The Pharmacokinetics of AVN-205 and its Metabolites, M1 and M2, in Humans Following Escalating Single Oral Doses

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Abstract

Objectives: To determine the pharmacokinetics of AVN-205 and its main metabolites, M1 and M2, in healthy volunteers following escalating single oral doses of AVN-205.

Introduction

AVN-205, a potent multi-target small molecule, is being developed by Avineuro Pharmaceuticals for the treatment of neurological disorders. Neurological disorders are a group of quite diverse, chronic and often disabling disorders that involve the central nervous system, the peripheral nervous system and the autonomic nervous system. This work presents the PK of AVN-205 and its main metabolites, M1 and M2, in healthy volunteers following escalating single oral doses of AVN-205.

Materials and Methods

A. Study
A healthy, volunteers, open-label, single-escalating oral dose, tolerability and pharmacokinetic study of AVN-205.

B. Dose
Four groups of eight subjects each were dosed orally with either 2, 4, 10 or 20 mg AVN-205.

C. Analytical Method
The plasma was analyzed for AVN-205, M1 and M2 by validated HPLC-MS/MS assay. The assay measures concentrations for the three analytes ranging from 10.0 to 2,050 pg/mL using 50.0 μL of plasma for extraction. Chromatograms for the LLOQ standards of AVN-205, M1, M2 and IS, are displayed in Figure 1.

D. PK Analysis
Cmax, Tmax, terminal half-life (T1/2) and AUC0-∞ were determined by standard model-independent methods. The harmonic mean half-life (T1/2) ranged from 2.48 to 3.85 hours. The dose-normalized Cmax and AUC0-∞ for AVN-205 and M1 also supported PK linearity.

Results and Discussion

AVN-205
Following single oral doses of AVN-205, AVN-205 was absorbed rapidly with median T1/2 ranging from 0.625 to 1.00 hour (Table 1 Figure 2).

AVN-205 exposure (Cmax and AUC0-∞) increased linearly as a function of the administered dose (Table 1 and Figures 3 and 4).

Table 1

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Cmax (pg/mL)</th>
<th>AUC0-∞ (μg h/mL)</th>
</tr>
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<tbody>
<tr>
<td>2</td>
<td>5.79</td>
<td>22.9</td>
</tr>
<tr>
<td>4</td>
<td>22.9</td>
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<tr>
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<td>53.7</td>
<td>220</td>
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<tr>
<td>20</td>
<td>220</td>
<td>843</td>
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</table>

Conclusions:

AVN-205 and M1 exhibited favorable PK in humans while M2 concentrations were markedly low. AVN-205 was rapidly absorbed and its T1/2 supports either QD or BIQ dosing. The metabolite M1 appeared rapidly in plasma and had higher concentration than AVN-205. The PK of AVN-205 and M1 in human were proportional to AVN-205 dose.

References


[Image 1: Chromatograms of a LLOQ Standard (10.0 pg/mL) for AVN-205, M1, M2 and IS.]

[Image 2: Mean Plasma Concentrations (pg/mL) of AVN-205, M1 and M2 in Humans Following Escalating Single Oral Doses of AVN-205 at 2, 4, 10 or 20 mg.]

[Image 3: Mean Cmax (pg/mL) of AVN-205, M1 and M2 in Humans Following Single Oral Doses of AVN-205 at 2, 4, 10 or 20 mg.]

[Image 4: Mean AUC0-∞ (μg h/mL) of AVN-205, M1 and M2 in Humans Following Single Oral Doses of AVN-205 at 2, 4, 10 or 20 mg.]

[Figure 1: Chromatograms of a LLOQ Standard (10.0 pg/mL) for AVN-205, M1, M2 and IS, in Human Plasma.]

[Figure 2: Mean Plasma Concentrations (pg/mL) of AVN-205, M1 and M2 in Humans Following Escalating Single Oral Doses of AVN-205 at 2, 4, 10 or 20 mg.]