Influence of CYP2B6 Pharmacogenetics on Stereoselective Inhibition and Induction of Bupropion Metabolism by Efavirenz in Healthy Volunteers.

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Running Title: Stereoselective bupropion-efavirenz drug interactions
Supplemental Table 1: Inclusion and Exclusion Criteria

I. Inclusion Criteria:

Subjects were included if they:

- Were 18 to 49 years old healthy (as decided from a pre-enrollment screening session described above) male and female participants within 32% of their ideal body weight.
- Were individuals who agree to refrain from taking any prescriptions medications, over-the-counter medications, hormonal agents, and herbal, dietary, and alternative supplements that may interact with the metabolism of those study drugs at least 2 weeks prior to the start of the study and until study completion.
- Were nonsmoker or individuals willing to refrain from smoking or use of tobacco or marijuana for at least one month prior to and until the completion of the study (the entire study lasts for approximately 38 days).

II. Exclusion Criteria:

Subjects were not allowed to participate in the study if they:

- were underweight (weigh less than 52 kg or 114 lb) or overweight [body mass index (BMI) greater than 32].
- had history or current alcohol or drug abuse (more than 4 alcoholic drinks per day on a regular basis).
- had history of intolerance, allergic reactions (e.g. rash) or other forms of hypersensitivities to any of the study medications (efavirenz, montelukast, bupropion and rosuvastatin).
- had history or current significant health conditions such as heart, liver, or kidney.
- had history or current psychiatric illness such as depression, anxiety, or nervousness that may be exacerbated by participation in study.
- had a history of suicidality including suicide attempts.
- had history or current gastrointestinal disorders such as persistent diarrhea or malabsorption that would interfere with the absorption of orally administered drugs.
- had a serious infection within the last week before study enrollment.
- had a baseline EKG reading that is abnormal that could place the patient at the higher risk as decided by the study medical doctor (MD)
- had donated blood within the past two months.
- had blood results that do not fall in a healthy range (e.g., blood hemoglobin less than 12.0 mg/dl).
- were taking on regular basis substances that may interfere with the metabolism (breakdown) of study medications by the body, including prescription medications, over the counter, herbal or dietary supplements, alternative medications, or hormonal agents (i.e. oral contraceptives, intra-uterine device with hormones).
- were female with a positive pregnancy urine test (indicating that you are pregnant) obtained just prior to each study.
- were female breastfeeding.
- were child-bearing potential unable or unwilling to either practice abstinence or use two non-hormonal forms of birth control (e.g., condom, contraceptive foams) up until the study completion, which will take a total of 38 days.
- had a lifestyle that places subjects at a higher risk for contracting HIV (e.g. drug abuse, excessive alcohol drinking, and having multiple sexual partners).
- had a history or current HIV infection.
- had participation in a research study or use of an investigational drug in the last one month.
- were employed or are student under supervision of any of the investigators of this study.
- were unable to state a good understanding of this study including risks and requirements; are unable to follow the rules of this study.
- were unable to commit the time requested for this study.
**Supplemental Table 2: Participant Demographics of Completed subjects (N=53)**

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<thead>
<tr>
<th></th>
<th>Men (n=29)</th>
<th>Women (n=24)</th>
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</thead>
<tbody>
<tr>
<td><strong>Age (years), median [range]</strong></td>
<td>23 [18-49]</td>
<td>23 [19-47]</td>
</tr>
<tr>
<td><strong>Height (cm), mean (SD)</strong></td>
<td>177.6 (7.0)</td>
<td>162.6 (7.2)</td>
</tr>
<tr>
<td><strong>Weight (kg), mean (SD)</strong></td>
<td>80.6 (12.5)</td>
<td>62.0 (7.9)</td>
</tr>
<tr>
<td><strong>BMI (kg/m^2), mean (SD)</strong></td>
<td>25.5 (3.2)</td>
<td>23.4 (2.5)</td>
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<td><strong>Self-identified race (n)</strong></td>
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<td>Caucasian</td>
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<td>5</td>
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<tr>
<td>Mixed</td>
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<tr>
<td>Non-Hispanic/Latino</td>
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<td>20</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
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<td>4</td>
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<td><strong>CYP2B6 genotype</strong></td>
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<tr>
<td>*1/*6</td>
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<tr>
<td>*6/*6</td>
<td>5</td>
<td>1</td>
</tr>
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</table>
Supplemental Figure 1: Enrollment Report

Phone pre-screen (N = 486)
- Phone pre-screen failed (N=293)
  - Failed (N=265)
  - Withdrew (N=28)
- Phone screen approved (N = 193)
- No show/withdraw at ICRC screen visit (N=68)
- ICRC screen visit (N = 125)
- Failed/withdraw ICRC screen (N=55)
  - Failed (N=36)
  - Withdrew (N=19)
- Enrolled (N = 70)
- Partially completed (N=17)
  - Consent withdrawn (N=8)
  - Difficulty with blood draw (N=4)
- Completed (N = 53)
Supplemental Figure 2. CYP2B6 Genotype-dependent ratios of concentration of racemic 4-hydroxybupropion (OHBUP) : concentration of racemic bupropion (BUP). Upper panel, concentrations up to 120 hours post dosing; and lower panel, concentrations up to 24 hours post dosing are shown. Each point represents geometric mean, with 95% confidence interval.
Supplemental Figure 3: CYP2B6 Genotype-dependent ratios of 0-120 hrs. concentration of RR-4-hydroxybupropion (RR-OHBUP) : concentration of R-bupropion (BUP) (upper panel); and 0-120 hrs. concentration of SS-4-hydroxybupropion (SS-OHBUP) : concentration of S-bupropion (S-BUP) (lower panel). Insets are 0-24 hrs. ratios of metabolite/parent drug. Each point represents geometric mean, with 95% confidence interval.
Supplemental Figure 4: Concentration ratios (full 0-120 hrs., and inset, 0-24 hrs.,) of each stereoisomer pair: R-BUP/S-BUP, R-bupropion/S-bupropion; RR-OHBUP/SS-OHBUP, RR-4-hydroxybupropion/SS-4-hydroxyBUP; RR-THBUP/SS-THBUP, RR-threohydrobupropion/SS-threohydrobupropion; and SR-EHBUP/RS-EHBUP, SR-erythrohydrobupropion/RS-erythrohydrobupropion. Each point represent geometric mean.