of indications for the listed subgroups.

EFFICACY AND SAFETY DETERMINATION TIME POINTS ACCORDING TO HIV PATIENT POPULATION

PATIENT POPULATION	EFFICACY DETERMINATION TIME POINT	SAFETY DETERMINATION TIME POINT
Treatment Naïve or limited previous treatment	Virologic response at 48 wks	Safety outcomes through 48 wks
Treatment-experienced with remaining options	Virologic response at 24 to 48 wks*	Safety outcomes through 24 to 48 wks
Treatment-experienced with few or no remaining options	Virologic response at 2 wks with follow-up at 24 wks	Safety outcomes through 24 wks

*24 wks is appropriate for drugs that show some advantages over existing options

Ending the accelerated approval designation will not prolong HIV drug development. The drug applications that are intended for treatment experienced patients, with few or no remaining options, or for drugs that show advantages over existing therapies in treatment experienced patients, can still be submitted with 24 weeks of treatment data. This is the same time frame used under accelerated approval designation. The new guidance results from years of experience using HIV-RNA as an endpoint. The new 2-week primary virologic endpoint for treatment experienced patients, with few or no remaining options, should help to expedite drug development.

TRIAL DESIGNS: TREATMENT NAÏVE PATIENTS

A trial design should be a randomized, active-controlled, non-inferiority trial. One arm is a preferred standard of care regimen being compared to the same regimen, with one of the drugs substituted for the investigational drug. This will be compared to a high-performing control regimen. Superiority may be observed, but this is not expected since the current standard of care is close to 90% with relatively few "virologic failures." The primary endpoint is the HIV-RNA will fall below the assay level of detection limit at 48 weeks of treatment.

TRIAL DESIGNS: TREATMENT-EXPERIENCED PATIENTS WITH AVAILABLE TREATMENT OPTIONS

The design option can be an active-controlled, non-inferiority comparison as with treatment naïve patient populations. Another design option is the add-on superiority trial, where patients are randomized to a new regimen of approved drugs plus the investigational

agent compared to approved drugs alone. If only approved drug are available, there is the dose response trial design option as well.

Factorial trial design can be utilized if multiple investigational agents available for testing.

Arm 1: Approved drugs + New Drug A + New Drug B

Arm 2: Approved drugs + New Drug A

Arm 3: Approved drugs + New Drug B

The primary efficacy endpoint will be the proportion of the patient population with HIV-RNA below assay level of detection limits at 48 weeks for early treatment-experienced patients. An analysis at 24 weeks of treatment is possible where the drug shows benefit over existing therapy (e.g., superiority over approved drug in the same class).

TRIAL DESIGNS: TREATMENT-EXPERIENCED PATIENTS WITH FEW OR NO AVAILABLE TREATMENT OPTIONS

This patient population lacks an appropriate active control due to limited treatment options. Therefore, active controlled, non-inferiority trials are not feasible for this population. If multiple investigational drugs are available for testing, a factorial superiority trial design would be possible. A dose response trial design is also possible; however, suboptimal doses should be determined and dropped early in development.

Another option is the superiority design of new drug vs. placebo. A primary efficacy analysis can be performed at 2 weeks (or less) and a safety analysis at 24 weeks. Treatment duration should be limited in order to prevent further resistance of background regimen and reduce disease progression risks.

There have been many treatment advances since the first HIV diagnosis. Zidovudine (AZT) was the first

antiretroviral medication approved in 1987; since then, 13 antiretroviral medications have been approved for the treatment of HIV/AIDS. The updated FDA guidance applies lessons learned and gives a clear path toward making additional progress. People are able to lead normal lives because of these treatments however the search for a vaccine still continues.

SOURCE

Guidance for Industry, Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment: Draft Guidance dated June 2013.

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