Initial Human Pharmacokinetics and Positron-Emission Tomography (PET) Occupancy of BTRX-335140, a Selective Kappa Opioid Receptor (KOR) Antagonist

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Introduction

- Dysregulation of the KOR system following exposure to stress has been implicated in the pathophysiology of neurobehavioral disorders, e.g., anxiety and major depression, and highlights the importance of targeting this system for therapeutic purposes[1].
- Data from preclinical and human studies have shown KORs are expressed in mesolimbic and mesocortical circuits, and their localization on dopamine-containing neurons within these circuits may underlie their involvement in motivation and executive functions[2, 3].
- Administration of KOR antagonists has been shown to reduce anhedonia and dysphoria in patients with anxiety and depressive disorders with actions attributed to activity within these circuits[4].
- In positron-emission tomography (PET) studies, KOR antagonists have lower binding potential in trauma-exposed individuals diagnosed with major depressive disorder, generalized anxiety disorder and/or post-traumatic stress disorder, highlighting the involvement of the KOR system across disorders[5].

BTRX-335140, a selective KOR antagonist, exhibited a favorable safety and tolerability profile in healthy subjects at doses and receptor occupancy levels projected to be effective in treating symptom domains relevant to neurobehavioral disorders.

Methods

- The pharmacokinetic study was divided into single ascending dose and multiple ascending dose cohorts and was conducted in a double-blind, placebo-controlled fashion.
- Six healthy volunteers were administered BTRX-335140, and two healthy volunteers received placebo in every cohort. Single doses were 5, 10, 20, 40, 80, 160, or 240 mg and multiple doses were 20, 40, 80, or 160 mg of BTRX-335140 once a day for 10 days. An additional cohort of 12 subjects was administered a single 80 mg dose under fed and fasted conditions to study the potential for a food effect.
- In the PET receptor occupancy study, single doses of 40 mg (3 subjects) or 160 mg (4 subjects) BTRX-335140 were administered. Receptor occupancy of BTRX-335140 (measured by blockade of the KOR antagonist radioligand [^{11}C]-LY2795050) and pharmacokinetics were measured at two time points post-dose.

BTRX-335140 Exhibits Increased Exposure with Dose Following Single Oral Administration

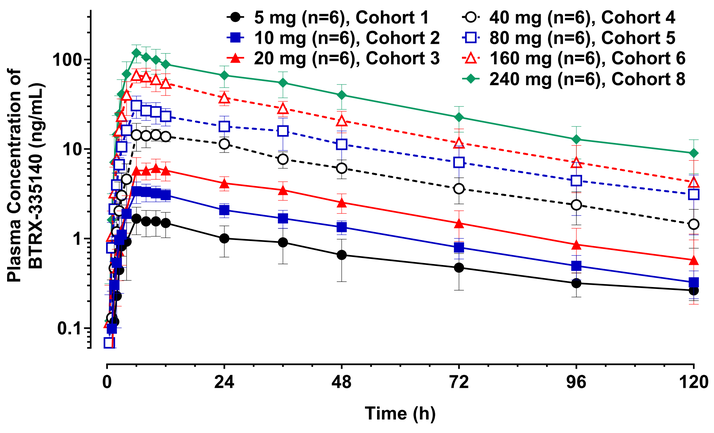

Figure 1. BTRX-335140 plasma concentrations (ng/ml) after a single dose generally showed a time to maximum concentration between 6 to 8 hours and a half-life of 31-42 hours. Analytical range of 0.2-100 ng/mL. 6 subjects per dose cohort.

BTRX-335140 Plasma Exposures are Consistent in both Fed and Fasted Conditions

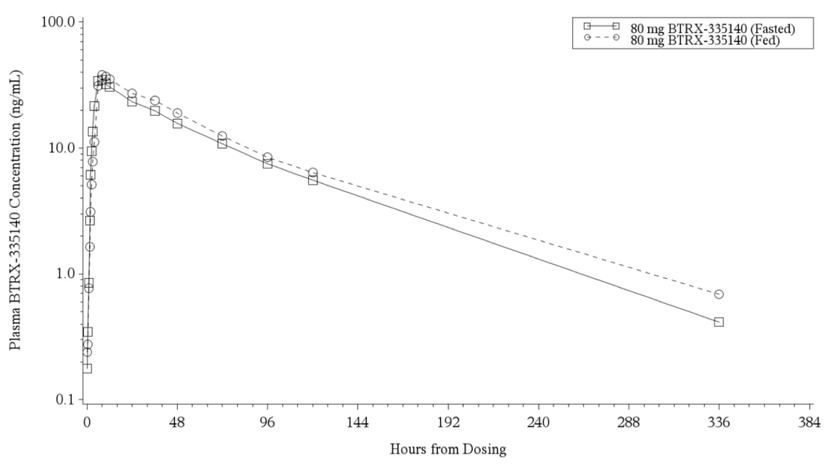

Figure 2. Plasma exposures of BTRX-335140 were similar between fed/fasted states. Analytical range of 0.2-100 ng/mL. 12 subjects per dose cohort.

BTRX-335140 Shows Increased Exposure with Dose After Oral Administration Once Daily for 10 Days

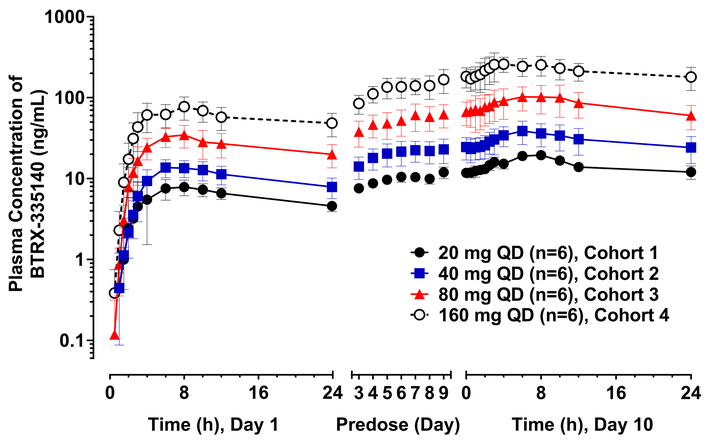

Figure 3. BTRX-335140 plasma concentration accumulates 2.5-4.5-fold over 10 days, where steady state is reached. Analytical range of 0.2-100 ng/mL. 6 subjects per dose cohort.

Summary of Pharmacokinetic Parameters for BTRX-335140 After 10 Days of Oral Dosing

Pharmacokinetic Parameters	20 mg	40 mg	80 mg	160 mg
AUC_{tau} (ng*hr/mL)	348.5 (9.0) [n=6]	683.0 (37.1) [n=6]	1860 (38.7) [n=6]	4960 (30.8) [n=6]
$C_{max,ss}$ (ng/mL)	19.47 (8.8) [n=6]	37.29 (32.9) [n=6]	102.6 (40.0) [n=6]	274.4 (29.1) [n=6]
$T_{max,ss}$ (hr)	8.000 (6.00, 8.01) [n=6]	6.002 (6.00, 10.00) [n=6]	8.001 (6.00, 10.01) [n=6]	4.004 (3.00, 8.00) [n=6]
C_{trough} (ng/mL)	11.8830 (18.2) [n=6]	22.6905 (42.0) [n=6]	56.9259 (38.1) [n=6]	170.3869 (38.6) [n=6]
K_{el} (1/hr)	0.01954 ± 0.0044416 [n=6]	0.01957 ± 0.0044465 [n=6]	0.01551 ± 0.0024163 [n=6]	0.01518 ± 0.0011574 [n=6]
$t_{1/2}$ (hr)	37.256 ± 9.6626 [n=6]	36.906 ± 7.9184 [n=6]	45.473 ± 6.0816 [n=6]	45.871 ± 3.2565 [n=6]
$CL_{ss/F}$ (L/hr)	53.27 ± 4.8059 [n=6]	57.26 ± 21.780 [n=6]	42.16 ± 15.776 [n=6]	31.05 ± 10.184 [n=6]

Figure 4. BTRX-335140 maximum plasma concentrations after multiple doses were between 4 to 8 hours and <2-fold peak to trough ratio. AUCs and C_{max} values are presented as geometric mean and geometric CV%; T_{max} values are presented as median (min, max); Other parameters are presented as arithmetic mean (± SD).

BTRX-335140 is Well-Tolerated after 10 Days of Dosing to Healthy Volunteers

	Placebo	20 mg	40 mg	80 mg	160 mg	Overall Active
# subjects	6	6	6	6	6	24
pruritis	0	1	0	0	2 (3)	3 (13%)
headache	0	0	0	1	1	2 (8%)
fatigue	0	0	0	2	1	3 (13%)
asthenia	0	0	0	2	0	2 (8%)
abnormal dreams	0	0	1	1	0	2 (8%)

Figure 5. Number of subjects (number of incidences) reporting an adverse event (AE) that occurred in >1 subject determined possibly related or related to BTRX-335140. No deaths or serious AEs, no adverse cardiac signals by EKG. All AEs classified as possibly related or related to treatment (investigator determined) were Grade 1. No treatment-related discontinuations.

BTRX-335140 Demonstrates KOR Target Engagement Using PET Imaging in Healthy Volunteers

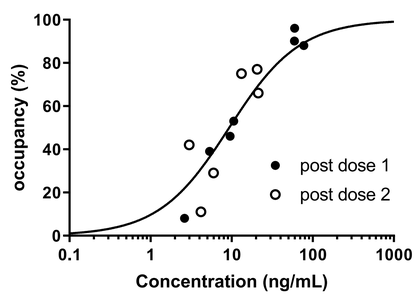

Figure 6. BTRX-335150 occupies KORs throughout the brain with an IC_{50} of 9.3 ± 1.4 ng/mL. A single 160 mg dose or daily repeated doses of 80 mg of BTRX-335140 maintain approximately 90% KOR receptor occupancy for a 24-hour period. Model fit using MAD PK data.

Next Steps

- Initiation of Phase 2 study in major depressive disorder Q4:19; Topline data anticipated Q1:21
- Study design includes a data-science driven patient selection strategy to identify patient subtypes with dysfunction in key KOR-mediated symptom domains.

References

1) Carlezon WA Jr, Krystal AD. Depress Anxiety. 2016 Oct;33(10):895-906.
2) Margolis EB, et al., PNAS. 2006 Feb 21;103(8):2938-42.
3) Van't Veer A, Carlezon WA Jr. Psychopharmacology (Berl). 2013 Oct;229(3):435-52.
4) Krystal AD. ACNP Annual Meeting. 2018; Hollywood Florida.
5) Pietrzak RH, et al., JAMA Psychiatry. 2014 Nov;71(11):1262-70.