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LB-102 for cognition in patients with schizophrenia: an exploratory *post hoc* analysis 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 poorly articulated and inadequately addressed by current treatments.[6]
- Most antipsychotics, while effective for positive symptoms, show little to no benefit for impaired cognitive performance, with only modest, or inconsistent, improvements observed for a small number of atypical agents. Overall, cognitive symptoms remain unmet in treatment strategies for patients with schizophrenia.[7-10]
- The dual M_1/M_4 muscarinic agonist xanomeline–trospium (KarXT) has demonstrated a treatment effect on cognition in acute schizophrenia that is limited to patients with severe cognitive impairment at baseline.
  - Across the total population in the phase 2 EMERGENT-1 trial, cognitive improvement was numerically but not statistically greater for KarXT (n=60) than placebo (n=65, p=0.16).[11]
  - A *post hoc* analysis of the subgroup with severe cognitive impairment at baseline showed that KarXT produced a treatment effect on the Cogstate Brief Battery, with a Cohen's *d* effect size of 0.50 (95% CI, 0.04–0.95; p=0.03), which was 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 a Cohen's *d* effect size of 0.54 (95% CI, 0.10–0.51; p=0.004) on the CANTAB, again independent of changes in psychotic symptoms.[12]
- LB-102 is an investigational novel benzamide D_2/D_3/5-HT_7 antagonist under development as a once-daily treatment for schizophrenia and other neuropsychiatric disorders.
- Preclinical studies have demonstrated that LB-102 exhibits improved receptor binding properties compared to amisulpride.[13,14]
- A phase 1, open-label PET study (NCT04588129) showed that LB-102 50 mg had a 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 acute schizophrenia (NCT06179108), LB-102 resulted in statistically significant improvements in Positive and Negative Syndrome Scale (PANSS) total score, including rapid onset as early as week 1, with sustained benefit across all doses. Additionally, statistically significant improvements in Clinical Global Impressions–Severity of illness (CGI-S) scores were observed at week 4 versus placebo. LB-102 was generally safe and well tolerated at dose levels up to 100 mg/day.[17]

Objective

- To evaluate the potential effects of LB-102 vs placebo on cognitive performance through prespecified and *post hoc* analyses of the NOVA[1] phase 2 clinical trial in the total trial population.

Methods

Study design and selection criteria

- NOVA[1] was a phase 2, multicenter, randomized, double-blind, placebo-controlled in-patient trial in adults with schizophrenia experiencing an acute 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 treatment.
- Eligible adults were aged 18–55 years, were diagnosed with schizophrenia, required hospitalization/continued hospitalization for a current acute exacerbation of psychotic symptoms, 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 used 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 arm exploratory (Nominal p-value).

Outcomes and analyses

- The primary efficacy endpoint of the NOVA[1] trial was the change from baseline to week 4 in the PANSS 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; simple reaction time)
  - Identification Test (IDN; choice reaction time)
  - One Back Test (ONB; working memory)
  - Groton Maze Learning Test (modified) (GMLT; executive function)
  - International Shopping List Test (ISLT; verbal list learning)
- Changes from baseline in the individual tests were prespecified exploratory endpoints, with composite scores generated *post hoc* in the total population:
  - **Global Cognition 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
- The main hypothesis tested was the effect of LB-102 on cognitive performace, as measured by the Global Cognition composite score. If an effect was observed, then further analysiss pf the effect of LB-102 on the specific cognitive domains that contributed to the global composite (Attention and Memory) was performed.
- Based on previously published literature, the threshold for clinical importance of the treatment effect size was pre-determined as 0.2.[18]

Results

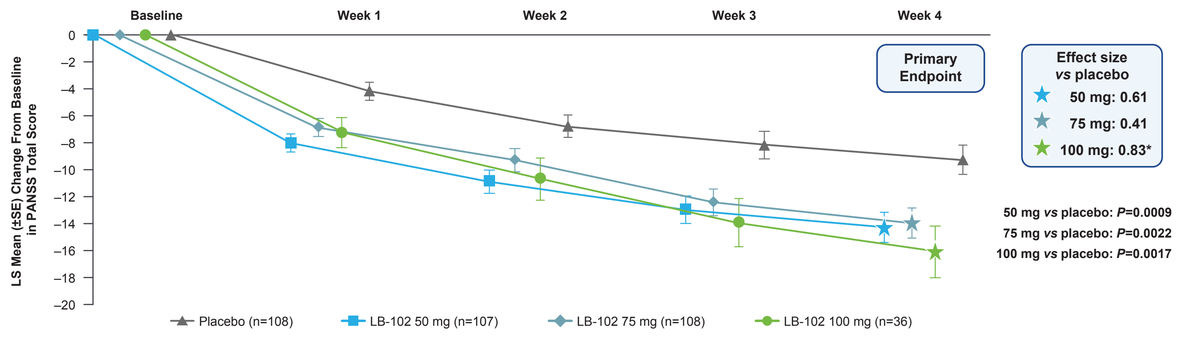
- A total of 359 participants were randomized and included in the safety and intent-to-treat populations (Table 1).
  - 293 participants (82%) completed the 4 week treatment phase with 261 participants completing the overall 6 week study.
  - 290 participants completed week 4, and provided both valid PANSS and Cogstate testing scores, with data included in the assessment of the Global Cognition composite score.
- 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 3243 administered tests indicating a usability rate of 99.4%.
  - There were 76 test performance failures from 2578 administered tests for which a test performance check was computed, for 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.
- Evaluation of the Global Cognition composite score across the NOVA[1] study population (N=290) 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 were observed on the Attention (Psychomotor Function) and Memory (Executive Function) composite scores after 4 weeks of treatment (Table 3).
- Simple bivariate correlation identified no significant relationship between change from baseline scores in Global Cognition composite score and the change from baseline scores in PANSS total score (Pearson's r=0.55, p=0.44, Figure 2).
- A causal mediation analysis using a counterfactual (potential outcomes) framework was condcuted, where the total effect of LB-102 on the Global Cognition composite score was decomposed into direct and indirect effects with respect to mediation by the effect of LB-102 on schizophrenia symptoms. This analysis demonstrated that the effect of LB-102 on cognitive performance was independent to any improvement in schizophrenia symptoms, as assessed by change from baseline to Week 4 in PANSS total score (Figure 3), or the change from baseline to Week 4 in PANSS Positive or Negative Symptom subscale scores (Data not shown).

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 to Week 4 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. Analysis of Effect Size based on completer population. * LB-102 100mg arm considered exploratory, with nominal p-value.
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 Global Cognition Composite Score After 4 Weeks of Treatment

	LB-102 50 mg vs. Placebo		LB-102 75 mg vs. Placebo		LB-102 100 mg vs. Placebo	
	Effect size	*P*-value	Effect size	*P*-value	Effect size	*P*-value
Global Cognition composite score (N=290)	***0.26***	***0.0476***	***0.41***	***0.0027***	***0.66***	***0.0018***
Attention (Psychomotor Function) composite score (n=290)	0.13	0.3331	***0.29***	***0.0277***	***0.24***	0.2062
Memory (Executive Function) composite score (n=265)	0.15	0.3128	0.19	0.1957	***0.53***	***0.0273***

Post hoc analysis. Analysis of Effect Size was calculated via ANCOVA with visit, treatment, and visit by treatment as fixed effects, and with baseline Global Cognition composite score as a covariate. Outliers on the Groton Maze Learning Test (i.e., total errors >150) were removed before generation of the Memory (Executive Function) composite scores.
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≥0.05).

Figure 2. Bivariate Analysis of the Association Between Treatment-Related Changes in PANSS Total Score and Global Cognition Composite Score for LB-102 in NOVA[1]

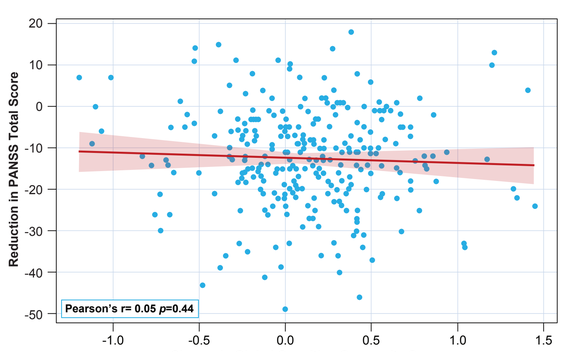
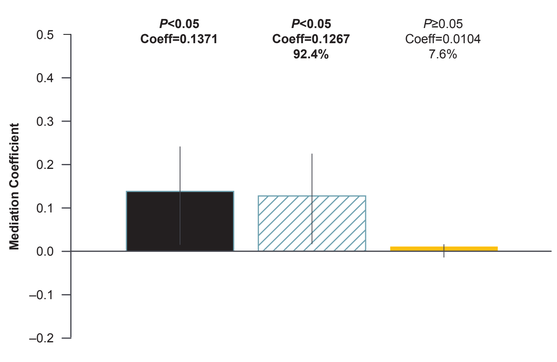


Figure 3. Mediation Analysis of the Effect of LB-102 on Global Cognition Composite Score



CONCLUSION

- **Analysis of the Global Cognition composite score demonstrated clinical improvement in cognitive performance at week 4 for LB-102 (all doses) compared to placebo in the total NOVA[1] population, with statistical significance achieved for each comparison.**
- **On the Attention (Psychomotor Function) composite score, LB-102 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 showed a moderate, clinically relevant, and statistically significant improvement on the Memory (Executive Function) composite score when compared with placebo at week 4.**
- **Mediation analysis highlighted a significant and direct effect of LB-102 on cognitive performance in all NOVA[1] participants with acute schizophrenia, with no impact mediated by the improvement in schizophrenia symptoms (r=0.05, p=0.44).**

DISCUSSION

- **Cognitive 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 an improvement in cognitive performance across the total population that was independent to the improvement in schizophrenia symptoms, with effect sizes on the Global Cognitive composite score of 0.26, 0.41, and 0.66 for the 50 mg, 75 mg, and 100 mg doses, respectively, exceeding the predefined clinical relevance threshold of 0.2 with statistical significance vs placebo.**
- **Additional analyses are planned to understand the durability and functional significance of the effects of LB-102 on cognitive performance, with a phase 3 clinical trial in patients with acute schizophrenia as well as Phase 2 studies in other neuropsychiatric disorders.**

References

1. Goonathilake P, et al. *BMC Psychiatry.* 2022;22(1):716.
2. Green MF, et al. *Schizophr Res.* 2004;72(1):41-51.
3. Kharawala S, et al. *Schizophr Res Cogn.* 2021;27:100217.
4. Correll CU, et al. *J Clin Psychiatry.* 2024;85(3):24r15316.
5. McCutcheon RA, et al. *Mol Psychiatry.* 2023;28(5):1902-1918.
6. Harvey PD, Bowie CR. *Psychiatric Clinics of North America.* 2022;45(3):395-408.
7. CURESZ. Published April 1, 2020. Accessed August 15, 2025. https://curesz.org/2020/04/01/cognitive-deficits-in-schizophrenia/
8. Citrome L. *J Clin Psychiatry.* 2014;75 Suppl 1:21-6.
9. Guilera G, et al. *Eur J Psychiatry.* 2009;23(2):77-89.
10. Haddad C, et al. *BMC Psychiatry.* 2023;23(1):61.
11. Sauder C, et al. *Transl Psychiatry.* 2022;12(1):491.
12. Horan WP, et al. *Am J Psychiatry.* 2025;182(3):297-306.
13. Grattan V, et al. *ACS Omega.* 2019;4(9):14151-4.
14. Neill JC, et al. *Eur Neuropsychopharmacol.* 2017;27(S4):S922-3.
15. Wong DF, et al. *Neuropsychopharmacology.* 2024;50(2):372-7.
16. Biernat L, et al. *Psychopharmacology (Berl).* 2022;239(9):3009-18.
17. Eramo A, et al. Poster presented at the 2025 Schizophrenia International Research Society (SIRS) Conference; Chicago, IL, USA; March 29–April 2, 2025.
18. Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdale, NJ: Lawrence Erlbaum Associates.

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