Efficacy and Safety of KarXT in Schizophrenia: Post Hoc Analysis of the Phase 3, Randomized, Double-Blind, Placebo-Controlled EMERGENT-2 Trial

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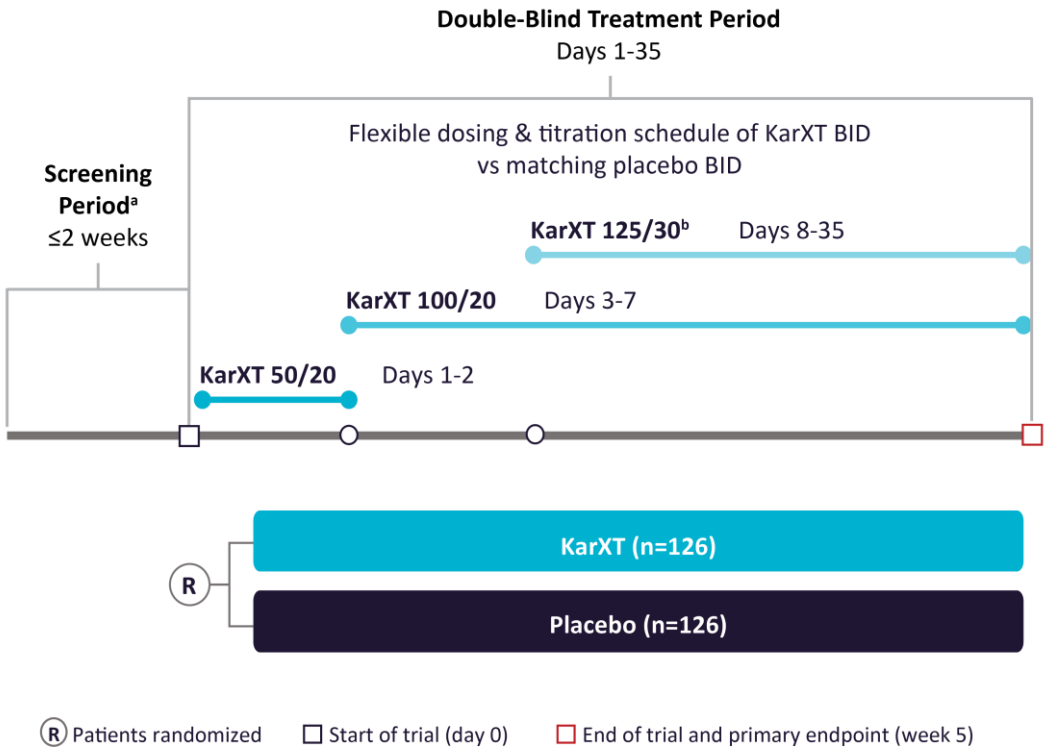
DISCLOSURES

Commercial Interests	Relationships
AbbVie, Acadia, Alkermes, Allergan, Angelini, Aristo Pharma, Boehringer Ingelheim, Cardio Diagnostics, Cerevel, CNX Therapeutics, Compass Pathways, Darnitsa, Gedeon Richter, Hikma, Holmusk, Intra-Cellular Therapies, Janssen/Johnson & Johnson, Karuna Therapeutics, LB Pharma, Lundbeck, MedAvante-ProPhase, MedinCell, Merck, Mindpax, Mitsubishi Tanabe Pharma, Mylan, Neurocrine Biosciences, Newron, Noven, Otsuka, Pharmabrain, PPD, Recordati, Relmada, Reviva, ROVI, Seqirus, SK Life Science, Sunovion, Sun Pharma, Supernus, Takeda, Teva, and Viatris	Consultant and/or advisor to or received honoraria
Janssen and Otsuka	Expert testimony
Lundbeck, Relmada, Reviva, ROVI, Supernus, and Teva	Data safety monitoring board
Janssen	Grant support
Cardio Diagnostics, Mindpax, and B Pharma	Stock option holder

EMERGENT-2: Randomized, Double-Blind, Placebo-Controlled Phase 3 Studies in Schizophrenia With Acute Psychosis

Trial Design



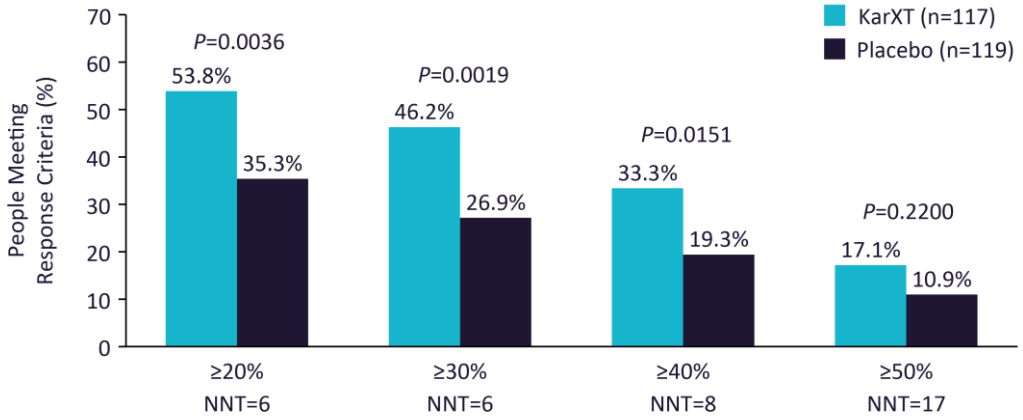
Primary Endpoint and Secondary Outcome Measures

	KarXT (n=117)	Placebo (n=119)	Difference (95% CI)	*P* value
Primary endpoint				
PANSS total score, LSM change (SE) from baseline	-21.2 (1.7)	--11.6 (1.6)	-9.6 (-13.9 to -5.2)	<0.0001
Prespecified Secondary outcome measures				
PANSS positive subscale score, LSM change (SE) from baseline	-6.8 (0.5)	-3.9 (0.5)	-2.9 (-4.3 to -1.5)	<0.0001
PANSS negative subscale score, LSM change (SE) from baseline	-3.4 (0.5)	-1.6 (0.5)	-1.8 (-3.1 to -0.5)	<0.01
PANSS Marder negative factor score, LSM change (SE) from baseline	-4.2 (0.5)	-2.0 (0.5)	-2.2 (-3.6 to -0.8)	<0.01
CGI-S scale score, LSM change (SE) from baseline	-1.2 (0.1)	-0.7 (0.1)	-0.6 (-0.9 to -0.3)	<0.0001
PANSS responders, n/N (%) (≥30% reduction in PANSS total score)	51/93 (54.8)	28/99 (28.3)	26.6% (12.6% to 39.1%)	<0.0001

KarXT dose is expressed as xanomeline/trospium chloride (mg/mg).
[a]Washout of prior oral lithium and/or antipsychotics. [b]Optional increase in dose based on tolerability determined by a clinician.
BID, twice daily; CGI-S, Clinical Global Impression–Severity; LSM, least squares mean; PANSS, Positive and Negative Syndrome Scale; SE, standard error.

Categorial Response Rates, Time Course of Response, and Symptom Domains of Response

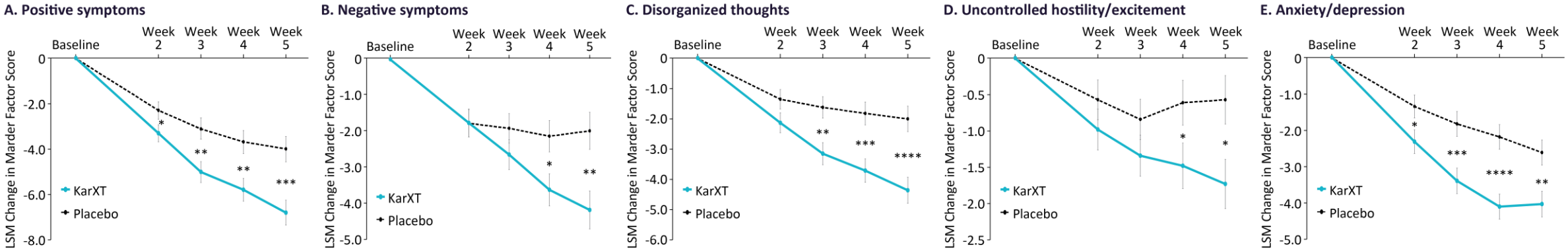
PANSS Categorial Response Rates at Week 5



PANSS: Marder 5-Factor Response by Treatment Assignment at Week 5

Marder Factor	Group	Baseline Score, Mean (SD)	LSM Change From Baseline to Week 5[a]	Week 5 KarXT-Placebo, LSM Difference	*P* value	Cohen's *d*
Positive symptoms	Placebo	30.8 (3.99)	-3.99	-2.82	0.0003	0.524
	KarXT	31.0 (4.01)	-6.80			
Negative symptoms	Placebo	22.5 (4.72)	-1.98	-2.20	0.0022	0.442
	KarXT	22.8 (5.08)	-4.18			
Disorganized thoughts	Placebo	21.8 (3.77)	-2.00	-2.36	<0.0001	0.581
	KarXT	21.8 (4.01)	-4.36			
Uncontrolled hostility	Placebo	10.0 (3.23)	-0.57	-1.15	0.0116	0.363
	KarXT	10.0 (3.36)	-1.73			
Anxiety/ depression	Placebo	12.5 (3.20)	-2.61	-1.42	0.0026	0.433
	KarXT	12.6 (3.44)	-4.03			

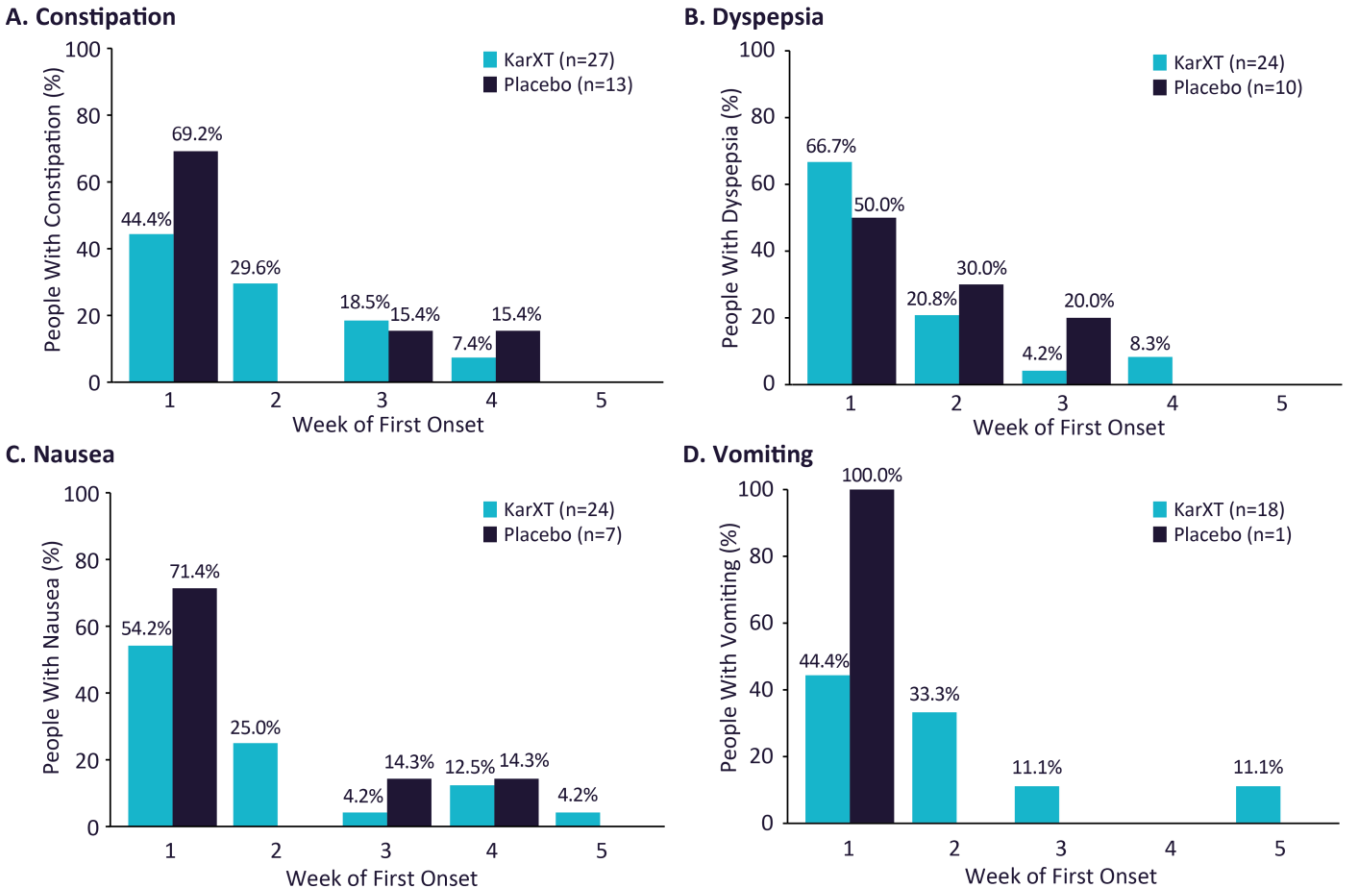
PANSS Marder 5-Factor Response Over Time



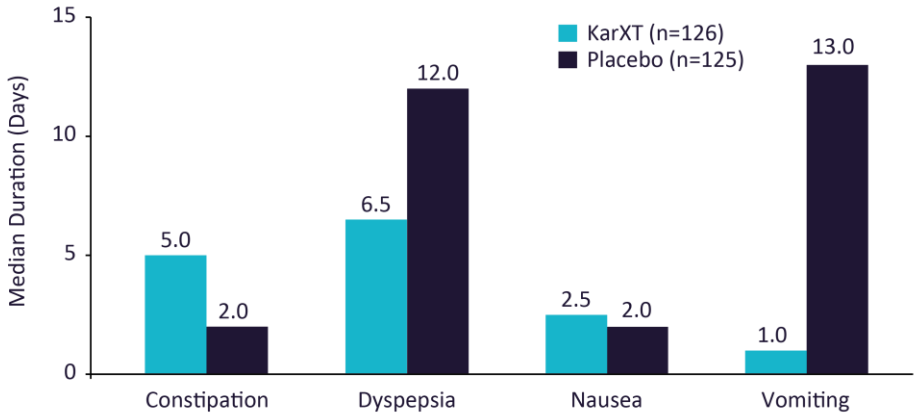
*P<0.05. **P<0.01. ***P<0.001. ****P<0.0001.
NNT, number needed to treat; LSM, least squares mean; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation.

Onset, Duration, and Severity of Procholinergic and Anticholinergic TEAEs

Onset



Duration[a]



Severity

	KarXT (n=126)		Placebo (n=125)		NNH (95% CI)
	Mild	Moderate	Mild	Moderate	
Constipation	24/27 (88.9%)	3/27 (11.1%)	11/13 (84.6%)	2/13 (15.4%)	10 (6 to 48)
Dyspepsia	18/24 (75.0%)	6/24 (25.0%)	9/10 (90.0%)	1/10 (10.0%)	10 (6 to 37)
Nausea	19/24 (79.2%)	5/24 (20.8%)	7/7 (100.0%)	0/7 (0.0%)	8 (5 to 19)
Vomiting	12/18 (66.7%)	6/18 (33.3%)	0/1 (0.0%)	1/1 (100.0%)	8 (6 to 14)

[a]Including TEAEs at the trial end.
CI, confidence interval; NNH, number needed to harm; TEAEs, treatment-emergent adverse events.