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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/m^2; 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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Drs. Dammerman, MD, PhD, Kim, PharmD, Adera, MBChB, Schwarz, PhD. Braeburn Pharmaceuticals, Princeton, New Jersey.

To whom correspondence will be forwarded to the proper author or authors. Please address correspondence to editorial@medworksmedia.com, C/O Michael E. Thase, MD.

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 nondominant 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

Demographic and Clinical Characteristics at Baseline

	IMPLANT 480 MG (N = 10)	IMPLANT 720 MG (N = 10)	IMPLANT 960 MG (N = 10)
Age, year			
Mean (SD)	45.2 (10.0)	41.3 (12.5)	40.3 (12.8)
Range (min–max)	27–56	25–56	24–60
Sex, n (%)			
Male	10 (100.0)	9 (90.0)	10 (100.0)
Female	0 (0)	1 (10.0)	0.(0)
Ethnicity, n (%)			
Non-Hispanic	10 (100.0)	9 (90.0)	10 (100.0)
Hispanic	0 (0)	1 (10.0)	0 (0)
Race, n (%)			
Black or African American	7 (70.0)	9 (90.0)	9 (90.0)
White	3 (30.0)	0 (0)	1 (10.0)
Other	0 (0)	1 (10.0)	0 (0)
BMI, kg/m^2			
Mean (SD)	29.3 (3.97)	30.2 (3.90)	26.3 (4.03)
Range (min–max)	23.8–33.6	23.2–34.5	19.2–31.5

Abbreviations: BMI, body mass index; max, maximum; min, minimum; SD, standard deviation.

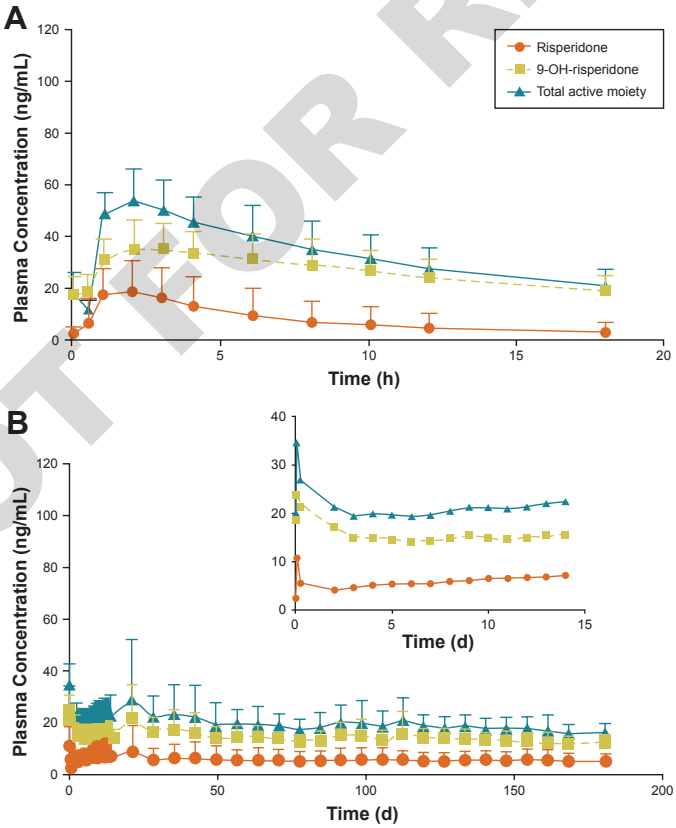
and 9-OH-risperidone following oral risperidone; plasma concentration at steady state (C_{ss}) was calculated for risperidone and 9-OH-risperidone following RI insertion
- Adverse events (AEs) were documented from informed consent signature through follow-up visit on day 203

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

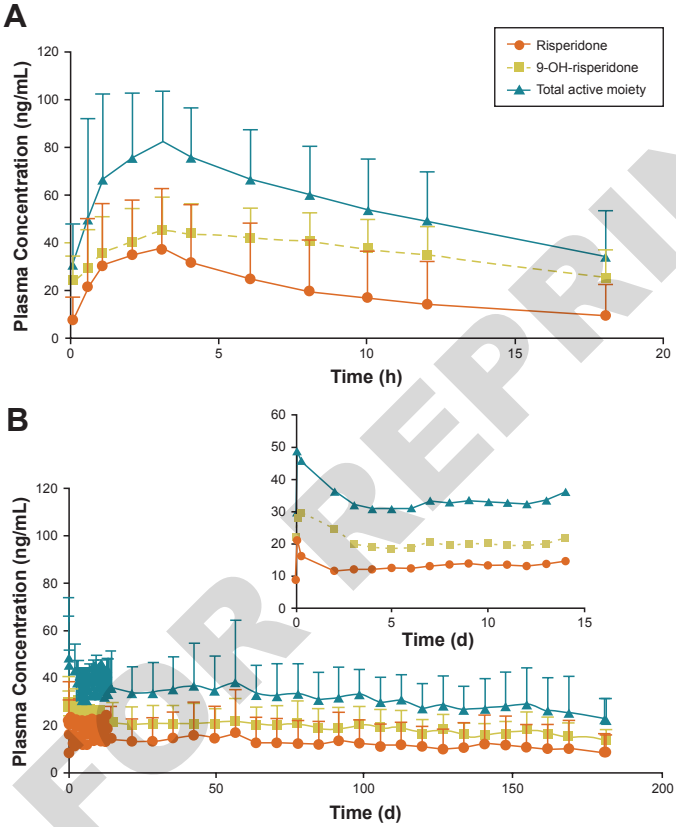
Plasma Concentration-Time Profiles of Risperidone, 9-OH-Risperidone, and Total Active Moiety (Risperidone Plus 9-OH-Risperidone) Following A) Oral Risperidone 4 mg/day and B) Risperidone Implant 480 mg



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.

FIGURE 2

Plasma Concentration-Time Profiles of Risperidone, 9-OH-Risperidone, and Total Active Moiety (Risperidone Plus 9-OH-Risperidone) Following A) Oral Risperidone 6 mg/day and B) Risperidone Implant 720 mg

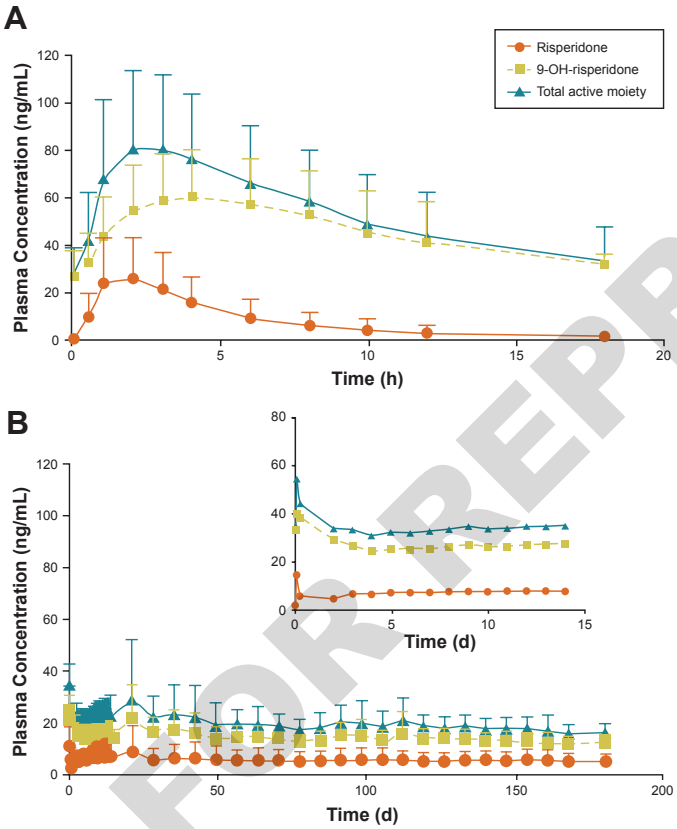


Notes: Inset in panel B shows expansion of days 0 to 14 without error bars. Error bars indicate SD.
Abbreviations: 9-OH-risperidone, 9-hydroxy-risperidone; SD, standard deviation.

- 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

	ORAL RISPERIDONE				IMPLANT
TREATMENT	C_{MAX} NG/ML	AUC_{0-24H} H*(NG/ML)	C_{AVG} NG/ML	C_{TROUGH} NG/ML	C_{SS} NG/ML
480-mg RI/4 mg oral	53.3	724.6	34.4	19.6	19.1
720-mg RI/6 mg oral	82.8	1203	56.2	29.7	31.0
960-mg RI/8 mg oral	80.6	1177	54.9	32.8	32.7

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.

TABLE 3

Summary of Treatment-Emergent Adverse Events Observed in ⩾5.0% of Subjects Overall

	480 MG RI (N = 10)	720 MG RI (N = 10)	960 MG RI (N = 10)
Incision site pain	1 (10.0)	7 (70.0)	4 (40.0)
Implant site hemorrhage	3 (30.0)	1 (10.0)	0 (0)
Incision site edema	0 (0)	4 (40.0)	0 (0)
Anxiety	1 (10.0)	2 (20.0)	1 (10.0)
Psychotic disorder	0 (0)	1 (10.0)	3 (30.0)
Implant site pain	1 (10.0)	0 (0)	2 (20.0)
Device difficult to use	0 (0)	3 (30.0)	0 (0)
Weight increased	2 (20.0)	1 (10.0)	0 (0)
Sluggishness	0 (0)	1 (10.0)	1 (10.0)
Incision site complication	2 (20.0)	0 (0)	0 (0)
Back pain	0 (0)	1 (10.0)	1 (10.0)
Dyspepsia	1 (10.0)	0 (0)	1 (10.0)
Vomiting	0 (0)	2 (20.0)	0 (0)
Schizophrenia	1 (10.0)	0 (0)	1 (10.0)

Note: Data presented as number (%).
Abbreviation: RI, risperidone implant.

- 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

1. Risperdal Consta® (risperidone) long-acting injection [prescribing information]. Janssen Pharmaceuticals, Inc. 2007.
2. Risperdal® (risperidone) [prescribing information]. Janssen Pharmaceuticals, Inc. 2014.
3. Morken G, et al. *BMC Psychiatry*. 2008;8:32.