Pharmacokinetics of Accordion Pill® Carbidopa/Levodopa Following Multiple Doses in Patients With Parkinson’s Disease

C. Warren Olanow1, Fabrizio Stocchi1, Mike Leinonen1, Nadav Navon1, Jeffrey A. Meckley2, R. Michael Gendreau2,3
1Cintrex LLC, Sarasota, FL, US; 2IRCSS San Raffaele Pisana, Tosinest Sanita, Rome, Italy; 3Intec Pharma, LTD, Jerusalem, Israel; 4Intec Pharma, Inc, New York, NY, US

BACKGROUND

Parkinson’s disease (PD) is a progressive neurodegenerative disorder that affects approximately 8 million people worldwide. Levodopa (LD) therapy is the gold standard for the treatment of motor fluctuations in PD, a condition that affects about 60% of PD patients within 10 years of diagnosis. However, motor complications such as dyskinesias continue to impact patients’ quality of life despite current therapeutic interventions. The Accordion Pill® (AP; Intec Pharma, Inc, New York, NY, US) is a novel drug formulation comprising multilayer films containing carbidopa (CD) as well as levodopa (LD) that is designed to deliver LD in a more continuous manner, thereby potentially minimizing motor fluctuations associated with standard levodopa therapy.

OBJECTIVE

To determine if AP-CD/LD provides a more consistent delivery of LD than IR-CD/LD, with the goal of reducing motor complications associated with CD/LD therapy in patients with PD.

STUDY DESIGN

This was an open-label, cross-over, pharmacokinetic (PK) study comparing AP-CD/LD 50/500 mg TID and IR-CD/LD 37.5/150 mg 5x daily in patients with PD (Figure 2).

PK samples were collected pre-dose (0 min) and at 30-minute intervals post-dose over 16 hours and again at 24 hours post-dose.

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RESULTS

AP-CD/LD Pharmacokinetics

- Primary Endpoint: Treatment with AP-CD/LD resulted in significantly less variability in stead-state LD plasma levels as compared to IR-CD/LD therapy, with a mean (95% confidence interval) FI4-16h difference of -0.63 (-1.03, -0.24; P=0.0057) (Table 2).

- Key Secondary Endpoint: Results were consistent with the primary endpoint, with a mean (95% confidence interval) CV4-16h difference of -11.2 (-22.2, -0.2; P=0.047) (Table 2).

The primary endpoint was the coefficient of variation (CV): standard deviation of plasma LD concentrations divided by the average concentration.

Multiple sensitivity analyses were performed.

Safety and Tolerability

- No statistically significant findings on laboratory tests, vital signs, or physical/neurological examinations were observed.

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CONCLUSIONS

- AP-CD/LD 50/500 mg TID provided stable plasma LD levels comparable to standard IR-CD/LD 37.5/150 mg 5x daily.

- AP-CD/LD was well tolerated, with no new safety signals.

- These results suggest that treatment with AP-CD/LD may reduce motor complications in patients with advanced PD versus standard IR-CD/LD treatment.

REFERENCES


TABLE 1: Baseline Demographics and Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Safety and PK Population (N = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>68.9 (16.6)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td>7 (58.3)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>9 (75.0)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>25.8 (2.2)</td>
</tr>
<tr>
<td>MI (kg/m²), mean (SD)</td>
<td>25.8 (2.2)</td>
</tr>
<tr>
<td>Height, mean (cm)</td>
<td>167.0 (8.2)</td>
</tr>
<tr>
<td>Weight, mean (kg)</td>
<td>72.2 (10.6)</td>
</tr>
<tr>
<td>ECOG status, n (%)</td>
<td>2 (16.7)</td>
</tr>
<tr>
<td>Cognitive impairment, n (%)</td>
<td>2 (16.7)</td>
</tr>
<tr>
<td>Dementia, n (%)</td>
<td>1 (8.3)</td>
</tr>
</tbody>
</table>

TABLE 2: Primary and Key Secondary Pharmacokinetic Endpoints (PK Population)

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Day 1 (IR-CD/LD)</th>
<th>Day 8 (AP-CD/LD)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FI4-16h</td>
<td>1.59 (0.57)</td>
<td>1.38 (0.17)</td>
<td>0.0320</td>
</tr>
<tr>
<td>CV4-16h</td>
<td>55.0 (12.0)</td>
<td>43.8 (11.7)</td>
<td>0.0114</td>
</tr>
</tbody>
</table>

FIGURE 1: Accordion Pill®

FIGURE 2: Study Design

FIGURE 3: Plasma LD Concentration-Time Curve (PK Population)

FIGURE 4: Fluctuation Index at 2-hour Intervals (PK Population)

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