RESULTS of the meta-analysis are presented in forest plots below:

**DSS + PPD SMO Broad Search: PI vs INSTI**

### Table 1: Summary of Trials

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>Total Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>START/MRK (Protocol 001)</td>
<td>563</td>
</tr>
<tr>
<td>GS-US-236-0102 (EFV + FTC/CTD)</td>
<td>700</td>
</tr>
<tr>
<td>GS-US-236-0103 (EVG + COB/FTC/CTD)</td>
<td>708</td>
</tr>
</tbody>
</table>

### Table 2: Summary of Frequently Reported NPAEs (Unweighted Totals)

<table>
<thead>
<tr>
<th>NPAE</th>
<th>INSTI vs PI</th>
<th>INSTI vs EFV</th>
<th>Risk Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression and Suicide/Self Injury (DSS SMO)</td>
<td>9.5% (3.8%, 15.2%)</td>
<td>10.9% (4.9%, 16.9%)</td>
<td>-1.4% (-6.3%, 3.5%)</td>
</tr>
<tr>
<td>Psychosis and Psychotic Disorders (PPD SMO)</td>
<td>13.1% (9.0%, 17.2%)</td>
<td>12.1% (8.1%, 16.1%)</td>
<td>-1.0% (-6.0%, 4.0%)</td>
</tr>
</tbody>
</table>

### Methods

**Background**

- There are currently 3 FDA approved Integrase Strand Transfer Inhibitors (INSTIs): raltegravir (RAL, approved 2007), elvitegravir (EVG, approved 2012 in a fixed dose combination tablet), and dolutegravir (DTG, approved 2013).
- INSTIs are a component of most recommended ART regimens in The Department of Health and Human Services HIV Treatment Guidelines for adults and adolescents [1], primarily because of their potent antiretroviral activity and favorable safety profile, as characterized in clinical trials.
- However, neuropsychiatric adverse events (NPAEs) were reported both pre- and post-marketing, including published reports in the medical literature describe new-onset or worsening of NPAEs among patients treated with INSTIs [2,3,4].
- FDA conducted a meta-analysis of clinical trial data to further evaluate the association between INSTIs and NPAEs.

**Design and Population**

- FDA conducted a meta-analysis of 5 randomized, double-blind, active-controlled Phase 3 trials in treatment-naive subjects (TN) comparing INSTIS (RAL, EVG, or DTG) vs elvitegravir (EVG) or ritonavir-boosted protease inhibitors: atazanavir or darunavir (ATV/r; DRV/r) [Table 1].
- Trials that did not have a head-to-head comparison of the treatments of interest were not included in the meta-analysis.
- NPAEs were identified using a standardized MedDRA Query (SMQ) Version 18.0. A broad search for terms in the Depression and Injury (DSS SMQ) and the Psychosis and Psychotic Disorders (PPD) SMQ was done. The event of highest toxicity grade was counted for each subject.

**Results**

- The adverse event of highest toxicity grade was counted for each subject.
- NPAEs during the first 96 weeks of treatment were identified using a broad search for preferred terms in two Standardized MedDRA Queries (SMQs) Version 18.0: Depression and Injury (DSS SMQ) and Psychosis and Psychotic Disorders (PPD) SMQ.
- The adverse event of highest toxicity grade was counted for each subject.
- Overall risk difference for INSTIs vs EFV and PI vs EFV was computed based on fixed effects and random effects analyses using inverse variance weights in both models. In the random effects model (DerSimonian-Laird estimate), the study variable was included as a random effect. Analyses were also performed by demographic subgroups (age, sex, race, region, and IV drug use).

**Conclusions**

- The meta-analysis shows the risk of NPAE in TN patients was similar for INSTIs vs EVF and INSTIs vs PI. The risk difference (95% CI) for DSS AEs and PPD AEs was: INSTIs vs EVF -3% (-5.0% and -1.2%) and INSTIs vs PI -2% (-4.4% and 0.2%).
- Results were identified for the fixed and random effects analyses. Grade 3 and 4 events occurred in 1% of INSTI and PI subjects and 2% of EVF subjects. Subgroup analyses were not interpretable due to small sample size (Table 2).

**Results**

- The majority of NPAEs were in the DSS SMO. PPD events were infrequent: Percent of Subjects with DSS events: INSTI 9.5%, PI 10.9%, EFV 13.1%.
- Percent of Subjects with PPD events: INSTI 0.4%, PI 0.9%, EFV 1.4%.
- Results of the secondary analysis are summarized in Table 2.

**Conclusions**

- Results of the meta-analysis demonstrate that the risk of NPAEs is similar for subjects treated with INSTIs compared to EFVs, with a trend towards higher risk for INSTIs relative to EVF.
- The risk for NPAEs is similar between INSTIs and PIs.
- Depression was the most frequently reported NPAE in all three ARV classes and accounts for the majority of NPAEs observed overall.
- Studies were not interpretable due to the infrequent events and may not be indicative of a trend across all trials and treatment groups.
- Analyses were unable to identify subgroups at increased risk for NPAEs.
- The relationship between ART and NPAEs remains confounded by numerous factors that were not evaluated, including exposure to concomitant medications, presence of pre-existing neuropsychiatric illness, and social stressors.
- In conclusion, although NPAEs were infrequent and risk was not increased with INSTIs, providers should be aware of the association between HIV infection, ART, and NPAEs.