Pharmacokinetic and 4-week safety/efficacy of dolutegravir (S/GSK1349572) dispersible tablets in HIV-infected children aged 4 weeks to <6 years: results from IMPAACT P1093

BACKGROUND

Dolutegravir (DTG) is recommended for first-line therapy for HIV-1 infection in adults due to its potency, high barrier to resistance, and tolerability. It is approved for children ≥6-24 months of age, in many settings. A 5 mg dispersible tablet (DTG DT) formulation is being evaluated in IMPAACT P1093, an ongoing phase 1/2 open-label pharmacokinetic (PK), safety, and dose-finding study. Here we present intensive PK and 4-week safety (primary outcome) and efficacy of the first doses of DTG DT tested in the youngest age-defined cohorts (V: 4 weeks to <6 months, IV: 6 months to <2 years, III: 2 to ≥6 years).

METHODS

On enrollment, children received DTG DT as monotherapy, or added to stable failing or empiric initial background regimens and dosed using weight band tables (Table 1). Intensive 24-hour PK sampling was completed between days 5-10, after which background regimens were optimized based on enrollment genotypes. Safety, tolerability, and plasma HIV RNA levels were assessed through week 4 (Figure 1). From adult data, targets range for geometric mean (GM) exposures were AUC$_{24h}$ 600-4610 (mg/L) and C$_{24h}$ 750 (500-2260) ng/mL.

RESULTS

BASELINE CHARACTERISTICS

In P1993 32 children were enrolled to achieve 30 (10 per age cohort) with evaluable data.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td>20 (10)</td>
<td>0-63</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>4 (4)</td>
<td>0.8-9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cohort</th>
<th>N (%)</th>
<th>Age (months)</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>1207 (55%)</td>
<td>0-63</td>
<td>4 (4)</td>
</tr>
<tr>
<td>III</td>
<td>61 (44%)</td>
<td>0-63</td>
<td>4 (4)</td>
</tr>
<tr>
<td>V</td>
<td>51 (38%)</td>
<td>0-63</td>
<td>4 (4)</td>
</tr>
</tbody>
</table>

PK

The GM AUC$_{24h}$ and C$_{24h}$ of each cohort were within target range, except for the C$_{24h}$ value in Cohort III (Table 1). From adult data, targets range for geometric mean (GM) exposures were AUC$_{24h}$ 48 (37.6-66) mg/L and C$_{24h}$ 750 (500-2260) ng/mL.

<table>
<thead>
<tr>
<th>Cohort</th>
<th>AUC$_{24h}$ (mg/L)</th>
<th>C$_{24h}$ (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>4.0 (2.0-6.0)</td>
<td>61 (44%)</td>
</tr>
<tr>
<td>III</td>
<td>1.2 (0.8-1.6)</td>
<td>711 (60%)</td>
</tr>
<tr>
<td>V</td>
<td>1.0 (0.8-1.6)</td>
<td>1207 (55%)</td>
</tr>
</tbody>
</table>

DISCUSSION OF PK FINDINGS

The 5 mg and 10 mg DT doses assessed in the youngest children (Cohort IV, 4 weeks to 6 months) achieved exposures comparable to adults. Enrolment into this cohort at these doses continues. The DTG doses assessed in children aged 6 months to <6 years (Cohorts III and IV) generally achieved doses in the protocol-defined range, however the C$_{24h}$ values trended lower. Higher doses in these cohorts are currently under assessment. Exposures in children in the 6 to <12 kg weight band were higher in younger children (i.e. <6 months of age). The age effect observed is not unexpected as clearances can be higher in older children (i.e. 2 to 6 years) compared to infants (Anderson & Holford, 2008).

REFERENCES AND RELATED ABSTRACTS


Conclusions

Data from these study cohorts will inform dosing of DTG DT in HIV-infected children 4 weeks to <6 years of age.

Because the dispersible tablet is a new pediatric formulation of DTG, the feasibility of administration and acceptability were assessed. Few issues with administration of the dispersible tablet were reported. The dispersion was well accepted by the children in this study.

ACKNOWLEDGEMENTS

The authors wish to acknowledge the full P1093 protocol team, NICHD and NIAID, ViiV Healthcare, and the P1093 sites and staff, and the P1093 participants and caregivers.

ADDITIONAL RESOURCES


ACKNOWLEDGEMENTS

The authors wish to acknowledge the full P1093 protocol team, NICHD and NIAID, ViiV Healthcare and GSK, the P1093 sites and staff, and the P1093 participants and caregivers.

REFERENCES AND RELATED ABSTRACTS


Conclusions

Data from these study cohorts will inform dosing of DTG DT in HIV-infected children 4 weeks to <6 years of age.

Because the dispersible tablet is a new pediatric formulation of DTG, the feasibility of administration and acceptability were assessed. Few issues with administration of the dispersible tablet were reported. The dispersion was well accepted by the children in this study.

ACKNOWLEDGEMENTS

The authors wish to acknowledge the full P1093 protocol team, NICHD and NIAID, ViiV Healthcare and GSK, the P1093 sites and staff, and the P1093 participants and caregivers.

REFERENCES AND RELATED ABSTRACTS


Poster Number: LPB823