Isentress®, raltegravir (MK-0518)
Position paper on NDA 022-128

High Hopes for the Next Generation
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September 5, 2007

The AIDS Treatment Activists Coalition's (ATAC) Drug Development Committee (DDC) works with government, academia, and the pharmaceutical industry to provide a community perspective into the development of new HIV drugs and the utilization of HIV therapies, focusing on issues such as clinical trials design and implementation, expanded access, and pricing concerns.

The DDC welcomes the public FDA Antiviral Drugs Advisory Committee hearing to discuss the accelerated approval of Isentress®, an HIV integrase inhibitor that represents an exciting new first in class HIV antiviral. We also welcome the opportunity to comment.

Introduction

Raltegravir (RAL) is a first-in-class integrase inhibitor that has been studied in treatment-experienced people. The current New Drug Application (NDA) and this paper deal only with the sponsor's current application for accelerated approval for RAL, formerly known as MK-0518, in treatment-experienced individuals, based on full 16- and partial 24-week data from the two pivotal studies, BENCHMRK-1 and –2, in 699 persons with advanced disease, (mean baseline CD4 cell count: RAL=151 cells/mm^3; comparator=158 cells/mm^3).

Development of RAL was a model of efficiency. It has been less than four years from RAL's 'first use in humans', and less than three years from its 'first use in HIV positive people'. While this is amazing progress, it is also a reminder of how much is yet to be learned about this drug, and the importance of long-term follow-up for adverse events as well as sustained efficacy. We are also very hopeful that longer-term safety data and the forthcoming data in naïve patients will establish the appropriateness of RAL combination therapy as first line therapy and will eventually also result in changes to the HIV treatment 'paradigm' in this population .

As we enter a new era of CCR5 inhibitors and integrase inhibitors, RAL combination therapy may well become a preferred first line therapy in treatment naïve patients. While it is slightly handicapped because it is administered twice daily, it does not require ritonavir boosting. We believe twice daily dosing is preferable to the many side effects and interactions presented by ritonavir (r) use.

The BENCHMRK studies permitted the use of experimental agents as part of the optimized background regimen at the initiation of the study. Some 20-50% of patients used darunavir/r, which was not FDA approved at the time. Of those who used both RAL and darunavir/r for the first time, 90% had viral loads of <400 copies/mL at 16 weeks.

Although we realize that experimental agents may not always be available, the DDC believes that the sponsor has continued to pave the way for new and exciting future trial designs in treatment experienced patients. We applaud the sponsor for continuing to include ingenious new trial design concepts and for listening to community concerns in this regard. We hope this major benchmark will serve to settle this issue once and for all. The sponsor was able to identify the effectiveness of RAL with one, two and more active drugs and also detect the RAL related side effects. We see this as a groundbreaking advancement and a new hallmark for study design inclusion criteria for treatment-experienced patients. In the future, the DDC will request that whenever possible, sponsors of all new antiviral compounds permit the use of appropriate experimental antiviral drugs in trials involving treatment-experienced patients. We also hope that the agency will require such innovative designs in future trials in treatment-experienced patients where appropriate.

WHAT ARE THE BENEFITS OF RAL?

The BENCHMRK 1 and 2 studies enrolled 350 and 349 people respectively, with triple-class drug failure defined as genotypic/phenotypic resistance to one or more drugs in each of three oral classes (NRTI, NNRTI, and PI), and HIV RNA viral load of more than 1000 copies/mL. The comparator arm included an optimized background therapy (OBT) plus placebo. Subjects were randomized to a RAL combination arm in a 2:1 ratio. The typical patient was male, in his mid-40s (~87% men), with a CD4+ cell count of ~153 cells/µL, and a baseline viral load of ~4.5 log HIV-1 RNA. Median duration of HIV therapy was ~10 years.

Although overall efficacy of RAL was superior to the comparator regimen, the efficacy varied depending on the activity of the OBT, defined by genotypic sensitivity scoring (GSS). Nevertheless, the RAL arm was superior to the comparator arm in each GSS category. With no active background agents, patients in the RAL arm did well, but with RAL plus one or two active drugs, the success rates were much greater, with up to 98% of viral loads at <400

copies/mL in patients using darunavir/r and enfuvirtide for the first time. Patients in the RAL arms also gained a mean of approximately 89 CD4 cells by week 24.

Since efficacy with RAL virtual monotherapy was much more limited, it appears that people will reap significant benefits from RAL when it is combined with at least one and preferably two active agents in the background regimen. Fortuitously, many people were able to combine RAL with new active drugs in the BENCHMRK studies. The results in the RAL subanalyses with one or two active agents and RAL with first-use of darunavir/r and/or enfuvirtide were astounding – up to 98% patients with viral loads of <400 copies/mL at 16 weeks.

Even the comparator arm achieved a record 33% of patients with viral loads of <50 copies/mL at week 24. This is a telling measure of the effectiveness of new antiviral therapies **AND** of allowing these heavily treated patients to use investigational agents like darunavir in these studies.

When the results of both BENCHMRK studies are combined, 37% of people in the RAL arms did not achieve virologic suppression below 50 copies/mL at week 24. We wonder if there is a subpopulation that will not benefit from RAL combination therapy and the effect of RAL resistance?

Sixteen percent (16%) of people were confirmed virologic failures in the RAL group by week 24. It will be very helpful to have mutation sequencing analyzed quickly. Based on limited data at this time, there appears to be primarily two distinct pathways to RAL resistance, involving the N155H and Q148K/R/H mutations. RAL resistance will hopefully be overcome by second generation integrase inhibitors since there appears to be significant cross-resistance to elvitegravir.

HOW SAFE IS RAL?

Preliminary data revealed that there was a significant imbalance of cancers between the RAL arm (10 cases), and the comparator group (1 case). The cancers included KS, lymphoma, squamous cell carcinoma, hepatocellular cancer and anal cancer. The sponsor claims that since more data has been collected in additional patients and the data has been adjusted for number of all patient years on RAL, the number of cancers in the RAL arm is no longer significantly larger than in the comparator arm. The agency must rigorously scrutinize the safety data in order to confirm these conclusions.

We wonder if any of the cancers were related to immune reconstitution syndrome (IRS). RAL viral load decreases occurred very rapidly in the first two weeks, much faster than in other HAART regimens. Could this rapid viral load decline actually cause IRS? We hope this phenomenon will be studied in the sponsor's trials in naïve patients. Of course, the cancers may be a consequence of the late stage nature of the trial participants. Long-term follow-up of RAL and anti-HIV

therapies are needed to effectively characterize such side effect signals.

All other related side effects, severe side effects, AIDS-defining events and lab abnormalities occurred with similar frequency across all groups, including placebo. There was no other safety-related RAL side effect signal. Adverse effects were generally mild to moderate in intensity. The most common adverse experiences (>10%) of all intensities reported in individuals receiving RAL, regardless of causality, were nausea, headache and diarrhea. In laboratory tests performed in routine monitoring during the studies, the most frequently reported laboratory adverse experiences (>3%), reported regardless of causality were increases in ALT, AST, triglycerides, and CPK.

Discontinuation due to adverse events was low. The BENCHMRK studies showed an overall ~1.6% rate; drug-related clinical adverse events were 47% at any grade; SAEs were 10%, and deaths were at 1.2%, all similar to the comparator arm. Investigator reported drug-related clinical adverse experiences of moderate or severe intensity included diarrhea (3.7%), nausea (2.2%), head ache (2.2%), and injection site reactions related to enfuvirtide (2.4%). In addition, using the DAIDS grading scale for laboratory abnormalities, grade 3 (2.6-5 X ULN) increases of bilirubin were seen in 3% of RAL subjects and 2.5% of the comparator group. Hypersensitivity was reported in 4 individuals in the RAL group; 2 people had therapy interrupted and upon re-challenge were able to resume RAL therapy; 2 had no interruption of therapy.

An analysis of correlated increases in serum bilirubin and ALT/AST liver functions was performed. No Hy's Law cases were identified. A QTc study also demonstrated that RAL did not prolong the QTc interval.

Due to its unique metabolic pathway, there are far fewer drug interaction issues. This is also very welcome news.

EXPANDED ACCESS PROGRAM (EAP)

We applaud the sponsor for its efforts to provide access to salvage patients in its EAP. Over 5,000 people were enrolled in the EAP in less than 10 months. This also provides us with a long awaited real time snapshot of the number of salvage patients in need of rescue therapy. An analysis of the safety data from the program should provide further insight into RALs toxicity/tolerability profile.

ACCELERATED APPROVAL?

The DDC believes that Merck's application for accelerated approval of RAL to treat antiretroviral-experienced patients with multi-class resistance should be approved, provided that the sponsor accepts the recommendations below, and initiates and timely completes the studies recommended below that include

follow-up periods sufficient to capture expected and non-expected side effect signals.

RECOMMENDATIONS

1. More women are needed in HIV clinical trials. Only 13% of people in the BENCHMRK studies were women. A number more reflective of the HIV population (27-30%) is desirable. Post-marketing studies in women that better reflect this reality need to be conducted. The sponsor should work with the agency and the community to design Phase IV PK and safety studies in women.

2. Standard PK and safety studies in people with hepatic insufficiency and people with compromised livers are also needed.

3. Because RAL is a first-in-class agent, frequent liver function tests and bilirubin measures are mandatory and such requirements should initially be included in the label.

4. Since resistance seems to be such an important issue in the sustained effectiveness of RAL, the label should also recommend resistance testing to help guarantee that the largest number of individuals use the greatest number of active background drugs when initiating RAL therapy.

5. We urge the sponsor to initiate a campaign to inform both the HIV community and heath care providers about the need to use RAL whenever possible with at least one and preferably two active agent in order to maintain sustained RAL effectiveness.

6. Because RAL represents a new drug class, FDA should require follow-up longer than the 96 weeks planned by the sponsor to confirm that the neoplasms seen were not caused by RAL use and to establish longer-term RAL safety.

7. The EAP data should be analyzed and made public by the sponsor in an effort to better characterize RAL's side effect profile.

8. PK, safety and efficacy studies need to be undertaken in pediatric patients.

9. Although we fully understand that the agency has no role in drug pricing, we firmly believe that the DDC should be on record as concurring with the Fair Pricing Coalition in recommending that the WAC price of RAL should be comparable to the median or even the low end price of protease inhibitor therapies.

The DDC appreciates the opportunity to comment on this very important new and exciting addition to the anti-HIV armamentarium. We look forward to the accelerated approval of RAL and to working with the agency and the sponsor to accomplish the recommendations and Phase IV requirements we have outlined above.