IMPACT (Invega in the Management of Patients in the ACute seTting): Results from a Belgian study using paliperidone extended-release in the management of psychotic patients with acute agitation and/or aggression.

Audenaert K[1], Godenir F[2], Geerts P[3], van Gils L[3], Detraux J[4]

[1]Ghent University Hospital, Belgium, [2]Mont-Godinne University Hospital, Godinne, Belgium, [3]Janssen-Cilag NV/SA, Belgium, [4]Sint-Jozef University Psychiatric Centre, Kortenberg, Belgium

BACKGROUND

- Oral atypical antipsychotics, alone or in combination with a benzodiazepine, are considered first line treatment for patients showing mild to moderate psychotic agitation at the emergency psychiatric ward[1]. However, often antipsychotics with sedating effects are used, not taking into consideration the fact that sedation may not be beneficial in the long term and cannot be titrated separately in this way.
- Paliperidone extended release (PALI ER) demonstrated significant efficacy in very acute patients during a Phase IIIb study[2]. Moreover, PALI ER has no or limited sedating effects. However, no data are currently available regarding the efficacy of PALI ER during the first two days of treatment of patients with acute agitation and/or aggression, nor regarding the efficacy of this compound on specific symptoms of agitation and/or aggression.

OBJECTIVES

- Evaluate the efficacy during the first 6 days of treatment of PALI ER in subjects with acute agitation and/or aggression in the context of psychosis in the psychiatric emergency setting, with special emphasis of the first 48 hours.
- Explore the tolerability and safety of the use of PALI ER in these subjects.

PATIENTS AND METHODS

- Fifty-six outpatients (≥ 18 years) with acute agitation and/or aggression, a PANSS-EC (PANSS-Excitement Component) score of ≥ 20 and in need of hospitalization were included in this study. Only patients presenting with acute agitation and/or aggression in the context of psychosis and suspected schizophrenia were eligible for this study. However, the most likely psychiatric diagnosis based on DSM-IV was recorded at endpoint. Patients who received benzodiazepines 4 hours or antipsychotics 72 hours prior to enrollment, as well as patients who received clozapine or a long-acting injectable antipsychotic drug during the last 3 months were excluded. Subjects presenting with agitation, aggression or violent behavior that necessitated the use of intramuscular or intravenous medication, showing a history of substance abuse, TD or NMS, or a high risk for suicidal behavior, as well as pregnant or breast-feeding subjects were also excluded.
- An open-label, single arm, multicenter 6-day study was used. The study ended after 5 days of treatment or at the day of discharge from the hospital, whatever came first. The recommended PALI ER dose was 6 mg/day throughout the study; however, the treating physician could decide to administer 9 mg, preferably from the beginning. The protocol specified that PALI ER should always be administered in the morning, and a given patient always needed to take it in either the fasting or fed state, not alternating between the two. The treating physician was responsible for this. A benzodiazepine (i.e., lorazepam 2.5 mg) for sedation and/or rescue medication could be added with a maximum of 7.5 mg/day at the investigators' discretion.
- Efficacy was evaluated by means of the PANSS-EC and the GAF (Global Assessment of Functioning) rating scales, as well as by the use of lorazepam; agitation and aggression were evaluated with the OAS (Overt Aggression Scale) and the BARS (Behavioural Activity Rating Scale). Safety parameters included adverse events and vital signs (blood pressure and pulse). All evaluations (with the exception of GAF) were conducted at baseline, 2 hours, 6-12 hours and 2, 3, 4, 5 and 6 days.

RESULTS

PATIENT CHARACTERISTICS.

Descriptive statistics of demographic and baseline disease characteristics are presented in **Table 1**.

Table 1 – Demographic and baseline disease characteristics of the subjects initiating PALI ER treatment.

Parameter	
Total number of patients enrolled	56
Male gender (%)	78.6
Mean age (years)	37.0
Mean weight at baseline (kg)	78.1
Mean BMI at baseline (kg/m²)	25.39
Median duration at baseline since first psychotic symptoms or first antipsychotic treatment (years)	3.0
Hospitalized before (%)	73.2

DOSING AND DISCONTINUATION RATE

Descriptive statistics of the subjects' exposure to PALI ER as well as discontinuation rates are presented in **Table 2**.

Table 2 – Study population: dosing & discontinuation information

	Pali ER 6 mg	Pali ER 9 mg	Pali ER 0 <> 6 mg	Pali ER 6 > 9 mg	Total
Treated N	35	15	4	2	56
Completed N (%)	28 (80)	14 (93)	1 (25)	2 (100)	45 (80)
Discontinued	7	1	3	0	11
Discharge	3				3
Lack efficacy	1				1
Trial nonadherence			1		1
Lost to FU			1		1
Other	3	1	1	0	5

Mean duration 4.8 days, mean dose 6.7 mg.
Hospital discharge counted as study end if it came before the end of 5 treatment days. – N = 56, 6 days.

The majority of subjects in this study (35 subjects, 62.5%) used a daily dose of 6 mg PALI ER. Fifteen subjects (26.8%) took a daily dose of 9 mg PALI ER. Two subjects had a PALI ER dose increase from 6 to 9 mg/day. Reasons for this dose increase were insufficient efficacy (1 subject) and not finding the 9-mg tablets at study entry (1 subject). Four subjects were not adherent with study medication intake (6 mg PALI ER) until completion of treatment or premature discontinuation and switched between taking no study medication and PALI ER doses 6 mg once daily. Overall, 45 out of 56 subjects (80.4%) completed the study. Eleven subjects (19.6%) discontinued the study prematurely. The main reason for study discontinuation was recovery of symptoms (3 subjects, 5.4%).

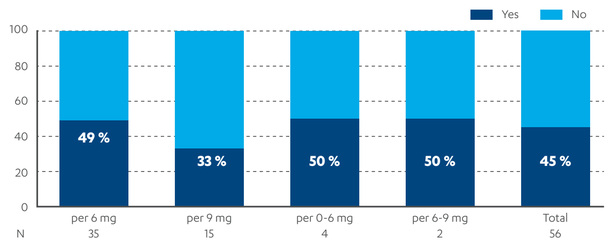
EFFICACY EVALUATIONS

The primary endpoint was the number of subjects having an improvement of 40% or more on the Positive and Negative Syndrome Scale-Excitement Component (PANSS-EC) at day 6 or early termination, compared to baseline.

PANSS-EC scores

The PANSS-EC allows the clinical assessment and the evaluation of the effectiveness of interventions on excitement symptoms, which is particularly important in acute treatment situations. The scale provides information regarding 5 items: poor-impulse control, tension, excitement, uncooperativeness and hostility. Each item is rated on a scale of 1 (absence of any symptom) to 7 (extremely severe symptoms).

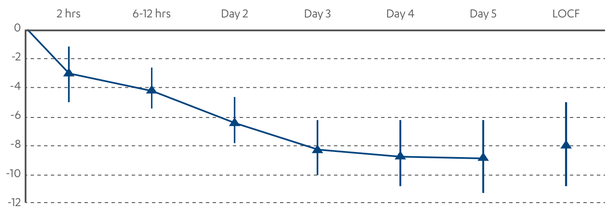
Figure 1 – Percentage of patients improving ≥ 40% on PANSS-EC



N = 56, 6 days
PANSS-EC: Positive and Negative Syndrome Scale - Excitement Component

Overall, 25 subjects (44.6%) had at least 40% improvement in total PANSS-EC score from baseline to endpoint (day 6) after treatment with PALI ER 6 or 9 mg once daily (**Figure 1**). The lower and upper limits of the 95% confidence interval were 31.6% and 57.7%, respectively.

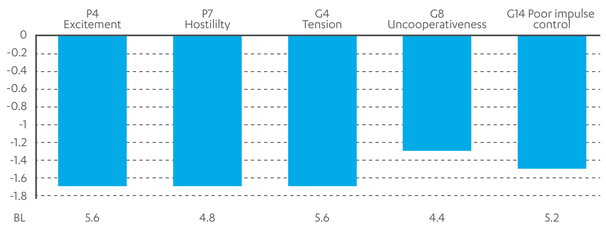
Figure 2 – PANSS-EC over time



BL score 25.6, potential range 5-35; ITT analysis set
PANSS-EC: Positive and Negative Syndrome Scale - Excitement Component – N = 56, 6 days

The total PANSS-EC scores showed consistent improvement of symptoms over the study period, indicated by a decrease in total PANSS-EC score from baseline. The mean (SD) total PANSS-EC baseline score was 25.6 (2.9). Changes from baseline to endpoint (day 6) showed a mean (SD) decrease in total PANSS-EC score of -7.9 (6.0). The mean decrease from baseline in total PANSS-EC score was the largest on day 5 (Δ = -8.7, SD = 5.12) (**Figure 2**).

Figure 3 – PANSS-EC by subscale



N = 56, 6 days
PANSS-EC: Positive and Negative Syndrome Scale - Excitement Component

Descriptive statistics of the PANSS-EC subscale scores at baseline and changes from baseline to endpoint (day 6) are presented in **Figure 3**. The PANSS-EC subscale scores excitement (BL = 5.6, Δ = -1.7), hostility (BL = 4.8, Δ = -1.7), tension (BL = 5.6, Δ = -1.7), uncooperativeness (BL = 4.4, Δ = -1.3), and poor impulse control (BL = 5.2, Δ = -1.5) decreased (improved) consistently over the study period. No obvious differences between subscales were observed in the changes from baseline to endpoint (day 6).

GAF scores

The GAF scale, taking into account the psychological, social, and occupational functioning of the subject, is used to rate the clinical progress of individuals in global terms, using a single measure. Mean GAF scores increased over the study period with a mean (SD) increase in GAF score of 11.7 (10.93) from baseline (BL=29.1, SD=7.40) to endpoint (day 6), indicating overall improvement of the patients' psychological, social and occupational functioning (**Table 3**).

Table 3: Global Assessment of Function (GAF)

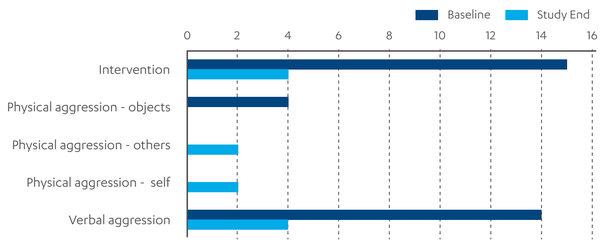
Time	GAF	Range
Baseline	29.1	Behaviour is considerably influenced by delusions or hallucinations OR serious impairment in communication or judgement (e.g. sometimes incoherent, acts grossly inappropriately, suicidal preoccupation) OR inability to function in almost all areas (e.g. stays in bed all day; no job, home, or friends).
Day 6 / Last	40.8	Some impairment in reality testing or communication (e.g. speech is at times illogical, obscure, or irrelevant) OR major impairment in several areas, such as work or school, family relations, judgement, thinking or mood (e.g. depressed man avoids friends, neglects family, and is unable to work; child frequently beats up younger children, is defiant at home, and is failing at school).

N = 56, 6 days

OAS (Overt Aggression Scale) scores

The Overt Aggression Scale is developed for the assessment of verbal and physical aggression. On the OAS, aggression is divided into 4 categories: verbal aggression, physical aggression against objects, physical aggression against self, and physical aggression against others. In addition, specific interventions related to each aggressive event can be recorded on the OAS. The recordings of verbal aggression incidents using the OAS scale decreased from 14 subjects (25.0%) at baseline to 4 subjects (7.1%) at endpoint (day 6). Intervention incidents decreased from 15 subjects (26.8%) at baseline to 4 subjects (7.1%) at endpoint (day 6). Physical aggression incidents were rare and reported in at most 2 subjects at any visit, except for physical aggression incidents against objects which were reported in 4 subjects (7.1%) at baseline (**Figure 4**).

Figure 4 – Overt Aggression Scale (OAS) - N patients with incidents

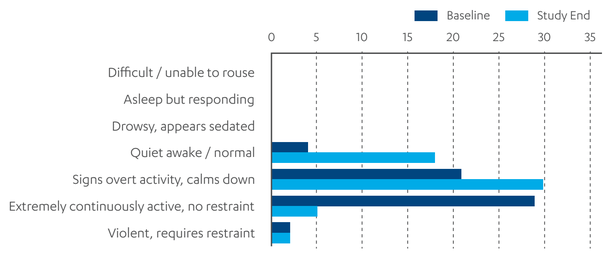


N = 56, 6 days

BARS scores

The BARS is a single item scale that differentiates between extreme agitation (score 7) and extreme sedation (difficult or unable to rouse) (score 1). At baseline, the majority of subjects had signs of overt activity (BARS score 5, 21 subjects [37.5%]) or were extremely or continuous active (BARS score 6, 29 subjects [51.8%]). At endpoint (day 6), the majority of subjects were quiet and awake (BARS score 4, 18 subjects [32.7%]) or had signs of overt activity (BARS score 5, 30 subjects [54.5%]) (**Figure 5**). The BARS is a single item scale that differentiates between extreme agitation (score 7) and extreme sedation (difficult or unable to rouse) (score 1).

Figure 5 – Behavioural Activity Rating Scale (BARS) - categorical

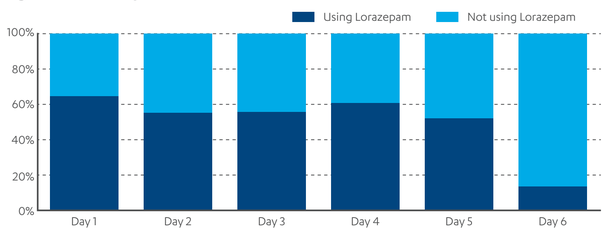


N = 56, 6 days

Use of lorazepam

The proportion of subjects using lorazepam remained approximately constant during the study period (range: 52.2% - 60.9%) but decreased at endpoint (day 6) (13.3%) (**Figure 6**). The mean daily dose of lorazepam ranged from 2.297 to 2.969 mg from study start until endpoint (day 6), with the lowest mean daily dose recorded at day 5 (2.297 mg).

Figure 6 – Lorazepam use



N = 56, 6 days

Psychiatric diagnosis (DSM-IV) at study end

At endpoint (day 6), approximately half of the subjects were diagnosed with schizophrenia (27 subjects, 49.1%). The remainder was diagnosed with psychotic disorder NOS (12 subjects, 21.8%), brief psychotic disorder (9 subjects, 16.4%), schizoaffective disorder (5 subjects, 9.1%), and mood disorder with psychotic features (2 subjects, 3.6%).

Efficacy: 6 mg vs. 9 mg

Table 4 – Efficacy: 6 mg vs 9 mg

	6 mg BL N=35	6 mg	9 mg BL N=15	9 mg
PANSS-EC	25.2	-7.9	26.5	-7.0
Hostility mean Δ	4.8	-1.7	4.9	-1.4
Tension mean Δ	5.5	-1.7	5.8	-1.5
Impulsivity mean Δ	5.2	-1.7	5.4	-1.3
Responders %		48.6		33.3
GAF mean Δ	30.3	+12.2	29.4	+8.9
OAS %	23	8	20	0
Verbal aggression %	20	6	20	0
Intervention %	23	6	20	0
BARS mean Δ	5.4	-0.7	5.9	-0.7
Quiet awake %	11	40	0	13.3
Lorazepam %	54	14	80	7

OAS: Overt Aggression Scale; BARS: Behavioural Activity Rating Scale
Responders = subjects with 40% improvement in total PANSS-EC from baseline to endpoint
BL : baseline measure Δ : change from baseline (PANSS-EC, GAF, BARS)

Baseline scores were similar for most measures except % lorazepam use and % quiet awake on BARS.
The reduction of ≥ 40% in the initial score on the PANSS-EC scale was observed in a higher proportion of patients in the PALI 6 mg/day dose group (N=35, 48.6%, BL=25.2, Δ=-7.9), compared to the PALI 9 mg/day group (N=15, 33.3%, BL=26.5, Δ=-7.0). Equally, the PALI 6 mg/day group showed a numerically greater increase in the GAF score (6 mg Δ=+12.2, N=35 versus 9 mg Δ=+8.9, N=15) % lorazepam use at endpoint was numerically half that of the 6 mg group (**Table 4**).

SAFETY EVALUATIONS

Adverse events

A summary of the treatment-emergent adverse events (TEAEs) during the study period is presented in **Table 5 and 6**.

Table 5 – Adverse events

Adverse event	N	%
Any TEAE	9	16.1
Any SAE	2	3.6
Any mild TEAE	7	12.5
Any moderate TEAE	1	1.8
Any severe TEAE	2	3.6
Any TEAE for which pali ER was temporarily or permanently stopped	0	0
Any TEAE at least possibly related to pali ER	2	3.6

TEAE = Treatment-Emergent Adverse Event; SAE = Serious Adverse Events
SAE: Schizophrenia, Psychotic disorder • Severe TEAE: Schizophrenia, Psychotic disorder • Possibly related TEAE: QTc prolongation, somnolence • N= 56, 6 days

No deaths or AEs leading to discontinuation of PALI ER treatment were reported in this study. Serious TEAEs were reported in 2 subjects (3.6%). Overall, 9 subjects (16.1%) had at least one TEAE during the study (**Table 5**). These TEAEs were observed in a higher proportion of patients in the PALI 6 mg/day dose group (N=35, 14.3%), compared to the PALI 9 mg/day group (N=15, 6.7%). The majority of TEAEs were mild in severity. Moderate TEAEs were reported in 1 subject (1.8%) and severe TEAEs in 2 subjects (3.6%). Most TEAEs were considered not or doubtfully related to PALI ER by the investigator. No TEAEs were considered very likely related to PALI ER by the investigator. TEAEs considered at least possibly related to PALI ER by the investigator were reported in 2 subjects (3.6%) during the study (electrocardiogram QT prolonged and somnolence each reported in 1 subject) (**Table 5**). All TEAEs occurred in only 1 subject during the study, except nausea which occurred in 3 subjects (5.4%) (**Table 6**).

Table 6 – Adverse events

	N	%
Nausea	3	5.4
Dyspepsia	1	1.8
Vomiting	1	1.8
Insomnia	1	1.8
Psychotic disorder	1	1.8
Schizophrenia	1	1.8
Headache	1	1.8
Somnolence	1	1.8
Gait disturbance	1	1.8
Malaise	1	1.8
QT prolongation	1	1.8
Hyponatremia	1	1.8
Rash	1	1.8

N = 56, 6 days

Vital signs

Mean changes from baseline to endpoint (day 6) in vital signs parameters (pulse rate, systolic and diastolic blood pressure) were generally small, and none of the changes were considered clinically relevant. No vital signs-related TEAEs were reported during the course of the study.

DISCUSSION AND CONCLUSION

Due to its extended-release formulation, the use of PALI ER could be regarded as less useful in the acute treatment of psychosis during the first days of hospitalisation. However, the OROS extended-release formulation provides a constant rise in plasma levels during those first days[3], without the peak-trough variation of normal immediate release oral formulations, providing a potential benefit in the second half of the first day. Hence it was of clinical interest to document the efficacy deployment during the first 48 hours, specifically during the first day.

Secondly, most recent studies of atypical antipsychotics in the first day of hospitalization used a treatment paradigm with standard lorazepam addition[4,5,6,7]. In spite of this, the baseline PANSS-EC score in this study was among the highest : 25.6 versus 19.0[5], 22.0[7] or 26.7[4]. In some of those studies, the very similar PANSS-PAS was used instead of the PANSS-EC (PANSS-EC : excitement, hostility, tension, uncooperativeness, poor impulse control ; PANSS-PAS : excitement, hostility, hallucinations, uncooperativeness, poor impulse control).

When looking at the OAS baseline data, it appears that this patient group had mostly verbal aggression as opposed to physical aggression ; a point to be taken into account when considering the clinical applicability of the data.

This is therefore the first study that documents the evolution of treatment efficacy and safety of PALI ER during the first two days of treating acutely agitated, verbally aggressive psychotic patients, and beyond up to 6 days. Although its conclusions are hampered by the fact that it is an open-label study without a comparator group, results of this study indicated that short-term treatment with PALI ER 6 or 9 mg once daily with discretionary lorazepam addition was associated with improvement in clinical and functional outcome in subjects with acute agitation and/or aggression in the context of psychosis. Consistent with earlier short-term data, treatment with PALI ER 6 mg or 9 mg once daily was generally safe and well tolerated in this patient population. Therefore, because of its fast onset of action and limited or no long-term sedating effects, it can be concluded that PALI ER can be a useful option in the management of psychotic patients with acute agitation and/or verbal aggression.

POSTER PRESENTED AT 11IÈME CONGRÈS DE L'ENCÉPHALE, PARIS, JANUARY 23-25, 2013.

1 : Allen MH, Currier GW, Carpenter D, Ross RW, Docherty JP; Expert Consensus Panel for Behavioral Emergencies 2005. The expert consensus guideline series. Treatment of behavioral emergencies 2005. J Psychiatr Pract 2005;11 Suppl 1: 5-108. • 2 : Schmauss M, Jukic V, Siracusano A et al. Flexible dosing with paliperidone ER in the treatment of patients with acutely exacerbated schizophrenia : results from a single-arm, open-label study (PERTAIN study). Current Medical Research and Opinion epub 2012. • 3 : Rossenu S, Cleton A, Talluri K et al. Evaluation of the pharmacokinetics of an extended-release formulation of paliperidone and an immediate –release formulation of risperidone. Poster presented at ASCPT congress, Anaheim, March 2007. • 4 : Currier GW, Simpson GM. Risperidone liquid concentrate and oral lorazepam versus intramuscular haloperidol and intramuscular lorazepam for treatment of psychotic agitation. J Clin Psychiatry 2001; 62(3): 153-157. • 5 : Currier GW, Chou JCY, Feifel D et al. Acute treatment of psychotic agitation : a randomized comparison of oral treatment with risperidone and lorazepam versus intramuscular treatment with haloperidol and lorazepam. J Clin Psychiatry 2004; 65(3): 386-394. • 6 : Veser FH, Veser BD, Mcmullan JT et al. Risperidone versus haloperidol, in combination with lorazepam, in the treatment of acute agitation and psychosis : a pilot, randomized, double-blind, placebo-controlled trial. J Psychiatric Practice 2006; 12(2): 103-108. • 7 : Lim HK, Kim JJ, Pae CU et al. Comparison of risperidone orodispersible tablet and intramuscular haloperidol in the treatment of acute psychotic agitation : a randomized open, prospective study. Neuropsychobiology 2010; 62 : 81-86.