Population Pharmacokinetic Analysis of the Sublingual Film Formulation of Dexmedetomidine (BXCL501) in Healthy Volunteers and Adults with Schizophrenia or Bipolar Disorder

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Introduction

BXCL501 is an orally dissolving film of dexmedetomidine HCl that was developed by BioXcel Therapeutics for sublingual or buccal self-administration as treatment for acute agitation associated with schizophrenia or bipolar disorder in adults. This population pharmacokinetic (PK) analysis integrates all currently available PK data on dexmedetomidine following BXCL501 administration, using data pooled from five studies where BXCL501 was given to patients and healthy volunteers.

Objectives

- Develop a population model that describes dexmedetomidine PK following BXCL501 administration
- Evaluate the impact of covariates (patient and study characteristics) on the PK of BXCL501

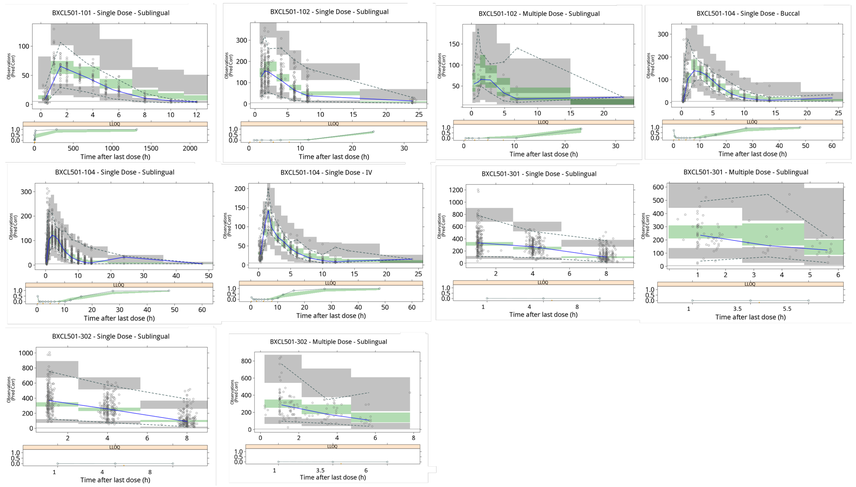
Methods

The analysis was carried out using NONMEM version 7.4. The final model was validated using goodness of fit plots and prediction corrected visual predictive checks (VPC).

Results

The final parameter estimates are presented in **Table 2** and a VPC is presented in Figure 1. The VPC results indicate that the model provides an adequate description of the data, as the confidence intervals around the predicted medians and percentiles include the observed ones.

Figure 1. VPC stratified by first dose



Solid Blue Line: Median of the observed BXCL501 concentrations. **Dashed Lines:** 2:5th and 97:5th percentiles of the observed BXCL501 concentrations**. Shaded Area:** The 95% CI around the median (green area) and 2:5th and 97:5th percentiles of the simulated concentrations (grey areas).

Population Pharmacokinetic Analysis of Dexmedetomidine Sublingual Film

- BXCL501 is an orally dissolving film formulation of dexmedetomidine developed for the treatment of agitation associated with schizophrenia or bipolar disorder
- PK was well-characterized by a 2-compartment PK model with linear elimination and a Transit Compartment Absorption Model

Table 1. Studies included in population PK analysis

Study ID	Design	N with PK Data	Observations per Participant	First Dose Regimen
BXCL501-101	Phase 1 randomized, single-blind, placebo-controlled, single ascending dose study of BXCL501 PK, safety, & tolerability in healthy adult volunteers	23	16	10, 20, 40 mcg single dose
BXCL501-102	Phase 1b multicenter, randomized, double-blind, placebo-controlled, multiple ascending dose study of BXCL501 efficacy, safety, and PK for agitation associated with schizophrenia	90	8	20, 60, 80, 120 180 mcg single dose
BXCL501-104	Phase 1, randomized, 7-way crossover in healthy adults to determine BXCL501 absolute bioavailability and the effect of drinking water on BXCL501 PK	35	19/arm	20 (IV), 40 (SL) mcg single dose
BXCL501-301	Phase 3 multicenter, randomized, double-blind, placebo-controlled, study of BXCL501 efficacy and safety for agitation associated with schizophrenia	253	4	120, 180 mcg single dose For persistent agitation a 2nd or 3rd dose of half the first dose could be given after 2 hours
BXCL501-302	Phase 3 multicenter, randomized, double-blind, placebo-controlled study of efficacy and safety of BXCL501 for agitation associated with bipolar disorder	252	4	120, 180 mcg single dose For persistent agitation a 2nd or 3rd dose of half the first dose could be given after 2 hours

Table 2. Parameter estimates of the final population PK Model for Sublingual Dexmedetomidine (BXCL501)

Parameter	Description	Estimate (%CV)	95% Confidence Interval	Estimated/Fixed
θ_1	CL, clearance (L/h)	34.6	(32.7-33.6)	Estimated
θ_2	V1, central distribution volume (L)	99.2	(92.5-106)	Estimated
θ_3	Q, intercompartmental clearance (L/h)	58.2	(29.5-115)	Fixed
θ_4	V2, peripheral distribution volume (L)	32.9	(21.1-51.3)	Fixed
θ_5	NTR, number of transit compartments (h)	0.937	(0.795-1.11)	Fixed
θ_6	MTT, mean transit time	1.16	(1.05-1.28)	Fixed
θ_7	F, bioavailability	0.712	(0.660-0.759)	Fixed
θ_8	buccal administration effect on F (on logit scale)	1.12	(0.696-1.55)	Estimated
θ_9	buccal administration effect on NTR	1.11	(0.530-1.66)	Fixed
θ_{10}	sublingual, drug side up effect on NTR	0.189	(-0.104-0.482)	Fixed
θ_{11}	Patient vs Healthy volunteer effect on F (on logit scale)	-0.902	(-1.02- -0.784)	Estimated
$\omega_{1.1}$	IIV-CL (variance (%CV))	0.028 (16.7)	(0.00178-0.0533)	Estimated
$\omega_{2.2}$	IIV-V1 (variance (%CV))	0.072 (27.4)	(0.0474-0.0969)	Estimated
$\omega_{4.4}$	IIV-V2 (variance (%CV))	0.26 (54.5)	(-0.159-0.679)	Fixed
$\omega_{5.5}$	IIV-MTT (variance (%CV))	0.087 (30.1)	(0.0474-0.126)	Fixed
$\omega_{6.6}$	IIV-F (variance (%CV))	0.455 (75.9)	(0.239-0.670)	Fixed
$\omega_{7.7}$	IIV-NTR (variance (%CV))	0.167 (42.6)	(0.0843-0.249)	Fixed
$\omega_{8.8}$	IOV-CL (variance (%CV))	0.104 (33.1)	(0.0730-0.134)	Estimated
$\sigma_{1.1}$	Proportional RUV (variance)	0.0492	(0.0418-0.0566)	Estimated
$\sigma_{2.2}$	Additive RUV (ng/L)	9.76	(2.58-16.9)	Estimated

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