PFIZER INC.

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COMPOUND NUMBER: PF-02545920

PROTOCOL NO.: A8241012

PROTOCOL TITLE: A Phase 2, Multicenter, Double-Blind, Randomized, Parallel Group, 4-Week Inpatient Study to Evaluate the Safety and Efficacy of Two Fixed Doses of PF-02545920 Compared to Placebo in the Treatment of Acute Exacerbation of Schizophrenia Using Risperidone as an Active Control

Study Centers: Twenty-nine (29) centers took part in the study and randomized subjects; 22 in the United States (US) and 7 in Ukraine.

Study Initiation and Final Completion Dates: 18 October 2010 to 04 August 2011

Phase of Development: Phase 2

Study Objectives: The primary objectives were 1) to evaluate the efficacy of PF-02545920 in the treatment of acute exacerbation of schizophrenia during a 4-week double-blind treatment period using the Positive and Negative Syndrome Scale (PANSS) to measure change in symptoms from Baseline compared to placebo, 2) to evaluate the safety and tolerability of 2 fixed dose regimens of PF-02545920 in the treatment of acute exacerbation of schizophrenia, and 3) to evaluate the incidence rate of dystonia associated with 2 doses of PF-02545920 compared to placebo in the treatment of acute schizophrenia.

The secondary objectives were 1) to assess the efficacy of PF-02545920 in the treatment of acute exacerbation of schizophrenia using the: Clinical Global Impression of Improvement (CGI-I) and Clinical Global Impression of Severity (CGI-S), PANSS Subscales: positive, negative, general, PANSS derived Marder factor scores (positive, negative, disorganized thought, hostility/excitement and anxiety/depression), PANSS derived Brief Psychiatric Rating Scale (BPRS) core psychosis items (conceptual disorganization, hallucinatory behavior, suspiciousness and unusual thought content), Global Assessment of Function (GAF), and Treatment Satisfaction Questionnaire for Medication (TSQM).

METHODS

Study Design:

This was a double-blind, parallel-group, fixed-dose, placebo-controlled, risperidone referenced, multicenter, randomized study in subjects with a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision 2000 (DSM-IV TR™) diagnosis of schizophrenia, who were experiencing an acute exacerbation of schizophrenia at the time of admission to the study. The study consisted of an inpatient Screening period of up to

7 days during which subjects were assessed for eligibility and discontinued from prior antipsychotic and prohibited medications, a 2-day, single-blind, placebo lead-in period, a 28 day, double-blind, randomized, inpatient treatment period, an optional inpatient restabilization phase of up to 7 days during which currently marketed antipsychotic therapy was re-introduced, and a follow-up safety evaluation 7 to 10 days after the completion of the double-blind treatment period. The subjects were randomized in a 2:2:2:1 ratio to the 4 treatment groups: PF-02545920 5 mg every 12 hours (Q12H) for 28 days, PF 02545920 15 mg (dose titrated: 5 mg Q12H for 2 days, 10 mg Q12H for 2 days, and 15 mg Q12H for 24 days), placebo Q12H for 28 days, risperidone 3 mg (dose titrated: 1 mg Q12H for 2 days, 2 mg Q12H for 2 days, and 3 mg Q12H for 24 days).

The complete schedule of events is presented in Table 1.

Table 1. Schedule of Events

Study Activity	Screen	Placebo Lead-In	Day 1	Day 3	Day 5	Day 7 (±1 Day)	Day 13	Day 14 (± 1 Day)	D 21 (± 1 Day)	Day 28/ET[a] (± 1 Day)	Optional Inpatient Re-Stabilization Phase Day 29-36	Follow Up 7-10 Days After Last Dose (Day 28/ET)
	Day -8 to Day -2	Day -1 to Day 0										
Informed consent	X											
Demographics	X											
Psychiatric history	X											
MINI diagnostic interview	X											
Medical history	X											
Prior treatment and concomitant medication	X											
Physical examination	X									X		
Neurological examination	X									X		
Height	X											
Weight	X		X							X		
Abdominal girth			X							X		
Retained serum sample			X									
De-identified molecular profiling prep D1 sample[b]			X									
De-identified molecular profiling prep B1 sample[b]			X			X				X		
Safety laboratory assessments	X		X			X		X	X	X		X
Nonanonymous pharmacogenomic sample			X									

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	Day -8 to Day -2	Day -1 to Day 0										
Serum prolactin, HDL, LDL, cholesterol, triglycerides, HbA1c and insulin			X			X				X		
WBC and ANC monitoring 3 times per week[c]			X----------							----------X		
Urine drug screen[d]	X											
Serum/urine pregnancy test[e]	X		X					X		X		
Serum FSH[f]	X											
Hepatitis B and C serology	X											
Vital signs[g] (supine and standing BP and pulse rate, body temperature)	X		X			X		X	X	X		
Vital signs[g] (sitting BP and pulse rate, body temperature)		X									X	X
12-lead ECG (single)[h]	X							X		X		X
12-lead ECG (triplicate)[h]			X									
PK sample[i]						X		X	X	X	X	
BPRS[j]	X		X									
PANSS[j]	X		X			X		X	X	X		
CGI-S[j]	X		X			X		X	X	X		
CGI-I[j]						X		X	X	X		
ESRS-A[j]	X		X			X		X	X	X		
GAF[j]			X			X		X	X	X		

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	Day -8 to Day -2	Day -1 to Day 0										
TSQM										X		
C-SSRS[j]	X		X			X		X	X	X		X
SBQ-R	X											
Dispense medication (IVRS)		X[k]	X	X	X		X		X[l]			
Single-blind placebo dosing Q12H		X→										
Study drug dosing Q12H[m]			X----------							----------X[m]		
AE monitoring		X----------										----------X
Update concomitant medication		X	X			X		X	X	X	X	X
Central confirmation of subject eligibility	X[n]		X[o]									
Randomization			X[p]									

AE = adverse event; ANC = absolute neutrophil count; BP = blood pressure; BPRS = Brief Psychiatric Rating Scale; CGI-I = Clinical Global Impression of Improvement; CGI-S = Clinical Global Impression of Severity; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; ESRS-A = Extrapyramidal Symptom Rating Scale- Abbreviated; ET = early termination; FSH = follicle stimulating hormone; GAF = Global Assessment of Function; HbA1c = glycosylated hemoglobin type A1c; HDL = high-density lipoprotein; IEC = Independent Ethics Committee; IRB = Institutional Review Board; IVRS = interactive voice response system; LDL = low densitylipoprotein; MINI = Mini International Neuropsychiatric Interview; PANSS = Positive and Negative Syndrome Scale; PK = pharmacokinetics; Q12H = every 12 hours; SBQ-R = Suicidal Behavior Questionnaire-Revised; TSQM = treatment Satisfaction Questionnaire for Medication; WBC =white blood cell.

a. Day 28 assessments were completed in the event of early subject withdrawal.
b. Subject to IRB/IEC approval and optional for individual subjects.
c. During the randomized treatment phase, WBC with differential including absolute cell counts were drawn and sent to the local laboratory in the morning 3 times per week on nonconsecutive days. Review of WBC and ANC results occurred within 36 hours of sample collection, and the Investigator confirmed that the results did not meet WBC/ANC stopping criteria prior to the subject receiving the next dose of study medication after review of WBC/ANC findings had occurred.
d. At the discretion of the Investigator a urine-drug screen and alcohol test could also have been performed upon return from supervised partial day leave.
e. Women of childbearing capacity only: serum pregnancy test was performed at Screening and Day 28. A urine pregnancy test was performed on Day 1 prior to dosing and on Day 14. Pregnancy tests could also have been repeated as per request of IRB/IECs or if required by local regulations.
f. Only performed in females aged 45-60 years to confirm postmenopausal status.
g. Vital signs were obtained once daily at approximately the same time of day. During the optional inpatient restabilization phase, vital signs were only obtained on Day 29.

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	Day -8 to Day -2	Day -1 to Day 0										

h. Triplicate ECGs were obtained prior to dosing on Day 1; single ECGs were to be obtained in the morning prior to the morning dose of study medication during the randomized treatment period.
i. The Day 21 PK sample was drawn at least 2 hours prior to administration of the symptom assessments.
j. To be completed at approximately 5 to 8 hours post morning dose, except on Day 1 (Baseline visit) when assessments were to be completed prior to the first dose of randomized study treatment. These assessments were recommended to take place in the following sequence: PANSS, CGI-S, CGI-I, GAF, ESRS-A, C-SSRS.
k. Dispensed medication (IVRS) on Day -1 only.
l. Dispensed medication (IVRS) on Day 21. The ±1 day window did not apply to this activity.
m. Study medication was administered approximately Q12H (range 10-14 hours), at least 1 hour prior to or 2 hours after meals. The Day 1 dose was administered only after administration of symptom assessments and confirmation that the subject continued to meet all study entry criteria. Only the morning dose was administered on Day 28.
n. Transmitted Screening worksheets and audio recording to central vendor.
o. Reviewed subject eligibility report from central vendor and confirmed subject eligible for randomization
p. Randomization occurred after the administration of the BPRS and other symptom assessments and confirmation that the subject met all entry criteria including the confirmation of eligibility by the central vendor.

Number of Subjects (Planned and Analyzed): A total of 260 subjects were planned and 259 subjects (74 each in the PF-02545920 5 mg, the PF-02545920 15 mg and the placebo treatment groups and 37 in the risperidone treatment group) were randomly assigned to treatment.

Diagnosis and Main Criteria for Inclusion: Male and female subjects aged 18-65 years, with a body mass index (BMI) of approximately 18 to 40 kg/m^2 and a total body weight >50 kg (110 lb) were included in the study. Subjects with a diagnosis of schizophrenia were assessed by a qualified psychiatrist using the DSM-IV-TR criteria. The Mini International Neuropsychiatric Interview (MINI) was used to confirm diagnosis and exclude comorbid diagnoses: total BPRS score of ≥45 at the Screening visit, score of ≥4 (moderate) on ≥2 items of the 4 BPRS core psychosis items (ie, Number 4 conceptual disorganization, Number 11 hallucinatory behavior, Number 12 suspiciousness and Number 15 unusual thought content) at Screening and Baseline, total score of ≥12 on the combination of the 4 BPRS core psychosis items (conceptual disorganization, hallucinatory behavior, suspiciousness and unusual thought content) at Screening and Baseline, and CGI-S scale score of ≥4 (moderately ill) at the Screening and Baseline Visits. Subjects who were diagnosed with schizophrenia with acute exacerbation of illness and whose current acute exacerbation of schizophrenia was <4 weeks duration prior to the initial evaluation were included in the study.

Exclusion Criteria: Subjects with current diagnosis of schizoaffective disorder, major depression, bipolar disorder, or obsessive compulsive disorder, subjects with evidence or history of clinically significant uncontrolled medical illness and the subjects who met DSM-IV defined diagnostic criteria for psychoactive substance dependence (excluding nicotine dependence) within 12 months of screening or DSM-IV defined substance abuse within 3 months prior to screening were excluded from the study.

Study Treatment: PF-02545920 was supplied as tablets containing 5 mg of active drug. A matching placebo tablet was also supplied. Risperidone 1 mg and 3 mg was supplied as a tablet and over-encapsulated using a capsule shell for blinding across treatment groups. The placebo corresponding to the risperidone 1 mg and 3 mg was also supplied using capsule shell. Subjects in all treatment groups received study medication at approximately the same time of day throughout the study (approximately Q12H [range 10-14 hours], at least 1 hour prior to or 2 hours after meals). Subjects swallowed the study medication whole and did not chew the medication prior to swallowing.

Efficacy, Safety and Pharmacokinetic Endpoints:

Primary Efficacy Endpoint:

- PANSS total change from Baseline.

Secondary Efficacy Endpoints:

Change from Baseline to Week 4 on the following scales:

- PANSS positive, negative, and general subscales,

- CGI-S,
- PANSS derived Marder factor scores (positive, negative, disorganized thought, hostility/excitement, anxiety/depression),
- PANSS derived BPRS core psychosis items (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content),
- Total score at Week 4 for CGI-I,
- GAF,
- TSQM.

Safety Endpoints:

Primary Safety Endpoint:

- Dystonia incidence rate.

Secondary Safety Endpoints:

- Adverse events (AEs), weight and abdominal girth, vital signs (pulse rate, blood pressure, and body temperature), physical examination, neurological examination, electrocardiogram (ECG) and clinical laboratory findings (hematology, biochemistry and urinalysis),
- White blood cells (WBC) and absolute neutrophil count (ANC) monitored at site 3 times per week on non-consecutive days with local laboratory,
- Fasting insulin, high-density lipoprotein, low-density lipoprotein, cholesterol, triglycerides, glycosylated hemoglobin type A1C and prolactin,
- Change from Baseline to endpoint (Week 4) on the individual domain scores and clinical global impression scores on the abbreviated version of the Extrapyramidal Symptom Rating Scale-Abbreviated (ESRS-A) was used to assess extrapyramidal symptoms (EPS),
- Change from Baseline to Week 4 in Movement Disorder Burden Score for dystonia (MDBS-D),
- Columbia-Suicide Severity Rating Scale (C-SSRS) (suicidality monitoring).

Pharmacokinetic Endpoint:

- Sparse pharmacokinetic (PK) sampling for population PK analysis.

Safety Evaluations: Safety evaluations included dystonia incidence rate, AE monitoring, weight and abdominal girth, vital signs (pulse rate, blood pressure, and body temperature), physical examination, neurological examination, electrocardiogram (ECG), clinical laboratory findings (hematology, biochemistry, and urinalysis), WBC and ANC, and suicidality risk assessment (C-SSRS).

Statistical Methods: The analysis population set used in the study were:

- Full Analysis Set (FAS) Population: It was based on modified Intent-to-treat (ITT) principle consisting of all subjects who received ≥1 dose of randomized study medication, and had a baseline and ≥1 post-baseline measurement for the primary endpoint.

- Per-Protocol (PP) Population: It included all subjects in the FAS but without any major protocol violations.

- Safety Population: All subjects with ≥1 dose of study medication was included in the study.

The primary objective was to compare mean change from Baseline to Week 4 in PANSS total score between each PF-02545920 treatment group and placebo. The primary time point was Week 4 and all other collection time points were considered secondary. The primary analysis was to test the differences in mean treatment effect using least square (LS) means based on a linear mixed effect repeated measures model (MMRM) with fixed effects for treatment, time (visit), baseline value of PANSS total score and investigator site, and a random effect for subject was used to analyze the change from Baseline in the PANSS total score. This model also included effects for treatment by time interaction and baseline value of PANSS total score by time interaction. The estimation method used was restricted maximum likelihood. The covariance structure among repeated measures was assumed to be adequately modeled using an unstructured variance covariance matrix. Other covariance structures could be examined if indicated by model diagnostics. Using this model, 90% upper confidence bound (obtained via 80% confidence interval [CI]) comparing the mean change from Baseline in the PANSS total score estimates at Week 4 for PF-02545920 15 mg versus placebo and PF-02545920 5 mg versus placebo was computed. No adjustments for multiple comparisons were made. For change from Baseline for the secondary endpoints (except the CGI-I), analyses were conducted using a MMRM (using SAS PROC MIXED) as described for the primary endpoint. For the CGI-I scores, analyses were conducted using a MMRM (using SAS PROC MIXED) analysis of variance (ANOVA) with subject as random effects, treatment, investigator site, visit and visit-by-treatment interaction as fixed effects. Comparisons to placebo for the secondary endpoints were conducted at Week 4 as described in the analysis of the primary endpoint. Descriptive statistics (number of subjects [n], mean, standard deviation, median, minimum and maximum) was provided for each efficacy endpoint for the baseline and change from Baseline values by treatment group and visit.

Safety analyses were evaluated using descriptive statistics.

Appropriate tabular and/or graphical summaries of observed PK data were generated. Population PK analysis was also performed.

RESULTS

Subject Disposition and Demography: A total of 259 subjects were randomized to receive study treatment, of which 74 subjects received PF-02545920 5 mg and 74 subjects received PF-02545920 15 mg, 36 subjects received risperidone 3 mg, and 74 subjects received placebo. Among 258 subjects who were treated, 63 subjects discontinued the study. Seven (7) subjects discontinued the study due to an AE judged to be related to the study treatment. Table 2 represents the disposition of subjects in the study.

Table 2. Subject Evaluation Groups

Number of Subjects in Category	PF-02545920 5 mg	PF-02545920 15 mg	Risperidone 3 mg	Placebo
	n (%)	n (%)	n (%)	n (%)
Assigned to study treatment	74	74	37	74
Treated	74	74	36[a]	74
Completed	58 (78.4)	52 (70.3)	25 (67.6)	60 (81.1)
Discontinued	16 (21.6)	22 (29.7)	11 (29.7)	14 (18.9)
Discontinuations				
Subject death	1 (1.4)	0	0	0
Relation to study drug not defined	13 (17.6)	17 (23.0)	8 (22.2)	10 (13.5)
Insufficient clinical response	4 (5.4)	5 (6.8)	0	5 (6.8)
Lost to follow-up	1 (1.4)	2 (2.7)	0	0
No longer willing to participate in study	4 (5.4)	8 (10.8)	5 (13.9)	5 (6.8)
Protocol violation	1 (1.4)	1 (1.4)	0	0
Other	3 (4.1)	1 (1.4)	3 (8.3)	0
Related to study drug	0	3 (4.1)	1 (2.8)	3 (4.1)
Adverse event	0	3 (4.1)	1 (2.8)	3 (4.1)
Not related to study drug	2 (2.7)	2 (2.7)	2 (5.6)	1 (1.4)
Adverse event	2 (2.7)	2 (2.7)	2 (5.6)	1 (1.4)

Discontinuations were attributed to the last study treatment received, and included the post treatment period and follow-up.
n = number of subjects
a. One (1) subject was not treated and withdrew consent due to family issues.

Table 3 summarizes the number of subjects included in the analyses. The primary efficacy analysis was based on the FAS included 254 subjects that received study drug, had a baseline evaluation, and ≥1 post-baseline evaluation. A total of 236 subjects in the PP analysis set completed the study with no major protocol violations which was determined before unblinding the study. A total of 184 subjects were in the PK analysis set and analyzed for PK.

Table 3. Data Sets Analyzed

Number of Subjects in Category	Number (%) of Subjects			
	PF-02545920 5 mg	PF-02545920 15 mg	Risperidone 3 mg	Placebo
Analyzed for PK				
PK analysis set	74 (100.0)	73 (98.6)	12 (32.4)	25 (33.8)
Analyzed for efficacy				
Full analysis set	74 (100.0)	73 (98.6)	34 (91.9)	73 (98.6)
Per protocol analysis set	69 (93.2)	67 (90.5)	33 (89.2)	67 (90.5)
Analyzed for safety				
Adverse events	74 (100.0)	74 (100.0)	36 (97.3)	74 (100.0)
Laboratory data	74 (100.0)	74 (100.0)	35 (94.6)	74 (100.0)

The demographics characteristics are summarized in Table 4.

Table 4. Demographic Characteristics

Subject Parameter	PF-02545920 5 mg	PF-02545920 15 mg	Risperidone 3 mg	Placebo
Number (%) of subjects	74	74	36	74
Gender				
Male	57	60	25	56
Female	17	14	11	18
Age group (years)				
<18	0	0	0	0
18-44	39 (52.7)	33 (44.6)	20 (55.6)	40 (54.1)
45-64	34 (45.9)	41 (55.4)	16 (44.4)	34 (45.9)
≥65	1 (1.4)	0	0	0
Mean (SD)	43.1 (11.2)	41.7 (10.5)	41.3 (10.9)	41.2 (10.9)
Range	21-65	20-60	21-60	18-63
Race				
White	21 (28.4)	15 (20.3)	11 (30.6)	21 (28.4)
Black	51 (68.9)	55 (74.3)	24 (66.7)	52 (70.3)
Asian	0	1 (1.4)	0	0
Other	2 (2.7)	3 (4.1)	1 (2.8)	1 (1.4)
Height (cm)				
Mean (SD)	173.6 (9.8)	175.9 (9.4)	172.7 (9.5)	174.3 (9.3)
Range	139.8-201.0	150.5-198.0	150.0-189.5	155.0-198.1
Weight (kg)				
Mean (SD)	85.7 (15.0)	87.4 (13.9)	83.8 (16.9)	83.9 (18.8)
Range	46.4-116.7	61.8-119.9	53.5-118.2	53.0-136.3
BMI (kg/m^2)				
Mean (SD)	28.5 (5.0)	28.3 (4.5)	28.1 (5.0)	27.6 (5.5)
Range	18.7-39.6	19.6-39.6	18.3-38.5	18.3-39.8

BMI = body mass index; SD = standard deviation.

Efficacy and Pharmacokinetic Results:

PANSS Total Change From Baseline: A summary of least square LS mean changes from Baseline to Week 4 for PANSS total score for the FAS is provided in Table 5. For the primary comparison of PANSS total score at Week 4, the difference in LS means (80% CI)

between PF-02545920 5 mg and placebo was -2.2 (-5.7, 1.2) and between PF-02545920 15 mg and placebo was -0.7 (-4.1, 2.8). The difference in response to placebo was not statistically significant for either of the PF-02545920 groups. The difference in LS means (80% CI) between risperidone 3 mg and placebo was -8.2 (-12.7, -3.8) and it was found to be was statistically significant (P=0.0090) when compared to placebo.

Table 5. PANSS Total Score - Least Squares Mean Changes From Baseline to Week 4 (FAS) and Pairwise (Treatment Placebo) Comparisons in Mean Change From Baseline

Visit	Test	N	Difference (Test-Placebo)					
			LS Mean	SE	Estimate	SE	80% CI of Difference	p-Value
Week 1/ET	PF-02545920 5 mg	74	-4.80	0.915	0.06	1.285	(-1.59, 1.72)	0.5201
	PF-02545920 15 mg	73	-4.01	0.913	0.85	1.292	(-0.81, 2.51)	0.7450
	Risperidone 3 mg	34	-5.40	1.334	-0.53	1.616	(-2.61, 1.54)	0.3705
	Placebo	73	-4.86	0.919				
Week 2/ET	PF-02545920 5 mg	69	-9.01	1.345	-1.31	1.897	(-3.75, 1.13)	0.2450
	PF-02545920 15 mg	70	-8.08	1.340	-0.38	1.899	(-2.82, 2.06)	0.4204
	Risperidone 3 mg	30	-10.40	2.001	-2.70	2.411	(-5.80, 0.40)	0.1317
	Placebo	69	-7.70	1.348				
Week 3/ET	PF-02545920 5 mg	67	-10.87	1.614	-0.62	2.280	(-3.55, 2.31)	0.3931
	PF-02545920 15 mg	66	-9.49	1.612	0.77	2.283	(-2.17, 3.70)	0.6313
	Risperidone 3 mg	27	-14.99	2.449	-4.74	2.934	(-8.51, -0.97)	0.0538
	Placebo	66	-10.25	1.619				
Week 4/ET	PF-02545920 5 mg	63	-13.03	1.898	-2.21	2.683	(-5.66, 1.24)	0.2053
	PF-02545920 15 mg	58	-11.49	1.915	-0.67	2.698	(-4.14, 2.80)	0.4024
	Risperidone 3 mg	26	-19.05	2.884	-8.24	3.453	(-12.68, -3.80)	0.0090
	Placebo	63	-10.82	1.904				

Estimates were from a MMRM model for PANSS total change from Baseline score with terms for baseline PANSS total score, investigator site, treatment, visit, a treatment by visit interaction, and a baseline PANSS total score by visit interaction were fixed effects and a random effect for subject. Center was obtained after implementing the pooling algorithm for small centers. The model was fit using an unstructured covariance matrix. The p-values reported were 1-sided.
CI = confidence interval; ET = early termination; FAS = full analysis set; LS = least square; MMRM = mixed effect repeated measures; N = number of subjects; PANSS = Positive and Negative Syndrome Scale; SE = standard error.

Change From Baseline in PANSS Subscales and PANSS Marder Scores: A summary of the analysis of the secondary endpoints change from Baseline in PANSS positive subscale, negative subscale, and general subscale and PANSS Positive Marder score, Negative Marder

Score, Disorganized Thought Marder score, Hostility/Excitement Marder score, and Anxiety/Depression Marder score is provided in Table 6, Table 7 and Table 8 respectively. At Week 4, the change from Baseline estimates for the PANSS positive subscales for PF-02545920 5 mg and 15 mg compared to placebo (80% CI) was -0.41 (-1.50, 0.68) and 0.15 (-0.95, 1.25), respectively, and general subscales for PF-02545920 5 mg and 15 mg compared to placebo (80% CI) was -0.74 (-2.45, 0.97) and -0.10 (-1.82, 1.62), respectively. At Week 4, the change from Baseline estimates for the PANSS negative subscale for PF-02545920 5 mg and 15 mg compared to placebo (80% CI) was -0.96 (-1.90, -0.02) and -0.61 (-1.56, 0.33), respectively. For the PANSS positive, negative, and PANSS general subscales change from Baseline, the risperidone group showed a mean effect (80% CI) of -3.0 (-4.4, -1.6), -1.26 (-2.48, -0.05), and -3.7 (-5.9, -1.5), respectively.

For the PANSS Positive Marder score, Disorganized Thought Marder score, Hostility/Excitement Marder score, and Anxiety/Depression Marder score, the risperidone group showed a mean effect (80% CI) of -2.6 (-4.1, -1.2), -1.5 (-2.5, -0.4), -1.7 (-2.5, -0.8), and -1.7 (-2.6, -0.8), respectively.

Table 6. Summary of Statistical Analysis of Change From Baseline at Week 4 in PANSS Positive, Negative, and General Subscales (FAS Population)

				Difference (Test-Placebo)			
Test	**N**	**LS Mean**	**SE**	**Estimate**	**SE**	**80% CI of Difference**	**p-Value**
Positive Subscale Score[a]							
PF-02545920 5 mg	63	-4.54	0.599	-0.41	0.845	(-1.50, 0.68)	0.3144
PF-02545920 15 mg	58	-3.98	0.605	0.15	0.854	(-0.95, 1.25)	0.5700
Risperidone 3 mg	26	-7.13	0.915	-2.99	1.093	(-4.40, -1.59)	0.0034
Placebo	63	-4.13	0.600				
Negative Subscale Score[b]							
PF-02545920 5 mg	63	-2.21	0.517	-0.96	0.730	(-1.90, -0.02)	0.0942
PF-02545920 15 mg	58	-1.86	0.522	-0.61	0.735	(-1.56, 0.33)	0.2030
Risperidone 3 mg	26	-2.51	0.788	-1.26	0.944	(-2.48, -0.05)	0.0907
Placebo	63	-1.25	0.519				
General Subscale Score[c]							
PF-02545920 5 mg	63	-6.47	0.942	-0.74	1.330	(-2.45, 0.97)	0.2904
PF-02545920 15 mg	58	-5.83	0.952	-0.10	1.339	(-1.82, 1.62)	0.4710
Risperidone 3 mg	26	-9.39	1.437	-3.66	1.718	(-5.86, -1.45)	0.0172
Placebo	63	-5.73	0.943				

Center was obtained after implementing the pooling algorithm for small centers. The model was fit using an unstructured covariance matrix. The p-values reported were 1-sided.

CI = confidence interval; FAS = full analysis set; LS = least square; MMRM = mixed effect repeated measures; N = number of subjects; PANSS = Positive and Negative Syndrome Scale; SE = standard error.

a. Estimates were from a MMRM model for PANSS Positive subscale change from Baseline score with terms for Baseline PANSS Positive subscale score, investigator site, treatment, visit, a treatment by visit interaction and a Baseline PANSS Positive subscale score by visit interaction were fixed effects and a random effect for subject.

b. Estimates were from a MMRM model for PANSS Negative change from Baseline score with terms for Baseline PANSS Negative subscale score, investigator site, treatment, visit, a treatment by visit interaction and a Baseline PANSS Negative subscale score by visit interaction were fixed effects and a random effect for subject.

c. Estimates were from a MMRM model for PANSS General change from Baseline subscale with terms for Baseline PANSS General subscale score, investigator site, treatment, visit, a treatment by visit interaction and a Baseline PANSS General subscale score by visit interaction were fixed effects and a random effect for subject.

Table 7. Summary of Statistical Analysis of Change From Baseline at Week 4 in PANSS Marder Positive, Negative, and Disorganized Thought Score (FAS Population)

Test	N	Diff erence(Test-Placebo)					
		LS Mean	SE	Estimate	SE	80% CI of Diff	p-Value
Marder Positive Factor Score[a]							
PF-02545920 5 mg	63	-5.03	0.611	-0.73	0.863	(-1.84, 0.38)	0.1999
PF-02545920 15 mg	58	-4.66	0.618	-0.36	0.870	(-1.48, 0.76)	0.3399
Risperidone 3 mg	26	-6.92	0.935	-2.62	1.117	(-4.06, -1.18)	0.0100
Placebo	63	-4.30	0.612				
Marder Negative Factor Score[b]							
PF-02545920 5 mg	63	-2.81	0.551	-0.77	0.778	(-1.77, 0.23)	0.1625
PF-02545920 15 mg	58	-2.60	0.557	-0.57	0.783	(-1.57, 0.44)	0.2354
Risperidone 3 mg	26	-2.83	0.837	-0.79	1.002	(-2.08, 0.50)	0.2161
Placebo	63	-2.04	0.552				
Marder Disorganized Thought Score[c]							
PF-02545920 5 mg	63	-2.09	0.444	-0.43	0.627	(-1.23, 0.38)	0.2480
PF-02545920 15 mg	58	-1.77	0.450	-0.10	0.632	(-0.92, 0.71)	0.4345
Risperidone 3 mg	26	-3.15	0.681	-1.48	0.813	(-2.53, -0.44)	0.0346
Placebo	63	-1.66	0.445				

Center was obtained after implementing the pooling algorithm for small centers. The model was fit using an unstructured covariance matrix. The p-values reported were 1-sided.
CI = confidence interval; FAS = full analysis set; LS = least square; MMRM = mixed effect repeated measures; N = number of subjects; PANSS = Positive and Negative Syndrome Scale; SE = standard error

a. Estimates were from a MMRM model for PANSS Marder Positive change from Baseline score with terms for Baseline PANSS Marder Positive score, investigator site, treatment, visit, a treatment by visit interaction and a Baseline PANSS Marder Positive score by visit interaction were fixed effects and a random effect for subject.
b. Estimates were from a MMRM model for PANSS Marder Negative change from Baseline score with terms for Baseline PANSS Marder Negative score, investigator site, treatment, visit, a treatment by visit interaction and a Baseline PANSS Marder Negative score by visit interaction were fixed effects and a random effect for subject.
c. Estimates were from a MMRM model for PANSS Marder Disorganized Thought Change from Baseline score with terms for Baseline PANSS Marder Disorganized Thought score, investigator site, treatment, visit, a treatment by visit interaction and a Baseline PANSS Marder Disorganized Thought score by visit interaction were fixed effect and a random effect for subject.

Table 8. Summary of Statistical Analysis of Change From Baseline at Week 4 in PANSS Marder Hostility/Excitement and Anxiety/Depression Score (FAS Population)

				Difference (Test-Placebo)			
Test	**N**	**LS Mean**	**SE**	**Estimate**	**SE**	**N**	**LS Mean**
Marder Hostility/Excitement Score[a]							
PF-02545920 5 mg	63	-0.78	0.352	-0.04	0.495	(-0.68, 0.60)	0.4685
PF-02545920 15 mg	58	-0.58	0.356	0.15	0.499	(-0.49, 0.80)	0.6214
Risperidone 3 mg	26	-2.40	0.538	-1.66	0.641	(-2.48, -0.84)	0.0052
Placebo	63	-0.74	0.351				
Marder Anxiety/Depression Score[b]							
PF-02545920 5 mg	63	-2.51	0.371	0.12	0.523	(-0.55, 0.79)	0.5894
PF-02545920 15 mg	58	-2.16	0.375	0.47	0.526	(-0.20, 1.15)	0.8155
Risperidone 3 mg	26	-4.31	0.568	-1.68	0.677	(-2.55, -0.81)	0.0069
Placebo	63	-2.63	0.370				

Center was obtained after implementing the pooling algorithm for small centers. The model was fit using an unstructured covariance matrix. The p-values reported were 1-sided.
CI = confidence interval; FAS = full analysis set; LS = least square; MMRM = mixed effect repeated measures: N = number of subjects; PANSS = Positive and Negative Syndrome Scale; SE = standard error.

a. Estimates were from a MMRM model for PANSS Marder Hostility/Excitement change from Baseline score with terms for Baseline PANSS Marder Hostility/Excitement score, investigator site, treatment, visit, a treatment by visit interaction and a Baseline PANSS Marder Hostility/Excitement score by visit interaction were fixed effect and a random effect for subject.
b. Estimates were from a MMRM model for PANSS Marder Anxiety/Depression change from Baseline score with terms for Baseline PANSS Marder Anxiety/Depression score, investigator site, treatment, visit, a treatment by visit interaction and a Baseline PANSS Marder Anxiety/Depression score by visit interaction were fixed effects and a random effect for subject.

Summary of Clinical Global Impression of Improvement:

A summary of the statistical analysis of CGI-I for the FAS population is provided in Table 9. The CGI-I took on integer scores ranging from 1 (very much improved compared to Baseline) to 7 (very much worse compared to Baseline). Differences in LS means for the CGI-I (80% CI) at Week 4 between placebo and PF-02545920 5 mg and 15 mg were: -0.1 (-0.3, 0.2) and 0.1 (-0.2, 0.4), respectively. The difference in LS means for the CGI-I (along with 80% CI) at Week 4 between placebo and risperidone 3 mg was -0.8 (-1.1, -0.4). Therefore, at Week 4, risperidone was statistically significant (P=0.0019) when compared to placebo.

Table 9. Summary of Statistical Analysis of CGI-I (FAS Population)

					Difference (Test-Placebo)			
Visit	**Test**	**N**	**LS Mean**	**SE**	**Estimate**	**SE**	**80% CI of Difference**	**p-Value**
Week 1/ET	PF-02545920 5 mg	74	3.70	0.082	0.06	0.115	(-0.09, 0.21)	0.6899
	PF-02545920 15 mg	73	3.70	0.082	0.06	0.116	(-0.09, 0.21)	0.6983
	Risperidone 3 mg	34	3.61	0.120	-0.03	0.145	(-0.22, 0.16)	0.4199
	Placebo	73	3.64	0.082				
Week 2/ET	PF-02545920 5 mg	69	3.43	0.101	-0.04	0.143	(-0.23, 0.14)	0.3823
	PF-02545920 15 mg	70	3.45	0.101	-0.03	0.143	(-0.21, 0.16)	0.4283
	Risperidone 3 mg	30	2.98	0.152	-0.49	0.182	(-0.73, -0.26)	0.0037
	Placebo	69	3.47	0.101				
Week 3/ET	PF-02545920 5 mg	67	3.25	0.124	-0.12	0.175	(-0.34, 0.11)	0.2541
	PF-02545920 15 mg	66	3.51	0.124	0.15	0.175	(-0.08, 0.37)	0.7973
	Risperidone 3 mg	27	2.61	0.189	-0.75	0.226	(-1.04, -0.46)	0.0005
	Placebo	66	3.36	0.124				
Week 4/ET	PF-02545920 5 mg	63	3.21	0.139	-0.07	0.196	(-0.32, 0.18)	0.3598
	PF-02545920 15 mg	58	3.40	0.141	0.12	0.198	(-0.13, 0.37)	0.7275
	Risperidone 3 mg	26	2.53	0.213	-0.75	0.255	(-1.07, -0.42)	0.0019
	Placebo	63	3.28	0.139				

Estimates were from a MMRM model predicting for CGI-I with terms for investigator site, treatment, visit, and a treatment by visit interaction were fixed effects and a random effect for subject. Center was obtained after implementing the pooling algorithm for small centers. The model was fit using an unstructured covariance matrix. The p-values reported were 1-sided.
CGI-I = Clinical Global Impression of Improvement, CI = confidence interval, Diff = difference, ET = early termination, FAS = full analysis set, LS = least square, MMRM = mixed effect repeated measures, N = number of subjects, SE = standard error.

Change at Week 4 in PANSS Derived Brief Psychiatric Rating Scale:

A summary of the analysis of change from Baseline in PANSS derived BPRS core score for the FAS population is provided in Table 10. At Week 4, none of the doses of PF-02545920 were statistically significant when compared to placebo for the PANSS derived BPRS core score. However, risperidone was statistically significant (P=0.0031) when compared to placebo.

Table 10. Summary of Statistical Analysis of Change From Baseline in PANSS Derived BPRS Core Score (FAS Population)

					Difference (Test-Placebo)			
Visit	**Test**	**N**	**LS Mean**	**SE**	**Estimate**	**SE**	**80% CI of Diff**	**p-Value**
Week 1/ET	PF-02545920 5 mg	74	-1.33	0.200	-0.23	0.281	(-0.59, 0.13)	0.2101
	PF-02545920 15 mg	73	-1.17	0.199	-0.06	0.282	(-0.42, 0.30)	0.4124
	Risperidone 3 mg	34	-1.58	0.291	-0.48	0.352	(-0.93, -0.03)	0.0878
	Placebo	73	-1.11	0.200				
Week 2/ET	PF-02545920 5 mg	69	-2.35	0.283	-0.21	0.400	(-0.72, 0.30)	0.3006
	PF-02545920 15 mg	70	-2.33	0.282	-0.19	0.399	(-0.70, 0.32)	0.3187
	Risperidone 3 mg	30	-3.05	0.423	-0.91	0.509	(-1.57, -0.26)	0.0372
	Placebo	69	-2.14	0.284				
Week 3/ET	PF-02545920 5 mg	67	-2.90	0.343	-0.09	0.484	(-0.72, 0.53)	0.4240
	PF-02545920 15 mg	66	-2.78	0.342	0.03	0.484	(-0.59, 0.66)	0.5284
	Risperidone 3 mg	27	-3.91	0.523	-1.10	0.625	(-1.90, -0.30)	0.0399
	Placebo	66	-2.81	0.344				
Week 4/ET	PF-02545920 5 mg	63	-3.43	0.396	-0.34	0.559	(-1.06, 0.38)	0.2727
	PF-02545920 15 mg	58	-3.12	0.399	-0.04	0.562	(-0.76, 0.69)	0.4747
	Risperidone 3 mg	26	-5.09	0.605	-2.00	0.723	(-2.93, -1.07)	0.0031
	Placebo	63	-3.09	0.396				

Estimates were from a MMRM model for PANSS derived BPRS core change from Baseline score with terms for Baseline PANSS derived BPRS core score, investigator site, treatment, visit, a treatment by visit interaction, and a Baseline PANSS derived BPRS core score by visit interaction were fixed effects and a random effect for subject. Center was obtained after implementing the pooling algorithm for small centers. The model was fit using an unstructured covariance matrix. The p-values reported were 1-sided.
BPRS = Brief Psychiatric Rating Scale; CI = confidence interval; Diff = difference; ET = early termination; FAS = full analysis set; LS = least square; MMRM = mixed effect repeated measures; N = number of subjects; PANSS = Positive and Negative Syndrome Scale; SE = standard error.

Change From Baseline in Clinical Global Impression of Severity:

The CGI-S takes on integer scores ranging from 1 (normal compared to Baseline) to 7 (among the most severely ill compared to Baseline). Differences in LS means for the CGI-S (80% CI) at Week 4 between placebo and PF-02545920 5 mg and 15 mg were: -0.1 (-0.3, 0.1) and -0.1 (-0.2, 0.2), respectively. The difference in LS means for the CGI-S (along with 80% CI) at Week 4 between placebo and risperidone 3 mg was -0.4 (-0.6, -0.1). Therefore, risperidone was statistically significant (P=0.0395) when compared to placebo (Table 11).

Table 11. Summary of Statistical Analysis of Change From Baseline in CGI-S (FAS Population)

Parameter: CGI – S					Difference (Test-Placebo)			
Visit	**Test**	**N**	**LS Mean**	**SE**	**Estimate**	**SE**	**80% CI of Difference**	**p-Value**
Week 1/ET	PF-02545920 5 mg	74	-0.17	0.052	0.00	0.074	(-0.09, 0.10)	0.5183
	PF-02545920 15 mg	73	-0.17	0.052	0.00	0.074	(-0.09, 0.10)	0.5202
	Risperidone 3 mg	34	-0.19	0.076	-0.02	0.093	(-0.14, 0.10)	0.4084
	Placebo	73	-0.17	0.053				
Week 2/ET	PF-02545920 5 mg	69	-0.35	0.075	0.03	0.106	(-0.10, 0.17)	0.6266
	PF-02545920 15 mg	70	-0.41	0.074	-0.03	0.105	(-0.16, 0.11)	0.4047
	Risperidone 3 mg	30	-0.49	0.111	-0.11	0.134	(-0.29, 0.06)	0.1992
	Placebo	69	-0.38	0.075				
Week 3/ET	PF-02545920 5 mg	67	-0.51	0.093	0.02	0.131	(-0.15, 0.19)	0.5495
	PF-02545920 15 mg	66	-0.42	0.093	0.11	0.131	(-0.06, 0.27)	0.7901
	Risperidone 3 mg	27	-0.86	0.142	-0.33	0.170	(-0.55, -0.11)	0.0265
	Placebo	66	-0.53	0.093				
Week 4/ET	PF-02545920 5 mg	63	-0.72	0.109	-0.13	0.154	(-0.33, 0.07)	0.1970
	PF-02545920 15 mg	58	-0.64	0.110	-0.05	0.154	(-0.24, 0.15)	0.3835
	Risperidone 3 mg	26	-0.94	0.166	-0.35	0.199	(-0.61, -0.10)	0.0395
	Placebo	63	-0.59	0.109				

Estimates were from a mixed effect repeated measures model predicting for change from Baseline in CGI-S with terms for baseline CGI-S, investigator site, treatment, visit, a treatment by visit interaction and a baseline CGI-S by visit interaction as fixed effects and a random effect for subject. Center was obtained after implementing the pooling algorithm for small centers. The model was fit using an unstructured covariance matrix. The p-values reported were 1-sided.
CI = confidence interval; CGI-S = Clinical Global Impression of Severity; ET = early termination; FAS = full analysis set; LS = least square; N = number of subjects; SE = standard error.

Global Assessment of Function:

A summary of statistical analysis of change from Baseline in GAF parameter (GAF score) in the FAS population is presented in Table 12.

Table 12. Summary of Statistical Analysis of Change From Baseline in GAF (FAS Population)

Parameter: GAF Score					Difference (Test-Placebo)			
Visit	Test	N	LS Mean	SE	Estimate	SE	80% CI of Difference	p-Value
Week 1/ET	PF-02545920 5 mg	73	1.84	0.515	-0.71	0.723	(-1.64,0.22)	0.8370
	PF-02545920 15 mg	71	1.50	0.516	-1.05	0.729	(-1.99,-0.11)	0.9245
	Risperidone 3 mg	34	2.11	0.745	-0.44	0.907	(-1.60,0.73)	0.6857
	Placebo	72	2.55	0.518				
Week 2/ET	PF-02545920 5 mg	68	3.42	0.753	-0.03	1.061	(-1.39,1.34)	0.5095
	PF-02545920 15 mg	68	3.88	0.752	0.43	1.064	(-0.93,1.80)	0.3420
	Risperidone 3 mg	30	5.11	1.117	1.66	1.347	(-0.07,3.40)	0.1092
	Placebo	68	3.45	0.754				
Week 3/ET	PF-02545920 5 mg	66	4.55	0.881	-0.71	1.244	(-2.31,0.89)	0.7164
	PF-02545920 15 mg	64	5.20	0.884	-0.06	1.249	(-1.67,1.55)	0.5192
	Risperidone 3 mg	27	7.44	1.336	2.18	1.601	(0.12,4.24)	0.0878
	Placebo	65	5.26	0.884				
Week 4/ET	PF-02545920 5 mg	62	5.69	1.046	-0.16	1.478	(-2.06,1.74)	0.5429
	PF-02545920 15 mg	57	6.09	1.062	0.24	1.492	(-1.68,2.16)	0.4354
	Risperidone 3 mg	26	8.38	1.594	2.53	1.907	(0.08,4.99)	0.0930
	Placebo	62	5.85	1.048				

GAF = Global Assessment of Function; ET = early termination; FAS = full analysis set.
Estimates were from a mixed effect repeated measures model predicting for GAF change from baseline score with terms for baseline GAF score, investigator site, treatment, visit, a treatment by visit interaction and a baseline GAF score by visit interaction as fixed effects and a random effect for subject. Center was obtained after implementing the pooling algorithm for small centers. The model was fit using an unstructured covariance matrix. The p-values reported were 1-sided.

Treatment Satisfaction Questionnaire for Medication: Descriptive statistics of TSQM parameters are provided in Table 13.

Table 13. Descriptive Statistics of Treatment Satisfaction Questionnaire for Medication (FAS Population)

Parameter	Statistics	PF-02545920 5 mg (N=74)	PF-02545920 15 mg (N=73)	Risperidone 3 mg (N=34)	Placebo (N=73)
Effectiveness	n	71	70	32	69
	Mean (SD)	53.68 (24.84)	51.90 (24.28)	63.37 (24.07)	53.70 (19.68)
	Median	55.56	55.56	66.67	55.56
	Min	0.0	0.0	16.7	0.0
	Max	100.0	100.0	100.0	88.9
Adverse events	n	70	70	32	69
	Mean (SD)	86.43 (24.45)	79.20 (28.67)	87.30 (22.02)	87.41 (24.00)
	Median	100.00	100.00	100.00	100.00
	Min	0.0	0.0	12.5	12.5
	Max	100.0	100.0	100.0	100.0
Convenience	n	71	70	32	69
	Mean (SD)	70.46 (17.46)	68.37 (18.49)	75.69 (15.44)	66.83 (15.12)
	Median	66.67	66.67	77.78	66.67
	Min	27.8	16.7	44.4	33.3
	Max	100.0	100.0	100.0	100.0
Global satisfaction	n	71	70	32	69
	Mean (SD)	56.84 (28.30)	51.02 (27.79)	66.07 (23.38)	49.48 (24.69)
	Median	57.14	53.57	67.86	50.00
	Min	0.0	0.0	14.3	0.0
	Max	100.0	100.0	100.0	92.9

FAS = full analysis set; Max = maximum, Min = Minimum, N = number of subjects per treatment group, n = number of subjects per prespecified criteria, SD = standard deviation.

Pharmacokinetic Results:

The PK of PF-02545920 and its metabolite PF-01001252 were assessed as trough concentration (predose) at Weeks 1, 2, 3, and 4; PK samples were also collected between 15 and 60 minutes postdose (targeting 20 minutes postdose) on Day 7, between 1 and 2 hours postdose (targeting 1.5 hours postdose) on Day 14, between 3 and 6 hours postdose (targeting 4.5 hours postdose) on Day 21 and, approximately 24 hours post the last dose on Day 28 to cover the exposures for the entire span of dosing regimen. As expected, PF-02545920 concentration increased proportionally from 5 mg to 15 mg (titrated) BID dose. Looking at the predose (trough) concentration at steady-state (C_{trough}) it appeared that PF-02545920 concentrations were stable over the multiple weeks of dosing. A summary of PF-02545920 C_{trough} during the study is provided in Table 14.

Table 14. Summary of Serum PF-02545920 Concentration (ng/mL) Versus Nominal Time (Postdose at Hour 0: C_{trough})

Visit[a]	PF-02545920 5 mg	PF-02545920 15 mg
Day 7		
N	71	71
NALQ	70	70
Median	12.8	48.4
Range	0.0-89.2	0.0-224.0
Day 14		
N	67	67
NALQ	66	66
Median	12.1	46.9
Range	0.0–85.5	0.0–208.0
Day 21		
N	64	58
NALQ	62	57
Median	11.4	44.6
Range	0.0–90.2	0.0–303.0
ET/Day 28		
N	62	56
NALQ	60	55
Median	12.4	42.7
Range	0.0–133.0	0.0 – 178.0

Summary statistics were calculated by setting concentration values below the LLOQ to 0. Samples not analyzed, unscheduled, collected outside allowable time window, or baseline samples collected postdose were excluded.

C_{trough} = predose (trough) concentration at steady-state; ET = early termination; LLOQ = lower limit of quantification; N = number of observations (nonmissing concentrations); NALQ = number of observations above lower limit of quantification.

a. The risperidone 3 mg treatment group and the placebo treatment group had no results, therefore these 2 treatment groups were not included.

Observed PF-02545920 exposures in this study at the 5 mg and 15 mg BID dose levels (Table 15) were similar to those observed earlier, after 2 weeks in the multiple ascending dose study in subjects with stable schizophrenia. This was also concluded in an additional PK analysis which suggested that steady state PF-02545920 concentrations of both the 5 mg and 15 mg BID dosing group were comparable to the exposures predicted by a population PK model.

Table 15. Summary of Serum PF-02545920 Concentration (ng/mL) Versus Nominal Time (Postdose at Specific Timepoints)

Visit[a]	PF-02545920 5 mg	PF-02545920 15 mg
Day 7		
N	71	68
NALQ	70	67
Median	22.4	78.7
Range	0.0–193.0	0.0–368.0
Day 14		
N	65	63
NALQ	65	62
Median	49.2	157.0
Range	2.4–197.0	0.0–422.0
Day 21		
N	64	58
NALQ	63	57
Median	20.3	81.7
Range	0.0–106.0	0.0–260.0
ET/Day 28		
N	58	52
NALQ	55	51
Median	4.3	21.2
Range	0.0–56.5	0.0–99.7

Summary statistics were calculated by setting concentration values below the LLOQ to 0. Samples not analyzed, unscheduled, collected outside allowable time window, or baseline samples collected postdose were excluded.

C_{trough} = predose (trough) concentration at steady-state; ET = early termination; LLOQ = lower limit of quantification; N = number of observations (nonmissing concentrations); NALQ = number of observations above lower limit of quantification.

a. The risperidone 3 mg treatment group and the placebo treatment group had no results, therefore these 2 treatment groups were not included.

Safety Results:

The incidence of the most frequent treatment-emergent AEs that occurred in ≥4% of subjects in any treatment group is presented in Table 16.

Table 16. Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) for Events Having a Frequency Rate ≥4%

	PF-02545920 5 mg	PF-02545920 15 mg	Risperidone 3 mg	Placebo
Number (%) of Subjects:	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Evaluable for AEs	**74**	**74**	**36**	**74**
With AEs	**53 (71.6)**	**47 (63.5)**	**22 (61.1)**	**51 (68.9)**
Number (%) of subjects with AEs by:				
System organ class MedDRA (v14.0) preferred term				
Blood and lymphatic system disorders	5 (6.8)	2 (2.7)	1 (2.8)	5 (6.8)
Neutropenia	5 (6.8)	2 (2.7)	1 (2.8)	4 (5.4)
Cardiac disorders	0	3 (4.1)	1 (2.8)	1 (1.4)
Tachycardia	0	3 (4.1)	1 (2.8)	0
Ear and labyrinth disorders	2 (2.7)	0	2 (5.6)	1 (1.4)
Ear pain	1 (1.4)	0	2 (5.6)	1 (1.4)
Gastrointestinal disorders	21 (28.4)	21 (28.4)	12 (33.3)	22 (29.7)
Abdominal discomfort	2 (2.7)	3 (4.1)	0	2 (2.7)
Abdominal pain	0	1 (1.4)	2 (5.6)	0
Constipation	8 (10.8)	2 (2.7)	2 (5.6)	6 (8.1)
Diarrhoea	3 (4.1)	2 (2.7)	1 (2.8)	4 (5.4)
Dry mouth	1 (1.4)	3 (4.1)	1 (2.8)	2 (2.7)
Dyspepsia	5 (6.8)	3 (4.1)	3 (8.3)	6 (8.1)
Nausea	3 (4.1)	6 (8.1)	3 (8.3)	5 (6.8)
Toothache	2 (2.7)	2 (2.7)	1 (2.8)	4 (5.4)
Vomiting	2 (2.7)	3 (4.1)	2 (5.6)	5 (6.8)
Infections and infestations	6 (8.1)	4 (5.4)	5 (13.9)	14 (18.9)
Upper respiratory tract infection	1 (1.4)	0	2 (5.6)	2 (2.7)
Musculoskeletal and connective tissue disorders	15 (20.3)	11 (14.9)	5 (13.9)	9 (12.2)
Back pain	4 (5.4)	2 (2.7)	2 (5.6)	3 (4.1)
Joint stiffness	0	3 (4.1)	0	0
Pain in extremity	4 (5.4)	1 (1.4)	1 (2.8)	0
Nervous system disorders	28 (37.8)	26 (35.1)	10 (27.8)	23 (31.1)
Akathisia	6 (8.1)	5 (6.8)	1 (2.8)	1 (1.4)
Dizziness	2 (2.7)	3 (4.1)	0	4 (5.4)
Dystonia	0	3 (4.1)	0	1 (1.4)
Headache	15 (20.3)	10 (13.5)	9 (25.0)	11 (14.9)
Sedation	3 (4.1)	5 (6.8)	1 (2.8)	3 (4.1)
Psychiatric disorders	13 (17.6)	10 (13.5)	2 (5.6)	6 (8.1)
Insomnia	4 (5.4)	3 (4.1)	0	2 (2.7)
Respiratory, thoracic and mediastinal disorders	6 (8.1)	5 (6.8)	2 (5.6)	3 (4.1)
Cough	3 (4.1)	0	0	0
Nasal congestion	3 (4.1)	1 (1.4)	1 (2.8)	0
Oropharyngeal pain	4 (5.4)	2 (2.7)	1 (2.8)	2 (2.7)
Skin and subcutaneous tissue disorders	5 (6.8)	2 (2.7)	1 (2.8)	5 (6.8)
Pruritus	3 (4.1)	1 (1.4)	0	1 (1.4)

Subjects were only counted once per treatment for each row. Includes data up to 999 days after last dose of study drug.
MedDRA (v14.0) coding dictionary applied.
AEs = adverse events; MedDRA = Medical Dictionary for Regulatory Affairs; n = number of subjects with AEs; v = version.

Table 17 provides the incidence of treatment-related, treatment-emergent AEs reported in ≥4% of subjects in any treatment group. Headache, constipation, akathisia, nausea, sedation, neutropenia, somnolence, dizziness, and insomnia were the most frequently reported as treatment-related AEs. Treatment-related neutropenia was reported by subjects in all treatment groups with the highest incidence in the placebo group (5.4% [4 subjects]), 4.1% (3 subjects) in the PF-02545920 5 mg group, 2.8% (1 subject) in the risperidone 3 mg group, and 1.4% (1 subject) in the PF-02545920 15 mg group. Treatment-related dizziness was reported by 4.1% (3 subjects) in the PF-02545920 15 mg group, and 5.4% (4 subjects) in the placebo group. Treatment-related dizziness was not reported in the PF-02545920 5 mg group or risperidone 3 mg group.

Table 17. Incidence of Most Frequent (≥4%) Treatment-Emergent Adverse Events (Treatment-Related)

System Organ Class Preferred Term	PF-02545920 5 mg N=74 n (%)	PF-02545920 15 mg N=74 n (%)	Risperidone 3 mg N=36 n (%)	Placebo N=74 n (%)
Blood and lymphatic system disorders				
Neutropenia	3 (4.1)	1 (1.4)	1 (2.8)	4 (5.4)
Gastrointestinal disorders				
Constipation	8 (10.8)	2 (2.7)	1 (2.8)	4 (5.4)
Nausea	3 (4.1)	5 (6.8)	2 (5.6)	3 (4.1)
Vomiting	1 (1.4)	3 (4.1)	2 (5.6)	2 (2.7)
Dyspepsia	3 (4.1)	3 (4.1)	2 (5.6)	0
Musculoskeletal and connective tissue disorders				
Joint stiffness	0	3 (4.1)	0	0
Nervous system disorders				
Akathisia	5 (6.8)	5 (6.8)	1 (2.8)	0
Dizziness	0	3 (4.1)	0	4 (5.4)
Dystonia[a]	0	3 (4.1)	0	0
Headache	9 (12.2)	8 (10.8)	9 (25.0)	6 (8.1)
Sedation	3 (4.1)	3 (4.1)	1 (2.8)	2 (2.7)
Somnolence	2 (2.7)	4 (5.4)	1 (2.8)	2 (2.7)
Psychiatric disorders				
Insomnia	4 (5.4)	1 (1.4)	0	1 (1.4)

Subjects were counted only once per treatment in each row. Included data up to 999 days after last dose of study drug. MedDRA (v14.0) coding dictionary applied.
Non SAE and SAE results are not separated out.
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects evaluable for adverse events; n = number of subjects with adverse events; SAE = serious adverse event; v = version.
a. Treatment-related dystonia (the information described here included data from dystonia, oromandibular dystonia, and oculogyric crisis) was more frequent in the PF-02545920 15 mg group 8.1% (6 subjects) compared to 0% (0 subjects) in the PF-02545920 5 mg group, 0% (0 subjects) in the risperidone 3 mg group, and 1.4% (1 subject) in the placebo group.

Dystonia Incidence Rate: The overall dystonia incidence rate in the PF-02545920 5 mg and 15 mg treatment groups was 1 and 6 subjects, respectively, 3 subjects in the placebo group, and no subjects in the risperidone 3 mg group. Table 18 presents the dystonia AEs that occurred during the study. Among the 6 subjects in the PF-02545920 15 mg group,

5 dystonia events occurred before Day 7, of which only 1 was reported as severe (oculogyric crisis).

Table 18. Dystonia Adverse Events

Serial Number	Event[a]	Sex/Age (Years)	Study Start Day[b]	Dose(s) at Onset[c]	Severity	Subject Action	Causality	Discontinuation
1	Oromandibular dystonia	Female/61	15	5 mg	Mild	Treatment given	Other-poor oral hygiene/care, excessive tobacco use, poor fitting dentures	No
2	Oromandibular dystonia	Female/46	13	15 mg	Mild	None	Study drug	No
3	Dystonia	Male/47	3 and 4	10 mg	Moderate	Treatment given	Study drug	Permanently discontinued
4	Dystonia	Male/42	5 and 25	15 mg	Mild	Treatment given	Study drug	No
5	Oromandibular dystonia	Male/42	5	15 mg	Mild	None	Study drug	No
6	Dystonia	Male/29	5 and 10	10 mg and 15 mg	Moderate	Treatment given	Study drug	No
7	Oculogyric crisis	Male/25	5	15 mg	Severe	Treatment given	Study drug	Stopped temporarily
8	Oromandibular dystonia	Male/47	23	Placebo	Moderate	Treatment given	Study drug	No
9	Dystonia[d]	Male/38	30	Placebo	Moderate	Treatment given	Concomitant treatment with Loxapine	No
10	Extrapyramidal disorder	Male/50	19	Placebo	Mild	Treatment given	Study drug	No

Age was recorded at Screening. MedDRA (v14.0) coding dictionary applied.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; v = version.
a. Treatment-emergent.
b. Day relative to start of study treatment. First day of study treatment = Day 1.
c. Dose at onset of AE.
d. The onset of this AE was after discontinuation of study treatment.

The differences in proportion (adjusted 80% CI, adjusted due interim) between PF-02545920 5 mg and 15 mg and placebo were -0.03 (-0.07, 0.01) and 0.04 (-0.02, 0.10). Based on the predefined criteria for dystonia, there was insufficient statistical evidence to suggest that the incidence of dystonia for both the PF-02545920 groups was worse than placebo (Table 19).

Table 19. Statistical Analysis of Dystonia Incidence Rate Between Treatment Groups

Statistics	PF-02545920 5 mg	PF-02545920 15 mg	Risperidone 3 mg	Placebo
N	**74**	**74**	**36**	**74**
Dystonia Incidence Rate Until Day 7				
Number of subjects with dystonia	0	5	0	0
Proportion of dystonia	0	0.07	0	0
Difference in proportion	0	0.07	0	NA
Adjusted 80% CI for difference in proportion	(0, 0)	(0.02, 0.12)	(0,0)	NA
Dystonia Incidence Rate Until the End of Study				
Number of subjects with dystonia	1	6	0	3
Proportion of dystonia	0.01	0.08	0	0.04
Difference in proportion	-0.03	0.04	-0.04	NA
Adjusted 80% CI for difference in proportion	(-0.07, 0.01)	(-0.02, 0.10)	(-0.08, -0.00)	NA

Subjects with dystonia AEs were only counted once per subject. The adjusted 80% CI equals 88.6% CI, adjusted due to 1 interim look. The test statistics for the end of study were 1.306 with the 90% repeated CI for the difference in dystonia rate equals (-0.013, 1.0).
AE = adverse event; CI=confidence interval; N = number of subjects; NA = not applicable.

Descriptive statistics for Baseline and change from Baseline for the MDBS-D is presented in Table 20.

Table 20. Descriptive Statistics of Movement Disorder Burden Score for Dystonia

	PF-02545920 5 mg	PF-02545920 15 mg	Risperidone 3 mg	Placebo
N	74	74	36	74
Mean (SD)	0.0019 (0.01648)	0.0163 (0.08087)	0.0000 (0.00000)	0.0126 (0.10349)
Median	0.0000	0.0000	0.0000	0.0000
Min	0.0000	0.0000	0.0000	0.0000
Max	0.1417	0.6236	0.0000	0.8900

Dystonia MDB Score (subject) = (S x D x C)/TTD (subject).
C = Concomitant Medication Factor (C = 1.5 if an anticholinergic or beta blocker was used for the treatment of a movement disorder; C = 1 if no concomitant medication was used); D = adverse event duration (days); Max = maximum; Min = minimum; MDB = Movement Disorder Burden Score; N = number of subjects; S = the Movement Disorder Severity Score for Dystonia; SD = standard deviation; TTD = total treatment days for the subject.

There were 15 serious adverse events (SAEs) reported in 13 subjects (1 subject had 1 SAE that occurred prior to bring treated); events in 2 subjects were fatal. Two (2) subjects experienced 2 SAEs each; all other subjects experienced 1 SAE each. The incidence of subjects with SAEs was highest in the PF-02545920 15 mg group (8.1%), followed by the risperidone 3 mg group (5.6%), PF-02545920 5 mg group (4.1%), and the placebo group (1.4%). There were 11 cases of nonfatal SAEs in the study, including 2 SAEs of suicidal ideation; 1 was reported on the same day the subject discontinued treatment (PF-02545920 5 mg) and 1 was reported 9 days after the subject discontinued treatment (risperidone 3 mg) and this subject also had homicidal ideation. One (1) SAE exacerbation of schizophrenia occurred before the subject was randomized, ie, the subject did not receive study treatment. Eight (8) subjects were diagnosed with "worsening/increase/exacerbation of schizophrenia/psychosis" (5 were in the PF 02545920 15 mg group, 1 each in the PF-02545920 5 mg group, risperidone 3 mg group, and the placebo group).

The incidence of treatment-emergent, all causality SAEs are presented in Table 21.

Table 21. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

System Organ Class Preferred Term	PF-02545920 5 mg	PF-02545920 15 mg	Risperidone 3 mg	Placebo
	N=74 n (%)	N=74 n (%)	N=36 n (%)	N=74 n (%)
Number of subjects with adverse events	3 (4.1)	6 (8.1)	2 (5.6)	1 (1.4)
Cardiac disorders	1 (1.4)	0	0	0
Acute myocardial infarction	1 (1.4)	0	0	0
Myocardial rupture	1 (1.4)	0	0	0
General disorders and administration	1 (1.4)	0	0	0
Sudden cardiac death	1 (1.4)	0	0	0
Psychiatric disorders	1 (1.4)	6 (8.1)	2 (5.6)	1 (1.4)
Homicidal ideation	0	0	1 (2.8)	0
Psychotic disorder	0	2 (2.7)	0	1 (1.4)
Schizophrenia	1 (1.4)	3 (4.1)	1 (2.8)	0
Suicidal ideation	0	1 (1.4)	1 (2.8)	0

Subjects are only counted once per treatment for each row. Includes data up to 999 days after last dose of study drug. MedDRA (v14.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Affairs; N = total number of subjects; n = number of subjects in pre-specified criteria; v = version.

A total of 14 subjects experienced treatment-emergent AEs resulting in discontinuation from the study: 2 of 74 subjects in the PF-02545920 5 mg group, 5 of 74 subjects in the PF-02545920 15 mg group, 3 of 36 subjects in the risperidone 3 mg group, and 4 of 74 subjects in the placebo group (Table 22). One (1) (risperidone 3 mg) subject discontinued due to an AE that started prior to dosing. All AEs resolved, with the exception of 2 subjects whose AEs were still present at the completion of study participation (psychotic disorder and neutropenia).

A total of 4 subjects experienced SAEs (schizophrenia [exacerbation] in 2 subjects, suicidal ideation, and psychotic disorder, 1 subject each) resulting in discontinuation from the study: 2 of 74 subjects in the PF-02545920 15 mg group, 1 of 36 subjects in the risperidone 3 mg group, and 1 of 74 subjects in the placebo group. All SAEs that resulted in permanent discontinuation were considered resolved.

Table 22. Discontinuations due to Adverse Events

Serial Number	Gender/Age (Years)	MedDRA (v14.0) Preferred Term	Severity	SAE	Outcome	Causality
PF-02545920 5 mg						
1	Male/31	Schizophrenia	Severe	No	Resolved	Disease under study
2	Male/48	Schizophrenia	Severe	No	Resolved	Disease under study
PF-02545920 15 mg						
3	Male/29	Neutropenia	Mild	No	Resolved	Study drug
4	Male/24	Schizophrenia	Moderate	Yes	Resolved	Disease under study
5	Male/47	Dystonia	Moderate	No	Resolved	Study drug
6	Male/25	Suicidal ideation	Moderate	Yes	Resolved	Disease under study
7	Male/53	Psychotic disorder	Moderate	No	Still present	Study drug
Risperidone 3 mg						
8	Male/46	Transaminases increased[a]	Severe	No	Resolved	Other illness – idiopathic liver enzyme elevation
9	Male/32	Schizophrenia	Moderate	Yes	Resolved	Disease under study
10	Male/21	Suicidal ideation	Moderate	No	Resolved	Study drug
Placebo						
11	Male/27	Psychotic disorder	Moderate	Yes	Resolved	Disease under study
12	Male/48	Schizophrenia	Severe	No	Resolved	Study drug
13	Male/28	Neutropenia	Moderate	No	Still present	Study drug
14	Male/37	Fatigue	Moderate	No	Resolved	Study drug

Age was recorded at Screening. MedDRA (v14.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event (according to investigators assessment); v = version.
a. Event began before treatment.

There were no dose reductions reported during the study. The most frequent AE resulting in temporary discontinuation was neutropenia. A total of 6 subjects experienced AEs resulting in temporary discontinuations of study treatment according to the study stopping criteria: 1 of 74 subjects in the PF-02545920 5 mg group, 2 of 74 subjects in the PF-02545920 15 mg group, 1 of 36 subjects in the risperidone 3 mg group, and 2 of 74 subjects in the placebo group. A summary of AEs resulting in temporary discontinuation of study drug is presented in Table 23.

Table 23. Temporary Discontinuations due to Adverse Events – Treatment-Emergent

Serial Number	Gender/Age (years)	MedDRA (v14.0) Preferred Term	Treatment	Severity	SAE	Duration (Hours)	Outcome	Causality
1	Male/46	Neutropenia	PF-02545920 5 mg	Mild	No	147.58	Resolved	Study drug
2	Male/60	Neutropenia	PF-02545920 15 mg	Moderate	No	628.32	Resolved	Other illness; benign ethnic neutropenia
3	Male/25	Oculogyric crisis	PF-02545920 15 mg	Severe	No	24.75	Resolved	Study drug
4	Male/34	Neutropenia	Risperidone 3 mg	Mild	No	73.77	Resolved	Study drug
5	Male/50	Neutropenia	Placebo	Mild	No	143.40	Resolved	Study drug
6	Female/31	Neutropenia	Placebo	Mild	No	72.25	Resolved	Study drug
		Neutropenia	Placebo	Mild	No	50.00	Resolved	Study drug

Age was recorded at Screening.
MedDRA (v14.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event according to investigators assessment; v = version.

Two (2) deaths occurred post-therapy and both subjects were in the PF-02545920 5 mg treatment group. One (1) subject died due to acute myocardial infarction and myocardium rupture and the other due to sudden cardiac death.

Abnormal laboratory test values meeting the criteria for potential clinical significance, regardless of Baseline abnormality, occurred in all treatment groups. Glucose was the most frequently reported abnormality, followed by insulin. None of the changes were considered clinically significant by the Investigator. A summary of abnormal laboratory test values by time is presented in Table 24.

Table 24. Categorical Summary of Laboratory Abnormalities by Early Termination/Day 28 Visit

Laboratory Test	Visit	Category	PF-02545920 5 mg (N=74)		PF-02545920 15 mg (N=74)		Risperidone 3 mg (N=36)		Placebo (N=74)	
			n	%	n	%	n	%	n	%
Glucose										
	ET/Day 28	n assessed	67		67		26		67	
		Within range	59	88.1	59	88.1	20	76.9	58	86.6
		≥126 mg/dL	8	11.9	8	11.9	6	23.1	9	13.4
LDL cholesterol										
	ET/Day 28	n assessed	70		64		30		63	
		Within range	69	98.6	64	100	30	100	63	100
		≥160 mg/dL	1	1.4	0		0		0	
Insulin										
	ET/Day 28	n assessed	62		58		25		58	
		Within range	57	91.9	56	96.6	19	76.0	52	89.7
		≥25 uIU/mL	5	8.1	2	3.4	6	24.0	6	10.3
Cholesterol										
	ET/Day 28	n assessed	71		64		31		64	
		Within range	71	100	63	98.4	31	100	63	98.4
		≥240 mg/dL	0		1	1.6	0		1	1.6
Triglycerides										
	ET/Day 28	n assessed	71		64		30		64	
		Within range	69	97.2	64	100	29	96.7	64	100
		≥200 mg/dL	2	2.8	0		1	3.3	0	

Baseline was defined as the last predose observation.
Only tests specifically labeled as fasting contributed to this summary.
ET = early termination; LDL = low-density lipoprotein; N = number of subjects per treatment group; n = number of subjects in pre-specified criteria.

Abnormal laboratory test values meeting the criteria for potential clinical significance, regardless of Baseline abnormality, occurred in all treatment groups: 55 of 74 (74%) subjects in the PF-02545920 5 mg group, 58 of 74 (78%) subjects in the PF-02545920 15 mg group, 34 of 35 (97%) subjects in the risperidone 3 mg group, and 56 of 74 (76%) subjects in the placebo group. A summary of laboratory test values meeting the criteria for potential clinical significance are presented in Table 25. A total of 6 subjects had parameters which were counted as abnormal due to incorrectly recorded units and reference ranges and these subjects are also included in Table 25. Of the 17 subjects that triggered the WBC/neutrophil stopping criteria, 5 were subjects with a documented history of benign ethnic neutropenia, 6 were subjects who exhibited a pattern of low neutrophil counts from the Screening Visit, and 6 subjects had no evidence of low neutrophil counts prior to dosing study drug. The proportion of subjects triggering the study stopping criteria did not differ substantively between the PF-02545920 5 mg (6 subjects), 15 mg (5 subjects), and placebo (5 subjects) treatment groups.

Table 25. Incidence of Laboratory Test Abnormalities (Without Regard to Baseline Abnormality)

			PF-02545920 5 mg	PF-02545920 15 mg	Risperidone 3 mg	Placebo
Number of subjects evaluable for laboratory abnormalities			74	74	35	74
Number (%) of subjects with laboratory abnormalities			55 (74)	58 (78)	34 (97)	56 (76)
Group Parameter	**Units**	**Criteria**	**N/n %**	**N/n %**	**N/n %**	**N/n %**
Hematology						
Lymphocytes (abs)	$10^3/mm^3$	<0.8 × LLN	74/2 (2.7)	74/2 (2.7)	35/3 (8.6)	74/7 (9.5)
		>1.2 × ULN	74/4 (5.4)	74/1 (1.4)	35/2 (5.7)	74/3 (4.1)
Total neutrophils (abs)	$10^3/mm^3$	<0.8 × LLN	74/6 (8.1)	74/6 (8.1)	35/0 (0)	74/8 (10.8)
		>1.2 × ULN	74/7 (9.5)	74/7 (9.5)	35/5 (14.3)	74/8 (10.8)
Basophils (abs)	$10^3/mm^3$	>1.2 × ULN	74/7 (9.5)	74/3 (4.1)	35/1 (2.9)	74/2 (2.7)
Eosinophils (abs)	$10^3/mm^3$	>1.2 × ULN	74/10 (13.5)	74/4 (5.4)	35/0 (0)	74/1 (1.4)
Monocytes (abs)	$10^3/mm^3$	>1.2 × ULN	74/8 (10.8)	74/6 (8.1)	35/2 (5.7)	74/3 (4.1)
Lipids						
Triglycerides	mg/dL	>1.3 × ULN	74/2 (2.7)	73/0 (0)	34/2 (5.9)	73/1 (1.4)
Hormones						
Prolactin	ng/mL	>1.1 × ULN	74/19 (25.7)	73/23 (31.5)	34/34 (100)	73/20 (27.4)
Clinical Chemistry						
Glucose	mg/dL	<0.6 × LLN	74/0 (0)	74/0 (0)	34/0 (0)	74/0 (0)
	mg/dL	>1.5 × ULN	74/4 (5.4)	74/5 (6.8)	34/5 (14.7)	74/10 (13.5)
Urinalysis (dipstick)						
Urine glucose (qual)		≥1	74/7 (9.5)	74/2 (2.7)	34/1 (2.9)	74/2 (2.7)
Urine ketones (qual)		≥1	74/0 (0)	74/7 (9.5)	34/2 (5.9)	74/7 (9.5)
Urine protein (qual)		≥1	74/3 (4.1)	74/4 (5.4)	34/2 (5.9)	74/0 (0)
Urine blood/Hgb (qual)		≥1	74/6 (8.1)	74/7 (9.5)	34/3 (8.8)	74/6 (8.1)
Urine nitrite		≥1	74/2 (2.7)	74/3 (4.1)	34/2 (5.9)	74/2 (2.7)
Urine leukocyte esterase		≥1	74/10 (13.5)	74/16 (21.6)	34/4 (11.8)	74/9 (12.2)

Percentages are displayed for the laboratory tests having a category with ≥50 evaluable subjects.
Abs = absolute; Hgb = hemoglobin; LLN = lower limit of normal; N = total number of subjects with at least 1 observation of the given laboratory test while on study treatment or during lag time; n = number of subjects with a laboratory abnormality meeting specified criteria while on study treatment or during lag time; qual = qualitative; ULN = upper limit of normal.

Mean changes from Baseline for vital signs data were minor and sitting, standing, and supine vital signs results were within normal ranges for this study population. The pattern of differences between treatment groups was small and varied across body positions without evidence for consistent treatment group effects. No subject was symptomatic as a result of these isolated occurrences. Table 26 presents the categorical summary of standing, sitting, and/or supine vital signs changes from Baseline that met prespecified criteria.

Table 26. Vital Signs Changes From Baseline

Parameter	Criteria	PF-02545920 5 mg		PF-02545920 15 mg		Risperidone 3 mg		Placebo	
		N	n (%)	N	n (%)	N	n (%)	N	n (%)
Increase from Baseline									
Maximum increase from Baseline in supine systolic BP (mm Hg)	≥30	74	2 (2.7)	73	0	34	0	73	1 (1.4)
Maximum increase from Baseline in sitting systolic BP (mm Hg)	≥30	68	1 (1.5)	67	2 (3.0)	30	1 (3.3)	70	2 (2.9)
Maximum increase from Baseline in standing systolic BP (mm Hg)	≥30	74	2 (2.7)	73	0	34	0	72	0
Maximum increase from Baseline in supine diastolic BP (mm Hg)	≥20	74	1 (1.4)	73	4 (5.5)	34	0	73	1 (1.4)
Maximum increase from Baseline in sitting diastolic BP (mm Hg)	≥20	68	2 (2.9)	67	7 (10.4)	30	1 (3.3)	70	6 (8.6)
Maximum increase from Baseline in standing diastolic BP (mm Hg)	≥20	74	1 (1.4)	73	2 (2.7)	34	0	72	5 (6.9)
Decrease from Baseline									
Maximum decrease from Baseline in supine systolic BP (mm Hg)	≥30	74	0	73	0	34	3 (8.8)	73	2 (2.7)
Maximum decrease from Baseline in sitting systolic BP (mm Hg)	≥30	68	1 (1.5)	67	0	30	0	70	2 (2.9)
Maximum decrease from Baseline in standing systolic BP (mm Hg)	≥30	74	0	73	2 (2.7)	34	2 (5.9)	72	2 (2.8)
Maximum decrease from Baseline in supine diastolic BP (mm Hg)	≥20	74	1 (1.4)	73	2 (2.7)	34	2 (5.9)	73	3 (4.1)
Maximum decrease from Baseline in sitting diastolic BP (mm Hg)	≥20	68	1 (1.5)	67	3 (4.5)	30	1 (3.3)	70	5 (7.1)
Maximum decrease from Baseline in standing diastolic BP (mm Hg)	≥20	74	0	73	3 (4.1)	34	1 (2.9)	72	8 (11.1)

Baseline was defined as the latest non- missing value from a range of pretreatment visits.
BP = blood pressure; N = number of subjects evaluated against criteria; n = number of subjects that met criteria.

ECG results, including mean Baseline and change from Baseline for ECG parameters (respiratory rate [RR], heart rate, PR, QRS, QT, QT corrected using Bazett's correction [QTcB], and QT corrected using Friericia's correction [QTcF]), were within normal limits, and no trends were observed over time. No changes from Baseline were of clinical concern. Categorical summary of maximum absolute values and maximum increases from Baseline for PR, QRS, QTcB, and QTcF, had no subjects that met the predefined criteria for potential clinical concern.

Body weight and waist circumference from Baseline and change from Baseline in the risperidone 3 mg group, demonstrated a greater mean weight gain and proportion of subjects gaining >7% of their body weight than the other treatment groups.

Table 27 presents the mean change from Baseline to Week 4 for the ESRS-A with observations of parkinsonism, dystonia, dyskinesia, and akathisia.

Table 27. Abbreviated Extrapyramidal Symptom Rating Scale Parameters for Mean Change From Baseline to Week 4

Parameter	PF-02545920 5 mg (N=74)	PF-02545920 15 mg (N=74)	Risperidone 3 mg (N=36)	Placebo (N=74)
CGI-S parkinsonism				
n	63	58	26	63
Mean (SD) change from Baseline to Week 4	0.000 (0.1796)	0.000 (0.2649)	0.154 (0.6127)	0.000 (0.3592)
CGI-S dystonia				
n	63	58	26	63
Mean (SD) change from Baseline to Week 4	0.016 (0.2194)	0.034 (0.1841)	0	0.016 (0.1260)
CGI-S dyskinesia				
n	63	58	26	63
Mean (SD) change from Baseline to Week 4	-0.016 (0.4916)	0.103 (0.6124)	-0.038 (0.1961)	0.016 (0.2194)
CGI-S akathisia				
n	63	58	26	63
Mean (SD) change from Baseline to Week 4	0.000 (0.3592)	0.155 (0.5864)	0.038 (0.7736)	-0.032 (0.3578)
ESRS-A parkinsonism score				
n	63	58	26	63
Mean (SD) change from Baseline to Week 4	0.143 (0.8397)	0.086 (1.3414)	-0.038 (0.9157)	-0.190 (1.4126)
ESRS-A dystonia score				
n	63	58	26	63
Mean (SD) change from Baseline to Week 4	0.000 (0.4016)	0.207 (1.1044)	0	0.032 (0.2520)
ESRS-A dyskinesia score				
n	63	58	26	63
Mean (SD) change from Baseline to Week 4	0.016 (0.4916)	0.207 (1.0884)	0.038 (0.4455)	-0.032 (0.3578)
ESRS-A akathisia score				
n	63	58	26	63
Mean (SD) change from Baseline to Week 4	0.032 (0.6713)	0.328 (1.3297)	0.154 (1.2866)	-0.095 (0.9283)

Baseline was defined as the last predose observation.
CGI-S = Clinical Global Impression of Severity; ESRS-A = Extrapyramidal Symptom Rating Scale-Abbreviated, N = total number of subjects per treatment group, n = number of subjects evaluable for parameters, SD = standard deviation.

A categorical summary of C-SSRS is presented in Table 28.

Table 28. Descriptive Summary of Columbia-Suicide Severity Rating Scale

	PF-02545920 5 mg	PF-02545920 15 mg	Risperidone 3 mg	Placebo
	N=74	N=74	N=36	N=74
Baseline				
Number assessed	74 (100%)	74 (100%)	36 (100%)	74 (100%)
Suicide attempt	1 (1.4%)	1 (1.4%)	0	1 (1.4%)
Actual attempt	1 (1.4%)	1 (1.4%)	0	1 (1.4%)
Preparatory acts towards imminent suicidal behavior	1 (1.4%)	0	0	2 (2.7%)
Aborted attempt	0	0	0	2 (2.7%)
Interrupted attempt	0	0	0	0
Preparatory acts or behavior	1 (1.4%)	0	0	0
Suicidal ideation	1 (1.4%)	4 (5.4%)	1 (2.8%)	3 (4.1%)
Wish to be dead	1 (1.4%)	3 (4.1%)	0	3 (4.1%)
Non-specific active suicidal thoughts	1 (1.4%)	3 (4.1%)	1 (2.8%)	2 (2.7%)
Active suicidal ideation with any methods (not plan) without intent to act	1 (1.4%)	1 (1.4%)	0	1 (1.4%)
Active suicidal ideation with some intent to act, without specific plan	1 (1.4%)	0	0	1 (1.4%)
Active suicidal ideation with specific plan and intent	0	1 (1.4%)	0	1 (1.4%)
Self-injurious behavior, no suicidal intent	0	1 (1.4%)	0	0
Has subject engaged in non-suicidal self-injurious behavior	0	1 (1.4%)	0	0
Week 1/ET				
Number assessed	74 (100%)	74 (100%)	34 (94.4%)	73 (98.6%)
Suicide attempt	0	0	0	0
Actual attempt	0	0	0	0
Preparatory acts towards imminent suicidal behavior	0	1 (1.4%)	0	0
Aborted attempt	0	0	0	0
Interrupted attempt	0	0	0	0
Preparatory acts or behavior	0	1 (1.4%)	0	0
Suicidal ideation	0	4 (5.4%)	0	0
Wish to be dead	0	2 (2.7%)	0	0
Non-specific active suicidal thoughts	0	3 (4.1%)	0	0
Active suicidal ideation with any methods (not plan) without intent to act	0	2 (2.7%)	0	0
Active suicidal ideation with some intent to act, without specific plan	0	1 (1.4%)	0	0
Active suicidal ideation with specific plan and intent	0	1 (1.4%)	0	0
Self-injurious behavior, no suicidal intent	0	0	0	0
Has subject engaged in non-suicidal self-injurious behavior	0	0	0	0
Week 2/ET				
Number assessed	71 (95.9%)	72 (97.3%)	32 (88.9%)	69 (93.2%)
Suicide attempt	0	0	0	0
Actual attempt	0	0	0	0
Preparatory acts towards imminent suicidal behavior	0	0	0	0
Aborted attempt	0	0	0	0
Interrupted attempt	0	0	0	0
Preparatory acts or behavior	0	0	0	0
Suicidal ideation	1 (1.4%)	3 (4.1%)	0	1 (1.4%)

Table 28. Descriptive Summary of Columbia-Suicide Severity Rating Scale

	PF-02545920 5 mg	PF-02545920 15 mg	Risperidone 3 mg	Placebo
	N=74	N=74	N=36	N=74
Wish to be dead	1 (1.4%)	3 (4.1%)	0	1 (1.4%)
Non-specific active suicidal thoughts	0	1 (1.4%)	0	0
Active suicidal ideation with any methods (not plan) without intent to act	0	1 (1.4%)	0	0
Active suicidal ideation with some intent to act, without specific plan	0	0	0	0
Active suicidal ideation with specific plan and intent	0	0	0	0
Self-injurious behavior, no suicidal intent	0	0	0	0
Has subject engaged in non-suicidal self-injurious behavior	0	0	0	0
Week 3/ET				
Number assessed	68 (91.9%)	69 (93.2%)	28 (77.8%)	69 (93.2%)
Suicide attempt	0	0	0	0
Actual attempt	0	0	0	0
Preparatory acts towards imminent suicidal behavior	0	0	0	0
Aborted attempt	0	0	0	0
Interrupted attempt	0	0	0	0
Preparatory acts or behavior	0	0	0	0
Suicidal ideation	0	2 (2.7%)	0	1 (1.4%)
Wish to be dead	0	2 (2.7%)	0	1 (1.4%)
Non-specific active suicidal thoughts	0	2 (2.7%)	0	1 (1.4%)
Active suicidal ideation with any methods (not plan) without intent to act	0	1 (1.4%)	0	1 (1.4%)
Active suicidal ideation with some intent to act, without specific plan	0	0	0	0
Active suicidal ideation with specific plan and intent	0	0	0	0
Self-injurious behavior, no suicidal intent	0	0	0	0
Has subject engaged in non-suicidal self-injurious behavior	0	0	0	0
Week 4/ET				
Number assessed	66 (89.2%)	63 (85.1%)	27 (75.0%)	64 (86.5%)
Suicide attempt	0	0	0	0
Actual attempt	0	0	0	0
Preparatory acts towards imminent suicidal behavior	0	0	0	0
Aborted attempt	0	0	0	0
Interrupted attempt	0	0	0	0
Preparatory acts or behavior	0	0	0	0
Suicidal ideation	3 (4.1%)	3 (4.1%)	1 (2.8%)	0
Wish to be dead	3 (4.1%)	3 (4.1%)	0	0
Non-Specific Active Suicidal Thoughts	1 (1.4%)	0	1 (2.8%)	0
Active suicidal ideation with any methods (not plan) without intent to act	1 (1.4%)	0	1 (2.8%)	0
Active suicidal ideation with some intent to act, without specific plan	0	0	1 (2.8%)	0
Active suicidal ideation with specific plan and intent	0	0	0	0

Table 28. Descriptive Summary of Columbia-Suicide Severity Rating Scale

	PF-02545920 5 mg	PF-02545920 15 mg	Risperidone 3 mg	Placebo
	N=74	N=74	N=36	N=74
Self-injurious behavior, no suicidal intent	0	0	0	0
Has subject engaged in non-suicidal self-injurious behavior	0	0	0	0
Follow-Up				
Number assessed	61 (82.4%)	53 (71.6%)	26 (72.2%)	63 (85.1%)
Suicide attempt	0	0	0	0
Actual attempt	0	0	0	0
Preparatory acts towards imminent suicidal behavior	0	0	0	0
Aborted attempt	0	0	0	0
Interrupted attempt	0	0	0	0
Preparatory acts or behavior	0	0	0	0
Suicidal ideation	1 (1.4%)	0	1 (2.8%)	0
Wish to be dead	1 (1.4%)	0	1 (2.8%)	0
Non-specific active suicidal thoughts	0	0	1 (2.8%)	0
Active suicidal ideation with any methods (not plan) without intent to act	0	0	1 (2.8%)	0
Active suicidal ideation with some intent to act, without specific plan	0	0	0	0
Active suicidal ideation with specific plan and intent	0	0	0	0
Self-injurious behavior, no suicidal intent	0	0	0	0
Has subject engaged in non-suicidal self-injurious behavior	0	0	0	0

Baseline is defined as the Week 0 measurement.
Percentages are based on the number of subjects in safety population.
ET = early termination; N = number of subjects per treatment group.

CONCLUSIONS:

At the a prior specified level of significance of 0.1 (1-sided), it can be concluded from the primary analysis for the mean change from Baseline in the PANSS total, that neither dose of PF-02545920 was different from placebo. The risperidone 3 mg group was statistically significant at a 0.1 (1-sided) level of significance when compared to placebo. The analysis of the secondary endpoints revealed a similar pattern for change from Baseline, with neither dose of PF-02545920 demonstrating a difference from placebo in the majority of the endpoints evaluated. The risperidone 3 mg group was statistically significant when compared to placebo in the majority of the study secondary efficacy endpoints.

It was observed that PF-02545920 concentration increased proportionally from 5 mg to 15 mg (titrated) BID dose. Also, as the C_{trough} at various visits was similar within groups it suggests that steady state was achieved after 1 week of PF-02545920 dosing. Further, the observed PK in this study was consistent with the model predicted exposures which are expected to be adequate for binding phosphodiesterase 10 enzyme.

The 5 mg and 15 mg BID dose groups of PF-02545920 appeared to be generally well tolerated, with an overall tolerability profile comparable to risperidone. In general, there

were few differences in AE frequency between the treatment groups, and most AEs were mild or moderate in severity. The most common AEs more frequent with PF-02545920 were akathisia in both PF-02545920 groups and dystonia and sedation/somnolence in the 15 mg group. Statistically, there was insufficient evidence to suggest that the incidence of dystonia for both the PF-02545920 groups was worse than placebo, although the greatest number of cases of dystonia occurred in the PF-02545920 15 mg group. Dystonia AEs were successfully managed with as occasion requires (prn) use of anticholinergic medication except in 1 case that required 4 days of prophylactic treatment. There were no substantive differences between the PF-02545920 groups and the placebo group in the proportion of subjects with neutropenia AEs or who met neutrophil count study stopping criteria. The pattern of differences between treatment groups in vital signs change from Baseline varied across body positions without evidence for consistent treatment group effects and there were no trends for differences between treatment groups in ECG parameters. The risperidone 3 mg group demonstrated greater mean weight gain and a greater proportion of subjects gaining >7% of their body weight than the other treatment groups.