Evaluation of Major Treatment Failures in Patients With Recent-Onset Schizophrenia: a Post Hoc Analysis From the Disease Recovery Evaluation and Modification (DREaM) Study

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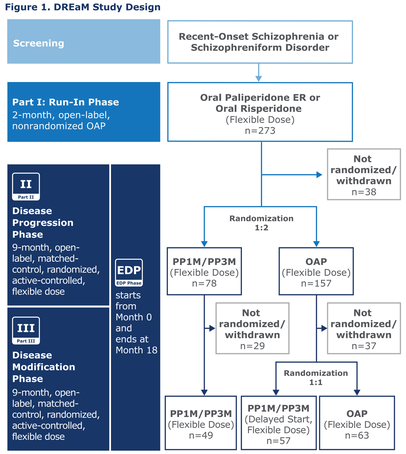
INTRODUCTION

- Relapse in the early stages of schizophrenia is often driven by nonadherence to oral antipsychotic medication and can have serious consequences, including psychiatric hospitalization and arrest/incarceration.[1-4] These outcomes are particularly relevant to public health because of their substantial economic and societal impact[4]
- Paliperidone palmitate (PP), available in once-monthly (PP1M)[5] and once-every-3-months (PP3M)[6] formulations, is a long-acting injectable antipsychotic indicated for the treatment of adults with schizophrenia
  - Real-world studies suggest that adult patients treated with PP have higher medication adherence and reduced risk of treatment failures, including hospitalization and arrest/incarceration, compared with patients treated with oral antipsychotics (OAPs)[4,7]
- An objective of the Disease Recovery Evaluation and Modification (DREaM, NCT02431702) study was to evaluate the effectiveness of PP versus OAPs in delaying disease progression as measured by time to first treatment failure (TtFTF) in participants with recent-onset schizophrenia or schizophreniform disorder
  - Treatment failure (TF) was defined as psychiatric hospitalization, suicidal/homicidal ideation, arrest/incarceration, medication discontinuation because of inadequate efficacy or safety/tolerability, treatment supplementation, or intervention to avert hospitalization
- The objective of this post hoc analysis of DREaM was to examine differences in time to first major treatment failure (TtFMTF), defined as psychiatric hospitalization or arrest/incarceration, between PP and OAPs

METHODS

- DREaM was a prospective, matched-control, double-randomized, open-label, flexible-dose, multicenter study that included 3 phases (**Figure 1**):
  - Part I: 2-month oral run-in
    - Participants received open-label, flexible-dose, oral paliperidone extended release (1.5-12 mg/day) or oral risperidone (1-6 mg/day) to establish tolerability before exposure to injectable PP
  - Part II: 9-month disease progression phase (PP or OAP)
    - Participants who had demonstrated adequate tolerability to oral paliperidone or risperidone in Part I were assigned to receive either PP or an OAP for 9 months in a 1:2 randomization ratio
  - Part III: 9 months of additional treatment in 3 groups
    - Participants who completed OAP treatment in Part II were matched and re-randomized to receive continued treatment with an OAP (OAP/OAP group) or to PP (delayed-start PP group, OAP/PP) in a 1:1 ratio
    - Participants previously assigned to treatment with PP in Part II continued with PP treatment in Part III (PP/PP group)
  - The Extended Disease Progression (EDP) phase began with the Part II start date (month 0) and continued through Part III. The EDP phase focused on comparisons between PP/PP and OAP/OAP in participants who received 18 months of consistent treatment with the same formulations of paliperidone during Parts II and III

Figure 1. DREaM Study Design



ER, extended release; EDP, extended disease progression; OAP, oral antipsychotic; PP, paliperidone palmitate; PP1M, paliperidone palmitate once monthly; PP3M, paliperidone palmitate once every 3 months.
In Part I, patients who tolerated oral paliperidone or risperidone but for whom paliperidone was inadequately effective (per clinical judgement) were eligible to be switched to another protocol-specified OAP: aripiprazole, haloperidol, perphenazine, quetiapine, or olanzapine. In Parts II and III, 9-month PP treatment was defined as PP1M for a minimum of 4 months (5 injections) followed by PP3M treatment. PP1M flexible dosing was 78 mg, 117 mg, 156 mg, or 234 mg. PP3M flexible dosing was 273 mg, 410 mg, 546 mg, or 819 mg.

- Key inclusion and exclusion criteria
  - Men and women aged 18-35 years
  - Current diagnosis of schizophrenia or schizophreniform disorder (DSM-5), confirmed by the Structured Clinical Interview for DSM-5 disorders and with a first psychotic episode within the past 24 months
  - Must have available a designated individual (eg, family member, significant other, friend) who also consents to participate in trial activities
  - Must not meet the DSM-5 definition of moderate or severe substance use disorder (except for nicotine) within 2 months before screening
- Major treatment failure (MTF)
  - Only MTF events that occurred after randomization in Part II and up to the end of Part III were assessed
  - MTF was determined by the investigator and defined as psychiatric hospitalization, arrest, or incarceration
- Safety was assessed by adverse event (AE) reporting, clinical laboratory tests, and physical examination
- Statistical methods
  - Efficacy and safety analyses were based on the intent-to-treat (ITT) analysis sets. Because there were different objectives for different periods of this study, separate ITT populations were defined. Analysis sets included all participants who received at least 1 dose of study medication (or any portion of the dose), regardless of their adherence to the protocol
  - TtFMTF in Part II, Part III, and EDP phases was examined first using log-rank test statistics. The cumulative distribution function of the TtFMTF was estimated by the Kaplan–Meier method, and the hazard ratio and 95% CI were provided based on Cox proportional hazards models
  - Reasons for TF, rates of treatment-emergent AEs (TEAEs), most common TEAEs (occurring in ≥10% participants), and discontinuations because of TEAEs were summarized
  - No adjustments were made for multiplicity

RESULTS

Disposition

- Participant disposition in each phase of DREaM is summarized in **Figure 1**
  - Part I: 273 participants entered, of whom 239 (87.5%) completed
  - Part II: 238 participants entered, of whom 78 were randomly assigned to receive PP, 157 were randomly assigned to receive an OAP, and 3 did not receive study drug; 52 PP participants (66.7%) and 128 OAP participants (81.5%) completed Part II
  - Part III: 169 participants entered, of whom 49 continued on PP, 57 were matched and re-randomized to PP (OAP/PP), and 63 were re-randomized to an OAP (OAP/OAP)
  - EDP: 112 participants entered (PP/PP: n = 49; OAP/OAP: n = 63), of whom 40 (81.6%, PP/PP) and 46 (73.0%, OAP/OAP) completed

Demographics

- Baseline demographics and disease characteristics were consistent across groups in Part II, Part III, and EDP phases (**Table 1**)
  - Most participants were male and had a diagnosis of schizophrenia; mean age was approximately 23 years (range, 23.0-24.1 years) and mean time since diagnosis was ≤1 year

Table 1. Demographic and Disease Characteristics in Part II, Part III, and EDP Phases

	II Part II		III Part III		EDP EDP Phase	
	PP n = 78	OAP n = 157	PP/PP n = 49	OAP/PP n = 57	OAP/OAP n = 63	PP/PP n = 49	OAP/OAP n = 63
Age, mean (SD), years	23.2 (4.38)	23.3 (4.44)	23.7 (4.65)	24.1 (4.85)	23.0 (4.30)	23.7 (4.65)	23.0 (4.30)
Sex, n (%)							
Male	62 (79.5)	125 (79.6)	41 (83.7)	46 (80.7)	47 (74.6)	41 (83.7)	47 (74.6)
Female	16 (20.5)	32 (20.4)	8 (16.3)	11 (19.3)	16 (25.4)	8 (16.3)	16 (25.4)
Race, n (%)							
White	38 (48.7)	69 (43.9)	24 (49.0)	24 (42.1)	23 (36.5)	24 (49.0)	23 (36.5)
Black/African American	28 (35.9)	54 (34.4)	17 (34.7)	21 (36.8)	25 (39.7)	17 (34.7)	25 (39.7)
Asian	4 (5.1)	8 (5.1)	2 (4.1)	2 (3.5)	4 (6.3)	2 (4.1)	4 (6.3)
Other[a]	8 (10.3)	26 (16.6)	6 (12.2)	10 (17.5)	11 (17.5)	6 (12.2)	11 (17.5)
Ethnicity, n (%)							
Hispanic or Latino	31 (39.7)	53 (33.8)	16 (32.7)	19 (33.3)	19 (30.2)	16 (32.7)	19 (30.2)
Not Hispanic or Latino	47 (60.3)	99 (63.1)	33 (67.3)	37 (64.9)	40 (63.5)	33 (67.3)	40 (63.5)
Unknown	0	5 (3.2)	0	1 (1.8)	4 (6.3)	0	4 (6.3)
Current diagnosis, n (%)							
Schizophrenia	61 (78.2)	120 (76.4)	41 (83.7)	43 (75.4)	49 (77.8)	41 (83.7)	49 (77.8)
Schizophreniform	17 (21.8)	37 (23.6)	8 (16.3)	14 (24.6)	14 (22.2)	8 (16.3)	14 (22.2)
Time since first psychotic episode, mean (SD), years	0.9 (0.65)	0.9 (0.59)	1.0 (0.66)	0.9 (0.57)	0.9 (0.62)	1.0 (0.66)	0.9 (0.62)
Prior psychiatric hospitalizations							
Total, mean (SD)	1.1 (1.24)	1.2 (1.11)	1.1 (1.30)	1.2 (1.11)	1.2 (1.12)	1.1 (1.30)	1.2 (1.12)
CGI-S, mean (SD)	3.3 (1.09)	3.3 (1.07)	3.0 (0.75)	3.1 (1.03)	2.9 (0.98)	3.3 (1.09)	3.2 (1.15)

CGI-S, Clinical Global Impression-Severity scale; OAD, oral antipsychotic; PP, paliperidone palmitate; SD, standard deviation.
[a]Other includes Other, American Indian/Alaskan Native, and Native Hawaiian/Other Pacific Islander.

Major Treatment Failure

- During Part II, 12.8% of participants in the PP group and 13.4% in the OAP group experienced a MTF (**Figure 2**)
  - There was no statistically significant difference in TtFMTF between groups (P = 0.918)
  - More participants had an FMTF because of psychiatric hospitalization than for arrest or incarceration: 4 (5.1%) versus 2 (2.6%) participants in the PP group and 11 (7.0%) versus 4 (2.5%) participants in the OAP group
- During Part III, no participants in the PP/PP group, 2 (3.5%) in the OAP/PP group, and 10 (15.9%) in the OAP/OAP group experienced a MTF (**Figure 3**)
  - The difference in TtFMTF among treatment groups was statistically significant (P = 0.021)
  - Risk of FMTF was 80% lower in participants in the OAP/PP group than in participants in the OAP/OAP group (HR [95% CI], 0.20 [0.04-0.92])
  - No participants in the PP/PP group, 2 participants (3.5%) in the OAP/PP group, and 8 participants (12.7%) in the OAP/OAP group had a psychiatric hospitalization, whereas no participants in the PP/PP and OAP/PP groups and 2 participants (3.2%) in the OAP/OAP group were arrested or incarcerated
- During the EDP phase, 10.2% of participants in the PP/PP group experienced an MTF compared with 25.4% in the OAP/OAP group (**Figure 4**)
  - The difference in TtFMTF between treatment groups was statistically significant (P = 0.045, Number Needed to Treat = 7)
  - The risk of FMTF was 63% lower in participants who received 18-month treatment with PP compared with those who received OAP (HR [95% CI], 0.37 [0.12-0.95])
  - FMTF because of psychiatric hospitalization was reported in 2 (4.1%, PP/PP) and 8 (12.7%, OAP/OAP) participants; arrest or incarceration was reported in no participants in the PP/PP group and in 3 participants (4.8%) in the OAP/OAP group

Figure 2. TtFMTF in Part II

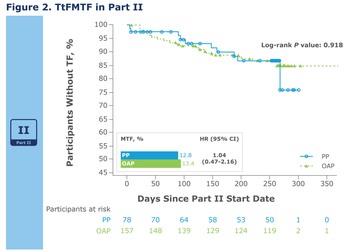


Figure 3. TtFMTF in Part III

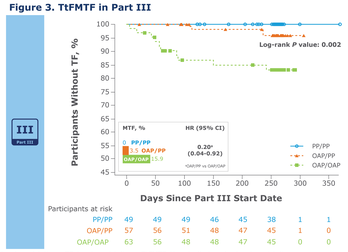
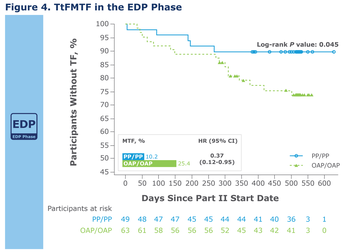


Figure 4. TtFMTF in the EDP Phase



CI, confidence interval; HR, hazard ratio; OAP, oral antipsychotic; PP, paliperidone palmitate; MTF, major treatment failure; TF, treatment failure; TtFMTF, time to first major treatment failure.

Safety

- Safety results were consistent with the known safety profile of PP in adult participants with schizophrenia,[4-6,8-10] and the safety profiles of PP and OAP were similar
- Overall, the percentages of participants who experienced at least 1 TEAE were similar across treatment groups
  - Part I: 57.9%
  - Part II: 76.9% (PP) and 76.4% (OAP)
  - Part III: 61.2% (PP/PP), 75.4% (OAP/PP), and 66.7% (OAP/OAP)
  - EDP: 91.8% (PP/PP) and 90.5% (OAP/OAP)
- Increased weight was the most common TEAE in Part I (16.1%), Part II (PP: 28.2%, OAP: 31.8%), Part III (PP: 16.3%, OAP/OAP: 11.1%, and OAP/PP: 17.5%), and EDP (PP/PP: 49.0%, OAP/OAP: 44.4%) phases
  - Although the percentage of participants who experienced weight gain was higher than that observed in previous PP trials, the rates in DREaM likely reflect the very early stage of disease course and the newness of the patient to treatment with antipsychotic medication
- The percentages of participants who experienced a serious AE were
  - Part I: 3.7%
  - Part II: 12.8% (PP) and 12.1% (OAP)
  - Part III: 2.0% (PP/PP), 5.3% (OAP/PP), and 12.7% (OAP/OAP)
  - EDP: 12.2% (PP/PP) and 20.6% (OAP/OAP)
- 1 patient (PP group) died during the study (inhalation of helium), where the investigator considered the causality to study medication to be doubtful. Another patient (OAP/PP) completed the study, and 9 days later, had a completed suicide. The investigator assessed the causality of this event to be doubtful

DISCUSSION

- This post hoc analysis of the DREaM study was conducted to evaluate the TtFMTF (psychiatric hospitalization or arrest/incarceration) in participants with recent-onset schizophrenia treated with PP versus OAP
- A large, persistent study effect was observed in Part I, possibly owing to increased early adherence to OAPs stemming from the involvement of a designated caregiver (inclusion criteria) and interactions at specialized treatment centers for first-episode schizophrenia
- No statistically significant difference in TtMTF was identified between groups in the first 9 months of treatment; however, with longer treatment (18-month extended disease progression phase; final 9 months of study), differences in TtFMTF became statistically significant, favoring PP
- The significant effects observed at the end of the study favoring PP suggest that, if introduced early in the course of illness, PP may improve long-term outcomes in schizophrenia

CONCLUSIONS

Although a statistically significant difference in time to first major treatment failure (psychiatric hospitalization or arrest/incarceration) between PP and OAP was not observed at the end of Part II, a statistically significant and clinically meaningful difference favoring PP was observed in Part III and the EDP phase

A large study effect was evident in the trial. However, data from this study suggest that, as time passes, the special study interventions do not sustain the degree of adherence necessary to prevent relapse

The results of this post hoc analysis suggest greater effectiveness of PP than OAPs in potentially improving long-term outcomes that are of particular relevance to public health in patients with schizophrenia

References

1. Kim B et al. *Schizophr Res Treatment*. 2012;2012:560836.
2. Emsley R et al. *BMC Psychiatry*. 2013;13:50.
3. Dufort A, Zipursky RB. *Clin Schizophr Relat Psychoses*. ePub Jan 3, 2019. doi: 10.3371/CSRP.ADRZ.121218.
4. Alphs L et al. *J Clin Psychiatry*. 2015;76(5):554-561.
5. Invega Sustenna (paliperidone palmitate) extended-release injectable suspension, for intramuscular use. Bearse, Belgium: Janssen Pharmaceutica NV; January 2019.
6. Invega Trinza (paliperidone palmitate) extended-release injectable suspension, for intramuscular use. Titusville, NJ: Janssen Pharmaceuticals Inc.; January 2019
7. Manjelievskaia J et al. *J Med Econ*. 2018;21(12):1221-1229.
8. Savitz AJ et al. *Int J Neuropsychopharmacol*. 2016;19(7):1-14.
9. Berwaerts J et al. *JAMA Psychiatry*. 2015;72(8):830-839.
10. Hough D et al. *Schizophr Res*. 2010;116(2-3):107-117.

Acknowledgments

The authors thank Susanna Bae, Madeline Pfau, and Lynn Brown of ApotheCom (Yardley, PA) for editorial and writing services, which were funded by Janssen Medical Affairs, LLC.

Disclosures

PB, BB, AO, and IT are employees of Janssen Pharmaceuticals, Inc., and hold stock in Johnson & Johnson, Inc. LA is a former employee of Janssen Pharmaceuticals, Inc. and holds stock in Johnson & Johnson, Inc.

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Supported by Janssen Scientific Affairs, LLC

Presented at the Psych Congress 2020 Virtual Experience; September 10-13, 2020