THE JOURNAL OF CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

Supplementary Material

Article Title: Lurasidone Dose Escalation in Early Nonresponding Patients With Schizophrenia: A Randomized, Placebo-Controlled Study

Author(s): Antony Loebel, MD; Robert Silva, PhD; Robert Goldman, PhD; Kei Watabe, MS; Josephine Cucchiaro, PhD; Leslie Citrome, MD, MPH; and John M. Kane, MD

DOI Number: 10.4088/JCP.16m10698

List of Supplementary Material for the article

1. **eAppendix 1** Pharmacokinetic Analysis
2. **eTable 1** Change From Week 2 to Week 6 on Secondary Efficacy Measures in Early Nonresponders Re-randomized at Week 2 to Lurasidone 80 mg/day or 160 mg/day (Intent-to-Treat Population; MMRM Analysis)
3. **eTable 2** Safety Assessments in Early Responders to Lurasidone 80 mg/day: Adverse Events Occurring From Study Baseline to Week 6 Endpoint in ≥5% of Early Responders and Baseline to Endpoint Change in Weight, Laboratory Parameters, and ECG (Last Observation Carried Forward)
4. **eTable 3** Adverse Events With Onset After Week 2 (Incidence ≥3% in Early Nonresponders Re-randomized at Week 2 to Lurasidone 80 mg/day or 160 mg/day; Safety Population)

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

eAppendix 1

Pharmacokinetic Analysis

Pharmacokinetic analysis was conducted to evaluate the relationship between lurasidone exposure and early response/nonresponse. Mean (SD) trough serum concentration of lurasidone at week 2 was 8.2 (5.3) ng/mL in early responders (n = 55) and 10.3 (8.9) ng/mL in early nonresponders (n = 71) to lurasidone 80 mg/day. At week 6, mean (SD) serum concentration at 14–15 hours postdose was 13.3 (10.2) ng/mL in early responders (n = 18), 14.7 (12.3) ng/mL in early nonresponders continued on lurasidone 80 mg/day (n = 15), and 29.1 (18.5) ng/mL in early nonresponders with dose increased to 160 mg/day (n = 11).

Supplementary eTable 1. Change From Week 2 to Week 6 on Secondary Efficacy Measures in Early Nonresponders Re-randomized at Week 2 to Lurasidone 80 mg/day or 160 mg/day (Intent-to-Treat Population; MMRM Analysis)

	Early Nonresponders Lurasidone 80 mg/d (n = 52)		Early Nonresponders Lurasidone 160 mg/d (n = 43)	
Outcome Measure	LS mean	SE	LS mean	SE
PANSS positive	–3.2	0.6	–5.2*	0.7
PANSS negative	–2.1	0.6	–3.0	0.7
PANSS general psychopathology	–4.0	1.1	–8.6**	1.3
PANSS excitability	–0.9	0.5	–3.4**	0.6
PANSS depression	–1.2	0.3	–2.1*	0.4

*$P < .05$ versus ENR 80 mg/day.

**$P < .01$ versus ENR 80 mg/day.

Abbreviations: ENR = early nonresponder; LS = least squares; PANSS = Positive and Negative Syndrome Scale; SE = standard error.

Supplementary eTable 2. Safety Assessments in Early Responders to Lurasidone 80 mg/day: Adverse Events Occurring From Study Baseline to Week 6 Endpoint in ≥5% of Early Responders[a] and Baseline to Endpoint Change in Weight, Laboratory Parameters, and ECG (Last Observation Carried Forward)[b]

Early Responders Lurasidone 80 mg/d (n = 100)						
Adverse Events			Weight and Laboratory Parameters			
	N	%		Mean	SD	Median
≥1 event	58	58.0	Weight (kg)[c]	0.5	1.9	0.5
Akathisia	16	16.0	Waist circumference (cm)	0.1	2.5	0.0
Insomnia	11	11.0	Total cholesterol (mg/dL)	1.3	28.7	–1.0
Nausea	9	9.0	LDL cholesterol (mg/dL)	0.1	22.7	2.0
Vomiting	6	6.0	Triglycerides (mg/dL)	4.4	72.4	–5.0
Diarrhea	5	5.0	Glucose (mg/dL)	–0.5	15.3	–2.0
	5	5.0	Prolactin (ng/mL)			
Parkinsonism			Men	–5.7	12.0	–2.2
			Women	5.6	46.4	–0.5
Extrapyramidal events[d,e]	8	8.0	QTcF (ms)	–1.4	18.2	0.0

[a]Suicidal ideation (assessed using the Columbia Suicide Severity Rating Scale) was noted in 1 patient (1.0%).

[b]Both confirmed and nonconfirmed fasting values are presented for metabolic parameters.

[c]Weight gain ≥7% was observed in 3.5% of patients.

[d]Combination term that included any of the following: cogwheel rigidity, drooling, dystonia, glabellar reflex abnormal, muscle rigidity, parkinsonism, torticollis, tremor, and trismus.

[e]Anticholinergic medication was used in 15.0% of patients.

Abbreviations: LDL = low-density lipoprotein; QTcF = heart rate–corrected QT interval, Fridericia's formula; SD = standard deviation.

Supplementary eTable 3. Adverse Events With Onset After Week 2 (Incidence ≥3% in Early Nonresponders Re-randomized at Week 2 to Lurasidone 80 mg/day or 160 mg/day; Safety Population)

	Early Nonresponders Lurasidone 80 mg/d (n = 55)		Early Nonresponders Lurasidone 160 mg/d (n = 43)	
Adverse Event	N	%	N	%
≥1 event	21	38.2	23	53.5
Insomnia	3	5.5	3	7.0
Akathisia	2	3.6	2	4.7
Anxiety	0	0	3	7.0
Abdominal discomfort	0	0	2	4.7
Nausea	2	3.6	1	2.3
Vomiting	2	3.6	1	2.3
Schizophrenia	2	3.6	1	2.3
Headache	3	5.5	0	0
Psychotic disorder	2	3.6	0	0
Respiratory tract infection (viral)	2	3.6	0	0
Suicidal ideation	2	3.6	0	0