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# Comparison of Paliperidone Palmitate and Risperidone Long-Acting Injection in Schizophrenic Patients

## Results From a Multicenter Retrospective Cohort Study in France

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### Abstract:

**Purpose/Background:** The study objective was to compare the impact of being treated by paliperidone palmitate (PP) or risperidone long-acting injection (RLAI) on the length of stay on initial hospitalization, rehospitalization risk, and treatment duration in schizophrenic patients.

**Methods:** We conducted an observational retrospective cohort study in 43 centers in France, including schizophrenic patients who initiated a treatment by PP or RLAI during initial hospitalization. The follow-up periods started in September 2012 for the RLAI group (median follow-up duration, 233 days) and in June 2013 for the PP group (259 days). Statistical analyses were based on Cox regression models, with propensity score weighting to account for differences in patients' characteristics.

**Findings/Results:** The analysis included 347 patients: 197 in the PP treatment group and 150 in the RLAI group. Compared with patients on RLAI, patients on PP were significantly more likely to have nonpsychiatric comorbidities, to have been on previous antipsychotic therapy, or to have been hospitalized for psychiatric care in the previous year. With regard to length of stay on initial hospitalization, there was no statistically significant difference between both groups (hazard ratio, 1.13 [0.97; 1.31]). Being on PP was associated with similar times to first rehospitalization compared with RLAI (hazard ratio, 0.92 [0.65; 1.30]).

**Implications/Conclusions:** We observed nonsignificant differences in initial hospitalization duration and time to rehospitalization between PP and RLAI, potentially due to lack of statistical power. A trend was observed in favor of PP with regard to time to treatment discontinuation, although this result was compromised by patients who switched between RLAI and PP.

**Key Words:** Paliperidone Palmitate, Antipsychotic Agents, schizophrenia, Retrospective Study, France

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Schizophrenia is a severe chronic mental disorder characterized by various “positive” symptoms (such as hallucinations and

disorganized speech) and “negative” symptoms (such as blunted affect and alogia). The course of the disease varies widely, alternating between periods of remission and relapse, where patients experience unpredictable patterns of symptoms. These symptoms are associated with isolation, alteration of daily functioning and feelings, as well as disorganized thoughts and behaviors. The public health and financial burdens of schizophrenia are considered to be substantial by the French authorities.<sup>1,2</sup> Indeed, patients affected by schizophrenia are the largest group of hospitalized patients for mental disorders in 2011.<sup>3</sup> In France, between 300,000 and 600,000 patients are affected by schizophrenia, with approximately 10,000 new patients per year.<sup>4–6</sup>

Long-acting injectable (LAI) antipsychotics are recommended for the maintenance treatment of schizophrenia especially for the prevention of relapse in noncompliant patients. Also, consensus-based guidance recommends using LAIs as first-line therapy in patients who will be treated with antipsychotics over the long term.<sup>7–9</sup> Relapses involve an increase of hospitalizations and disease deterioration such as treatment resistance and socialization issues. Compliance is a key challenge in treatment management, as noncompliance is strongly associated with relapses or hospitalizations. Paliperidone palmitate (PP) long-acting injection and risperidone long-acting injection (RLAI) are two long-acting antipsychotics recommended in the prevention of relapses. Paliperidone palmitate long-acting injection is administered once monthly, whereas RLAI is administered fortnightly. Advantages of PP include a quick onset of action, a one-monthly injection, and the absence of oral supplementation at treatment initiation. Thus, PP may help patient compliance.<sup>10</sup>

To date, several observational studies have been conducted assessing the effectiveness of RLAI.<sup>11–13</sup> One study evaluated the comparative effectiveness of RLAI versus PP in the United States.<sup>14</sup> However there is still a lack of real-life data on patients treated with PP in Europe.

The Long Acting Outcomes Study in Schizophrenia (LAOS) was a multicenter observational retrospective cohort study conducted in 43 centers in France. It included schizophrenic patients who initiated a treatment by PP or RLAI during the initial hospitalization.

The primary objective of the study was to evaluate and compare the impact of being treated by PP or long-acting risperidone injection on the length of stay on initial hospitalization of schizophrenic patients. Secondary objectives included evaluation and comparison of risk of rehospitalization and treatment duration.

Our hypothesis is that PP is associated with better patient compliance and reduced disease management costs through a decrease in health resource use compared with long-acting risperidone injection.

## MATERIALS AND METHODS

### LAOS Study

#### Study Objectives

This study was designed to assess and compare, in patients with schizophrenia who were hospitalized full-time for symptomatic

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decompensation and in whom treatment (with PP or RLAI) was initiated during the initial hospitalization period, the duration of maintenance treatments, the duration of the initial hospitalizations periods, and the hospitalization rates and cumulative hospitalization periods for psychiatric reasons during exposure to treatment (either PP or RLAI).

### Study Design

The LAOS study was an observational, retrospective, multicenter, and national cohort and was carried out in public and private health care establishments equipped for the full-time hospitalization of patients in psychiatric units. Although the study was retrospective, monitoring visits equivalent to quality-check visits were conducted to ensure optimal quality and completeness of data.

Psychiatrists were identified from exhaustive national listings of practicing physicians by specialty (CEGEDIM OneKey registries; Cegedim, Boulogne-Billancourt, France [www.cegedim.com](http://www.cegedim.com)), where the sponsor (Janssen-Cilag) has a list of e-mail addresses provided by practitioners. On 3,615 contacted French psychiatrists, 193 sites sent a confidentiality agreement and received a feasibility questionnaire, notably about their patient recruitment potential. On these 193 sites, 89 feasibility questionnaires were received and site selection was organized (by visit or remote contact). On these 89 sites, 64 sites, with a potential to take more than 5 patients per treatment group, were preselected. Psychiatrists did not receive any specific incentive to report cases.

As psychiatric services are organized per sector<sup>15</sup> (sectors are established based on population density) with the sectors essentially proposing state-run services (92% of state-run structures: general or specialized hospitals, medicopsychological consultation services), to ensure the whole of France was represented in the study, the geographic localization of the centers was based on 7 large French metropolitan areas.

On the 64 preselected sites, the study was carried out in 50 selected centers representative of the French centers, with sampling being stratified per region according to the aforementioned distributions.

In each center, the first 6 to 18 patients meeting the inclusion criteria were selected and 3 to 9 patients were allocated to each treatment group. This method of cluster sampling within the centers and systematic assessment of the first eligible patients (chronologic selection) with equivalent numbers of patients being selected per center guarantees representativeness.

Patients were eligible for inclusion in the study if they satisfied the following criteria: at least 18 years of age; with confirmed schizophrenia according to the criteria of the International Classification of Diseases (CIM10), except for schizoaffective disorders; hospitalized full-time for symptomatic decompensation (acute psychotic episode, behavior disorders/aggressive behavior toward self or others, thymic state, intoxication with alcohol or other substances, etc.); and in whom the following treatment was initiated during hospitalization: either RLAI from September 1, 2012 (before PP French market access) or PP from June 1, 2013. The LAI prescription was initiated before the onset of the study.

Participants were excluded if they were with schizoaffective disorder or another psychotic disorder, hospitalized full-time chronically (hospitalized for more than 60 consecutive days) at the time of treatment initiation (RLAI or PP), whose previous treatment included RLAI or PP (in the 6 months preceding treatment initiation with PP or RLAI long-acting injection), who had already been treated with clozapine or patients participating in another clinical trial at the time of the initial hospitalization.

### Monitoring Plan

Data were directly collected in electronic case report form, with automatic controls and alerts when potential incorrect data were entered (outlier data check), by investigators. To ensure the quality of data collected in this study, on-site monitoring visits were carried out by independent clinical research assistants trained in the study protocol. A first monitoring visit was performed, after the sixth patient, to check that patients were informed by investigators about the collection of their medical data and were not opposed to it, to control that all required data entered into the electronic case report form were in accordance with data from medical records and to check that sites performed the study in compliance with the study protocol and current regulations. A total of 60 monitoring visits were carried out and allowed to monitor 308 patients (75% of the patients included) by direct access to medical data records or by investigator interview (depending on hospital's practices on medical records access). In addition to monitoring, data quality testing based on the comparison of rates of missing data on the monitored variables and on the number of deviant patients was carried out.

### Data Collection

For each patient, a patient case report form was filled retrospectively by participating psychiatrists, in providing information on patient attributes. These related to demographics, type of schizophrenia, disease history and severity, initial full-time hospitalization (admission and discharge dates, reason having led to hospitalization, antipsychotic treatment at the time of admission to hospital, treatment compliance issues, treatment resistance, treatments related to the disorder prescribed and administered during the hospital stay (with start and end dates, dosage, and administration route), other nonmedical therapeutic measures during hospitalization and other concurrent disorders).

At the end of the initial hospitalization and throughout the follow-up period, were also been collected all the types of hospitalizations, all the consultations as an outpatient, all the visits to an emergency unit, taking part in activities organized by part-time therapeutic reception centers, the number of suicide attempts and forced hospitalizations, all the other nonmedical therapeutic measures and the hospitalization alternatives. Treatments related to the disorder prescribed and administered during the hospital stay, with start and end dates, dosage, and administration route were also collected. Finally, date and circumstances of the last contact, initiated treatment (PP or RLAI) continued or discontinued (with discontinuation data and reason).

Patients were informed about the study and were not opposed to the use of their data. They also signed a consent form to authorize the access to their medical data.

The study protocol was approved by an independent scientific committee and in accordance with French law, the Ethics Committee's approval was not required as the protocol was strictly observational and usual practice was unchanged. However, the study protocol was approved by the Advisory Committee on Information Processing in Research in the Field of Health and by the French Data Protection Authority.

### Outcome Measures

The primary outcome was length of stay on initial hospitalization, which was defined as the number of days between the admission to the hospital and the last day of this initial hospitalization. Secondary outcomes were the time to first rehospitalization after the initial hospitalization and the time to treatment discontinuation.

The individual study period started from the beginning of the initial hospitalization and ended 30 days after the last injection of treatment or at the date of last contact. If a patient switched from

RLAI to PP (or vice versa), the study period ended at the time of the treatment switch. Consequently, each patient was included in a single treatment group. A switch from RLAI to PP (and vice versa) was considered to be a treatment withdrawal for the analysis of time to discontinuation (treatment duration).

Patients who deviated from the protocol and patients who never left the initial hospitalization were excluded from the analysis in order to minimize bias. Patients from center 69 were also excluded from the analysis as the monitoring in this center could not be conducted according to the study protocol.

### Statistical Analyses

Time to end of initial hospitalization, time to first rehospitalization and time to treatment discontinuation were analyzed through Kaplan-Meier survival analyses and Cox regression models. In nonrandomized studies, there is a risk that the allocation of a treatment may be dependent on patient characteristics. Therefore, to control for this potential selection bias, the propensity score weighting method was used to account for differences in individual patient's characteristics. The propensity score corresponds to the probability for a patient to receive PP rather than RLAI as a function of patients' and prescribers' characteristics. The propensity score was estimated with a logistic regression using the following variables (selected based on statistical significance): nonpsychiatric comorbidities, number of hospitalizations for psychiatric care during the last 12 months, monitoring method, admission method, prior therapies and compliance, alcohol addiction, concomitant psychotic treatment, psychiatric comorbidities, sex, age, sex of the investigator, education level, and psychoeducation received (Supplemental Digital Content, Table S1 Results of the propensity score estimation, <http://links.lww.com/JCP/A489>).

Sensitivity analyses were conducted to assess the robustness of the results. Several statistical models were tested (nonadjusted, multivariate Cox regressions and use of the propensity score as an adjustment variable). Sensitivity analyses excluding patients with extreme propensity scores were conducted. Based on discussions with a clinical expert, covariates used for the propensity score estimation were selected based on clinical relevance instead of statistical significance. For the duration of initial hospitalization only, a sensitivity analysis including patients still in initial hospitalization at the end of follow-up was conducted. For the time to first rehospitalization and treatment discontinuation, an analysis was restricted on patients with at least one injection after initial hospitalization. For the time to treatment discontinuation

only, a switch from RLAI to PP (and vice versa) was considered as a censoring event in a sensitivity analysis.

Outputs are reported as hazard ratios (HRs) with their corresponding 95% confidence intervals (95% CIs). Statistical analyses were conducted using SAS® version 9.4.

## RESULTS

### Descriptive Statistics

Descriptive data on the baseline characteristics of the study population is reported for each treatment group in Table 1 and patient's characteristics over the follow-up period are described in Table 2. A total of 347 patients were included in the analysis: 197 from the PP treatment group (mean dose of 106.3 mg) and 150 from the RLAI treatment group (mean dose of 45.3 mg; Table 1 and Fig. 1).

Both treatment groups were well balanced with regard to sex, alcohol addiction, drug addiction, and type of schizophrenia (paranoid vs other types of schizophrenia). Compared with patients on RLAI, patients on PP were significantly more likely to have nonpsychiatric comorbidities ( $P = 0.007$ ), to have been on previous antipsychotic therapy ( $P = 0.04$ ), or to have been hospitalized for psychiatric care in the previous year ( $P = 0.001$ ). High rates of involuntary hospitalizations were observed in both groups (67% in the RLAI group and 69% in the PP group). This may be associated with the use of injectable antipsychotics, which are frequently administered in more severe and less compliant patients.

### Length of Stay on Initial Hospitalization and Time to First Re-Hospitalization

Results from the base case and sensitivity analyses for both the length of stay on initial hospitalization and the time to first rehospitalization are reported in Figure 2.

The average length of stay on initial hospitalization was comparable among PP patients compared with RLAI patients (38 vs 42 days). There was no statistically significant difference between both treatment groups (hazard ratio [HR], 1.13 [0.97; 1.31]). Conclusions were similar across all sensitivity analyses: no statistically significant results were identified across analyses. When including patients still in their initial hospitalization at the end of follow-up, results remained similar between both treatment groups (HR, 1.00 [0.86; 1.16]).

**TABLE 1.** Baseline Characteristics of the Study Population

	Paliperidone Palmitate n = 197	Risperidone Long-Acting Injection n = 150	P
Age, mean (SD), yrs	37.8 (12.3)	37.8 (12.1)	0.97*
Sex (male), n (%) patients	126 (64%)	107 (71%)	0.15 <sup>†</sup>
At least one nonpsychiatric comorbidity, n (%) patients	28 (14%)	8 (5%)	0.01 <sup>†</sup>
At least one psychiatric comorbidity, n (%) patients	37 (19%)	29 (19%)	0.90 <sup>†</sup>
Alcohol abuse, n (%) patients	37 (19%)	37 (25%)	0.18 <sup>†</sup>
Substance abuse (other than nicotine), n (%) patients	64 (32%)	50 (33%)	0.87 <sup>†</sup>
Paranoid schizophrenia, n (%) patients	142 (72%)	105 (70%)	0.67 <sup>†</sup>
At least one prior antipsychotic therapy, n (%) patients	84 (43%)	48 (32%)	0.04 <sup>†</sup>
At least one hospitalization for psychiatric care in the last 12 months, n (%) patients	136 (69%)	77 (51%)	0.001 <sup>†</sup>
Involuntary hospitalization, n (%) patients	136 (69%)	101 (67%)	0.74 <sup>†</sup>
Psychoeducation received, n (%) patients	88 (45%)	64 (43%)	0.71 <sup>†</sup>

\*Wilcoxon test; <sup>†</sup> $\chi^2$  test.

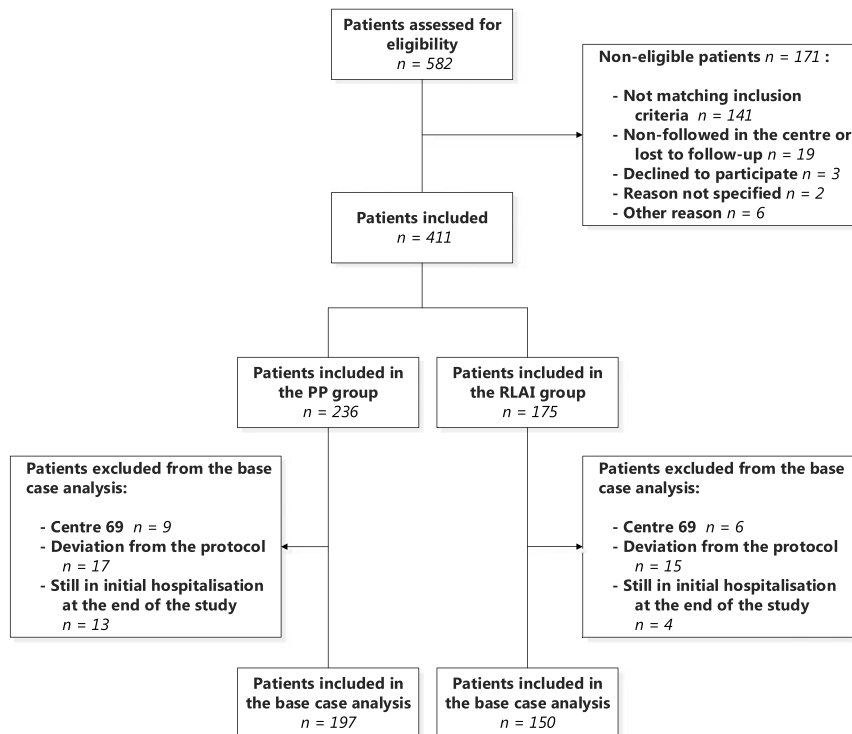
**TABLE 2.** Patient's Characteristics over the Follow-Up Period

	Paliperidone Palmitate n = 197	Risperidone Long-Acting Injection n = 150	P
Treatment dose, mean (SD), mg	106.3 (22.1)	45.3 (8.9)	—
At least one emergency room visit, n (%)	84 (43%)	61 (41%)	0.71*
At least one adverse event, n (%)	25 (13%)	12 (8%)	0.16*
Concomitant therapies, n (%)			
Antipsychotics <sup>†</sup>	80 (41%)	76 (51%)	0.06*
Anticholinergic agents	55 (28%)	44 (29%)	0.77*
Anxiolytics	59 (30%)	49 (33%)	0.59*
Antidepressants	19 (10%)	17 (11%)	0.61*
Antiepileptic agents	21 (11%)	16 (11%)	0.99*
Hypnotics and sedatives	26 (13%)	20 (13%)	0.97*
Other	13 (7%)	3 (2%)	0.04*
Length of stay on initial hospitalization, mean (SD), days	38.1 (24.6)	41.6 (38.1)	0.95 <sup>‡</sup>
No. patients rehospitalized during the study, n (%)	39 (20%)	33 (22%)	0.62*
Cumulative duration of rehospitalizations among patients with at least one rehospitalization, mean (SD)	42.1 (36.8)	44.4 (30.7)	0.36 <sup>‡</sup>
No. rehospitalizations among patients with at least one rehospitalization, mean (SD) per patient	1.56 (0.9)	1.4 (0.8)	0.34 <sup>‡</sup>
No. patients who discontinued their treatment, §n (%)	39 (20%)	67 (45%)	<0.001*
No. patients who discontinued their treatment during the initial hospitalization, §, ¶n (%)	14 (7%)	20 (13%)	0.05*
No. patients with at least one rehospitalization and who discontinued their treatment during a rehospitalization, §, ¶n (%)	13 (20%)	6 (11%)	0.16*

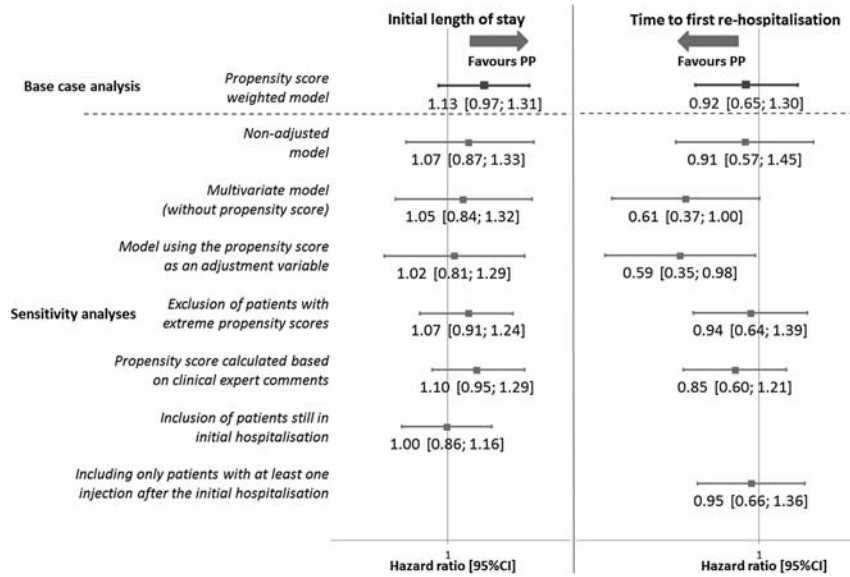
\* $\chi^2$  test; <sup>†</sup>only 2 patients received chlorpromazine as concomitant therapy (100 mg and 300 mg) both in the PP group; <sup>‡</sup>Wilcoxon test; <sup>§</sup>considering a switch as a treatment withdrawal; <sup>¶</sup>3 missing values; <sup>‡</sup>2 missing values.

The percentages of patients being rehospitalized after the initial hospitalization were low and comparable in both treatment groups (20% in PP patients and 22% in RLAI patients, as reported

in Table 2). The treatment discontinuation rates during a rehospitalization in patients with at least one rehospitalization were also comparable in both treatment groups (20% in PP patients and



**FIGURE 1.** Patient's eligibility for the base case analysis.



**FIGURE 2.** Base case and sensitivity analyses results for both outcomes: length of stay on initial hospitalization and time to first rehospitalization. For the length of stay on initial hospitalization an HR higher than 1 indicates a shorter duration in favor of PP. For the time to first rehospitalization, an HR lower than 1 indicates a lower risk of rehospitalization in favor of PP.

11% in RLAI patients). Being on PP was associated with similar times to first rehospitalization compared with being on RLAI (HR, 0.92 [0.65; 1.30]). Conclusions were similar across sensitivity analyses (with HRs ranging from 0.61 to 0.95), except for one analysis testing a methodological assumption which resulted in an HR significantly in favor of PP (HR, 0.59 [0.35; 0.98]). These differences in results across analyses were due to the low number of patients being rehospitalized after the initial hospitalization (39 in the PP group and 33 in the RLAI group).

**Treatment Duration**

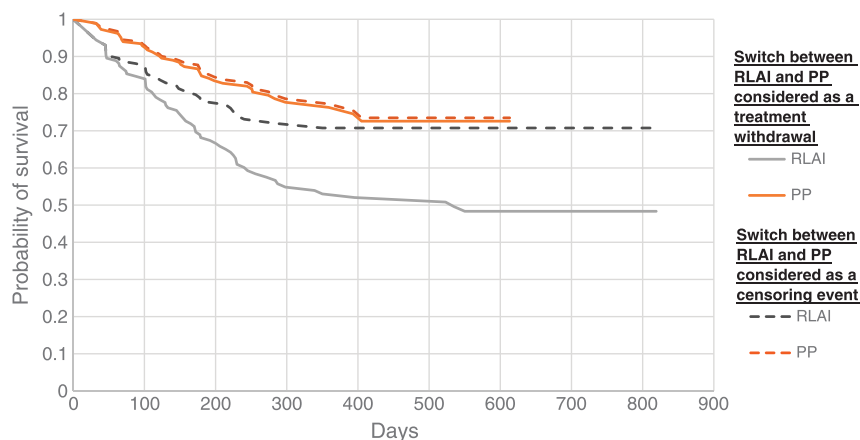
Figure 3 shows the Kaplan-Meier survival curves for time to treatment discontinuation, considering a treatment switch as a treatment withdrawal (base case assumption). As reported in Table 2, the percentage of patients who discontinued their treatment was significantly higher in the RLAI group (45%) than in the PP group (20%). The probability of remaining on treatment after one year was higher with PP (76%) than with RLAI (53%). The percentage of patients who discontinued their treatment during the initial

hospitalization was significantly higher in the RLAI group (13%) than in the PP group (7%).

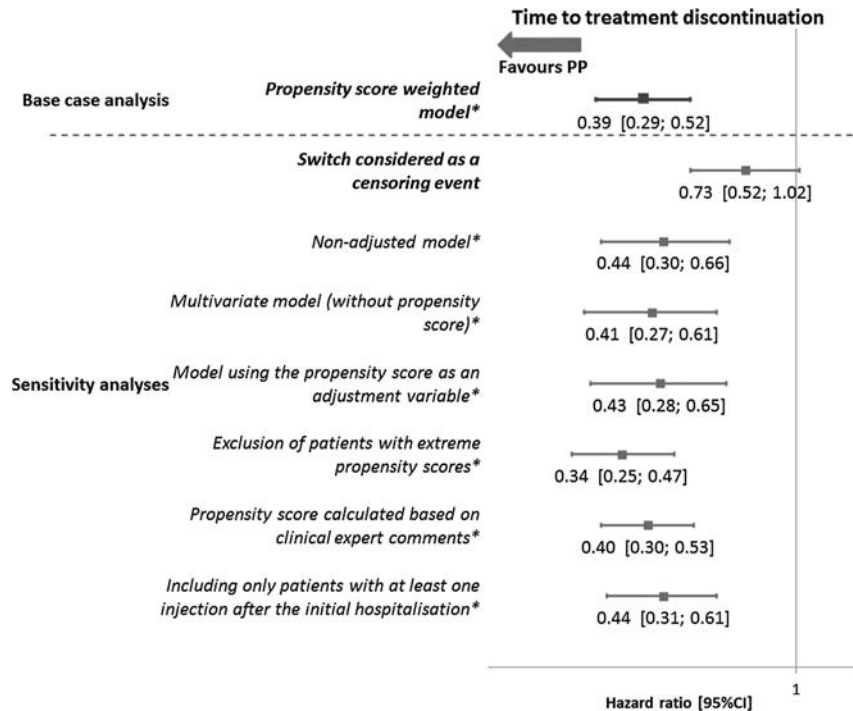
Results from the base case and sensitivity analyses are reported in Figure 4. When considering a switch as a treatment withdrawal, patients on PP were associated with a 61% risk reduction in treatment discontinuation compared with patients on RLAI (HR, 0.39 [0.29; 0.52]). However, when a switch was considered as a censoring event, the results indicated a nonstatistically significant trend in favor of PP (HR, 0.73 [0.52; 1.02]). All other sensitivity analyses were also associated with significantly longer treatment duration for PP compared with RLAI. When focusing on patients with at least one injection after the initial hospitalization, the treatment duration remained significantly longer among patients on PP than among patients on RLAI (HR, 0.44 [0.31; 0.61]).

**DISCUSSION**

This retrospective observational study assesses PP versus RLAI among schizophrenic patients with regard to length of stay on initial hospitalization, time to first rehospitalization and time to



**FIGURE 3.** Time to treatment discontinuation: Kaplan-Meier curves.



**FIGURE 4.** Base case and sensitivity analyses results for the time to treatment discontinuation. \*Switch considered as a treatment withdrawal. For the time to treatment discontinuation, an HR lower than 1 indicates a lower risk of treatment discontinuation in favor of PP, that is, a longer treatment duration.

treatment discontinuation. Overall, the study population was representative of the general French schizophrenic patient population. Mean age was 38 years and 67% of patients were male. This is very comparable to the Cohort for the General study of Schizophrenia, which included more than 1,500 patients (mean age, 38 years; 68% of male).<sup>10</sup>

Length of stay on initial hospitalization was comparable between treatment groups (average duration of 38 days in the PP group and 42 days in the RLAI group). Fewer days of hospitalization for PP compared to RLAI were expected given that the initiation of RLAI requires an oral supplementation (pretreatment by oral risperidone during at least 2 weeks followed by a 3-week oral supplementation). However, these lengths of stay were not significantly different between treatments potentially owing to a lack of statistical power. Indeed, fewer patients than initially planned were included. In addition patients with protocol deviations or patients from center 69 were excluded. This resulted in 347 of the 500 patients initially planned being included in the statistical analyses.

There was only a few number of rehospitalization in both treatment groups: 39 in the PP group (20% of patients) and 33 in the RLAI group (22% of patients). This low number of rehospitalization may be because all patients received a treatment (either PP or RLAI) throughout the study and were followed until 30 days after the last injection of treatment or until the date of last contact. Rehospitalization rates were comparable between PP and RLAI groups and results were nonsignificant for most of the analyses conducted. Those results are consistent with noninferiority results with regard to efficacy between PP and RLAI demonstrated in a randomized controlled trial.<sup>16</sup>

The assumption made regarding the switch between PP and RLAI (and vice versa) impacted the conclusion of the treatment discontinuation analysis as a total of 30 patients switched from RLAI to PP and 2 patients switched from PP to RLAI. Results for the analysis of treatment discontinuations were significantly in favor of PP

when considering a switch as a treatment failure. It should be noted that considering a switch as a censoring event changed the conclusion of this analysis (results are no longer statistically significant).

Little bias was expected on the primary and secondary end points as the duration of hospitalization, time to rehospitalization, and time to treatment discontinuation are robust end points, which are not subject to interpretation. The absence of randomization is usually associated with a potential selection bias, which was adjusted for by using the propensity score method. This statistical technique is recommended in guidelines such as the ones from the National Institute for Health and Care Excellence and International Society for Pharmacoeconomics and Outcomes Research.<sup>17,18</sup> Several sensitivity analyses were conducted to assess the robustness of the results, accounting for patient selection, differences in outcome definitions, and for the implementation of different statistical methods. Overall, the results were considered to be robust, as the conduct of these different analyses did not significantly change the interpretation of the results.

Few studies have been published on the association between long-acting antipsychotic treatments and hospitalization. In particular, there is a lack of studies investigating the factors influencing the duration of hospital stay and the consequences on patients' outcomes of shorter hospital stays.<sup>19</sup> Nevertheless, some recent studies have been identified. Results from previous observational studies<sup>9,10</sup> indicate that RLAI is associated with lower hospitalization rates compared to oral antipsychotics. A Hungarian registry-based observational follow-up study including 9,567 schizophrenic patients<sup>10</sup> also reported longer time to treatment discontinuations with RLAI than with oral antipsychotics. Moreover, our results are consistent with those obtained in previous studies comparing PP versus RLAI. An American retrospective longitudinal cohort study demonstrated that the use of PP was associated with better adherence, lower discontinuation rates, and longer treatment durations compared to RLAI. Paliperidone palmitate was also associated with

a lower risk of hospitalization and shorter hospitalization lengths.<sup>13</sup> A double-blind randomized trial also showed that PP was non-inferior to RLAI based on the change in the PANSS total score from baseline<sup>11</sup> and a French retrospective study based on pharmacy treatment issuance reported significantly longer treatment duration for PP compared with RLAI.<sup>20</sup>

Our study also has some limitations. For instance, length of hospital stay is driven by the diversity of health care institutions in France. In 2011, an IRDES study reported a mean length of stay of 83 days over 1 year, varying from 75 to 78 days in multidisciplinary public institutions to 85 to 97 in specialized public structures.<sup>3</sup> The variety of type of institutions participating in the LAOS study could thus have introduced some heterogeneity in length and frequency of hospital stays.

Moreover, the study design was also associated with some limitations. Indeed, owing to the retrospective design, data collected can be biased (unreliable recorded data). Therefore, to ensure the quality of data collected, on-site monitoring visits were conducted by independent clinical research assistants. The different periods of data collection for PP and RLAI could also lead to differences between the 2 groups (e.g., changes in patient's profile or current practice). To account for differences in individual patient characteristics, the propensity score weighting method was used. Finally, the launch date of PP was January 2013, and PP patients included in the study were patients who initiated PP from July 2013. The period between the launch date of PP and the first date of inclusion of PP patients was relatively short. Therefore, the treatment may have not yet been available in some of the participating centers before July 2013. As such, physicians may not have been used to prescribing it, especially since PP was one of the first once-monthly antipsychotics on the market. Some physicians may even have been reluctant to prescribe PP given that the new injection schedule would increase the interval between hospital visits, which may not be adequate for patients needing a closer follow-up.

It is difficult to conclude on the clinical practice in France given that RLAI and PP are long-term maintenance treatment. It would have been interesting to follow included patients until their next treatment line to highlight the full impact of LAI antipsychotics. Our study indicates a trend in favor of PP compared to RLAI with regard to time to treatment discontinuations, with an HR of 0.39 [0.29; 0.52] when considering a switch as a treatment withdrawal, and of 0.73 [0.52; 1.02] when considering a switch as a censoring event. Yet, a major challenge of schizophrenia management is to maintain patients under treatment in the long term. Indeed, it has been demonstrated that lack of adherence is frequent in the use of antipsychotic medications. Half of patients with schizophrenia experience poor adherence,<sup>21,22</sup> and a previous Finnish study showed a low adherence to the initial antipsychotic treatment during the first 60 days after patient's first hospitalization for schizophrenia.<sup>23</sup> A lack of adherence to antipsychotics is often associated with relapses; indeed, it has been shown that the risk of relapse is 5 times higher among patients who discontinued their antipsychotic treatment after a first episode of schizophrenia.<sup>24</sup> Relapses usually lead to hospitalizations and substantial changes in the disease management. As a result, relapses are associated with a high economic burden.<sup>25</sup> Thus, maintaining schizophrenic patients under treatment for a longer period of time may have a positive impact on both clinical outcomes and the economic burden of schizophrenia.

To conclude, this observational retrospective study indicated nonsignificant differences in duration of initial hospitalization and time to rehospitalization between PP and RLAI, potentially due to a lack of statistical power. A trend was observed in favor of PP with regard to time to treatment discontinuation, although this

result is compromised by patients who switched between RLAI and PP and would need to be confirmed by a dedicated study.

#### AUTHOR DISCLOSURE INFORMATION

*F Limosin received honorarium from Janssen for his participation in the LAOS study design, writing the protocol, data interpretation, and approving the final manuscript. F Limosin received also honorarium as consultant or board participation from AstraZeneca, Euthérapie-Servier, Janssen, Lundbeck, Otsuka Pharmaceuticals France, and Roche. D Belhadi and M Pacou work for Amaris Company and report no conflict of interest. D Comet works for Axonal-Biostatem Company and reports no conflict of interest. P Guillon, S Bouju, and K Van Impe are employees of Janssen-Cilag.*

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