A Phase-1, 6-Month Open-Label, Dose-Ranging Pharmacokinetic Study in Stabilized Patients with Schizophrenia Following Risperidone Implant

By Ryan Dammerman, Sonnie Kim, Mathews Adera, Alex Schwarz

BACKGROUND

• Risperidone is a second-generation antipsychotic approved in the US and European Union for treatment of schizophrenia
• Traditional oral and injectable formulations of risperidone require frequent dosing,1,2 which poses a barrier to treatment compliance in the schizophrenic population, in which medication nonadherence rates range from 37% to 74%3
• This phase-1, 6-month, open-label, multisite, dose-ranging study evaluated the safety and pharmacokinetics (PK) of a long-acting subcutaneous risperidone implant (RI) in clinically stable subjects diagnosed with schizophrenia

METHODS

• This was a phase-1, 6-month, open-label, multisite, dose-ranging study (NCT01774435)
• Inclusion criteria included a DSM-IV diagnosis of schizophrenia; age ≥18 to ≤60 years; body mass index ≥18.5 to ≤35.0 kg/m²; and clinical stability on oral risperidone 4, 6, or 8 mg for 30 days prior to enrollment
• Exclusion criteria included a known hypersensitivity to any local amide anesthetic agent, polyurethane, or risperidone; hospitalization or acute crisis intervention


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for symptom exacerbation within 30 days prior to admission; a history of attempted suicide within the past year; a positive and negative syndrome scale total score of >75 at the screening visit; presence of any clinically significant skin disorder; and positive screen for substances of abuse at screening or history of abuse within the past 6 months as defined by DSM-IV criteria

- Subjects were stratified into 3 dosing groups based on preimplant oral dosing regimens
  - Subjects stable on 4-mg, 6-mg, or 8-mg daily oral risperidone received one 480-mg, one 480-mg plus one 240-mg (total 720 mg), or two 480-mg (total 960 mg) RI, respectively
  - On day 1, RIs were inserted in the inner aspect of the upper non-dominant arm
- Serial blood samples for assessment of the PK of oral risperidone were collected prior to implantation; serial PK samples for RI were collected beginning 2 hours postimplantation, once daily from days 2 to 14, and weekly for 22 weeks
- Risperidone and active metabolite, 9-hydroxy-risperidone (9-OH-risperidone), plasma concentrations were determined by validated liquid chromatography-tandem mass spectrophotometry
  - PK measures for average plasma concentration (C_{avg}), maximum plasma concentration (C_{max}), and concentration 24 hours following dosing (C_{trough}) were calculated for risperidone

### TABLE 1

<table>
<thead>
<tr>
<th>Demographic and Clinical Characteristics at Baseline</th>
<th>IMPLANT 480 MG (N = 10)</th>
<th>IMPLANT 720 MG (N = 10)</th>
<th>IMPLANT 960 MG (N = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, year Mean (SD)</td>
<td>45.2 (10.0)</td>
<td>41.3 (12.5)</td>
<td>40.3 (12.8)</td>
</tr>
<tr>
<td>Range (min–max)</td>
<td>27–56</td>
<td>25–56</td>
<td>24–60</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10 (100.0)</td>
<td>9 (90.0)</td>
<td>10 (100.0)</td>
</tr>
<tr>
<td>Female</td>
<td>0 (0)</td>
<td>1 (10.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>10 (100.0)</td>
<td>9 (90.0)</td>
<td>10 (100.0)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0 (0)</td>
<td>1 (10.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td>7 (70.0)</td>
<td>9 (90.0)</td>
<td>9 (90.0)</td>
</tr>
<tr>
<td>White</td>
<td>3 (30.0)</td>
<td>0 (0)</td>
<td>1 (10.0)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0)</td>
<td>1 (10.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>29.3 (3.97)</td>
<td>30.2 (3.90)</td>
<td>26.3 (4.03)</td>
</tr>
<tr>
<td>Range (min–max)</td>
<td>23.8–33.6</td>
<td>23.2–34.5</td>
<td>19.2–31.5</td>
</tr>
</tbody>
</table>

**Abbreviations:** BMI, body mass index; max, maximum; min, minimum; SD, standard deviation.
and 9-OH-risperidone following oral risperidone; plasma concentration at steady state (C_{ss}) was calculated for risperidone and 9-OH-risperidone following RI insertion.

- Adverse events (AEs) were documented from informed consent signature through follow-up visit on day 203.

RESULTS

- A total of 35 patients enrolled; 5 patients discontinued before implantation and were not included in the PK population.
- Ten subjects each were randomized to 480, 720, and 960 mg RI; 23 (65.7%) patients completed the study, of whom 9 subjects each received 480 and 720 mg RI and 5 subjects received 960 mg RI.

FIGURE 1

**Plasma Concentration-Time Profiles of Risperidone, 9-OH-Risperidone, and Total Active Moiety (Risperidone Plus 9-OH-Risperidone) Following A) Oral Risperidone 4 mg/day and B) Risperidone Implant 480 mg**

Notes: Inset in panel B shows expansion of days 0 to 14 without error bars. Error bars indicate SD. Abbreviations: 9-OH-risperidone, 9-hydroxy-risperidone; SD, standard deviation.
Subject demographics and baseline characteristics were balanced across the 3 dosing groups. Mean plasma concentrations of active drug following RI displayed a slow and steady increase with peak concentrations markedly lower than those of oral doses. Peak concentrations of active moiety occurred at day 21 for the 480 (28.9 ng/mL) and 960 mg (43.3 ng/mL) RI, and at day 56 for the 720 mg (38.4 ng/mL) RI. Plasma drug levels remained relatively stable throughout the study and were detectable at the last study day (day 180). Following oral risperidone administration, maximal concentrations were reached 2 to 3 hours postdose.
FIGURE 3

Plasma Concentration-Time Profiles of Risperidone, 9-OH-Risperidone, and Total Active Moiety (Risperidone Plus 9-OH-Risperidone) Following A) Oral Risperidone 8 mg/day and B) Risperidone Implant 960 mg

Notes: Inset in panel B shows expansion of days 0 to 14 without error bars. Error bars indicate SD. Abbreviations: 9-OH-risperidone, 9-hydroxy-risperidone; SD, standard deviation.

TABLE 2

Pharmacokinetic Parameters for Total Active Moiety (Risperidone Plus 9-OH-Risperidone) Following Oral Risperidone and Risperidone Implants

<table>
<thead>
<tr>
<th>Treatment</th>
<th>C_{MAX}</th>
<th>AUC_{0-24h}</th>
<th>C_{AVG}</th>
<th>C_{TROUGH}</th>
<th>C_{SS}</th>
</tr>
</thead>
<tbody>
<tr>
<td>480-mg RI/4 mg oral</td>
<td>53.3</td>
<td>724.6</td>
<td>34.4</td>
<td>19.6</td>
<td>19.1</td>
</tr>
<tr>
<td>720-mg RI/6 mg oral</td>
<td>82.8</td>
<td>1203</td>
<td>56.2</td>
<td>29.7</td>
<td>31.0</td>
</tr>
<tr>
<td>960-mg RI/8 mg oral</td>
<td>80.6</td>
<td>1177</td>
<td>54.9</td>
<td>32.8</td>
<td>32.7</td>
</tr>
</tbody>
</table>

Abbreviations: AUC_{0-24}, area under the concentration vs. time curve from time 0 to 24 hours; C_{avg}, average steady-state concentration; C_{max}, observed maximum plasma concentration; C_{ss}, plasma concentration at steady state; C_{trough}, concentration at 24 hours postdose.
Overall, 25 of 30 subjects (83.3%) in the safety population had at least one treatment-emergent AE (TEAE) during the study; most were considered mild to moderate in severity.

A total of 7 subjects (70.0%) with 480-mg RI, 10 subjects (100.0%) with 720-mg RI, and 8 subjects (80.0%) with 960-mg RI experienced TEAEs; 4 subjects (40.0%) in the RI 960 mg group discontinued study drug due to TEAEs.

CONCLUSION

• Mean peak concentrations of risperidone plus metabolite were numerically lower following RI relative to oral risperidone; steady-state risperidone and metabolite concentrations were similar to observed trough values for oral risperidone.
• Plasma active moiety concentrations reached therapeutic levels within approximately 2 days following implantation, and systemic drug concentrations associated with RI should be sufficient for maintenance treatment of schizophrenia for up to 6 months.
• The safety profile of RI was consistent with the known effects of risperidone or the implantation procedures.
• The constant concentrations of active moiety over 6 months post-implant, favorable safety profile, and preliminary efficacy suggest...
patients with schizophrenia may be successfully transitioned from oral risperidone to RI.

ACKNOWLEDGMENTS

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DISCLOSURES

Drs. Dammerman, Kim, Adera, and Schwarz are all current employees of Braeburn Pharmaceuticals.

REFERENCES

2. Risperdal® (risperidone) [prescribing information]. Janssen Pharmaceuticals, Inc. 2014.