Safety and Efficacy of KarXT in Patients With Schizophrenia in the Randomized, Double-Blind, Placebo-Controlled, Phase 3 EMERGENT-2 and EMERGENT-3 Trials

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KARUNA THERAPEUTICS™

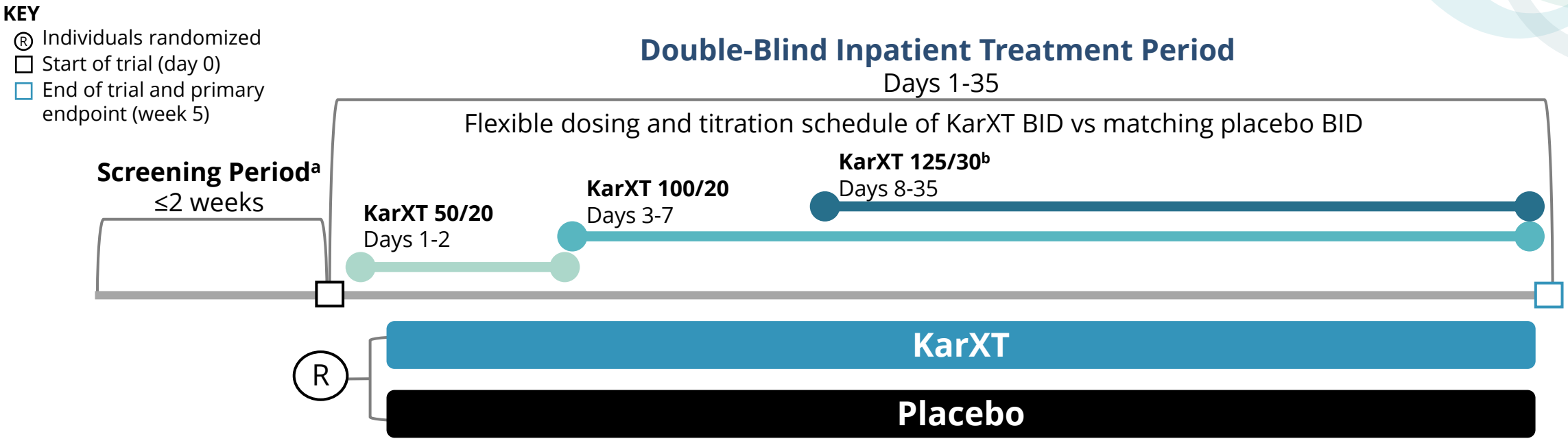
KarXT in Schizophrenia: EMERGENT Clinical Development Program

EMERGENT-1[1,2] NCT03697252	**EMERGENT-2**[2-4] NCT04659161	**EMERGENT-3**[5-7] NCT04738123	**EMERGENT-4**[7,8] NCT04659174	**EMERGENT-5**[7,9] NCT04820309
Phase 2	**Phase 3**	**Phase 3**	**Phase 3**	**Phase 3**
Efficacy and safety of KarXT vs placebo		Efficacy and safety of KarXT vs placebo	Long-term safety and tolerability of KarXT	Long-term safety and tolerability of KarXT
5-week, 1:1 randomized, double-blind, placebo-controlled inpatient trial		5-week, 1:1 randomized, double-blind, placebo-controlled inpatient trial	52-week, open-label, outpatient extension of EMERGENT-2 and EMERGENT-3	52-week, open-label, outpatient trial in newly enrolled participants
People with schizophrenia experiencing acute psychosis (baseline PANSS score of 80-120)		People with schizophrenia experiencing acute psychosis (baseline PANSS score of 80-120)	People with schizophrenia who participated in EMERGENT-2 or EMERGENT-3	People with stable schizophrenia (baseline PANSS score ≤80)
Flexible dosing of KarXT up to 125/30		Flexible dosing of KarXT up to 125/30	Flexible dosing of KarXT up to 125/30	Flexible dosing of KarXT up to 125/30
Primary outcome: PANSS total score		**Primary outcome:** PANSS total score	**Primary outcome:** Incidence of TEAEs	**Primary outcome:** Incidence of TEAEs
Secondary outcomes: PANSS positive subscale score, PANSS negative subscale score, PANSS Marder negative factor score, CGI-S, CGI-S responders	**Secondary outcomes:** PANSS positive subscale score, PANSS negative subscale score, PANSS Marder negative factor score, CGI-S, PANSS responders	**Secondary outcomes:** PANSS positive subscale score, PANSS negative subscale score, PANSS Marder negative factor score, CGI-S, PANSS responders	**Secondary outcomes:** Incidence of serious TEAEs, TEAEs leading to withdrawal, PANSS total score, PANSS positive subscale score, PANSS negative subscale score, PANSS Marder negative factor score, CGI-S, PANSS responders	**Secondary outcomes:** Incidence of serious TEAEs, TEAEs leading to withdrawal, PANSS total score, PANSS positive subscale score, PANSS negative subscale score, PANSS Marder negative factor score, CGI-S, PANSS responders
Complete EMERGENT-1, EMERGENT-2, and EMERGENT-3 met their primary endpoint: KarXT demonstrated significant reductions in PANSS total score vs placebo			**Active, not recruiting**	**Enrolling**

CGI-S, Clinical Global Impression–Severity; PANSS, Positive and Negative Syndrome Scale; TEAEs, treatment-emergent adverse events. 1. Brannan SK, et al. *N Engl J Med*. 2021;384(8):717-726. 2. Brannan SK. Presented at: ECNP; Oct 15-18, 2022; Vienna, Austria. Oral presentation. 3. Karuna Therapeutics. Accessed Feb 22, 2023. https://investors.karunatx.com/news-releases/news-release-details/karuna-therapeutics-announces-positive-results-phase-3-0. 4. NIH. Accessed Nov 20, 2022. https://clinicaltrials.gov/ct2/show/NCT04659161. 5. Karuna Therapeutics. Accessed Nov 20, 2022. https://investors.karunatx.com/news-releases/ news-release-details/karuna-therapeutics-reports-second-quarter-2022-financial. 6. NIH. Accessed Feb 22, 2023. https://clinicaltrials.gov/ct2/show/NCT04738123. 7. Karuna Therapeutics. Data on file. 8. NIH. Accessed Feb 22, 2023. https://clinicaltrials.gov/ct2/show/NCT04659174. 9. NIH. Accessed Nov 20, 2022. https://clinicaltrials.gov/ct2/show/NCT04820309.

KarXT in Schizophrenia: EMERGENT-2 and -3 Trial Design[1,2]

Randomized, Double-Blind, Placebo-Controlled, Phase 3 Studies in Schizophrenia



Select Eligibility Criteria[c]

- 18-65 years of age
- Confirmed diagnosis of schizophrenia and experiencing symptoms of psychosis
- Positive and Negative Syndrome Scale (PANSS) total score between 80 and 120

Primary Endpoint: Change from baseline (CFB) in PANSS total score compared with placebo at week 5

Key Prespecified Secondary Outcome Measures:

- CFB in PANSS positive subscale score compared with placebo at week 5
- CFB in PANSS negative subscale score compared with placebo at week 5
- CFB in PANSS Marder negative factor score compared with placebo at week 5
- Clinical Global Impression–Severity (CGI-S) score at week 5
- Percentage of PANSS responders (≥30% change in PANSS total score) at week 5

KarXT dose is expressed as xanomeline/trospium chloride (mg/mg). BID, twice daily.
[a]Washout of prior oral lithium and/or antipsychotics. [b]Optional increase in dose based on tolerability determined by a clinician. [c]Does not include all inclusion and exclusion criteria.
1. Correll CU, et al. Presented at: NPA; Feb 15-18, 2023; Las Vegas, NV. Poster presentation. 2. Tamminga C, et al. Presented at: SIRS; May 11-15, 2023; Toronto, Canada. Oral presentation.

Baseline Demographics and Characteristics

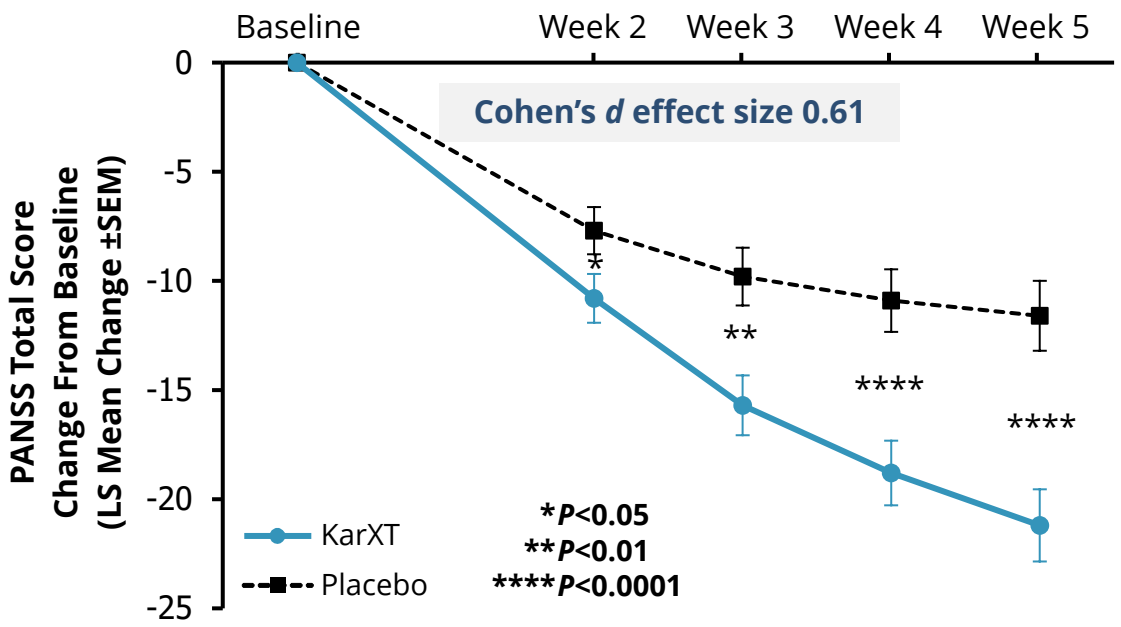
	EMERGENT-2[1]		EMERGENT-3[2]	
	KarXT (n=126)	Placebo (n=126)	KarXT (n=125)	Placebo (n=131)
Mean age, years (SD)	45.6 (10.4)	46.2 (10.8)	43.6 (11.4)	42.6 (12.2)
Sex, n (%)				
Male	95 (75.4)	95 (75.4)	87 (69.6)	104 (79.4)
Female	31 (24.6)	31 (24.6)	38 (30.4)	27 (20.6)
Race, n (%)				
Asian	2 (1.6)	1 (0.8)	1 (0.8)	0
Black	97 (77.0)	92 (73.0)	79 (63.2)	77 (58.8)
White	26 (20.6)	31 (24.6)	45 (36.0)	53 (40.5)
Other	1 (0.8)	2 (1.6)	0[3]	0[3]
Not reported	0[3]	0[3]	0	1 (0.8)
PANSS total score, mean (SD)	98.3 (8.9)	97.9 (9.7)	97.3 (8.9)	96.7 (8.9)
PANSS positive subscale score, mean (SD)	26.8 (3.7)	26.7 (4.0)	26.9 (3.7)	26.4 (3.3)
PANSS negative subscale score, mean (SD)	22.9 (4.0)	22.9 (3.8)	22.6 (3.2)	22.0 (3.7)
PANSS Marder negative factor score, mean (SD)	22.9 (5.0)	22.5 (4.7)	22.0 (3.7)	21.8 (4.2)

Intent-to-treat population.
1. Correll CU, et al. Presented at: NPA; Feb 15-18, 2023; Las Vegas, NV. Poster presentation. 2. Tamminga C, et al. Presented at: SIRS; May 11-15, 2023; Toronto, Canada. Oral presentation.
3. Karuna Therapeutics. Data on file.

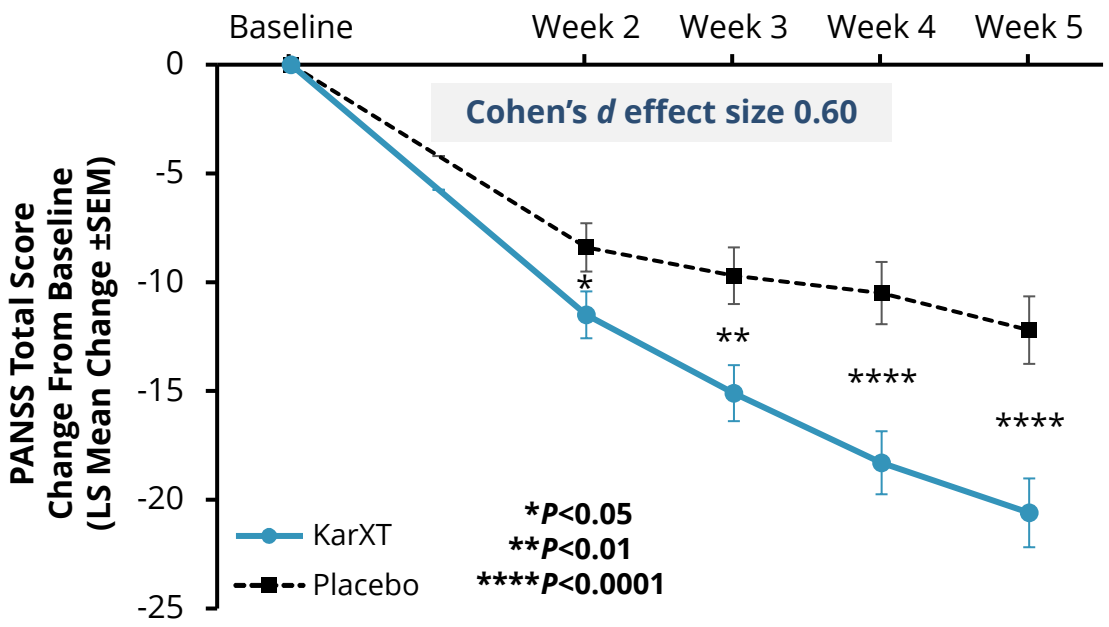
PANSS Total Score at Week 5

Primary Endpoint

EMERGENT-2[1]



EMERGENT-3[2]



All efficacy analyses performed using the mITT analysis set, defined as all randomized individuals who received ≥1 dose of trial medication at baseline and ≥1 postbaseline PANSS assessment (EMERGENT-2: KarXT n=117, placebo n=119; EMERGENT-3: KarXT n=114, placebo=120).[1-3]

LS, least squares; mITT, modified intent-to-treat; PANSS, Positive and Negative Syndrome Scale; SEM, standard error of the mean.

1. Correll CU, et al. Presented at: NPA; Feb 15-18, 2023; Las Vegas, NV. Poster presentation. 2. Tamminga C, et al. Presented at: SIRS; May 11-15, 2023; Toronto, Canada. Oral presentation.
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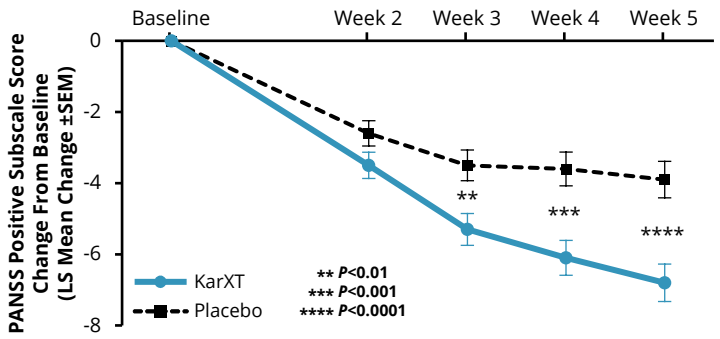
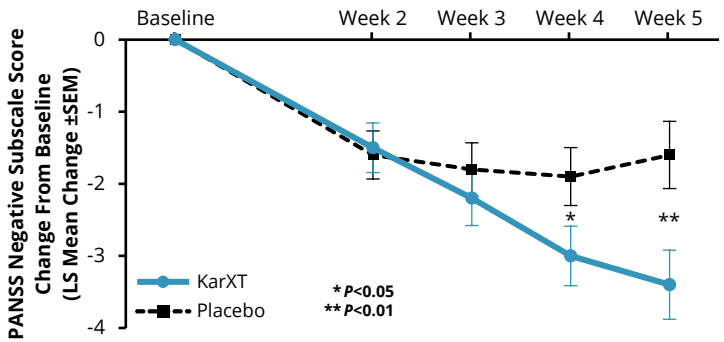
Key Secondary Efficacy Endpoints

EMERGENT-2[1,2]

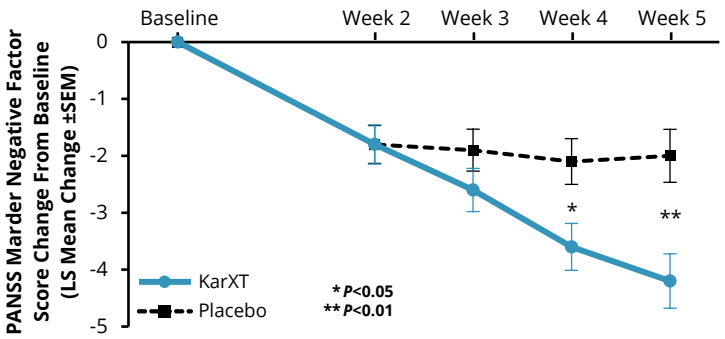
PANSS Positive Subscale



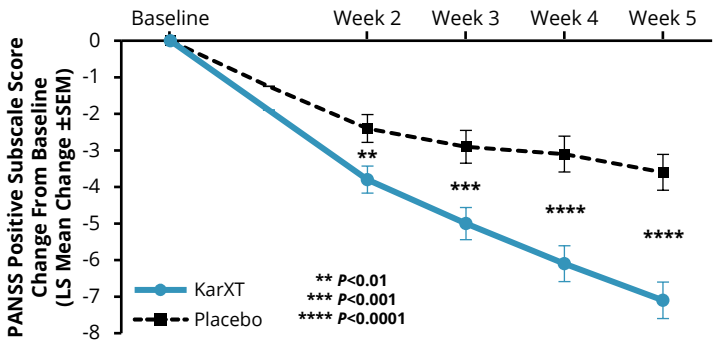
PANSS Negative Subscale

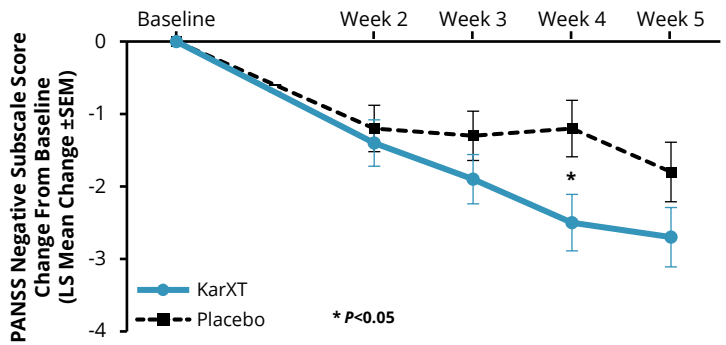


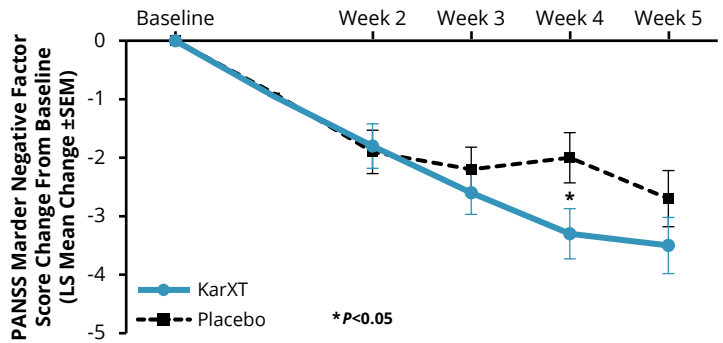
PANSS Marder Negative Factor



EMERGENT-3[3]







All efficacy analyses performed using the mITT analysis set, defined as all randomized individuals who received ≥1 dose of trial medication at baseline and ≥1 postbaseline PANSS assessment (EMERGENT-2: KarXT n=117, placebo n=119; EMERGENT-3: KarXT n=114, placebo n=120).[1,2,4] LS, least squares; mITT, modified intent-to-treat; PANSS, Positive and Negative Syndrome Scale; SEM, standard error of the mean.

1. Correll CU, et al. Presented at: NPA; Feb 15-18, 2023; Las Vegas, NV. Poster presentation. 2. Correll CU, et al. Presented at: ECNP; Oct 15-18, 2022; Vienna, Austria. Poster P.0193. 3. Tamminga C, et al. Presented at: SIRS; May 11-15, 2023; Toronto, Canada. Oral presentation. 4. Karuna Therapeutics. Data on file.

Safety and Tolerability During the 5-Week Treatment Period

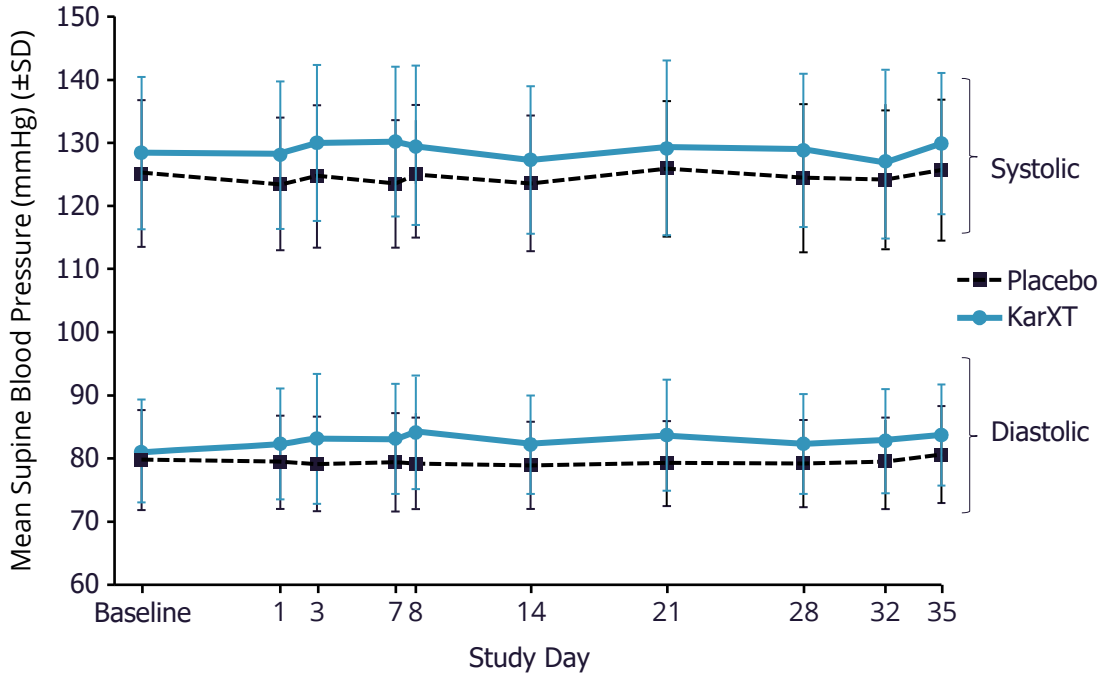
	EMERGENT-2[1]		EMERGENT-3[2]	
	KarXT (n=126)	Placebo (n=125)	KarXT (n=125)	Placebo (n=128)
Any TEAE, n (%)	95 (75.4)	73 (58.4)	88 (70.4)	64 (50.0)
Serious TEAE,[a,b] n (%)	2 (1.6)	2 (1.6)	1(0.8)	0
TEAE leading to discontinuation, n (%)	9 (7.1)	7 (5.6)	8 (6.4)	7 (5.5)
TEAE occurring in ≥5% of people in the KarXT group in either trial, n (%)				
Constipation	27 (21.4)	13 (10.4)	16 (12.8)	5 (3.9)
Dyspepsia	24 (19.0)	10 (8.0)	20 (16.0)	2 (1.6)
Nausea	24 (19.0)	7 (5.6)	24 (19.2)	2 (1.6)
Vomiting	18 (14.3)	1 (0.8)	20 (16.0)	1 (0.8)
Headache	17 (13.5)	15 (12.0)	14 (11.2)[3]	15 (11.7)[3]
Hypertension[c]	12 (9.5)	1 (0.8)	8 (6.4)	2 (1.6)
Dizziness	11 (8.7)	4 (3.2)	2 (1.6)[3]	1 (0.8)[3]
Gastroesophogeal reflux disease	8 (6.3)	0	5 (4.0)[3]	1 (0.8)[3]
Abdominal discomfort	7 (5.6)	4 (3.2)	2 (1.6)[3]	3 (2.3)[3]
Diarrhea	7 (5.6)	4 (3.2)	7 (5.6)	1 (0.8)
Insomnia	3 (2.4)	6 (4.8)	7 (5.6)	10 (7.8)
Body weight: mean change from baseline to week 5, kg±SD	1.36±3.31[3]	2.49±6.92[3]	1.41±3.37	2.0±3.08
Body weight: ≥7% increase from baseline to week 5, n/N (%)	6/94 (6.4)[3]	13/100 (13.0)[3]	5/78 (6.4)	12/92 (13.0)
Simpson-Angus Scale score: mean change from baseline to week 5, ±SD	0.0±0.61	-0.1±0.70	-0.1±0.56	-0.1±0.36
Barnes Akathisia Rating Scale score: mean change from baseline to week 5, ±SD	-0.1±1.09	-0.2±0.98	-0.1±0.75	-0.1±0.88

[a]Serious TEAEs in EMERGENT-2 were 2 cases of suicidal ideation in the KarXT group, 1 case of appendicitis in the placebo group, and 1 case of worsening of schizophrenia in the placebo group. [b]The single serious TEAE observed in EMERGENT-3 was a case of gastroesophageal reflux disease in the KarXT group. [c]Hypertension is the MedDRA preferred term and is not necessarily reflective of clinical hypertension.
MedDRA, Medical Dictionary for Regulatory Activities; SD, standard deviation; TEAE, treatment-emergent adverse event.
1. Correll CU, et al. Presented at: NPA; Feb 15-18, 2023; Las Vegas, NV. Poster presentation. 2. Tamminga C, et al. Presented at: SIRS; May 11-15, 2023; Toronto, Canada. Oral presentation. 3. Karuna Therapeutics. Data on file.

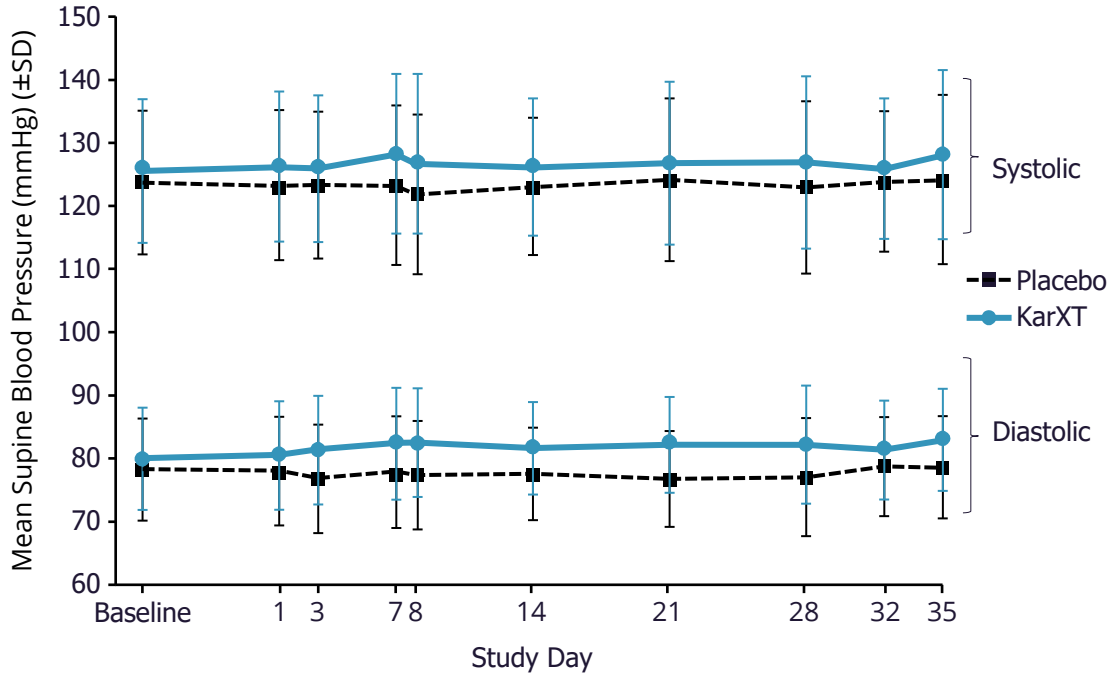
Mean Supine Blood Pressure

Systolic and Diastolic Blood Pressure Measures Recorded at 2 Hours Post Dose (C_{max})

EMERGENT-2[1]



EMERGENT-3[2]

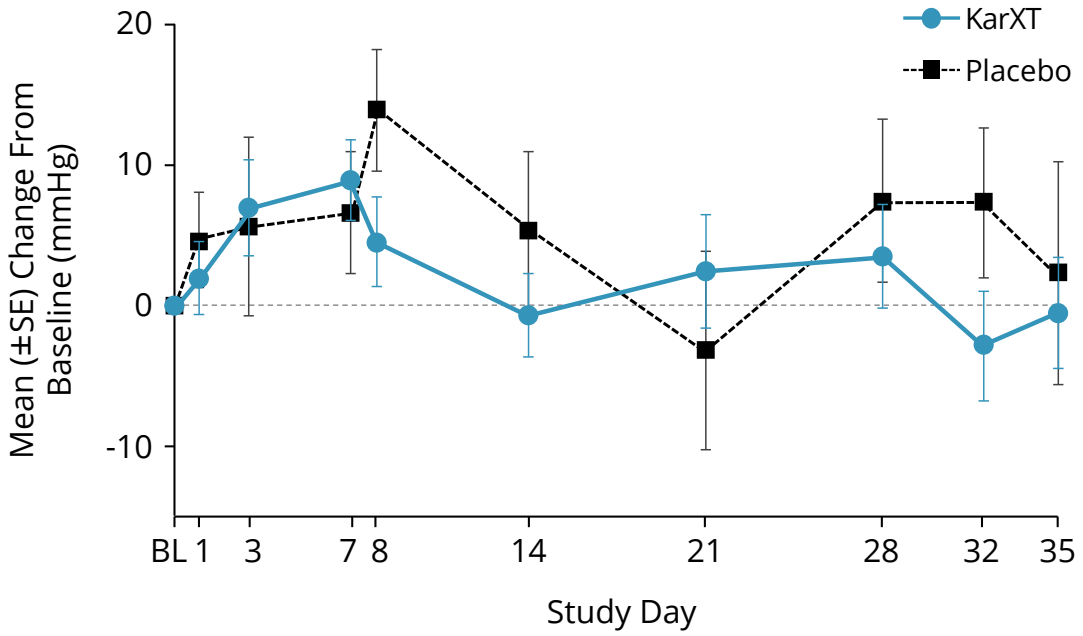


During treatment, beginning on day 1, blood pressure was measured 2 (±1) hours after morning dose of trial treatment.
C_{max}, maximum concentration; SD, standard deviation.

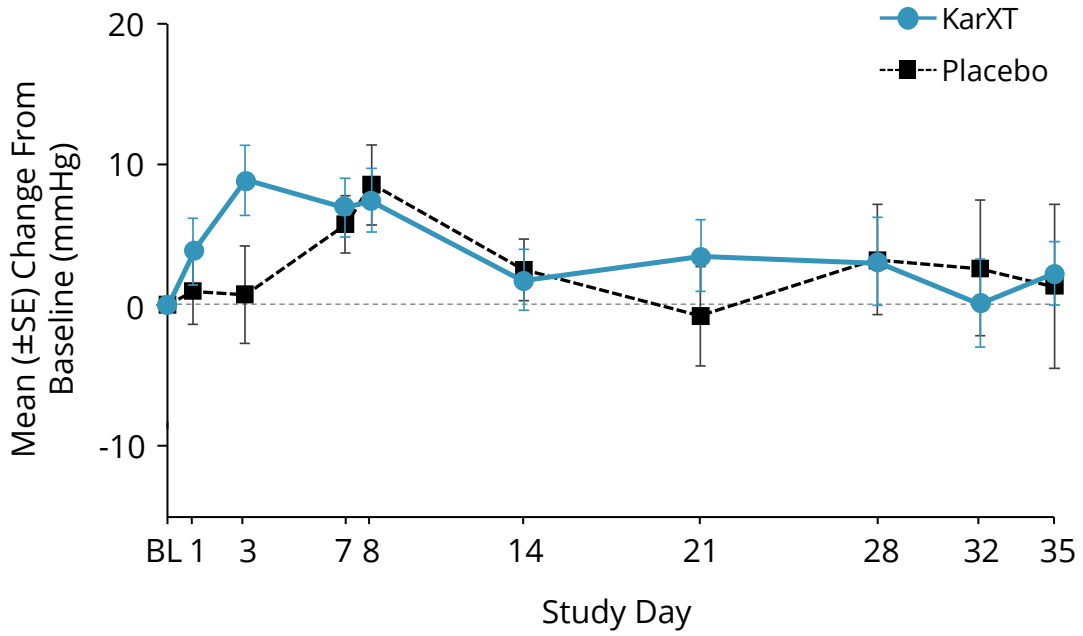
Change in Supine (A) Systolic and (B) Diastolic Blood Pressure in Participants With a TEAE of Hypertension

Combined Results From EMERGENT-1, EMERGENT-2, and EMERGENT-3

A



B



During treatment, beginning on day 1, blood pressure was measured 2 (±1) hours after morning dose of trial treatment.
BL, baseline; SE, standard error; TEAE, treatment-emergent adverse event.

EMERGENT-2[1] and EMERGENT-3[2] Overall Summary

- KarXT was associated with clinically meaningful and statistically **significant improvement in symptoms** of schizophrenia as measured by PANSS total score
- In both trials, KarXT was associated with a significantly greater improvement in **PANSS positive subscale** score at week 5 compared with placebo
- Improvement in **PANSS negative subscale** and **PANSS Marder negative factor** scores at week 5 with KarXT achieved statistical significance compared with placebo only in EMERGENT-2
- KarXT was associated with an **early and sustained** reduction of symptoms observed at week 2 that was maintained through all time points in the trial
- KarXT was **generally well tolerated**; the most common TEAEs with KarXT were **mild to moderate in severity**
- The most common TEAEs mostly occurred within the first 2 weeks of treatment and were generally transient in nature
- **Measures of weight gain, somnolence, and EPS/motor symptoms were similar between KarXT and placebo**

Long-term safety and efficacy of KarXT are currently under study in the open-label EMERGENT-4 and EMERGENT-5 trials[3,4]

EPS, extrapyramidal symptoms; PANSS, Positive and Negative Syndrome Scale; TEAE, treatment-emergent adverse event.

1. Correll CU, et al. Presented at: NPA; Feb 15-18, 2023; Las Vegas, Nevada. Poster presentation. 2. Tamminga C, et al. Presented at: SIRS; May 11-15, 2023; Toronto, Canada. Oral presentation.
3. NIH. Accessed January 20, 2023. https://clinicaltrials.gov/ct2/show/NCT04659174. 4. NIH. Accessed January 20, 2023. https://clinicaltrials.gov/ct2/show/NCT04820309.

Karuna Therapeutics: KarXT Clinical Development Program

PROGRAM	PRECLINICAL / PHASE 1 / PHASE 2 / PHASE 3	STATUS
Schizophrenia	EMERGENT-1[1]	Complete
	EMERGENT-2[2]	Complete
	EMERGENT-3[3,4]	Complete
	EMERGENT-4 (open-label extension of EMERGENT-2 and EMERGENT-3)[4,5]	Active, not recruiting
	EMERGENT-5 (open-label trial, newly enrolled participants)[4,6]	Enrolling
Schizophrenia (adjunctive) Psychosis in people with inadequately controlled symptoms of schizophrenia	ARISE[7]	Enrolling
	ARISE-2 (open-label extension)[8]	Enrolling
Psychosis in Alzheimer's disease	ADEPT-1[9]	Enrolling
	ADEPT-2	Planned initiation 2023
	ADEPT-3 (open-label extension)	Planned initiation 2023

Updated March 2023.
References 1-3. ClinicalTrials.gov records for: 1. EMERGENT-1. www.clinicaltrials.gov/ct2/show/NCT03697252. 2. EMERGENT-2. www.clinicaltrials.gov/ct2/show/NCT04659161. 3. EMERGENT-3. www.clinicaltrials.gov/ct2/show/NCT04738123. 4. Press Release (Aug 8, 2022). investors.karunatx.com/node/8661/pdf. References 5-9. ClinicalTrials.gov records for: 5. EMERGENT-4. www.clinicaltrials.gov/ct2/show/NCT04659174. 6. EMERGENT-5. www.clinicaltrials.gov/ct2/show/NCT04820309. 7. ARISE. www.clinicaltrials.gov/ct2/show/NCT05145413. 8. ARISE OLE. www.clinicaltrials.gov/ct2/show/NCT05304767. 9. ADEPT-1. www.clinicaltrials.gov/ct2/show/NCT05511363. All accessed Jan 20, 2023.