Analysis of Protocol-Defined Virologic Failure Through Week 96 From a Phase 2 Trial (P011) of Islatravir and Doravirine in Treatment-Naive Adults With HIV-1 Infection

Background

- Islatravir (ISL, MK-8591) is the first nucleoside reverse transcriptase translocation inhibitor (NRTTI) in development for the treatment and prevention of HIV-1 infection.
- Doravirine (DOR) is a next-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) approved for the treatment of HIV-1.
- The combined attributes of ISL and DOR create the potential for a potent, simple, 2-drug regimen that may address some of the long-term safety and toxicity concerns of traditional regimens.

Current Analysis Objectives

Objective: To characterize participants who discontinued with protocol-defined virologic failure from the PARTNERS Phase 2b trial of islatravir (ISL) and doravirine (DOR) through week 96.

Protocol-Defined Virologic Failure (PDVF) is defined as:

- Viral rebound: HIV-1 RNA >200 copies/mL after initial response of HIV-1 RNA <50 copies/mL at any time during the study or
- Confirmation HIV-1 RNA >1 log increase from HIV-1 RNA nadir after a >1 log decrease in HIV-1 RNA baseline from any time during the study
- Nonresponse: 
  - >2000 copies/mL at any time from week 24 through week 48
  - Confirmed HIV-1 RNA >50 copies/mL at any time during the study

Initial PDVF HIV-1 must be confirmed by an additional measurement within 2 weeks

Figure 1. Virologic Outcomes at Week 96 (FDA Snapshot Approach)

The numerically lower response rates for ISL (2.25 mg) + DOR group was largely driven by discontinuations through week 48.

Table 1. Protocol-Defined Virologic Failure (PDVF) at Week 96

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline HIV-1 RNA &gt;200 copies/mL (%)</th>
<th>HIV-1 RNA &gt;50 copies/mL (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISL (0.25 mg) + DOR</td>
<td>5.6%</td>
<td>6.9%</td>
</tr>
<tr>
<td>ISL (0.75 mg) + DOR</td>
<td>10.6%</td>
<td>6.9%</td>
</tr>
<tr>
<td>ISL (2.25 mg) + DOR</td>
<td>2.2%</td>
<td>6.5%</td>
</tr>
</tbody>
</table>

Background: Protocol-defined virologic failure

- Nonresponder: Confirmed HIV-1 RNA ≥200 copies/mL at any time from week 24 through week 48 or confirmed HIV-1 RNA ≥50 copies/mL at week 48.
- Rates of PDVF were low, and all participants who discontinued due to PDVF had confirmed HIV-1 RNA <50 copies/mL at any time from week 24 through week 48.
- The protocol violation exclusionary criteria discontinued occurred at week 2.

Conclusions

- Participants who initiated on ISL+DOR in combination with 3TC and switched to ISL+DOR had high efficacy at week 96 as measured by HIV-1 RNA <50 copies/mL, comparable to that of DOR/3TC/TDF.
- Rates of PDVF were low, and all participants who discontinued due to PDVF had confirmed HIV-1 RNA levels <80 copies/mL.
- Between weeks 48 and 96 one participant discontinued due to PDVF.
- No participant in any treatment group met criteria for resistance testing (>400 copies/mL). During the limited 42-day follow-up period, 3 out of 7 participants who discontinued due to PDVF continued to have low-level viremia after switching to a new regimen.

Acknowledgments

We are grateful to all the trial participants, as well as the trial investigators and staff members, for their contributions to this study.

Principal Investigators:


References

1. Momsen J, et al. Islatravir (ISL, MK-8591) at doses of 0.25 mg, 0.75 mg, and 2.25 mg in combination with doravirine (DOR) was evaluated in two randomized phase 2 trials in treatment-naive and treatment-experienced HIV-positive adult subjects. Presented at Conference on Retroviruses and Opportunistic Infections (CROI) 2020.