Longitudinal Efficacy Analysis of the Sublingual Film Formulation of Dexmedetomidine (BXCL501) for the Treatment of Acute Agitation Associated with Schizophrenia and Bipolar Disorder

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Introduction

Dexmedetomidine sublingual film (DSF, BXCL501) is an orally dissolving film of dexmedetomidine HCl that was developed by BioXcel Therapeutics and approved for sublingual self-administration for the treatment for acute agitation associated with schizophrenia or bipolar disorder.

Objectives

Develop an integrated population PKPD model describing the effect of placebo treatment and dexmedetomidine plasma concentrations on PANSS-Excited Component (PEC) and Agitation-Calmness Evaluation Score (ACES).
Simulate efficacy profiles of various dose levels, treatment regimens, and patient populations to help inform dose and dosage regimen selection decisions.

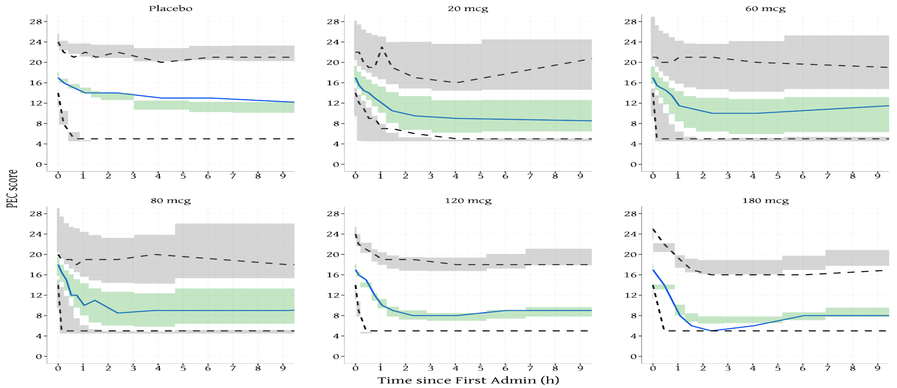
Methods

Data analyzed were derived from one Phase 1b and two Phase 3 studies in adults with schizophrenia or bipolar disorder (Table 1). Efficacy was quantified using an integrated analysis of the relationship between DSF exposure and response data on the PEC and ACES. Efficacy was simulated using the final model

Results

The final model was a joint continuous model for ACES and PEC describing a direct linear relationship between plasma dexmedetomidine concentration and response on the PEC scale without effect delay. Placebo response was considerable and highly variable. The final parameter estimates are presented in Table 2 and a VPC is presented in Figure 1.
Simulation results with the final model are presented in Table 3. Simulations indicated high levels of efficacy at both the 120 mcg and 180 mcg dose (Table 1).

Figure 1. PEC Score VPC stratified by (First) Dose



Longitudinal Efficacy Analysis of Dexmedetomidine Sublingual Film

- No time delay in the effect of dexmedetomidine sublingual film (BXCL501) in the treatment of agitation associated with schizophrenia or bipolar disorder in adults
- Notable and variable placebo effect
- Significant efficacy in reducing symptoms of agitation
- Sedation was generally minimal, and no study participant was unarousable

Table 1: Studies included in the exposure-response analysis

Study Identifier5	Design	N	Observations per subject	Regimen (first dose)
BXCL501-102	Phase 1b Multicenter, Randomized, Double-blind, Placebo-controlled, Multiple Ascending Dose Study to determine Efficacy, Pharmacokinetics and Safety of BXCL501 in Agitation associated with Schizophrenia	135	12 PEC 3 ACES	20, 60, 80, 120 180 mcg single dose
BXCL501-301	Phase 3 multicenter, randomized, double-blind, placebo-controlled study to determine efficacy and safety of BXCL501 for the treatment of agitation associated with schizophrenia	379	13 PEC 4 ACES	Pbo, 120, 180 mcg single dose. In the case of persistent agitation, a repeat dose of half of first dose could be given after 2-hour time point with a maximum of 2 half doses
BXCL501-302	Phase 3 multicenter, randomized, double-blind, placebo-controlled study to determine efficacy and safety of BXCL501 for the treatment of agitation associated with bipolar disorder	378	13 PEC 4 ACES	Pbo, 120, 180 mcg single dose. In the case of persistent agitation, a repeat dose of half of first dose may be given after the 2-hour time point. A maximum of 2 half doses may be given.

Note: 27 participants in study BXCL501-102 also participated in study BXCL501-301

Table 2: Parameter estimates of the final PK-PEC and –ACES Model

Parameter	Description	Estimate (%CV)	95% Confidence Interval	Estimated/Fixed
Θ_1	Baseline PEC score	13	(12.7-13.2)	Estimated
θ_2	Max Placebo effect – 1st administration - responders	0.567	(0.492-0.653)	Estimated
θ_3	Placebo effect onset	0.582	(0.344-0.984)	Estimated
θ_4	Placebo effect drift	0.0819	(0.0597-0.112)	Estimated
θ_5	Max Placebo effect – administration 2 or 3	0.046	(0.0282-0.0751)	Estimated
θ_6	Max Placebo effect – non-responders	0	-	Fixed
θ_7	Fraction placebo responders	0.782	-	Fixed
θ_8	Slope of linear exposure effect on PEC score	0.000723	(0.000547-0.000955)	Estimated
θ_9	Fraction baseline ACES=1 (logit scale)	-2.55	-	Fixed
θ_{10}	Fraction baseline ACES>2 (logit scale)	3.2	(12.7-13.2)	Estimated
θ_{11}	Slope of linear relation between predicted PEC change from baseline and ACES	5.07	(4.79-5.37)	Estimated
$\omega_{1,1}$	IIV-Baseline PEC	0.036 (19.3)	(0.0322-0.0408)	Estimated
$\omega_{2,2}$	IIV-Max Placebo effect – 1st administration- responders	1.04 (135)	(0.162-1.92)	Estimated
$\omega_{3,3}$	IIV-Placebo effect onset	0 (0)	-	Fixed
$\omega_{4,4}$	IIV-Placebo effect drift	0.973 (128)	(0.508-1.44)	Estimated
$\omega_{5,4}$	Covariance Placebo drift-Max Placebo effect 2/3	2.05 (260)	(1.39-2.71)	Estimated
$\omega_{5,5}$	IIV-Max placebo effect 2/3	5.58 (1630)	(3.09-8.08)	Estimated
$\omega_{6,6}$	IIV-Max placebo effect non-responders	0 (0)	-	Fixed
$\omega_{7,7}$	IIV-Slope linear exposure effect	1.96 (241)	(1.34-2.51)	Estimated
$\omega_{8,8}$	IIV-Slope PEC CFB-ACES	0.0600 (24.8)	(0.0367-0.0827)	Estimated
$\sigma_{2,2}$	Additive RUV PEC	3.35	(3.01-3.68)	Estimated
$\sigma_{4,4}$	Additive RUV ACES	0.705	(0.600-0.810)	Estimated

Note: The PEC predictions were shifted by a value of 4.5 in order to prevent (rounded) PEC predictions below the lower limit of the scale (a PEC score of 5.). Therefore, the actual baseline PEC score is 17.5, with the baseline parameter was estimated to a value of 13. ωX: variance of the inter-individual variability (IIV) of parameter X, IIV as a %CV was derived from variance according to 100 √(⟦ e^ωx "−1" ⟧^" ")

Table 3. Simulated PEC responder and ACES response category fractions at 2 h after last administration

Time post 1st dose (h)	Regimen	Responder Rate (%)	ACES Scores			
			1 - 3 Marked, Moderate, Mild Agitation	4 Normal Behavior	5 - 7 Mild, Moderate, Marked Calm	8 - Deep Sleep 9 - Unarousable
2	Placebo	30.5	53.3	17.4	27.1	2.2
2	120 mcg	65.1	19.5	19.4	56.8	4.3
2	180 mcg	72.0	16.1	18.6	60.3	5.0
6	Pbo + 2 x Pbo (Q2h)	54.8	30.8	21.0	45.0	3.2
6	120 + 2x60mcg	84.9	7.7	17.5	69.4	5.4
6	180 + 2x90 mcg	87.1	6.8	15.6	71.8	5.8

Responder Rate defined as 2-hour PEC change from baseline ≥ 40%; Pbo, Placebo

Reference
1 Lagraauw, H.M. et al. Population Pharmacokinetic Analysis of the Sublingual Film Formulation of Dexmedetomidine (BXCL501) in Healthy Volunteers and Adults with Schizophrenia or Bipolar Disorder. Poster ASCPT Annual Meeting, Atlanta 2023. Poster PII-100

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