# Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

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**eAppendix 2. Supplemental Methods: Pharmacokinetic Assessments, Sample Size Determination, and Analysis Set**

**Pharmacokinetic Assessments**

Pharmacokinetic samples were collected during the transition phase predose on day 1, 64 and 92 and postdose on day 99. Additionally, PK samples were collected every 4 weeks (+/- 7 days) starting at day 120 and further at 1 and 2 weeks after the fourth PP3M cycle (weeks 54 and 55). The PK assessments included: $C_{predose}$ (plasma concentration measured immediately before the last intramuscular [i.m] injection), $C_{max}$ (observed maximum plasma concentration after the last i.m. injection), $t_{max}$ (time to reach the maximum plasma concentration after last i.m injection) and $AUC_{\tau}$ (area under the plasma concentration-time curve after the last i.m injection).

**Sample Size Determination**

This study was designed with 90% power to detect a relative risk of 0.44 between 12-month relapse rates for placebo (40%) and PP3M (20%), with a significance level of 0.05 (2-sided). Accordingly, with an expected total of at least 392 patients enrolled and assuming a 50% dropout rate during the OL phase, 196 patients were expected to be randomized in the DB phase to either PP3M or placebo (1:1 ratio) to obtain 70 relapse events to show that PP3M was significantly different from placebo at the 2-sided significance level of 0.05. A 2-stage group sequential design with one interim analysis was planned; study termination was to occur if efficacy was established at interim analysis after 60% (42 events) of the projected relapse events had occurred.

**Analysis Set**

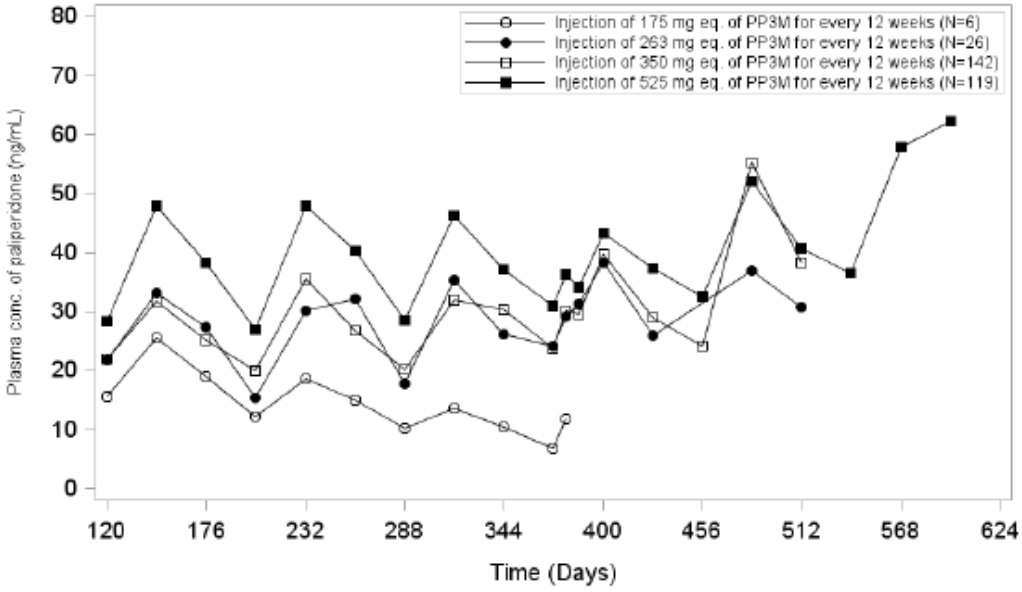
Interim intent-to-treat (ITT) (DB) analysis set: Included all patients who received ≥ 1 dose of study drug in the DB phase when the 42$^{nd}$ relapse event occurred; was used for analyzing the primary efficacy end point at interim lock.
ITT (DB) analysis set: Included all patients who received ≥ 1 dose of study drug in the DB phase; used for all other efficacy analyses during the DB phase.
Safety analysis set: For DB safety summaries; defined identical to ITT (DB) analysis set.
ITT (OL) analysis set: Included all patients who received ≥ 1 dose of study drug in the OL phase; was used for summarizing safety and efficacy during the OL phase.

**eAppendix 3. Supplemental Results: Pharmacokinetics**

**Pharmacokinetics**

Details on the pharmacokinetics of PP3M will be published elsewhere. Median plasma concentrations of paliperidone during the DB phase after PP3M injections were overlapping with plasma concentrations observed in the transition phase after corresponding PP1M injections for all dose groups (50 mg eq.PP1M vs. 175 mg eq.PP3M; 75 mg eq.PP1M vs. 263 mg eq. PP3M; 100 mg eq. PP1M vs. 350 mg eq. group). However, predose paliperidone concentrations were slightly higher in the PP3M 525 mg eq. group (maintenance and DB phase) compared with the PP1M 150 mg eq. group (transition phase), likely because steady-state was not fully reached by the time of transitioning from PP1M to PP3M. Predose paliperidone concentrations were lower in the PP3M 175 mg eq. group (DB phase) vs the PP1M 50 mg eq. group (transition phase) due to the 150 mg eq. initiation dose, which may have increased the paliperidone exposure during the next PP1M cycles. The predose mean plasma concentrations of paliperidone after PP3M 175, 263, 350 and 525 mg eq. injections were comparable across time points (eFigure). Deltoid muscle administration resulted in slightly higher exposure parameters at steady state compared with gluteal muscle administration.

## eFigure. Median Linear and Semi-Logarithmic Plasma Concentration-Time Profiles of Paliperidone per Dosage




**The eFigure must be interpreted with caution: while patients drop-out during the DB phase, the sample sizes drop from the indicated number to N=3 per dose group at the last visit depicted.**

## eTable 1. Dosing Administration Schedule

| | Transition phase (17 weeks) | | | | | Maintenance phase (12 weeks) | | | Double-blind phase (variable length) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Day** | **1** | **8** | **36** | **64** | **92** | **120** | **148** | **176** | **204** | **232** | **260** | **Every 12 weeks** |
| **PP1M dose** | 150 mg eq.[a] | 100 mg eq.[a]<br>Fixed dose (50, 75, 100, or 150 mg eq.)[b]<br>150 mg eq.[c] | Flexible doses[d] (50, 75, 100, or 150 mg eq.) | Flexible doses[d] (50, 75, 100, or 150 mg eq.) | Same dose as day 64 | - | - | - | - | - | - | - |
| **PP3M dose / Placebo** | - | - | - | - | - | 3.5-fold multiple of PP1M dose received on day 64 and 92 (175, 263, 350 or 525 mg eq.) | - | - | Fixed dose PP3M (as day 120) or placebo | - | - | Fixed dose PP3M (as day 120) or placebo |

Abbreviations: mg eq, milligram equivalents; PP1M, paliperidone palmitate 1 month formulation; PP3M, paliperidone palmitate 3 month formulation.
[a]Patients not switching from other LAI antipsychotics.
[b]Patients switching from risperidone (Ris) LAI or were continuing on PP1M at study entry (doses based on knowledge of previous dose levels of antipsychotic medication needed to keep symptoms under control).
[c]Patients switching from other LAI antipsychotic (other than Ris LAI or PP1M).
[d]Based on the severity of symptoms, safety and tolerability issues, and knowledge of previous dose levels of antipsychotic medication needed to keep symptoms under control.
Note: An oral tolerability test was conducted during screening phase for patients not previously exposed to oral or injectable risperidone or paliperidone. Study consisted of 4 phases: screening (up to 3 weeks), open-label (OL) transition phase (17 weeks, partly flexible dose), OL maintenance phase (12 weeks, fixed dose), and DB phase (variable length, fixed dose). In the transition phase, all patients except those switching from other LAI antipsychotics or who were on PP1M before study entry received PP1M for 120 days; day 1: 150 mg eq. (deltoid), day 8: 100 mg eq. (deltoid), days 36 and 64: 50, 75, 100, or 150 mg eq. flexible doses (deltoid or gluteal), and day 92: same dose of PP1M as administered on day 64. During the 12-week maintenance phase, patients received a single dose of PP3M in either the deltoid or gluteal muscle (3.5-fold multiple of the final PP1M dose administered on day 92). This was followed by a DB phase (variable length, fixed dose: as on day 120) during which patients were randomly assigned (1:1) to either PP3M or placebo.

## eTable 2. Conversion Between PP1M and PP3M Doses

| PP1M Dose | PP3M Dose (3.5-Fold Multiple) | PP1M Dose | PP3M Dose (3.5-Fold Multiple) |
|---|---|---|---|
| (mg paliperidone palmitate) | | (mg eq. paliperidone) | |
| 78 mg | 273 mg | 50 mg eq. | 175 mg eq. |
| 117 mg | 410 mg | 75 mg eq. | 263 mg eq. |
| 156 mg | 546 mg | 100 mg eq. | 350 mg eq. |
| 234 mg | 819 mg | 150 mg eq. | 525 mg eq. |

Abbreviations: PP3M, paliperidone palmitate 3-month formulation; PP1M, paliperidone palmitate 1 month formulation.

## eTable 3. Frequency Distribution of Relapse Types and Reasons During Double-Blind Phase—Interim and Final Analyses (Intent-to-Treat [DB] Analysis Set)

| | No. (%) | | | | | |
|---|---|---|---|---|---|---|
| | Interim Analysis | | | Final Analysis | | |
| | Placebo (N=135) | PP3M (N=148) | Total (N=283) | Placebo (N=145) | PP3M (N=160) | Total (N=305) |
| Total patients with relapse | 31 (23) | 11 (7) | 42 (15) | 42 (29) | 14 (9) | 56 (18) |
| Psychiatric hospitalization | 6 (4) | 2 (1) | 8 (3) | 10 (7) | 2 (1) | 12 (4) |
| PANSS total score | 26 (19) | 8 (5) | 34 (12) | 35 (24) | 10 (6) | 45 (15) |
| Increase of ≥25% in total PANSS score | 25 (19) | 8 (5) | 33 (12) | 34 (23) | 10 (6) | 44 (14) |
| 10-point increase in total PANSS score | 1(1) | 0 | 1(<1) | 1(1) | 0 | 1(<1) |
| Deliberate self-injury, violent behavior | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (1) | 1 (<1) |
| Suicidal or homicidal ideation | 1 (1) | 2 (1) | 3 (1) | 2 (1) | 3 (2) | 5 (2) |
| PANSS items (P1, P2, P3, P6, P7, G8) | 5 (4) | 1 (1) | 6 (2) | 7 (5) | 1 (1) | 8 (3) |

Abbreviations: PANSS, Positive and Negative Syndrome scale; PP3M, paliperidone palmitate 3-month formulation.
For PANSS items P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), P6 (suspiciousness/persecution), P7 (hostility), and G8 (uncooperativeness).

## eTable 4. Cox Regression of Time to Relapse of Symptoms of Schizophrenia With Treatment as a Factor and Age Group, Sex, Baseline (OL) BMI Category at Screening, and Region (US, Europe, ROW) as Cofactors

| Descriptive[a] | Placebo | PP3M | Total |
|---|---|---|---|
| **Time to Relapse** | | | |
| Number of Assessed | 145 | 160 | 305 |
| Number of Censored, No. (%) | 103 (71) | 146 (91) | 249 (82) |
| Number of Events, No. (%) | 42 (29) | 14 (9) | 56 (18) |
| 25% Quantile (95% CI) | 141.0 (111.0; 196.0) | ( ; ) | 274.0 (180.0 to - ) |
| Median (95% CI) | 395.0 (274.0; ) | ( ; ) | ( 395.0 to - ) |
| 75% Quantile (95% CI) | ( 395.0 to - ) | ( ; ) | ( ; ) |
| *P* value (over PP3M)[b] | <.0001 | | |
| Hazard Ratio (95% CI)[b] | 4.65 (2.49 to 8.69) | | |

Abbreviation: PP3M, paliperidone palmitate 3-month formulation
[a]Based on Kaplan-Meier product limit estimates
[b]Regression analysis of survival data based on Cox proportional hazards model with treatment, age group, sex, baseline (OL) BMI category at screening, and region (US, Europe, ROW) as factors.

## eTable 5. Cox Regression of Time to Relapse of Symptoms of Schizophrenia With Treatment as a Factor and Region (US, Europe, ROW) as a Cofactor

| Descriptive[a] | Placebo | PP3M | Total |
|---|---|---|---|
| Time to Relapse | | | |
| Number of Assessed | 145 | 160 | 305 |
| Number of Censored (%) | 103 (71) | 146 (91) | 249 (82) |
| Number of Events (%) | 42 (29) | 14 (9) | 56 (18) |
| 25% Quantile (95% CI) | 141.0 ( 111.0; 196.0) | ( ; ) | 274.0 ( 180.0; ) |
| Median (95% CI) | 395.0 ( 274.0; ) | ( ; ) | ( 395.0; ) |
| 75% Quantile (95% CI) | ( 395.0; ) | ( ; ) | ( ; ) |
| P-value(over PP3M)[b] | <0.0001 | | |
| Hazard Ratio (95% CI)[b] | 3.96 (2.16;7.26) | | |

Abbreviation: ROW, rest of the world
(a) Based on Kaplan-Meier product limit estimates.
(b) Regression analysis of survival data based on Cox proportional hazards model with treatment and Region (US, Europe, ROW) as factors.

## eTable 6. Change in Secondary Efficacy Measures During Double-Blind Phase (Intent-to-Treat [DB] Analysis Set)

| | Placebo (N=145) | PP3M (N=160) | *P* Value* |
|---|---|---|---|
| PANSS Total Score[a], mean (SD) | | | |
| Baseline | 54.3 (9.20) | 54.8 (9.96) | |
| Change from Baseline[b] | 6.7 (14.40) | −0.5 (8.36) | <.001 |
| PANSS Subscales Scores[a], mean (SD) | | | |
| Positive Subscale | | | |
| Baseline | 11.4 (2.99) | 11.7 (3.20) | |
| Change from Baseline | 2.7 (4.92) | -0.1 (2.84) | <.001 |
| Negative Subscale | | | |
| Baseline | 16.2 (3.91) | 16.4 (4.42) | |
| Change from Baseline | 0.8 (3.76) | -0.1 (2.96) | .013 |
| General Psychopathology Subscale | | | |
| Baseline | 26.6 (4.92) | 26.8 (4.98) | |
| Change from Baseline | 3.2 (7.88) | -0.3 (4.77) | <.001 |
| PANSS Marder Standardized Factor Scores[a], Mean (SD) | | | |
| Positive symptoms | | | |
| Baseline | 14.6 (3.71) | 14.9 (3.72) | |
| Change from Baseline | 2.5 (5.25) | -0.1 (2.74) | <.001 |
| Negative Symptoms | | | |
| Baseline | 15.0 (3.70) | 15.2 (4.28) | |
| Change from Baseline | 0.4 (4.01) | -0.3 (3.21) | .080 |
| Disorganized Thoughts | | | |
| Baseline | 13.8 (3.25) | 13.8 (3.41) | |
| Change from Baseline | 0.7 (3.38) | -0.2 (2.53) | .005 |
| Uncontrolled Hostility/Excitement | | | |
| Baseline | 5.2 (1.77) | 5.2 (1.80) | |
| Change from Baseline | 1.7 (3.18) | -0.0 (1.89) | <.001 |
| Anxiety/Depression | | | |
| Baseline | 5.7 (2.02) | 5.8 (2.10) | |
| Change from Baseline | 1.4 (3.28) | 0.1 (2.34) | <.001 |
| CGI-S Score[a] - Mean±SD | | | |
| Baseline | 2.8 (0.65) | 2.7 (0.68) | |
| Change from Baseline[b] | 0.4 (0.87) | 0.1 (0.60) | <.001 |
| PSP Score[a] - Mean±SD | | | |
| Baseline | 68.5 (8.93) | 68.9 (9.34) | |
| Change from Baseline[c] | -4.2 (9.70) | -0.5 (6.63) | <.001 |

Abbreviation: PP3M denotes paliperidone palmitate 3-month formulation

*Based on analysis of covariance (ANCOVA) model with treatment (placebo, PP3M) and country as factors and baseline value as a covariate.

[a]Explanation of scores: Decrease in PANSS scores and CGI-S scores indicate improvement; Decrease in PSP scores indicate worsening.

[b]N: placebo==142, PP3M==159

[c]N: placebo==142, PP3M==157

## eTable 7. Personal and Social Performance Scores (10-Point Categories) During Double-Blind Phase (Intent-to-Treat [DB] Analysis Set)

| PSP Scores | No. (%) | | | |
|---|---|---|---|---|
| | Placebo (N=145) | | PP3M (N=160) | |
| | Baseline | Endpoint | Baseline | Endpoint |
| Poor ( ≤ 30) | 0 | 1 (1) | 0 | 2 (1) |
| 1-10 | 0 (0) | 0 (0) | 0 (0) | 0 (0.0) |
| 11-20 | 0 (0) | 0 (0) | 0 (0) | 0 (0.0) |
| 21-30 | 0 (0) | 1 (1) | 0 (0) | 2 (1) |
| Variable (>30 - ≤ 70) | 84 (58) | 96 (68) | 87 (54) | 83 (53) |
| 31-40 | 1 (1) | 3 (2) | 1 (1) | 1 (1) |
| 41-50 | 4 (3) | 22 (15) | 5 (3) | 9 (6) |
| 51-60 | 18 (12) | 19 (13) | 24 (15) | 22 (14) |
| 61-70 | 61 (42) | 52 (37) | 57 (36) | 51 (33) |
| Good (>70) | 61(42) | 45 (32) | 73 (46) | 72 (46) |
| 71-80 | 55 (38) | 42 (30) | 66 (41) | 59 (38) |
| 81-90 | 5 (3) | 2 (1) | 5 (3) | 11 (7) |
| 91-100 | 1 (1) | 1 (1) | 2 (1) | 2 (1) |
| Total | 145 | 142 | 160 | 157 |

Abbreviations: PP3M, paliperidone palmitate 3-month formulation; PSP, Personal and Social Performance
Categorical analyses of the PSP scores were performed by grouping them into10-point increment categories to represent a clinically meaningful change in patient response

## eTable 8. Loss of Remitter Status-Double-Blind Phase (Intent-to-Treat [DB] Analysis Set)

| Visits[d] (Week) | No. (%) | | | | | |
|---|---|---|---|---|---|---|
| | Placebo (N=145)[a] | | | PP3M (N=160)[b] | | |
| | Baseline Remitter[c] | | | Baseline Remitter[c] | | |
| | n=82 | | | n=80 | | |
| | N | Remitter | Nonremitter | N | Remitter | Nonremitter |
| 4 | 80 | 76 (95) | 4 (5) | 80 | 75 (94) | 5 (6) |
| 8 | 74 | 68 (92) | 6 (8) | 74 | 65 (88) | 9 (12) |
| 12 | 70 | 63 (90) | 7 (10) | 69 | 61 (88) | 8 (12) |
| 16 | 64 | 55 (86) | 9 (14) | 64 | 57 (89) | 7 (11) |
| 20 | 49 | 40 (82) | 9 (18) | 58 | 57 (98) | 1 (2) |
| 24 | 33 | 28 (85) | 5 (15) | 46 | 41 (89) | 5 (11) |
| 28 | 18 | 11 (61) | 7 (39) | 31 | 28 (90) | 3 (10) |
| 32 | 15 | 10 (67) | 5 (33) | 25 | 22 (88) | 3 (12) |
| 36 | 12 | 7 (58) | 5 (42) | 13 | 12 (92) | 1 (8) |
| 40 | 8 | 5 (63) | 3 (38) | 8 | 0 (0) | 8 (100) |
| 44 | 2 | 0 | 2 (100) | 7 | 6 (86) | 1 (14) |
| 48 | 1 | 0 | 1 (100) | 4 | 2 (50) | 2 (50) |

Abbreviation: PP3M, paliperidone palmitate 3-month formulation.
Percentage during the DB phase was based on the total number of patients in a group at each visit (N).
[a]At baseline nonremitters=63.
[b]At baseline nonremitters=80.
[c]Being a remitter at double-blind baseline (DB) meant that a patient had individual scores of ≤3 for Positive and Negative Syndrome Scale (PANSS) positive-symptom (P) items P1, P2, and P3; negative-symptom (N) items N1, N4, and N6; and general-psychopathology (G) items G5 and G9 throughout the 3-month maintenance phase (at open-label weeks 17, 21, 25 and week 29)
[d]Being a remitter at a DB visit meant that a patient had individual scores ≤3 for PANSS items P1, P2, P3, N1, N4, N6, G5 and G9 at a particular DB visit.

Note: Of the patients randomized in the DB phase, 50% of patients assigned to PP3M and 57% to placebo, met criteria for remission at DB baseline. For PP3M patients who had been remitters at DB baseline, the remission status was maintained at each visit in the DB phase with 12 of 13 patients (92.3%) in remission at week 36. However, the percentage of placebo patients in remission at each visit decreased over time to 58.3% (7/12 patients) at week 36.

**eTable 9. Treatment-Emergent Adverse Events Reported in Maintenance Phase (Intent-to-Treat Analysis Set)**

| | No. (%) |
|---|---|
| | **Pali palmitate (N=379)** |
| TEAEs (≥6 patients) in the Maintenance phase | |
| Anxiety | 22 (6) |
| Insomnia | 18 (5) |
| Headache | 11 (3) |
| Weight increased | 17 (4) |
| Psychotic disorder | 6 (2) |
| Schizophrenia | 6 (2) |
| EPS-related TEAEs | |
| Total number of patients with EPS-related TEAEs | 12 (3) |
| Restlessness | 4 (1) |
| Akathisia | 2 (1) |
| Musculoskeletal stiffness | 2 (1) |
| Drooling | 1 (0.3) |
| Muscle rigidity | 1 (0.3) |
| Parkinsonism | 1 (0.3) |
| Dyskinesia | 1 (0.3) |
| Dystonia | 1 (0.3) |
| Tremor | 1 (0.3) |
| Diabetes mellitus and hyperglycemia-related TEAEs | |
| Number of patients with TEAEs | 1 (0.3) |
| Type-2 diabetes mellitus | 1 (0.3) |

Abbreviations: EPS, extrapyramidal symptoms; TEAE, treatment-emergent adverse events.

## eTable 10. Extrapyramidal Symptoms Assessed By Rating Scale Incidence (Relative to Baseline, Open-Label) and Use of Anticholinergic Medication During Double-Blind Phase (Safety Analysis Set)

| | No. (%) | |
|---|---|---|
| | Placebo (N=145) | PP3M (N=160) |
| Use of anticholinergic medications[a] | 13 (9) | 18 (11) |
| Parkinsonism[b] | 2 (1) | 7 (4) |
| Akathisia[c] | 1 (1) | 8 (5) |
| Dyskinesia[d] | 4 (3) | 5 (3) |

Abbreviation: PP3M, paliperidone palmitate 3-month formulation.
[a]Use of Anti-EPS Medication During the Double-Blind Phase
[b]Percent of patients with Simpson-Angus Scale Global Score > 0.3 (Global Score defined as total sum of items score divided by the number of items)
[c]Percent of patients with Barnes Akathisia Rating Scale Global Clinical Rating Score ≥ 2
[d]Percent of patients with a score ≥ 3 on any of the first seven items or a score ≥ 2 on two or more of any of the first seven items of the Abnormal Involuntary Movement Scale

## eTable 11. QTc Change From Double-Blind Baseline to Maximum Corrected QT Interval (Safety Analysis Set)

| | No. (%) | |
|---|---|---|
| | Placebo (N=145) | PP3M (N=160) |
| QTc change from baseline to maximum | 141 | 155 |
| QTcB | | |
| ≤ 30 msec | 130 (92) | 139 (90) |
| >30-60 msec | 11 (8) | 15 (10) |
| >60 msec | 0 | 1 (1) |
| QTcF | | |
| ≤ 30 msec | 133 (94) | 145 (94) |
| >30-60 msec | 8 (6) | 10 (6) |
| QTLc | | |
| ≤ 30 msec | 134 (95) | 147 (95) |
| >30-60 msec | 7 (5) | 8 (5) |
| QTcLD | | |
| ≤ 30 msec | 135 (96) | 148 (95) |
| >30-60 msec | 6 (4) | 7 (5) |

Abbreviations: PP3M, paliperidone palmitate 3-month formulation; QTc, corrected QT interval; QTcB, QTc interval calculated using the Bazett formula; QTcF, QTc interval calculated using the Fridericia formula; QTLc, QTc interval calculated using the Sagie formula; QTcLD, interval calculated using the linear-derived formula.

## eTable 12. Patient Evaluation of Injection Pain Over Time During Double-Blind Phase (Safety Analysis Set)

| Time points (DB) | Placebo | | PP3M | |
|---|---|---|---|---|
| | N | Mean (SD) | N | Mean (SD) |
| Baseline | 145 | 12.9 (15.50) | 160 | 15.8 (19.06) |
| Week 12 | 111 | 14.5 (16.04) | 129 | 15.3 (17.43) |
| Week 24 | 43 | 12.4 (12.24) | 74 | 14.1 (16.57) |
| Week 36 | 14 | 14.6 (14.97) | 25 | 12.0 (18.62) |
| Week 48 | 2 | 15.5 (20.51) | 7 | 9.7 (10.95) |
| Week 60 | 0 | NA | 1 | 17.0 (NA) |
| Endpoint | 111 | 13.0 (13.61) | 129 | 15.1 (17.92) |

Abbreviation: PP3M, paliperidone palmitate 3-month formulation.
Injection site pain assessed using visual analog scale (VAS) ranging from 0 to 100 mm within 30 min after each injection.

## eTable 13. Treatment-Emergent Abnormal ECG Values Relative to Average Predose at Any Time During the Double-Blind Phase (Safety Analysis Set)

| | No. (%) | |
|---|---|---|
| | Placebo (N=145) | PP3M (N=160) |
| Abnormally high heart rate[a] | 10 (7) | 3 (2) |
| Abnormally low heart rate[b] | 4 (3) | 4 (3) |
| Abnormally high PR duration[c] | 3 (2) | 2 (1) |

[a]Abnormally high heart rate: ≥100 bpm
[b]Abnormally low heart rate: ≤ 50 bpm
[c]Abnormally high PR duration: ≥ 210 msec

**eTable 14. Antipsychotic Medication Usage ≥ 5% of Patients in Either Group Before Start of Open-Label Phase (Intent-to-Treat (DB) Analysis Set)**

| | No. (%) | | |
|---|---|---|---|
| | **Placebo (N=145)** | **PP3M (N=160)** | **Total (N=305)** |
| Depot antipsychotics | 27 (19) | 33 (21) | 60 (20) |
| Paliperidone Palmitate | 12 (8) | 15 (9) | 27 (9) |
| Atypical antipsychotics | 85 (59) | 99 (62) | 184 (60) |
| Risperidone oral | 48 (33) | 57 (36) | 105 (34) |
| Quetiapine | 13 (9) | 15 (9) | 28 (9) |
| Olanzapine | 9 (6) | 12 (8) | 21 (7) |
| Paliperidone | 9 (6) | 11 (7) | 20 (7) |
| Amisulpride | 7 (5) | 5 (3) | 12 (4) |
| Aripiprazole | 2 (1) | 8 (5) | 10 (3) |
| Typical antipsychotics | 39 (27) | 36 (23) | 75 (25) |
| Haloperidol | 14 (10) | 8 (5) | 22 (7) |
| Chlorpromazine | 8 (6) | 6 (4) | 14 (5) |
| Trifluoperazine | 9 (6) | 5 (3) | 14 (5) |
| Zuclopenthixol | 8 (6) | 6 (4) | 14 (5) |
| Levomepromazine | 10 (7) | 3 (2) | 13 (4) |

Abbreviation: PP3M, paliperidone palmitate 3-month formulation

**eTable 15. Psychotropic Medications Received Prior to the Open-Label Phase (Intent-to-Treat [OL] Analysis Set)**

| | Pali Palmitate |
|---|---|
| **Psychotropic Drug Category** | **(N=506)** |
| **Generic Term Category** | **n (%)** |
| Total no. patients with prior psychotropic medications | 462 ( 91) |
| Atypical antipsychotics | 318 ( 63) |
| Risperidone oral | 159 ( 31) |
| Quetiapine | 54 ( 11) |
| Olanzapine | 46 ( 9) |
| Paliperidone | 40 ( 8) |
| Aripiprazole | 19 ( 4) |
| Amisulpride | 16 ( 3) |
| Lurasidone | 8 ( 2) |
| Ziprasidone | 7 ( 1) |
| Clozapine | 3 ( 1) |
| Asenapine | 1 ( <1) |
| Iloperidone | 1 ( <1) |
| Typical antipsychotics | 118 ( 23) |
| Haloperidol | 43 ( 8) |
| Chlorpromazine | 22 ( 4) |
| Levomepromazine | 19 ( 4) |
| Zuclopenthixol | 18 ( 4) |
| Trifluoperazine | 17 ( 3) |
| Chlorprothixene | 14 ( 3) |
| Flupentixol | 5 ( 1) |
| Fluphenazine | 5 ( 1) |
| Thioridazine | 4 ( 1) |
| Perphenazine | 3 ( 1) |
| Melperone | 1 ( <1) |
| Sertindole | 1 ( <1) |
| Tiapride | 1 ( <1) |
| Depot antipsychotics | 89 ( 18) |
| Paliperidone palmitate | 36 ( 7) |
| Haloperidol decanoate | 15 ( 3) |
| Risperidone | 13 ( 3) |
| Zuclopenthixol decanoate | 9 ( 2) |
| Fluphenazine decanoate | 8 ( 2) |

Percentages calculated with the number of subjects in each group as denominator.

## eTable 16. Completion/Withdrawal Rates of Patients During Open-Label and Double-Blind Phase

| | No. (%) | | | | |
|---|---|---|---|---|---|
| | Open-label | | Double-blind | | |
| | Transition phase (N=506) | Maintenance phase[b] (N=379) | Placebo (N=145) | PP3M (N=160) | Total (N=305) |
| Withdrawn | 127 (25) | 74 (20) | 23 (16) | 12 (8) | 35 (11) |
| Adverse event | 16 (3) | 10 (3) | 1 (1) | 0 | 1 (<1) |
| Death | 1 (<1) | 0 | 0 | 0 | 0 |
| Exposure to prohibited medications | 4 (1) | 10 (3) | 1 (1) | 0 | 1 (<1) |
| Lack of efficacy | 19 (4) | 9 (2) | NA | NA | NA |
| Lost to follow-up | 19 (4) | 5 (1) | 1 (1) | 3 (2) | 4 (1) |
| Patients failing to meet criteria to enter next phase | 8 (2) | 13 (3) | NA | NA | NA |
| Withdrawal of consent | 51 (10) | 15 (4) | 10 (7) | 7 (4) | 17 (6) |
| Study terminated by sponsor | 0 | 2 (1) | NA | NA | NA |
| Blind broken by investigator | NA | NA | 1 (1) | 0 | 1 (<1) |
| Pregnancy | 0 | 0 (0) | 1 (1) | 0 | 1 (<1) |
| Other | 9 (2) | 8 (2) | 8 (6) | 2 (1) | 10 (3) |
| Completed[a] | 379 (75) | 305 (80) | 122 (84) | 148 (93) | 270 (89) |
| Completed DB phase due to study termination | NA | NA | 80 (55) | 134 (84) | 214 (70) |
| Relapse during DB phase | | | 42 (29) | 14 (9) | 56 (18) |

Abbreviation: PP3M, paliperidone palmitate 3-month formulation.

[a]Completed the transition or maintenance phase means a patient completed last visit in that phase, completed DB phase included patients who experienced relapse in the DB phase, 'completed DB phase due to study termination' included patients who remained relapse-free at study termination.

[b]2 patients failed to meet criteria to enter maintenance phase, but continued into the maintenance phase by mistake and received visit 8 PP3M injections. These two patients withdrew from the maintenance phase due to the reason of not meeting criteria to enter the maintenance phase.