Pharmacokinetics of VM1500A Long Acting Injectable Formulations for HIV-1 Infections Treatment and Prevention after Repeat-Dose Administration in Dogs

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1. BACKGROUND

VM1500A is a new, potent non-nucleoside HIV-1 reverse transcriptase inhibitor (NNRTI). Its orally-bioavailable prodrug, Efuslavirine (Efudexâ„¢, VM100), is currently marketed in Eastern Europe as an oral QD regimen for HIV/AIDS treatment. Unique pharmacokinetic properties (7.2±3.9 days) of VM1500A suggest a possibility for long-acting formulation development.

2. MATERIALS & METHODS

Polymer analysis of VM1500A resulted in selection of 2 aqueous nanosuspensions of VM1500A polymers with 2 specific particle size distribution and development of corresponding formulations. Formulation safety and pharmacokinetics (PK) were studied in beagle dogs, following three once-monthly 10 mg/kg dose administration by intramuscular (IM) injection. Three animals per group were used for each formulation. Blood samples were collected frequently up to 72 h after administration and every week up to 3 months after last administration. VM1500A plasma concentrations were measured using LC-MS/MS.

3. RESULTS

VM1500A Advantage for LAI Development: Prolonged HalfElimination Time

Figure 1. Treatment-naïve HIV-infected patients received 30 or 40 mg oral doses of Efuslavirine QD for 7-days

<table>
<thead>
<tr>
<th>Parameter</th>
<th>30 mg (n=10)</th>
<th>40 mg (n=10)</th>
</tr>
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<tbody>
<tr>
<td>Plasma (ng/mL)</td>
<td>1.65±0.3</td>
<td>4.3±0.8</td>
</tr>
<tr>
<td>AUC (ng*h/mL)</td>
<td>11.1±1.9</td>
<td>25.6±4.8</td>
</tr>
<tr>
<td>Mean (ng/mL)</td>
<td>1.65±0.3</td>
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The half-elimination time suggests the potential for once weekly oral dosing as well as an advantage for long-acting injectable (LAI) formulations development.

4. RESULTS (cont.)

LAI formulation development: PK Study in Dogs

Figure 2. Proof-of-concept that VM1500A nanosuspensions could be developed into long-acting injectable (LAI) formulations

Figure 4. VM1500A-LAI PK in plasma. Doses, 10 mg/kg IM, Lot740-1-141

5. CONCLUSIONS

This study supports further development of VM1500A long-acting injectable formulations to enable infrequent dosing. It was discovered that variation of a particle size affects pharmacokinetic properties. Future formulation development will be directed at decreasing the particle size and increasing the half-elimination time of the substance, which can potentially allow for a once per quarter administration. This new development is very promising for both HIV treatment and prevention.