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LB-102 for cognitive impairment in schizophrenia: exploratory *post hoc* analyses from a randomised, double-blind, placebo-controlled phase 2 study

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Background

- Cognitive impairment is highly prevalent in schizophrenia, affecting approximately 70–90% of patients, and encompasses broad deficits across working memory, attention, learning, and executive function.[1-5]
- Given their persistence and functional impact, cognitive impairments are recognized as a core therapeutic target in schizophrenia, yet they remain inadequately addressed by current treatments.[6]
- Most antipsychotics, while effective for positive symptoms, show little to no benefit for cognitive dysfunction, with only modest, or inconsistent, improvements observed for a small number of atypical agents. Overall, cognitive symptoms remain unmet in treatment strategies.[7-10]
- The dual M_1/M_4 muscarinic agonist xanomeline–trospium (KarXT) has demonstrated effects on cognition in acute schizophrenia populations when limited to patients with cognitive impairment at baseline.
  - In the phase 2 EMERGENT-1 trial, analysis of cognitive performance in the impaired subgroup showed that KarXT produced a significant improvement on the Cogstate, with a Cohen's *d* effect size of 0.50 (95% CI, 0.04–0.95; *p*=0.03), independent of changes in psychotic symptoms.[11]
    - The effect size increased to *d*=0.79 (95% CI, 0.16–1.10; *p*=0.009) when outliers were excluded.
  - In a pooled analysis of the cognitively impaired subgroup in the phase 3 EMERGENT-2 and EMERGENT-3 trials, KarXT yielded an Cohen's *d* effect size of 0.54 (95% CI, 0.10–0.51; *p*=0.004) on the CANTAB, independent of changes in psychotic symptoms.[12]
- LB-102 is a novel $D_2/D_3/5\text{-}HT_7$ antagonist under development for the treatment of schizophrenia and other central nervous system disorders.
- Preclinical assays have demonstrated that LB-102 exhibits similar receptor binding, pharmacokinetics, and behavior-modifying properties to amisulpride.[13,14]
- A phase 1, open-label PET study (NCT04588129) showing that LB-102 50 mg exhibits similar dopamine receptor occupancy under steady-state conditions to amisulpride 400 mg.[15]
- A phase 1, double-blind, placebo-controlled trial (NCT04187560) in 64 healthy volunteers showed that LB-102 in doses up to 150 mg/day was generally safe and well tolerated.[16]
- In the phase 2 NOVA[1] clinical trial in adults with schizophrenia (NCT06179108), LB-102 resulted in significant improvements in Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impressions–Severity of illness (CGI-S) scores after 4 weeks versus placebo, and was generally safe and well tolerated at dose levels up to 100 mg/day (see ECNP 2025 presentation: **PS02-1273**).[17]

Objective

- To evaluate the potential cognitive effects of LB-102 vs placebo through prespecified and *post hoc* analyses of the NOVA[1] phase 2 clinical trial, based on the Cogstate computerized cognitive battery of tests.

Methods

Study design and selection criteria

- NOVA[1] was a phase 2, multicenter, randomized, double-blind, placebo-controlled in-patient trial in adults with acute schizophrenia experiencing a psychotic relapse conducted in the United States.
- The trial comprised a 7- to 14-day inpatient screening, 28-day inpatient treatment, 5-day inpatient stabilization, and outpatient safety follow-up after the end of treatment.
- Eligible adults (aged 18–55 years) were diagnosed with schizophrenia, required hospitalization/continued hospitalization for a current acute exacerbation of psychotic symptoms, and had a PANSS total score of 80–120, a PANSS Positive Symptoms subscale item score of ≥4 on at least two key items, and a CGI-S score of ≥4.
  - No cognitive impairment assessment was conducted at screening or baseline to determine clinical trial eligibility.
- Participants were randomised (3:3:3:1) to oral once-daily placebo, LB-102 50 mg, LB-102 75 mg, or LB-102 100 mg, with the 100 mg treatment arm considered exploratory.

Outcomes and analyses

- The primary efficacy endpoint was the change from baseline to week 4 in the PANSS total score.
- The Cogstate computerized cognitive battery of tests was administered at baseline and at the end of the 4-week treatment period, and included the following 5 tests:
  - Detection Test (DET; measures simple reaction time)
  - Identification Test (IDN; measures choice reaction time)
  - One Back Test (ONB; measures working memory)
  - Groton Maze Learning Test (GMLT; measures executive function)
  - International Shopping List Test (ISLT; measures verbal list learning)
- Changes from baseline in the individual tests were prespecified exploratory endpoints, and the following composite scores were generated *post hoc* in the total trial population:
  - **Cogstate Brief Battery global composite score**
    - Aggregates performance on the DET, IDN, ISLT, GMLT, ONB (speed)
  - **Attention (Psychomotor Function) composite score**
    - Aggregates performance on the DET and IDN
  - **Memory (Executive Function) composite score**
    - Aggregates performance on the ISLT and GMLT
- Based on previously published literature, the threshold for clinical relevance of the treatment effect size was pre-determined as 0.2.[18]

Results

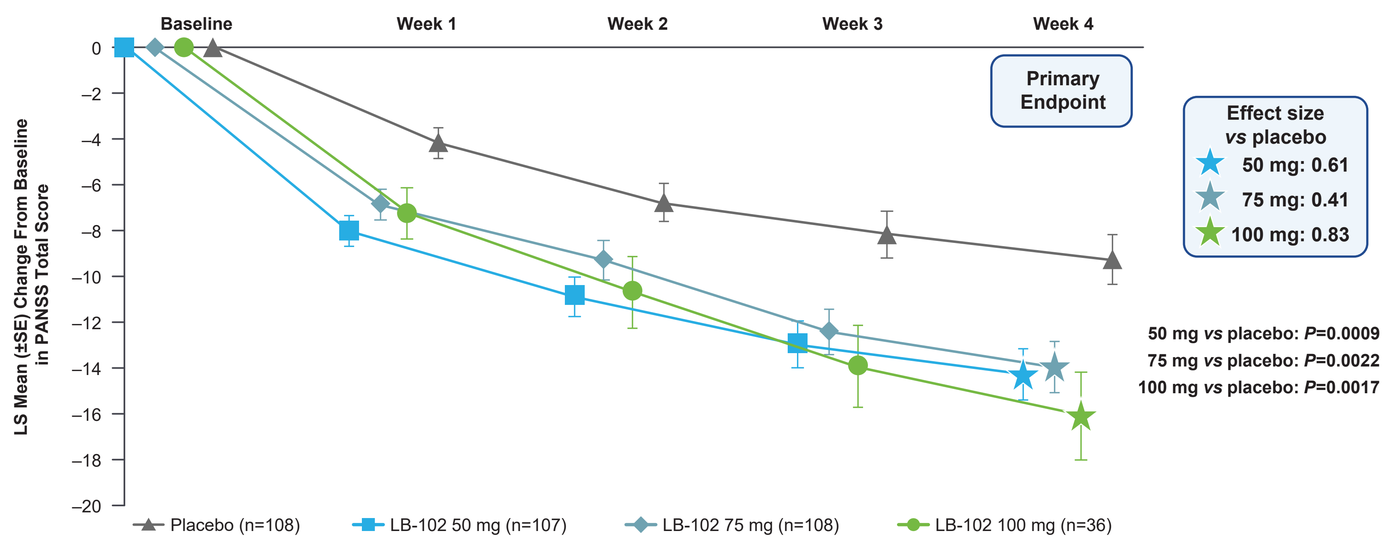
- A total of 359 participants were randomized and included in the safety and intent-to-treat populations (**Table 1**).
  - 293 participants (82%) completed week 4.
  - 261 participants (73%) completed the trial.
- LB-102 met the primary endpoint, with least-squares mean changes from baseline to week 4 in PANSS total score of −9.3 (placebo), −14.3 (50 mg, *p*=0.0009; effect size=0.61), −14.0 (75 mg, *p*=0.0022; effect size=0.41), and −16.1 (100 mg, nominal *p*=0.0017; effect size=0.83) (**Figure 1**).
- A usability and acceptability assessment of the total NOVA[1] trial population and the Cogstate dataset was performed prior to conducting the *post hoc* analyses (**Table 2**).
  - There were 18 test completion failures from a total of 3243 administered tests indicating a usability rate of 99.4%.
  - There were 76 test performance failures from a total of 2578 administered tests for which a test performance check was computed, providing an acceptability rate of 97.1%.
- As a result of the usability and acceptability analysis, the total NOVA[1] clinical trial population was deemed appropriate for further analysis.
- Analysis of the Cogstate Brief Battery global composite score demonstrated a significant dose-related treatment effect for LB-102 compared to placebo after 4 weeks of treatment (**Table 3**).
  - LB-102 50 mg, effect size=0.26, *p*=0.0476
  - LB-102 75 mg, effect size=0.41, *p*=0.0027
  - LB-102 100 mg, effect size=0.66, *p*=0.0018
- Clinical improvements with LB-102 treatment on the Attention (Psychomotor Function) and Memory (Executive Function) composite scores were also observed after 4 weeks of treatment (**Table 3**).

Table 1. Demographics and Baseline Characteristics

		Placebo (n=108)	LB-102 50 mg (n=107)	LB-102 75 mg (n=108)	LB-102 100 mg (n=36)	Overall (N=359)
Age at informed consent, mean (SD)		39.1 (9.1)	39.0 (9.6)	39.2 (9.2)	39.1 (9.2)	39.1 (9.3)
Sex, n (%)	Male	85 (79%)	87 (81%)	90 (83%)	28 (78%)	290 (81%)
	Female	23 (21%)	20 (19%)	18 (17%)	8 (22%)	69 (19%)
Ethnicity, n (%)	Latino	17 (16%)	12 (11%)	8 (7%)	6 (17%)	43 (12%)
Race, n (%)	White	24 (22%)	17 (16%)	18 (17%)	9 (25%)	68 (19%)
	Black	80 (74%)	87 (81%)	83 (77%)	25 (69%)	275 (77%)
	Asian	1 (1%)	0	2 (2%)	0	3 (1%)
	Native American	0	0	2 (2%)	0	2 (1%)
Weight at baseline (kg), mean (SD)		85.6 (17.2)	84.0 (19.5)	88.4 (18.5)	85.9 (18.0)	86.0 (18.4)
BMI at baseline (kg/m^2), mean (SD)		28.2 (5.2)	27.4 (6.0)	28.8 (5.6)	28.0 (6.0)	28.1 (5.6)
Baseline PANSS total score at baseline, mean (SD)		93.8 (8.2)	93.9 (7.5)	93.6 (7.8)	93.9 (9.0)	–
Years since diagnosis, mean (range)		16.4 (2–41)	15.2 (2–38)	16.2 (2–39)	13.5 (2–36)	15.8 (2–41)

BMI, body mass index; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation.

Figure 1. Change from Baseline in PANSS Total Score



Analyzed using a mixed model for repeated measures (MMRM) that included treatment, visit, treatment-by-visit interaction, and study site as categorical effects, and baseline PANSS total score as continuous covariate.
LS, least squares; PANSS, Positive and Negative Syndrome Scale; SE, standard error.

Table 2. Cogstate Usability and Acceptability Analysis

Visit	Flag		Detection Test n (%)	Groton Maze Learning Test n (%)	Identification Test n (%)	One Back Test n (%)	International Shopping List Test n (%)
Vist 2 (Baseline, Study Day 1)	Completion	Pass	355 (98.6)	355 (98.9)	358 (99.4)	356 (98.9)	359 (99.7)
		Fail	5 (1.4)	4 (1.1)	2 (0.6)	4 (1.1)	1 (0.3)
	Performance	Pass	353 (99.4)	328 (92.4)	351 (98.0)	342 (96.1)	
		Fail	2 (0.6)	27 (7.6)	7 (2.0)	14 (3.9)	
Visit 6 (Study Day 28)	Completion	Pass	289 (100)	287 (99.7)	289 (100)	289 (100)	288 (99.7)
		Fail		1 (0.3)			1 (0.3)
	Performance	Pass	287 (99.3)	272 (94.8)	287 (99.3)	282 (97.6)	
		Fail	2 (0.7)	15 (5.2)	2 (0.7)	7 (2.4)	

Table 3. Impact of LB-102 vs Placebo on Cogstate Composite Scores After 4 Weeks of Treatment

	LB-102 50 mg (n=90) vs. Placebo (n=94)		LB-102 75 mg (n=82) vs. Placebo (n=94)		LB-102 100 mg (n=22) vs. Placebo (n=94)	
	Effect size	*P*-value	Effect size	*P*-value	Effect size	*P*-value
Global cognition composite score	***0.26***	***0.0476***	***0.41***	***0.0027***	***0.66***	***0.0018***
Attention (Psychomotor Function) composite score	0.13	0.3331	***0.29***	***0.0277***	***0.24***	0.2062
Memory (Executive Function) composite score	0.15	0.3128	0.19	0.1957	***0.53***	***0.0273***

Post hoc analysis. Outliers on the Groton Maze Learning Test (i.e., total errors >150) were removed before generating composite scores.
Effect size (Cohen's *d*) interpretation: <0.2 = trivial, 0.2–0.5 = small, >0.5–0.8 = moderate, >0.8–1.1 = large, >1.1 = very large. Bold and italic indicates a clinically relevant value (effect size ≥0.2) with statistical significance favoring LB-102 over placebo ($p<0.05$). Bold without italic indicates a clinically relevant value (effect size ≥0.2) not considered statistically significant ($p\geq0.05$).

CONCLUSION

- **Performance on the Cogstate Brief Battery global composite score demonstrated clinical improvement in cognition at week 4 for all LB-102 dose levels compared to placebo in the total study population, with statistical significance achieved for each comparison.**
- **On the Cogstate Attention (Psychomotor Function) composite score, LB-102 at 75 mg and 100 mg produced small but clinically meaningful improvements relative to placebo at week 4, with statistical significance observed for the 75 mg dose.**
- **LB-102 100 mg group showed a moderate, clinically relevant, and statistically significant improvement on the Cogstate Memory (Executive Function) composite score when compared with placebo at week 4.**

DISCUSSION

- **Cognitive deficits, such as impairments in memory, attention, executive function, and social cognition, are common in patients with schizophrenia, persist even when psychotic symptoms are controlled, and remain a core driver of functional disability.[7]**
  - **Current antipsychotic treatments largely fail to address this domain.**
- **In the phase 2 NOVA[1] clinical trial, all doses of LB-102 demonstrated improvements in cognition across the total study population, with effect sizes on the Cogstate Brief Battery global composite of 0.26, 0.41, and 0.66 for the 50 mg, 75 mg, and 100 mg dose levels, respectively, exceeding the predefined clinical relevance threshold of 0.2 and achieving statistical significance vs. placebo.**
- **Additional analyses and clinical trials are planned to understand the durability and functional significance of the effects of LB-102 on cognition in patients with acute schizophrenia and other neuropsychiatric disorders.**

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