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Trial record **1 of 1** for: R076477BIM3004

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A Study to Evaluate the Effectiveness and Safety of Extended-Release (ER) Paliperidone Compared With Placebo in Delaying the Recurrence of Symptoms in Bipolar I Disorder

This study has been completed.

Sponsor:
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

Information provided by (Responsible Party):
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

ClinicalTrials.gov Identifier:
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History of Changes

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Results First Received: April 26, 2011

Study Type:	Interventional
Study Design:	Allocation: Randomized; Endpoint Classification: Efficacy Study; Intervention Model: Parallel Assignment; Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor); Primary Purpose: Treatment
Condition:	Bipolar Disorder
Interventions:	Drug: Olanzapine Drug: Paliperidone ER Drug: Placebo

Participant Flow

Hide Participant Flow

Recruitment Details

Key information relevant to the recruitment process for the overall study, such as dates of the recruitment period and locations
No text entered.

Pre-Assignment Details

Significant events and approaches for the overall study following participant enrollment, but prior to group assignment
The double-blind (ie, niether physician nor patient knows the treatment that the patient receives) study has 15-week acute/continuation phase followed by variable-duration maintenance phase (lasting until patient had recurrence or discontinued treatment) to assess effect of paliperidone on maintenance of remission of Bipolar I Disorder

Reporting Groups

	Description
Paliperidone Extented Release (ER)	Acute and continuation period. Paliperidone ER: Oral tablet, 3 mg/day to 12 mg/day, Once daily.
Olanzapine	Acute and continuation period. Olanzapine: Oral tablet, 5 mg/day to 20 mg/day, Once daily.
Pali/Placebo	Maintenance period. Placebo (Paliperidone in the acute and continuation period).
Pali/Pali	Maintenance period. Paliperidone ER: Oral tablet, 3 mg/day to 12 mg/day, Once daily (Paliperidone in

	the acute and continuation period)
Olan/Olan	Maintenance period. Olanzapine Oral tablet, 5 mg/day to 20 mg/day, Once daily (Olanzapine in the acute and continuation period)

Participant Flow for 2 periods

Period 1: Acute/Continuation

	Paliperidone Extented Release (ER)	Olanzapine	Pali/Placebo	Pali/Pali	Olan/Olan
STARTED	614 [1]	148 [2]	0 [3]	0 [3]	0 [3]
COMPLETED	308	86	0 [3]	0 [3]	0 [3]
NOT COMPLETED	306	62	0	0	0
Adverse Event	62	13	0	0	0
Death	2	0	0	0	0
Lack of Efficacy	106	12	0	0	0
Lost to Follow-up	23	7	0	0	0
Protocol Violation	10	2	0	0	0
Withdrawal by Subject	92	24	0	0	0
Not specified	11	4	0	0	0

[1] 617 participants were assigned to paliperidone, out of which 614 took the study medication.
[2] 149 participants were assigned to paliperidone, out of which 148 took the study medication.
[3] "0" indicates this group is not relevant to acute and continuation period.

Period 2: Maintenance

	Paliperidone Extented Release (ER)	Olanzapine	Pali/Placebo	Pali/Pali	Olan/Olan
STARTED	0 [1]	0 [1]	147 [2]	149 [3]	83
COMPLETED	0 [1]	0 [1]	96	96	44
NOT COMPLETED	0	0	51	53	39
Adverse Event	0	0	4	5	7
Death	0	0	0	2	0
Lost to Follow-up	0	0	5	8	10
Pregnancy	0	0	1	0	0
Protocol Violation	0	0	4	1	1
Withdrawal by Subject	0	0	26	28	18
Not specified	0	0	11	9	3

[1] "0" indicates this group is not relevant to maintenance period.
[2] 148 participants were assigned to pali/placebo, out of which 147 took the study medication.
[3] 152 participants were assigned to pali/pali, out of which 149 took the study medication.

Baseline Characteristics

Hide Baseline Characteristics

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
No text entered.

Reporting Groups

	Description
Paliperidone ER	Acute and continuation period. Paliperidone ER: Oral tablet, 3 mg/day to 12 mg/day, Once daily.
Olanzapine	Acute and continuation period. Olanzapine: Oral tablet, 5 mg/day to 20 mg/day, Once daily.
Total	Total of all reporting groups

Baseline Measures

	Paliperidone ER	Olanzapine	Total
Number of Participants [units: participants]	**614**	**148**	**762**
Age [units: participants]			
<=18 years	**7**	**3**	**10**
Between 18 and 65 years	**606**	**145**	**751**
>=65 years	**1**	**0**	**1**
Age [units: years] Mean (Standard Deviation)	**39.7 (11.93)**	**39.2 (11.49)**	**39.6 (11.84)**
Gender [units: participants]			
Female	**310**	**80**	**390**
Male	**304**	**68**	**372**
Region of Enrollment [units: participants]			
Asia	**162**	**36**	**198**
Eastern Europe	**129**	**31**	**160**
European Union	**71**	**19**	**90**
North America	**177**	**41**	**218**
Other	**75**	**21**	**96**
India	**69**	**14**	**83**
Malaysia	**7**	**2**	**9**
China	**86**	**20**	**106**
Russian Federation	**51**	**11**	**62**
Serbia	**32**	**8**	**40**
Ukraine	**46**	**12**	**58**
Bulgaria	**27**	**6**	**33**
Germany	**6**	**3**	**9**
Poland	**16**	**5**	**21**
Romania	**22**	**5**	**27**
Costa Rica	**12**	**4**	**16**
Morocco	**6**	**2**	**8**
Panama	**3**	**1**	**4**
South Africa	**26**	**6**	**32**

Tunisia	**10**	**4**	**14**
Turkey	**18**	**4**	**22**
United States	**177**	**41**	**218**
AgeCategorical [units: participants]			
18-25	**98**	**25**	**123**
26-50	**378**	**96**	**474**
51-65	**138**	**27**	**165**
>65	**0**	**0**	**0**
<18	**0**	**0**	**0**

Outcome Measures

Hide All Outcome Measures

1. Primary: Time to Recurrence of Any Mood Symptoms (Manic or Depressive) Associated With Bipolar I Disorder [Time Frame: Date of randomization into the maintenance phase until the first occurrence of recurrence of any symptoms or discontinuation from the study, assessed over a period of 41 months.]

Measure Type	Primary
Measure Title	Time to Recurrence of Any Mood Symptoms (Manic or Depressive) Associated With Bipolar I Disorder
Measure Description	Time to first recurrence of any mood symptoms (ie, manic or depressive) associated with bipolar I disorder during the maintenance phase, after maintaining clinical stability during continued treatment with paliperidone ER over a period of 15 weeks. The time period was from occurrence of acute manic or mixed episode to Week 15. This outcome was measured using combination of various scales, hospitalization for any mood symptoms, use of any medicines for an mood episode and clinical events suggestive of recurrent mood episode associated with bipolar I disorder.
Time Frame	Date of randomization into the maintenance phase until the first occurrence of recurrence of any symptoms or discontinuation from the study, assessed over a period of 41 months.
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intent-to-treat analysis set (ITT) in maintenance (MA) phase, which included participants who entered the MA phase and took at least 1 dose of study medication.

Reporting Groups

	Description
Paliperidone ER	Acute and continuation period. Paliperidone ER: Oral tablet, 3 mg/day to 12 mg/day, Once daily.
Olanzapine	Acute and continuation period. Olanzapine: Oral tablet, 5 mg/day to 20 mg/day, Once daily.
Pali/Placebo	Maintenance period. Placebo (Paliperidone in the acute and continuation period).
Pali/Pali	Maintenance period. Paliperidone ER: Oral tablet, 3 mg/day to 12 mg/day, Once daily (Paliperidone in the acute and continuation period)
Olan/Olan	Maintenance period. Olanzapine Oral tablet, 5 mg/day to 20 mg/day, Once daily (Olanzapine in the acute and continuation period)

Measured Values

	Paliperidone	**Olanzapine**	**Pali/Placebo**	**Pali/Pali**	**Olan/Olan**

	ER				
Number of Participants Analyzed [units: participants]	**0**	**0**	**144**	**146**	**82**
Time to Recurrence of Any Mood Symptoms (Manic or Depressive) Associated With Bipolar I Disorder [units: Days] Number (95% Confidence Interval)					
25% Quantile of Time to Recurrence			**85.0 (72.0 to 141.0)**	**140.0 (72.0 to 274.0)**	**541 (386.0 to N/A) [1]**
Median Time to Recurrence			**283.0 (203.0 to 531.0)**	**558.0 (401.0 to 804.0)**	**NA [2]**

[1] There were 23% of the subjects in Olan/Olan treatment group who reported recurrence. Hence 25% quantile of time to recurrence was not observed

[2] There were 23% of the subjects in Olan/Olan treatment group who reported recurrence. Hence median time to recurrence was not observed

Statistical Analysis 1 for Time to Recurrence of Any Mood Symptoms (Manic or Depressive) Associated With Bipolar I Disorder

Groups [1]	Pali/Placebo
Method [2]	Weighted Z- test
P Value [3]	0.017

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	Null hypothesis: there is no difference between Pali/Pali and Pali/Placebo in the time to recurrence of any mood symptoms related to bipolar I disorder. An interim analysis was performed when approximately 85% of the required number of recurrences were reported in Pali/Pali and Pali/Placebo treatment groups. A flexible group-sequential approach was adopted. The general family of alpha spending function based on the rho-family with rho=2.5 at overall type I error of 0.025 (1-sided) was employed.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	No text entered.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	The two treatment groups were compared using a weighted z-statistic based on rho-family of alpha spending function at information fraction of 85.0% at interim analysis analysis (rho=2.5) at 0.025 (1-sided) level. One-sided alpha at final was 0.0195.

2. Secondary: Time to Recurrence of Manic Symptoms Associated With Bipolar I Disorder [Time Frame: Date of randomization into the maintenance phase until the first occurrence of recurrence of manic symptoms or discontinuation from the study, assessed over a period of 41 months.]

Measure Type	Secondary
Measure Title	Time to Recurrence of Manic Symptoms Associated With Bipolar I Disorder
Measure Description	This was the key secondary efficacy end-point. Pali/Pali and Pali/Placebo were compared with each other with respect to time to recurrence of manic symptoms. The criterias used for this analysis were similar to criterias used for primary analysis.
Time Frame	Date of randomization into the maintenance phase until the first occurrence of recurrence of manic symptoms or discontinuation from the study, assessed over a period of 41 months.
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intent-to-treat analysis set in MA phase, which included participants who entered the MA phase and took at least 1 dose of study medication.

Reporting Groups

	Description
Paliperidone ER	Acute and continuation period. Paliperidone ER: Oral tablet, 3 mg/day to 12 mg/day, Once daily.
Olanzapine	Acute and continuation period. Olanzapine: Oral tablet, 5 mg/day to 20 mg/day, Once daily.
Pali/Placebo	Maintenance period. Placebo (Paliperidone in the acute and continuation period).
Pali/Pali	Maintenance period. Paliperidone ER: Oral tablet, 3 mg/day to 12 mg/day, Once daily (Paliperidone in the acute and continuation period)
Olan/Olan	Maintenance period. Olanzapine Oral tablet, 5 mg/day to 20 mg/day, Once daily (Olanzapine in the acute and continuation period)

Measured Values

	Paliperidone ER	**Olanzapine**	**Pali/Placebo**	**Pali/Pali**	**Olan/Olan**
Number of Participants Analyzed [units: participants]	**0**	**0**	**144**	**146**	**82**
Time to Recurrence of Manic Symptoms Associated With Bipolar I Disorder [units: Days] Number (95% Confidence Interval)					
25% Quantile of Time to Recurrence			**194.0 (125.0 to 283.0)**	**498.0 (294.0 to 813.0)**	**NA (595.0 to N/A) [1]**
Median Time to Recurrence			**550.0 (419.0 to 878)**	**NA (813 to N/A) [2]**	**NA [3]**

[1] There were 11% of the subjects in the Olan/Olan group who reported recurrence of manic symptoms. Hence 25% quartile of time to recurrence was not observed.

[2] There were 21% of the subjects in the Pali/Pali group who reported recurrence of manic symptoms. Hence median time to recurrence was not observed.

[3] There were 11% of the subjects in the Olan/Olan group who reported recurrence of manic symptoms. Hence median time to recurrence was not observed.

Statistical Analysis 1 for Time to Recurrence of Manic Symptoms Associated With Bipolar I Disorder

Groups [1]	Pali/Placebo
Method [2]	Weighted z-test
P Value [3]	<0.001

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	At the time of interim analysis of the primary efficacy endpoint, the proportion of recurrence of manic symptoms was 81.9% of the number of recurrence of manic symptoms at final analysis. A flexible group-sequential approach was adopted. The general family of alpha spending function based on the rho-family with rho=2.5 at overall type I error of 0.025 (1-sided) was employed.
[2]	Other relevant method information, such as adjustments or degrees of freedom:

	No text entered.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	The two treatment groups were compared using a weighted z-statistic based on rho-family of alpha spending function at information fraction of 81.9% at interim analysis analysis (rho=2.5) at 0.025 (1-sided) level. One-sided alpha at final was 0.0198.

3. Secondary: Time to Recurrence of Depressive Symptoms Associated With Bipolar I Disorder [Time Frame: Date of randomization into the maintenance phase until the first occurrence of recurrence of depressive symptoms or discontinuation from the study, assessed over a period of 41 months.]

Measure Type	Secondary
Measure Title	Time to Recurrence of Depressive Symptoms Associated With Bipolar I Disorder
Measure Description	Pali/Pali and Pali/Placebo were compared with each other with respect to time to recurrence of depressive symptoms. The criterias used for this analysis were similar to criterias used for primary analysis.
Time Frame	Date of randomization into the maintenance phase until the first occurrence of recurrence of depressive symptoms or discontinuation from the study, assessed over a period of 41 months.
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intent-to-treat analysis set in MA period, which included participants who entered the maintenance phase and took at least 1 dose of study medication.

Reporting Groups

	Description
Paliperidone ER	Acute and continuation period. Paliperidone ER: Oral tablet, 3 mg/day to 12 mg/day, Once daily.
Olanzapine	Acute and continuation period. Olanzapine: Oral tablet, 5 mg/day to 20 mg/day, Once daily.
Pali/Placebo	Maintenance period. Placebo (Paliperidone in the acute and continuation period).
Pali/Pali	Maintenance period. Paliperidone ER: Oral tablet, 3 mg/day to 12 mg/day, Once daily (Paliperidone in the acute and continuation period)
Olan/Olan	Maintenance period. Olanzapine Oral tablet, 5 mg/day to 20 mg/day, Once daily (Olanzapine in the acute and continuation period)

Measured Values

	Paliperidone ER	Olanzapine	Pali/Placebo	Pali/Pali	Olan/Olan
Number of Participants Analyzed [units: participants]	**0**	**0**	**144**	**146**	**82**
Time to Recurrence of Depressive Symptoms Associated With Bipolar I Disorder [units: Days] Number (95% Confidence Interval)			**503.0 (203.0 to N/A)** [1]	**448.0 (170.0 to 750.0)**	**NA (651.0 to N/A)** [2]

[1] There were 18% of the participants in the Pali/Placebo group who reported recurrence of depressive symptoms.

[2] There were 12% of the participants in the Olan/Olan group who reported recurrence of depressive symptoms. Hence the 25% quartile of the time to recurrence of depressive symptoms was not observed.

Statistical Analysis 1 for Time to Recurrence of Depressive Symptoms Associated With Bipolar I Disorder

Groups [1]	Pali/Placebo vs. Pali/Pali
Method [2]	Regression, Cox
Hazard Ratio (HR) [3]	0.88
95% Confidence Interval	0.53 to 1.46

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	The percent of participants who reported recurrence of depressive symptoms was: 18% Pali/Placebo, 24% Pali/Pali.
[3]	Other relevant estimation information:
	Hazard ratio was estimated with Pali/Placebo in the numerator and Pali/Pali in the denominator

4. Other Pre-specified: Young Mania Rating Scale (YMRS): Change From Baseline [Time Frame: From 1st randomization into acute phase to end of acute/continuation phase (ie, up to 15 weeks after 1st randomization), or from randomization into maintenance (MA) phase to the end of MA phase (ie, up to 175 weeks (or 41 months) after 2nd randomization).]

Measure Type	Other Pre-specified
Measure Title	Young Mania Rating Scale (YMRS): Change From Baseline
Measure Description	This is method by which condition of patient suffering with mania is checked. In this scale patient's condition is assessed using 11 items. A severity rating is assigned to each of 11 items based on the how subject feels of his or her condition and the physicians observation of patients behavior. The range of the scale is 0 to 60. A higher score indicates a more severe condition. Change from baseline (Day 105) in the double-blind maintenance phase to the last postbaseline assessment.
Time Frame	From 1st randomization into acute phase to end of acute/continuation phase (ie, up to 15 weeks after 1st randomization), or from randomization into maintenance (MA) phase to the end of MA phase (ie, up to 175 weeks (or 41 months) after 2nd randomization).
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intent-to-Treat

Reporting Groups

	Description
Paliperidone ER	Acute and continuation period. Paliperidone ER: Oral tablet, 3 mg/day to 12 mg/day, Once daily.
Olanzapine	Acute and continuation period. Olanzapine: Oral tablet, 5 mg/day to 20 mg/day, Once daily.
Pali/Placebo	Maintenance period. Placebo (Paliperidone in the acute and continuation period).
Pali/Pali	Maintenance period. Paliperidone ER: Oral tablet, 3 mg/day to 12 mg/day, Once daily (Paliperidone in the acute and continuation period)
Olan/Olan	Maintenance period. Olanzapine Oral tablet, 5 mg/day to 20 mg/day, Once daily (Olanzapine in the acute and continuation period)

Measured Values

	Paliperidone ER	**Olanzapine**	**Pali/Placebo**	**Pali/Pali**	**Olan/Olan**
Number of Participants Analyzed					

[units: participants]	602	145	143	144	81
Young Mania Rating Scale (YMRS): Change From Baseline [units: Scores on the scale] Mean (Standard Deviation)	-19.2 (11.23)	-19.3 (10.25)	9.0 (11.78)	4.2 (9.33)	1.3 (6.26)

Statistical Analysis 1 for Young Mania Rating Scale (YMRS): Change From Baseline

Groups [1]	Pali/Placebo vs. Pali/Pali
Method [2]	ANCOVA
P Value [3]	<0.001
Mean Difference (Final Values) [4]	-4.5
95% Confidence Interval	-6.92 to -1.98

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	Change from Baseline (Maintenance Phase) to Endpoint (Maintenance Phase)
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	ANCOVA model with treatment group (Pali/Pali, Pali/Placebo) and country as factors with baseline value as covariate
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.
[4]	Other relevant estimation information:
	No text entered.

5. Other Pre-specified: Montgomery-Asberg Depression Rating Scale (MADRS) [Time Frame: From 1st randomization into acute phase to end of acute/continuation phase (ie, up to 15 weeks after 1st randomization), or from randomization into maintenance (MA) phase to the end of MA phase (ie, up to 175 weeks (or 41 months) after 2nd randomization).]

Measure Type	Other Pre-specified
Measure Title	Montgomery-Asberg Depression Rating Scale (MADRS)
Measure Description	The MADRS consists of 10 items covering all the important complaints which patient with depression have (apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts). Item is scored from 0 (normal) to 6 (severe). Total score (0 to 60) is calculated by adding the scores of all 10 items. A higher score represents a more severe condition. Negative Change in Score Indicates Improvement.
Time Frame	From 1st randomization into acute phase to end of acute/continuation phase (ie, up to 15 weeks after 1st randomization), or from randomization into maintenance (MA) phase to the end of MA phase (ie, up to 175 weeks (or 41 months) after 2nd randomization).
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intent-to-Treat

Reporting Groups

	Description

Paliperidone ER	Acute and continuation period. Paliperidone ER: Oral tablet, 3 mg/day to 12 mg/day, Once daily.
Olanzapine	Acute and continuation period. Olanzapine: Oral tablet, 5 mg/day to 20 mg/day, Once daily.
Pali/Placebo	Maintenance period. Placebo (Paliperidone in the acute and continuation period).
Pali/Pali	Maintenance period. Paliperidone ER: Oral tablet, 3 mg/day to 12 mg/day, Once daily (Paliperidone in the acute and continuation period)
Olan/Olan	Maintenance period. Olanzapine Oral tablet, 5 mg/day to 20 mg/day, Once daily (Olanzapine in the acute and continuation period)

Measured Values

	Paliperidone ER	Olanzapine	Pali/Placebo	Pali/Pali	Olan/Olan
Number of Participants Analyzed [units: participants]	**597**	**144**	**143**	**144**	**81**
Montgomery-Asberg Depression Rating Scale (MADRS) [units: Scores on the scale] Mean (Standard Deviation)	**-2.7 (8.21)**	**-2.7 (7.82)**	**6.0 (9.16)**	**6.1 (10.10)**	**2.5 (7.10)**

Statistical Analysis 1 for Montgomery-Asberg Depression Rating Scale (MADRS)

Groups [1]	Pali/Placebo vs. Pali/Pali
Method [2]	ANCOVA
P Value [3]	0.763
Mean Difference (Final Values) [4]	0.3
95% Confidence Interval	-1.87 to 2.55

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	Change from Baseline (Maintenance Phase) to Endpoint (Maintenance Phase)
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	ANCOVA Model with treatment (Pali/Pali, Pali/Placebo) and country as factors with baseline value as covariate
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.
[4]	Other relevant estimation information:
	No text entered.

6. Other Pre-specified: Global Assessment of Functioning (GAF): Change From Baseline [Time Frame: From 1st randomization into acute phase to end of acute/continuation phase (ie, up to 15 weeks after 1st randomization), or from randomization into maintenance (MA) phase to the end of MA phase (ie, up to 175 weeks (or 41 months) after 2nd randomization).]

Measure Type	Other Pre-specified
Measure Title	Global Assessment of Functioning (GAF): Change From Baseline
Measure Description	This scale is used when the clinical progress of a subject needs to be assessed in global terms, using a single measure. The GAF scale is rated with respect to psychological, social, and occupational functioning at the time of the assessment only. A higher score indicates a better functioning, with an overall range from 1 to 100. Positive Change in Score Indicates Improvement.

Time Frame	From 1st randomization into acute phase to end of acute/continuation phase (ie, up to 15 weeks after 1st randomization), or from randomization into maintenance (MA) phase to the end of MA phase (ie, up to 175 weeks (or 41 months) after 2nd randomization).
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intent-to-Treat

Reporting Groups

	Description
Paliperidone ER	Acute and continuation period. Paliperidone ER: Oral tablet, 3 mg/day to 12 mg/day, Once daily.
Olanzapine	Acute and continuation period. Olanzapine: Oral tablet, 5 mg/day to 20 mg/day, Once daily.
Pali/Placebo	Maintenance period. Placebo (Paliperidone in the acute and continuation period).
Pali/Pali	Maintenance period. Paliperidone ER: Oral tablet, 3 mg/day to 12 mg/day, Once daily (Paliperidone in the acute and continuation period)
Olan/Olan	Maintenance period. Olanzapine Oral tablet, 5 mg/day to 20 mg/day, Once daily (Olanzapine in the acute and continuation period)

Measured Values

	Paliperidone ER	**Olanzapine**	**Pali/Placebo**	**Pali/Pali**	**Olan/Olan**
Number of Participants Analyzed [units: participants]	**575**	**137**	**131**	**135**	**77**
Global Assessment of Functioning (GAF): Change From Baseline [units: Scores on the scale] Mean (Standard Deviation)	**19.6 (17.38)**	**20.8 (18.26)**	**-15.2 (20.93)**	**-8.9 (17.75)**	**-4.2 (13.98)**

Statistical Analysis 1 for Global Assessment of Functioning (GAF): Change From Baseline

Groups [1]	Pali/Placebo vs. Pali/Pali
Method [2]	ANCOVA
P Value [3]	0.010
Mean Difference (Final Values) [4]	5.7
95% Confidence Interval	1.40 to 10.09

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	Change from Baseline (Maintenance Phase) to Endpoint (Maintenance Phase)
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	ANCOVA Model with treatment (Pali/Pali, Pali/Placebo) and country as factors with baseline value as covariate
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.
[4]	Other relevant estimation information:
	No text entered.

7. Other Pre-specified: Clinical Global Impression - Bipolar Disorder - Severity of Illness (CGI-BP-S): Change From Baseline [Time Frame: From 1st randomization into acute phase to end of acute/continuation phase (ie, up to 15 weeks after 1st randomization), or from randomization into maintenance (MA) phase to the end of MA phase (ie, up to 175 weeks (or 41 months) after 2nd randomization).]

Measure Type	Other Pre-specified
Measure Title	Clinical Global Impression - Bipolar Disorder - Severity of Illness (CGI-BP-S): Change From Baseline
Measure Description	The CGI-BP-S rating scale is used to rate the severity of bipolar disorder, including both depressed and manic components, on a 7-point scale ranging from 1 (not ill) to 7 (very severely ill). This scale permits a global evaluation of the subject's bipolar condition at a given time. Negative Change in Score Indicates Improvement.
Time Frame	From 1st randomization into acute phase to end of acute/continuation phase (ie, up to 15 weeks after 1st randomization), or from randomization into maintenance (MA) phase to the end of MA phase (ie, up to 175 weeks (or 41 months) after 2nd randomization).
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intent-to-Treat

Reporting Groups

	Description
Paliperidone ER	Acute and continuation period. Paliperidone ER: Oral tablet, 3 mg/day to 12 mg/day, Once daily.
Olanzapine	Acute and continuation period. Olanzapine: Oral tablet, 5 mg/day to 20 mg/day, Once daily.
Pali/Placebo	Maintenance period. Placebo (Paliperidone in the acute and continuation period).
Pali/Pali	Maintenance period. Paliperidone ER: Oral tablet, 3 mg/day to 12 mg/day, Once daily (Paliperidone in the acute and continuation period)
Olan/Olan	Maintenance period. Olanzapine Oral tablet, 5 mg/day to 20 mg/day, Once daily (Olanzapine in the acute and continuation period)

Measured Values

	Paliperidone ER	**Olanzapine**	**Pali/Placebo**	**Pali/Pali**	**Olan/Olan**
Number of Participants Analyzed [units: participants]	**601**	**145**	**143**	**144**	**81**
Clinical Global Impression - Bipolar Disorder - Severity of Illness (CGI-BP-S): Change From Baseline [units: Scores on the scale] Median (Full Range)	**-2 (-6 to 2)**	**-3 (-5 to 2)**	**2 (-1 to 6)**	**0 (-2 to 5)**	**0 (-1 to 4)**

Statistical Analysis 1 for Clinical Global Impression - Bipolar Disorder - Severity of Illness (CGI-BP-S): Change From Baseline

Groups [1]	Pali/Placebo vs. Pali/Pali
Method [2]	ANCOVA
P Value [3]	0.007

[1]	Additional details about the analysis, such as null hypothesis and power calculation:

	Change from Baseline (Maintenance Phase) to Endpoint (Maintenance Phase)
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	ANCOVA Model on ranks with treatment (Pali/Pali, Pali/Placebo) and country as factors with baseline value as covariate
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.

Serious Adverse Events

Hide Serious Adverse Events

Time Frame	No text entered.
Additional Description	No text entered.

Reporting Groups

	Description
Paliperidone ER	Acute and continuation period. Paliperidone ER: Oral tablet, 3 mg/day to 12 mg/day, Once daily.
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Pali/Pali	Maintenance period. Paliperidone ER: Oral tablet, 3 mg/day to 12 mg/day, Once daily (Paliperidone in the acute and continuation period)
Olan/Olan	Maintenance period. Olanzapine Oral tablet, 5 mg/day to 20 mg/day, Once daily (Olanzapine in the acute and continuation period)

Serious Adverse Events

	Paliperidone ER	Olanzapine	Pali/Placebo	Pali/Pali	Olan/Olan
Total, serious adverse events					
# participants affected / at risk	**42/614 (6.84%)**	**10/148 (6.76%)**	**33/147 (22.45%)**	**16/149 (10.74%)**	**8/83 (9.64%)**
Cardiac disorders					
Myocardial infarction [*1]					
# participants affected / at risk	**2/614 (0.33%)**	**0/148 (0.00%)**	**0/147 (0.00%)**	**0/149 (0.00%)**	**0/83 (0.00%)**
Eye disorders					
Vision blurred [*1]					
# participants affected / at risk	**1/614 (0.16%)**	**0/148 (0.00%)**	**0/147 (0.00%)**	**0/149 (0.00%)**	**0/83 (0.00%)**
Gastrointestinal disorders					
Gastritis [*1]					
# participants affected / at risk	**0/614 (0.00%)**	**1/148 (0.68%)**	**0/147 (0.00%)**	**0/149 (0.00%)**	**0/83 (0.00%)**
Pancreatitis [*1]					
# participants affected / at risk	**0/614 (0.00%)**	**0/148 (0.00%)**	**0/147 (0.00%)**	**0/149 (0.00%)**	**1/83 (1.20%)**
General disorders					

Death [*1]					
# participants affected / at risk	**1/614 (0.16%)**	**0/148 (0.00%)**	**0/147 (0.00%)**	**1/149 (0.67%)**	**0/83 (0.00%)**
Infections and infestations					
Abdominal infection [*1]					
# participants affected / at risk	**1/614 (0.16%)**	**0/148 (0.00%)**	**0/147 (0.00%)**	**0/149 (0.00%)**	**0/83 (0.00%)**
Hepatitis viral [*1]					
# participants affected / at risk	**0/614 (0.00%)**	**0/148 (0.00%)**	**0/147 (0.00%)**	**1/149 (0.67%)**	**0/83 (0.00%)**
Pneumonia [*1]					
# participants affected / at risk	**0/614 (0.00%)**	**0/148 (0.00%)**	**0/147 (0.00%)**	**1/149 (0.67%)**	**0/83 (0.00%)**
Sinusitis [*1]					
# participants affected / at risk	**0/614 (0.00%)**	**1/148 (0.68%)**	**0/147 (0.00%)**	**0/149 (0.00%)**	**0/83 (0.00%)**
Injury, poisoning and procedural complications					
Chest injury [*1]					
# participants affected / at risk	**0/614 (0.00%)**	**0/148 (0.00%)**	**0/147 (0.00%)**	**0/149 (0.00%)**	**1/83 (1.20%)**
Head injury [*1]					
# participants affected / at risk	**0/614 (0.00%)**	**0/148 (0.00%)**	**0/147 (0.00%)**	**0/149 (0.00%)**	**1/83 (1.20%)**
Multiple fractures [*1]					
# participants affected / at risk	**1/614 (0.16%)**	**0/148 (0.00%)**	**0/147 (0.00%)**	**0/149 (0.00%)**	**0/83 (0.00%)**
Post procedural complication [*1]					
# participants affected / at risk	**1/614 (0.16%)**	**0/148 (0.00%)**	**0/147 (0.00%)**	**0/149 (0.00%)**	**0/83 (0.00%)**
Investigations					
Blood potassium decreased [*1]					
# participants affected / at risk	**0/614 (0.00%)**	**0/148 (0.00%)**	**0/147 (0.00%)**	**0/149 (0.00%)**	**1/83 (1.20%)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
Breast cancer stage III [*1]					
# participants affected / at risk	**1/614 (0.16%)**	**0/148 (0.00%)**	**0/147 (0.00%)**	**0/149 (0.00%)**	**0/83 (0.00%)**
Nervous system disorders					
Akathisia [*1]					
# participants affected / at risk	**2/614 (0.33%)**	**0/148 (0.00%)**	**0/147 (0.00%)**	**0/149 (0.00%)**	**0/83 (0.00%)**
Extrapyramidal disorder [*1]					
# participants affected / at risk	**2/614 (0.33%)**	**0/148 (0.00%)**	**0/147 (0.00%)**	**0/149 (0.00%)**	**0/83 (0.00%)**
Hypoxic encephalopathy [*1]					
# participants affected / at risk	**0/614 (0.00%)**	**0/148 (0.00%)**	**1/147 (0.68%)**	**0/149 (0.00%)**	**0/83 (0.00%)**
Neuroleptic malignant syndrome [*1]					

# participants affected / at risk	1/614 (0.16%)	0/148 (0.00%)	0/147 (0.00%)	0/149 (0.00%)	0/83 (0.00%)
Psychomotor hyperactivity [*1]					
# participants affected / at risk	2/614 (0.33%)	0/148 (0.00%)	0/147 (0.00%)	0/149 (0.00%)	0/83 (0.00%)
Psychiatric disorders					
Agitation [*1]					
# participants affected / at risk	1/614 (0.16%)	0/148 (0.00%)	0/147 (0.00%)	0/149 (0.00%)	0/83 (0.00%)
Alcohol abuse [*1]					
# participants affected / at risk	2/614 (0.33%)	1/148 (0.68%)	0/147 (0.00%)	0/149 (0.00%)	0/83 (0.00%)
Anger [*1]					
# participants affected / at risk	0/614 (0.00%)	0/148 (0.00%)	1/147 (0.68%)	0/149 (0.00%)	0/83 (0.00%)
Anxiety [*1]					
# participants affected / at risk	1/614 (0.16%)	0/148 (0.00%)	0/147 (0.00%)	0/149 (0.00%)	0/83 (0.00%)
Bipolar I disorder [*1]					
# participants affected / at risk	1/614 (0.16%)	0/148 (0.00%)	0/147 (0.00%)	0/149 (0.00%)	0/83 (0.00%)
Catatonia [*1]					
# participants affected / at risk	0/614 (0.00%)	1/148 (0.68%)	0/147 (0.00%)	0/149 (0.00%)	0/83 (0.00%)
Completed suicide [*1]					
# participants affected / at risk	1/614 (0.16%)	0/148 (0.00%)	0/147 (0.00%)	0/149 (0.00%)	0/83 (0.00%)
Depression [*1]					
# participants affected / at risk	4/614 (0.65%)	1/148 (0.68%)	8/147 (5.44%)	4/149 (2.68%)	1/83 (1.20%)
Depressive symptom [*1]					
# participants affected / at risk	0/614 (0.00%)	0/148 (0.00%)	0/147 (0.00%)	1/149 (0.67%)	0/83 (0.00%)
Hypomania [*1]					
# participants affected / at risk	1/614 (0.16%)	0/148 (0.00%)	0/147 (0.00%)	1/149 (0.67%)	0/83 (0.00%)
Insomnia [*1]					
# participants affected / at risk	1/614 (0.16%)	0/148 (0.00%)	0/147 (0.00%)	0/149 (0.00%)	0/83 (0.00%)
Major depression [*1]					
# participants affected / at risk	0/614 (0.00%)	0/148 (0.00%)	1/147 (0.68%)	1/149 (0.67%)	0/83 (0.00%)
Mania [*1]					
# participants affected / at risk	10/614 (1.63%)	6/148 (4.05%)	22/147 (14.97%)	3/149 (2.01%)	4/83 (4.82%)
Pressure of speech [*1]					
# participants affected / at risk	0/614 (0.00%)	0/148 (0.00%)	0/147 (0.00%)	1/149 (0.67%)	0/83 (0.00%)
Psychotic disorder [*1]					
# participants affected / at risk	0/614 (0.00%)	1/148 (0.68%)	1/147 (0.68%)	0/149 (0.00%)	0/83 (0.00%)

Self-injurious ideation * 1					
# participants affected / at risk	**0/614 (0.00%)**	**0/148 (0.00%)**	**0/147 (0.00%)**	**1/149 (0.67%)**	**0/83 (0.00%)**
Suicidal behaviour * 1					
# participants affected / at risk	**1/614 (0.16%)**	**0/148 (0.00%)**	**0/147 (0.00%)**	**0/149 (0.00%)**	**0/83 (0.00%)**
Suicidal ideation * 1					
# participants affected / at risk	**6/614 (0.98%)**	**0/148 (0.00%)**	**0/147 (0.00%)**	**0/149 (0.00%)**	**0/83 (0.00%)**
Suicide attempt * 1					
# participants affected / at risk	**1/614 (0.16%)**	**0/148 (0.00%)**	**0/147 (0.00%)**	**0/149 (0.00%)**	**0/83 (0.00%)**
Tachyphrenia * 1					
# participants affected / at risk	**0/614 (0.00%)**	**0/148 (0.00%)**	**0/147 (0.00%)**	**1/149 (0.67%)**	**0/83 (0.00%)**
Skin and subcutaneous tissue disorders					
Leukoplakia * 1					
# participants affected / at risk	**1/614 (0.16%)**	**0/148 (0.00%)**	**0/147 (0.00%)**	**0/149 (0.00%)**	**0/83 (0.00%)**
Surgical and medical procedures					
Breast operation * 1					
# participants affected / at risk	**1/614 (0.16%)**	**0/148 (0.00%)**	**0/147 (0.00%)**	**0/149 (0.00%)**	**0/83 (0.00%)**
Mastectomy * 1					
# participants affected / at risk	**0/614 (0.00%)**	**0/148 (0.00%)**	**0/147 (0.00%)**	**1/149 (0.67%)**	**0/83 (0.00%)**
Nasal operation * 1					
# participants affected / at risk	**0/614 (0.00%)**	**0/148 (0.00%)**	**0/147 (0.00%)**	**1/149 (0.67%)**	**0/83 (0.00%)**
Sinus operation * 1					
# participants affected / at risk	**1/614 (0.16%)**	**0/148 (0.00%)**	**0/147 (0.00%)**	**0/149 (0.00%)**	**0/83 (0.00%)**
Vascular disorders					
Hypertension * 1					
# participants affected / at risk	**2/614 (0.33%)**	**0/148 (0.00%)**	**0/147 (0.00%)**	**0/149 (0.00%)**	**0/83 (0.00%)**
Orthostatic hypotension * 1					
# participants affected / at risk	**1/614 (0.16%)**	**0/148 (0.00%)**	**0/147 (0.00%)**	**0/149 (0.00%)**	**0/83 (0.00%)**

* Events were collected by non-systematic assessment
1 Term from vocabulary, 12.1

Other Adverse Events

Hide Other Adverse Events

Time Frame	No text entered.
Additional Description	No text entered.

Frequency Threshold

Threshold above which other adverse events are reported	5%

Reporting Groups

	Description
Paliperidone ER	Acute and continuation period. Paliperidone ER: Oral tablet, 3 mg/day to 12 mg/day, Once daily.
Olanzapine	Acute and continuation period. Olanzapine: Oral tablet, 5 mg/day to 20 mg/day, Once daily.
Pali/Placebo	Maintenance period. Placebo (Paliperidone in the acute and continuation period).
Pali/Pali	Maintenance period. Paliperidone ER: Oral tablet, 3 mg/day to 12 mg/day, Once daily (Paliperidone in the acute and continuation period)
Olan/Olan	Maintenance period. Olanzapine Oral tablet, 5 mg/day to 20 mg/day, Once daily (Olanzapine in the acute and continuation period)

Other Adverse Events

	Paliperidone ER	Olanzapine	Pali/Placebo	Pali/Pali	Olan/Olan
Total, other (not including serious) adverse events					
# participants affected / at risk	**351/614 (57.17%)**	**79/148 (53.38%)**	**38/147 (25.85%)**	**38/149 (25.50%)**	**26/83 (31.33%)**
Gastrointestinal disorders					
Dry mouth [*1]					
# participants affected / at risk	**28/614 (4.56%)**	**14/148 (9.46%)**	**2/147 (1.36%)**	**1/149 (0.67%)**	**1/83 (1.20%)**
Nausea [*1]					
# participants affected / at risk	**33/614 (5.37%)**	**2/148 (1.35%)**	**2/147 (1.36%)**	**1/149 (0.67%)**	**0/83 (0.00%)**
Investigations					
Weight decreased [*1]					
# participants affected / at risk	**7/614 (1.14%)**	**0/148 (0.00%)**	**9/147 (6.12%)**	**4/149 (2.68%)**	**1/83 (1.20%)**
Weight increased [*1]					
# participants affected / at risk	**51/614 (8.31%)**	**18/148 (12.16%)**	**10/147 (6.80%)**	**12/149 (8.05%)**	**7/83 (8.43%)**
Metabolism and nutrition disorders					
Increased appetite [*1]					
# participants affected / at risk	**23/614 (3.75%)**	**13/148 (8.78%)**	**0/147 (0.00%)**	**1/149 (0.67%)**	**0/83 (0.00%)**
Nervous system disorders					
Akathisia [*1]					
# participants affected / at risk	**83/614 (13.52%)**	**11/148 (7.43%)**	**1/147 (0.68%)**	**1/149 (0.67%)**	**2/83 (2.41%)**
Dizziness [*1]					
# participants affected / at risk	**41/614 (6.68%)**	**4/148 (2.70%)**	**1/147 (0.68%)**	**4/149 (2.68%)**	**0/83 (0.00%)**
Extrapyramidal disorder [*1]					
# participants affected / at risk	**54/614 (8.79%)**	**4/148 (2.70%)**	**1/147 (0.68%)**	**2/149 (1.34%)**	**1/83 (1.20%)**
Headache [*1]					
# participants affected / at risk	**78/614 (12.70%)**	**14/148 (9.46%)**	**7/147 (4.76%)**	**4/149 (2.68%)**	**7/83 (8.43%)**
Sedation [*1]					
		25/148 (16.89%)			

# participants affected / at risk	38/614 (6.19%)		0/147 (0.00%)	0/149 (0.00%)	2/83 (2.41%)
Somnolence [*1]					
# participants affected / at risk	76/614 (12.38%)	23/148 (15.54%)	0/147 (0.00%)	5/149 (3.36%)	1/83 (1.20%)
Tremor [*1]					
# participants affected / at risk	34/614 (5.54%)	4/148 (2.70%)	0/147 (0.00%)	1/149 (0.67%)	3/83 (3.61%)
Psychiatric disorders					
Insomnia [*1]					
# participants affected / at risk	83/614 (13.52%)	15/148 (10.14%)	14/147 (9.52%)	13/149 (8.72%)	7/83 (8.43%)

* Events were collected by non-systematic assessment
1 Term from vocabulary, 12.1

Limitations and Caveats

Hide Limitations and Caveats

Limitations of the study, such as early termination leading to small numbers of participants analyzed and technical problems with measurement leading to unreliable or uninterpretable data
The study employed a randomized withdrawal design, and as such, was enriched for responders to the study drug. Thus, the long-term efficacy demonstrated cannot be extrapolated to a population of patients without prior exposure to paliperidone ER.

More Information

Hide More Information

Certain Agreements:

Principal Investigators are **NOT** employed by the organization sponsoring the study.
There **IS** an agreement between Principal Investigators and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.
The agreement is: ☐ The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is **less than or equal to 60 days**. The sponsor cannot require changes to the communication and cannot extend the embargo. ☑ The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is **more than 60 days but less than or equal to 180 days**. The sponsor cannot require changes to the communication and cannot extend the embargo. ☐ Other disclosure agreement that restricts the right of the PI to discuss or publish trial results after the trial is completed.

Results Point of Contact:

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Organization: Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
phone: 609-730-2436

Publications automatically indexed to this study by ClinicalTrials.gov Identifier (NCT Number):

Berwaerts J, Melkote R, Nuamah I, Lim P. A randomized, placebo- and active-controlled study of paliperidone extended-release as maintenance treatment in patients with bipolar I disorder after an acute manic or mixed episode. J Affect Disord. 2012 May;138(3):247-58. doi: 10.1016/j.jad.2012.01.047. Epub 2012 Feb 27.

Responsible Party:	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
ClinicalTrials.gov Identifier:	NCT00490971 History of Changes
Other Study ID Numbers:	CR010825 **R076477BIM3004** (Other Identifier: Johnson & Johnson Pharmaceutical Research & Development, L.L.C.)
Study First Received:	June 18, 2007
Results First Received:	April 26, 2011
Last Updated:	March 25, 2015
Health Authority:	United States: Food and Drug Administration Ukraine: State Pharmacological Center - Ministry of Health

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