

A Flexible-dose Study of Paliperidone ER in Non-acute Patients With Schizophrenia Previously Unsuccessfully Treated With Aripiprazole

A. Schreiner¹, D. Hoeben², M. Lahaye³, C. Tessier⁴, D. Naber⁵, J. Peuskens⁶, R. Vauth⁷, M. Jasovic-Gasic⁸, E. Rancans⁹, R. Didi¹⁰

¹Medical Affairs EMEA, Janssen-Cilag, Neuss, Germany; ²Medical Affairs EMEA, Janssen Pharmaceutica N.V., Beerse, Belgium; ³Janssen-Cilag Netherlands B.V., Tilburg, Netherlands; ⁴Medical Affairs EMEA, Janssen-Cilag France, Paris, France; ⁵Department of Psychiatry and Psychotherapy, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany; ⁶University Psychiatric Centre St-Jozef, Kortenberg, Belgium; ⁷Psychiatric Outpatient Department, University Hospital of Basel, Basel, Switzerland; ⁸Institute for Psychiatry, Clinical Center of Serbia, Belgrade, Serbia; ⁹Department of Psychiatry, Riga Stradins University, Riga, Latvia; ¹⁰CHS La Chartrouse, Dijon, France

INTRODUCTION

- Extended-release paliperidone (paliperidone ER) uses an innovative osmotic controlled-release oral delivery system (OROS[®]) in order to achieve minimal peak-to-trough fluctuations over 24 hours with once-daily dosing.¹
- Paliperidone ER is approved for the treatment of schizophrenia, with efficacy, tolerability, and safety demonstrated in randomized controlled clinical trials.^{2,3}

OBJECTIVE

To explore tolerability, safety, and treatment response of flexible doses of paliperidone ER in adult patients with non-acute schizophrenia, previously unsuccessfully treated with aripiprazole.

Table 1. Baseline characteristics (N = 141).

Characteristic	n (%)
Sex, n (%)	
Male	79 (56.0)
Female	62 (44.0)
Age, mean years ± SD	37.8 ± 10.9
Duration since diagnosis of schizophrenia, mean years ± SD	8.5 ± 7.4
Diagnosis of paranoid schizophrenia, n (%)	98 (69.5)
Last used total daily dose of previous treatment with aripiprazole, mg/day	
Mean ± SD	19.4 ± 11.4
Median	15
Main reason for switching from aripiprazole, n (%)	
Lack of efficacy	94 (66.7)
Lack of tolerability	31 (22.0)
Lack of compliance	9 (6.4)
Other	7 (5.0)

SD, standard deviation.

Table 2. Patient disposition (N = 141).

Patient disposition	n (%)
Completed 6 months of treatment	95 (67.4)
Reasons for early discontinuation of paliperidone ER	
Withdrew consent	14 (9.9)
AE	9 (6.4)
AE plus lack of efficacy	7 (5.0)
Lost to follow-up	5 (3.5)
Lack of efficacy	5 (3.5)
Non-compliance	4 (2.8)
Other	2 (1.4)

METHODS

Patients

Inclusion criteria for analyses

- Adult in- or outpatients aged ≥ 18 years, with a DSM-IV diagnosis of schizophrenia.
- Definition of non-acute schizophrenia: patient treated with aripiprazole with a change in Clinical Global Impression – Severity (CGI-S) score of ≤ 1 during the 4 weeks before enrolment.
- Patient previously received an adequate dose of aripiprazole for an adequate period of time prior to enrolment, per investigator judgment.

Exclusion criteria

- Patients were excluded if they had: been treated with clozapine or a long-acting injectable antipsychotic during the preceding 3 months; significant medical illness; tardive dyskinesia; neuroleptic malignant syndrome; high risk for adverse events (AEs) or self-harm; substance dependence over the past 6 months; or known hypersensitivity to paliperidone ER or aripiprazole.

Treatment

- Flexibly dosed paliperidone ER (3–12 mg/day).
 - Recommended dose 6 mg once daily
 - Transitioned to effective dose without titration
 - Treated for up to 6 months

Outcome measures

Efficacy assessments

- Primary efficacy outcome was based on main reason for transitioning to paliperidone ER.
 - Patients switching for the main reason of lack of efficacy: response defined by ≥ 20% improvement in Positive and Negative Syndrome Scale (PANSS) total score from baseline to endpoint
 - Patients switching for main reasons other than lack of efficacy: change in PANSS total score from baseline to endpoint
- Additional efficacy measures: PANSS total, subscale, and Marder factor scores, CGI-S score, Personal and Social Performance (PSP) scale score, and patient satisfaction with previous treatment measured at baseline and with paliperidone ER at week 26 (or endpoint). Satisfaction was rated as: very poor (1); poor (2); moderate (3); good (4); or very good (5).

Safety and tolerability

- Treatment-emergent AEs.
- Extrapyramidal Symptom Rating Scale (ESRS) score and body weight.

Data analysis

- For response, 95% confidence intervals (CIs) were estimated.
- Non-inferiority, defined by a difference of 5 points in change versus baseline on the PANSS total score, was evaluated using the Schuirmann 1-sided test ($\alpha = 0.025$).
- Within-group changes versus baseline were evaluated using the 2-tailed Wilcoxon signed-rank test ($\alpha = 0.05$).
- All patients who received paliperidone ER at least once are included in the analysis (ITT analysis set). Post-baseline efficacy and safety data were available for 138 patients (ITT analysis set for efficacy) and 141 patients (ITT analysis set for safety), respectively.

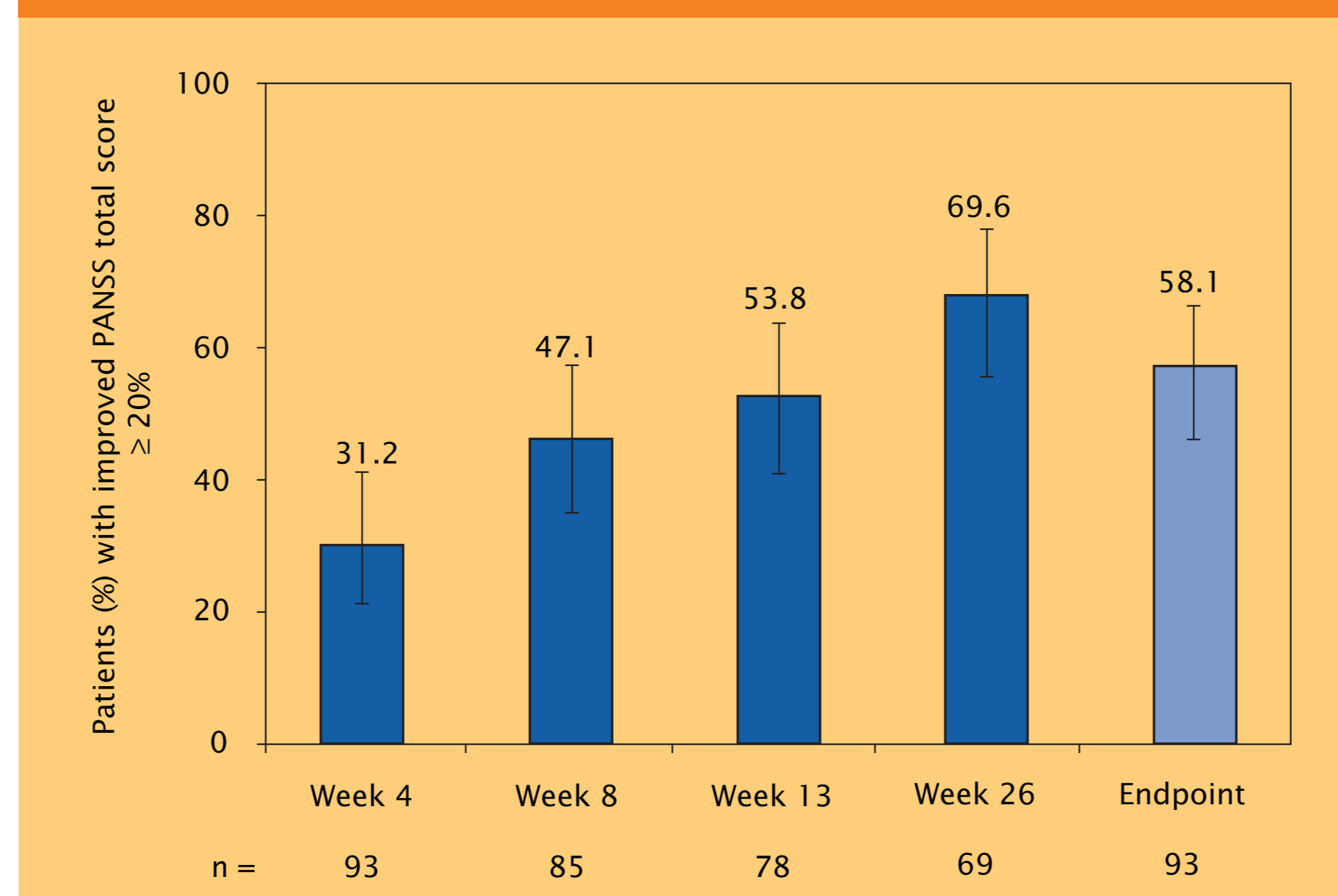
RESULTS

Table 3. Paliperidone ER treatment* (N = 141).

Paliperidone ER dosing	
Initial dose, mean mg/day ± SD	5.1 ± 1.8
Mode dose, mg/day	
Mean mode dose ± SD	6.8 ± 2.8
Median mode dose	6.0
Duration of exposure, mean days ± SD	145.7 ± 59.4
Patients with a change in dosing, n (%)	
Increase	93 (66.0)
Decrease	29 (20.6)

*Paliperidone ER dosing was comparable for patients switching for reasons other than lack of efficacy but slightly higher for patients switching for the reason of lack of efficacy.

Figure 1. Primary efficacy outcome for patients transitioned due to lack of efficacy.



Primary efficacy measure was the improvement in PANSS total score ≥ 20% from baseline to endpoint in patients transitioned due to lack of efficacy with previous aripiprazole treatment (shown in the lighter blue bar, n = 93).

Table 4. Primary efficacy measure for patients switching for reasons other than lack of efficacy was change in PANSS total score from baseline to endpoint.

Main reason for switching to paliperidone ER	Change in PANSS total score, mean ± SD
Lack of tolerability (n = 31)	–6.6 ± 19.1***
Lack of compliance (n = 7)	–3.9 ± 16.4
Other (n = 7)	–13.7 ± 10.9**

Schuirmann's 1-sided test confirmed that equivalence to within the specified equivalence bounds can be claimed: ** $P = 0.0019$; *** $P = 0.001$.

Figure 2. Mean PANSS total scores for the entire population.

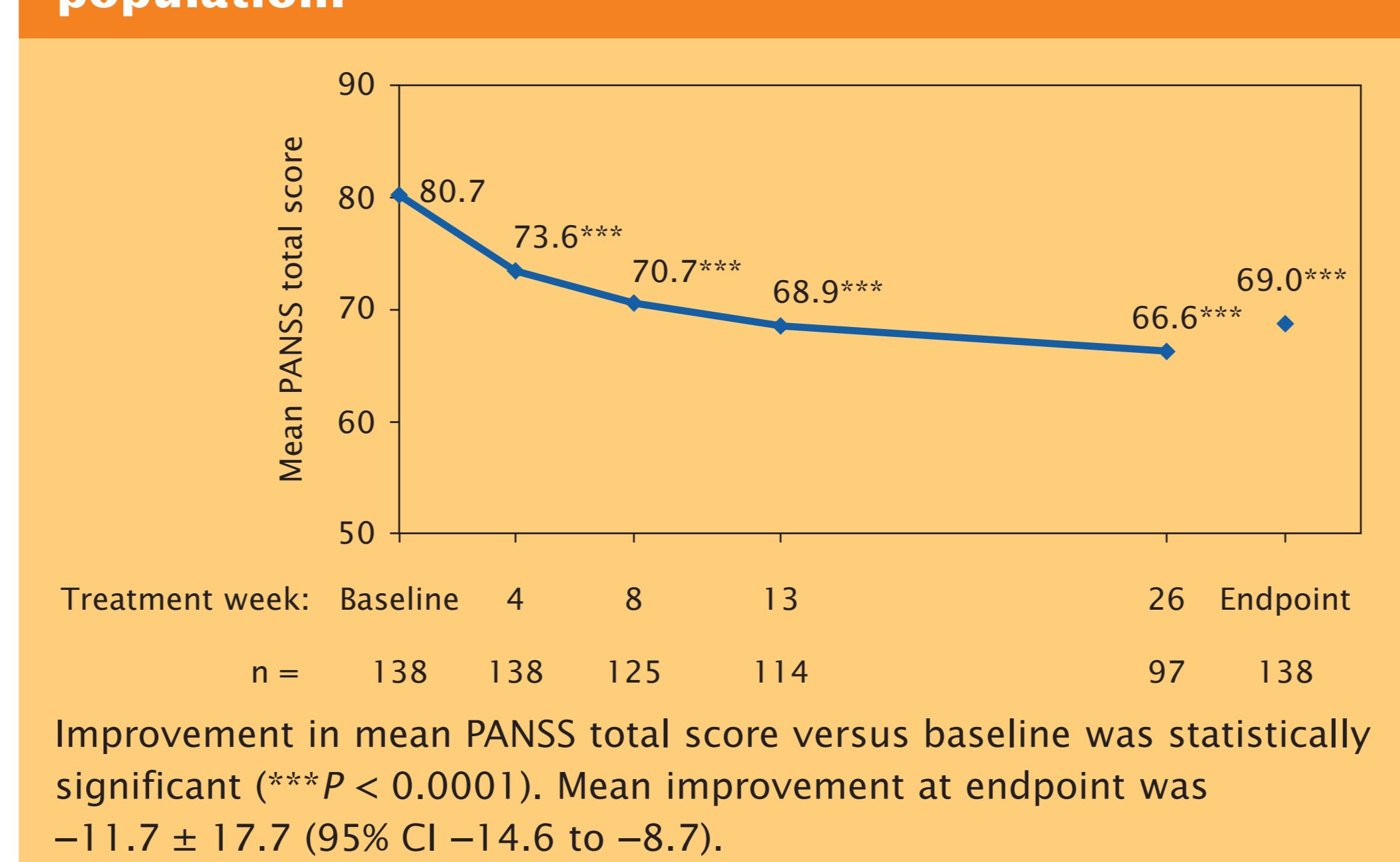


Table 5. Mean PANSS scores at baseline and endpoint (N = 138).

PANSS score ± SD	Baseline	Endpoint	P value
Total	80.7 ± 20.8	69.0 ± 19.1	< 0.0001
Subscale			
Positive	17.5 ± 5.8	14.6 ± 5.5	< 0.0001
Negative	23.0 ± 7.2	19.5 ± 6.2	< 0.0001
General psychopathology	40.1 ± 11.0	34.9 ± 10.0	< 0.0001
Marder factors			
Positive	21.7 ± 6.7	18.3 ± 6.2	< 0.0001
Negative	22.8 ± 7.2	19.1 ± 6.3	< 0.0001
Disorganized thoughts	17.6 ± 5.8	15.2 ± 5.0	< 0.0001
Uncontrolled hostility/excitement	7.6 ± 3.3	7.1 ± 3.2	0.0162
Anxiety/depression	11.1 ± 4.0	9.3 ± 3.4	< 0.0001

Figure 3. CGI-S categories at baseline and endpoint.

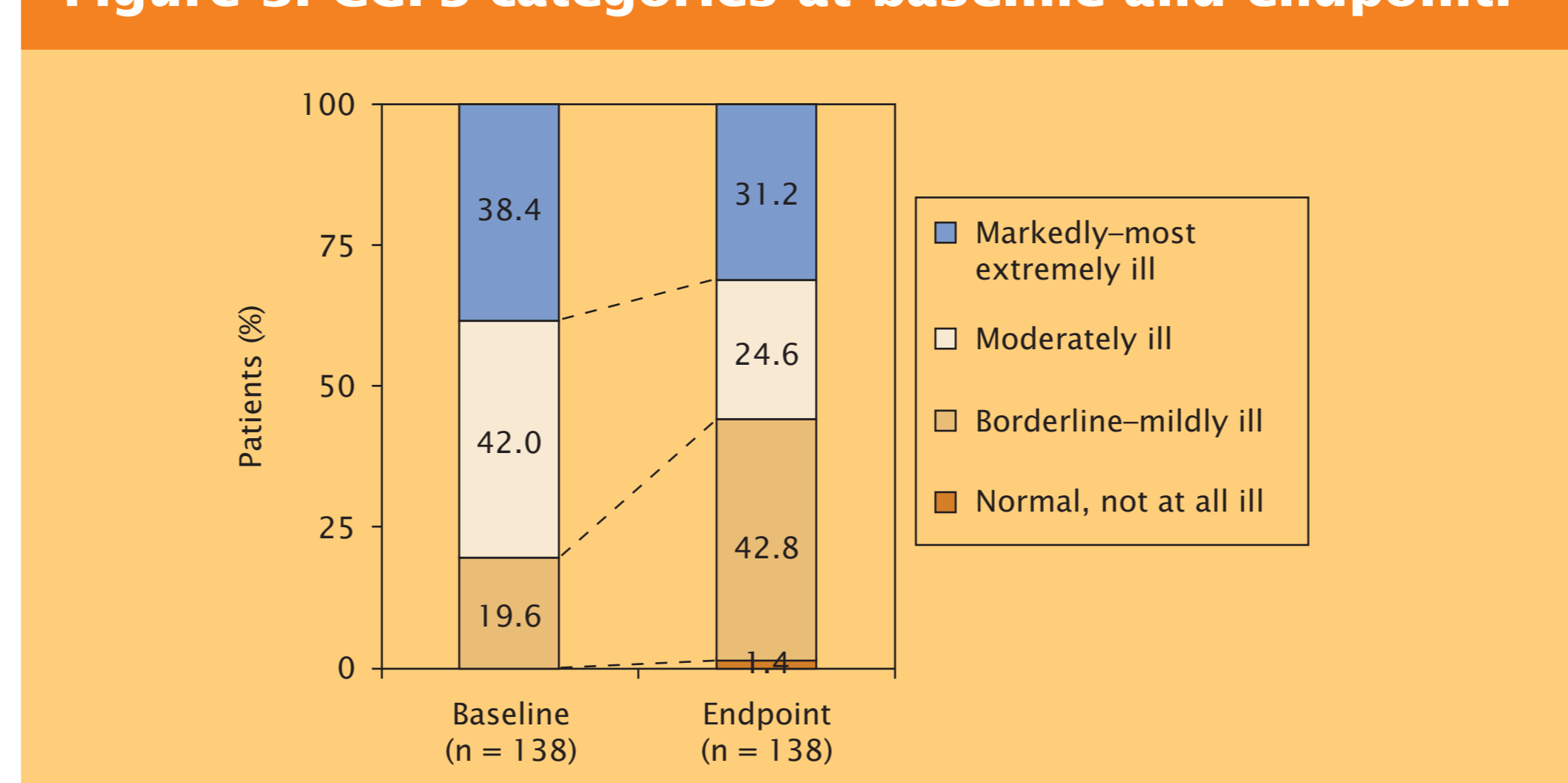


Figure 4. Patient functioning (PSP categories) at baseline and endpoint.

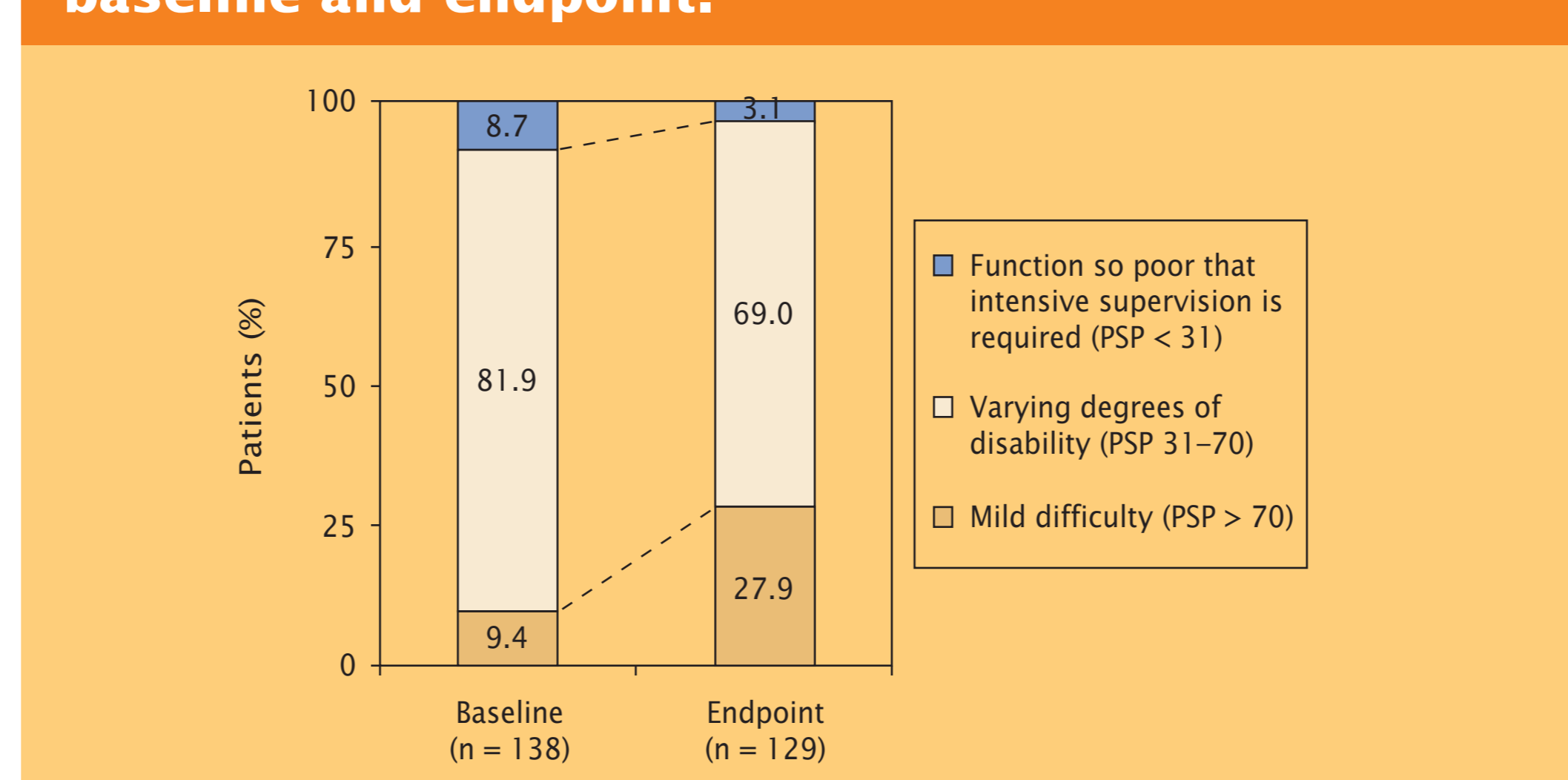


Figure 5. Patient satisfaction with previous antipsychotic treatment at baseline and with paliperidone ER at endpoint.

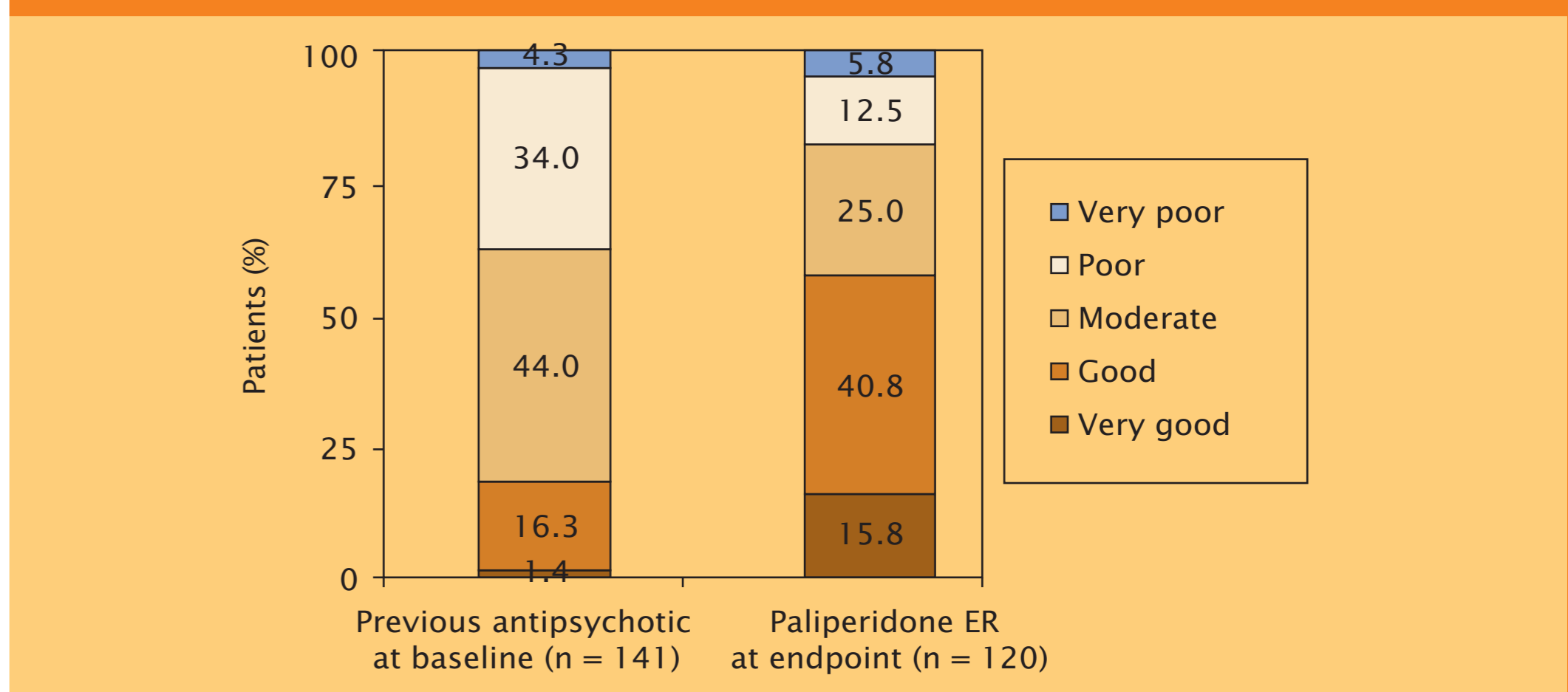


Table 6. Treatment-emergent adverse events (TEAEs) (N = 141).

TEAE	n (%)
Any TEAE*	85 (60.3)
TEAE causally related to paliperidone ER	60 (42.6)
Serious TEAEs†	14 (9.9)
TEAEs occurring in ≥ 5% of patients	
Anxiety	11 (7.8)
Insomnia	11 (7.8)
Somnolence	10 (7.1)
Weight increase	9 (6.4)
Akathisia	7 (5.0)
Action taken due to TEAE‡	
None	176 (73.0)
Dose adjustment	38 (15.8)
Permanent discontinuation	27 (11.2)

*Most TEAEs (93.4%) were mild to moderate in intensity.
 †Most commonly reported serious TEAEs based on number of patients were psychotic disorder (2.8%), schizophrenia (2.1%), and anxiety (2.1%).
 ‡Based on number of TEAEs (n = 241) rather than number of patients.

Figure 6. Mean ESRS total scores.

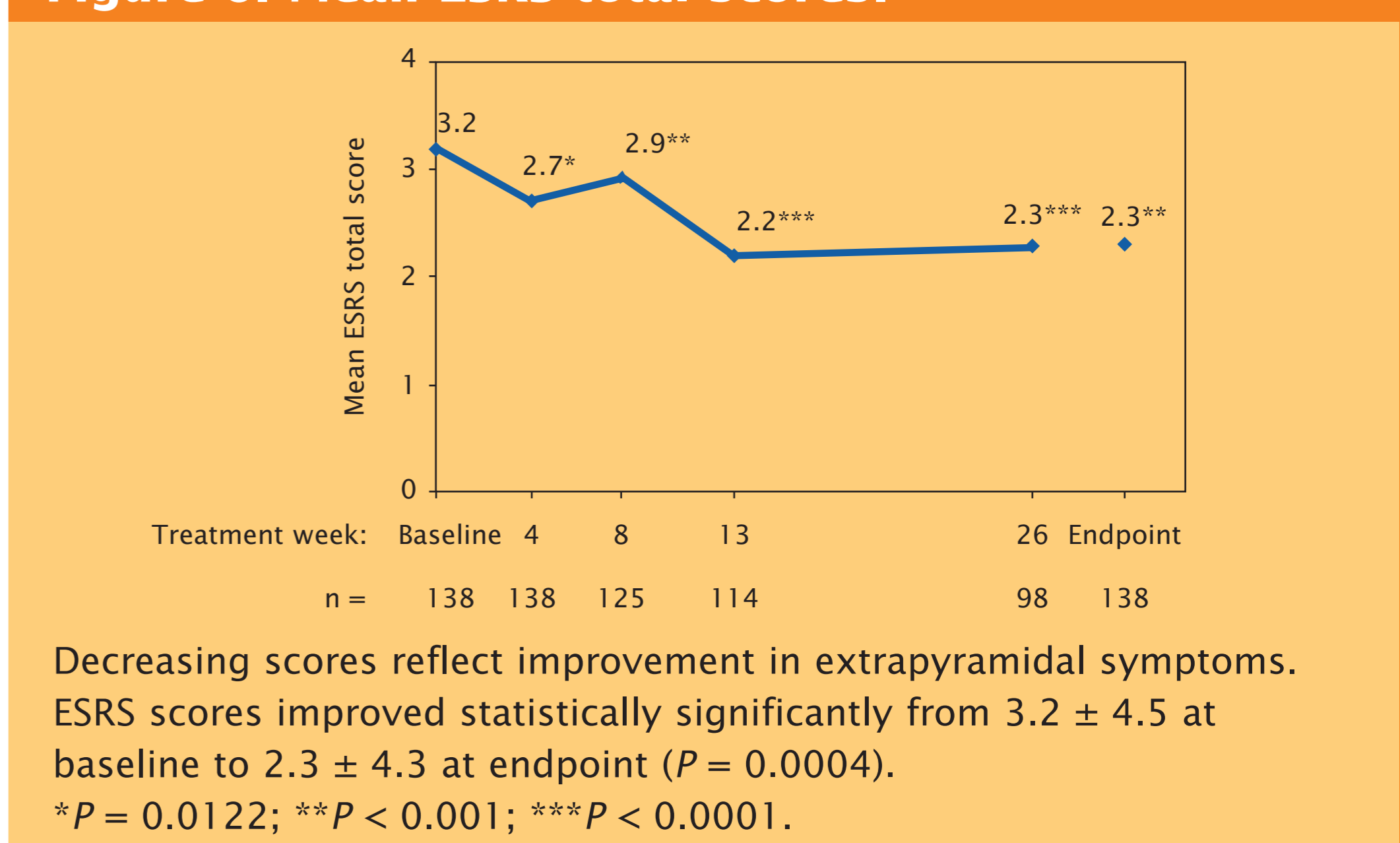
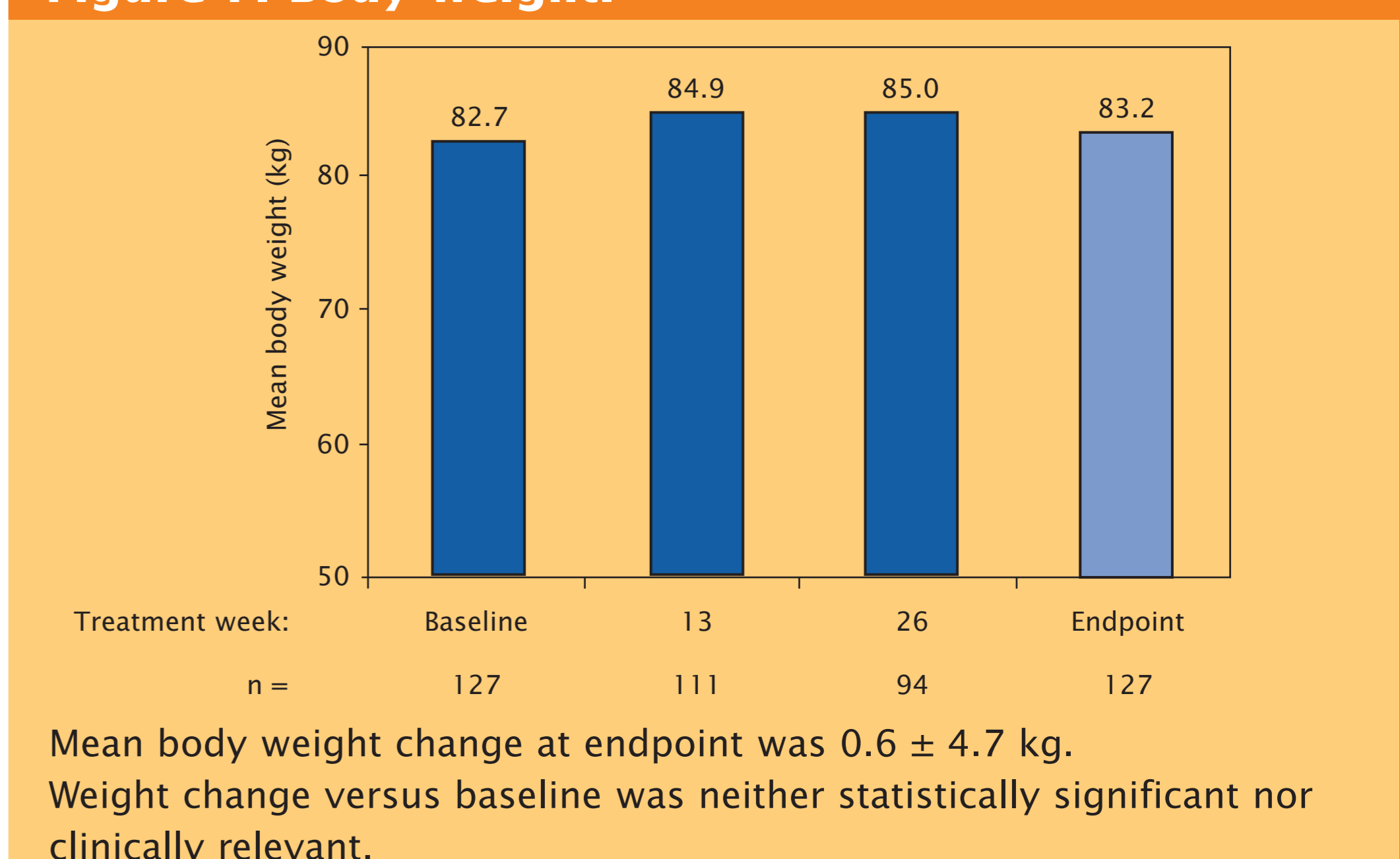


Figure 7. Body weight.



SUMMARY and CONCLUSION

- Among non-acute patients with schizophrenia transitioned to paliperidone ER for the main reason of lack of efficacy with previous aripiprazole treatment, more than 58% had an improvement in PANSS total scores of ≥ 20% from baseline to endpoint.
- Among patients switching to paliperidone ER from aripiprazole for main reasons of lack of tolerability and reasons other than lack of efficacy, tolerability, or compliance, PANSS total scores at endpoint met prespecified non-inferiority criteria.
- For all patients, PANSS total score from baseline to endpoint improved significantly ($P < 0.0001$).
- Clinically relevant and statistically significant improvements occurred in PANSS total, subscale, and Marder factor scores ($P < 0.05$), with significant improvements in PANSS total scores noted from the first post-baseline assessment (4 weeks after initiating paliperidone ER).
- The percentage of patients with severe or varying degrees of functional impairment decreased from 91% at baseline to 72% at endpoint.
- Patient satisfaction, an important predictor for adherence to treatment, was good or very good in 18% of patients previously unsuccessfully treated with aripiprazole. Patient satisfaction after treatment with paliperidone ER was good or very good in 57% of patients.
- TEAEs occurring in ≥ 5% of patients were anxiety (7.8%), insomnia (7.8%), somnolence (7.1%), weight increase (6.4%), and akathisia (5.0%).
- ESRS scores decreased (i.e. improved) statistically significantly from 3.2 ± 4.5 to 2.3 ± 4.3 ($P = 0.0004$). This statistically significant, while numerically small, improvement may be clinically relevant as aripiprazole is generally considered to be well tolerated.
- Mean body weight change from baseline to endpoint after switching to paliperidone ER was only 0.6 ± 4.7 kg.
- Flexibly dosed paliperidone ER treatment over 6 months was safe, well tolerated, and associated with meaningful treatment response in patients previously unsuccessfully treated with aripiprazole.

REFERENCES

- Conley R, et al. *Curr Med Res Opin.* 2006;22:1879-92.
- Meltzer HY, et al. *J Clin Psychiatry.* 2008;69:817-29.
- Emsley R, et al. *Int Clin Psychopharmacol.* 2008;23:343-56.