Number Needed to Treat and Number Needed to Harm From Two Phase 3 Studies of Dexmedetomidine Orally Dissolving Film (BXCL501) for Treating Acute Agitation in Patients With Schizophrenia and Bipolar Disorder

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INTRODUCTION

- Because episodes of acute agitation in patients with schizophrenia or bipolar disorder can lead to injuries among patients and staff, disruption of care, and hospital admissions,[1,2] they require urgent clinical attention
- Dexmedetomidine orally dissolving film (ODF) is an investigational formulation of dexmedetomidine, a selective α_{2A} adrenergic receptor agonist, designed to rapidly dissolve and be absorbed sublingually or buccally, bypassing first-pass liver metabolism
- In Phase 3 studies, dexmedetomidine ODF significantly reduced acute agitation in patients with schizophrenia or bipolar disorder at 2 hours postdose, as measured by the 5-item Positive and Negative Syndrome Scale-Excited Component (PEC)
- When evaluating a new drug, the numbers needed to treat (NNT) and needed to harm (NNH) can facilitate formulary and prescribing decisions
- In general, medications with a low NNT (≥10% better than placebo = NNT <10) and a high NNH (no more than a 10% disadvantage, resulting in an NNH >10) are preferred

OBJECTIVES

Use the metrics of NNT and NNH to provide clinically meaningful estimates of the efficacy and tolerability of dexmedetomidine ODF in adults with agitation associated with schizophrenia or bipolar disorder

METHODS

- Post hoc analysis of data from 2 randomized, double-blind, placebo-controlled Phase 3 trials in adults (18-75 years) with acute agitation and DSM-5 schizophrenia or schizoaffective disorder (NCT04268303)[3] or bipolar disorder I or II (NCT04276883)[4]
- Participants were clinically agitated at screening and baseline, with a PEC total score ≥14 and baseline score of ≥4 on ≥1 of 5 PEC items
- They self-administered dexmedetomidine ODF 180 mcg, 120 mcg, or placebo

Assessments

- Screening, predose (within 15 minutes of the first dose), 10, 20, 30, 45, 60, 90 minutes and 2, 4, 6, and 8 hours after the first dose

Endpoints

- Primary efficacy: change from baseline on the PEC total score at 2 hours postdose (PEC scale 1=minimum to 7=maximum; total score range 5-35)
- PEC response: ≥40% reduction from baseline in PEC total score at 2 hours postdose
- NNT: 1/absolute risk reduction (ARR) for PEC response (dexmedetomidine ODF response minus placebo response)
- NNH: derived from incidence of adverse events vs placebo

RESULTS

- Schizophrenia: 380 enrolled, 380 received ≥1 dose of study drug, and 372 completed; most were male (63.4%) and Black or African American (77.9%)
- Bipolar: 380 enrolled, 378 received ≥1 dose of study drug, and 362 completed; most were female (54.8%) and Black or African American (56.1%)
- In both trials, mean age was 45.6 years, and baseline agitation was mild-moderate; mean PEC scores were 17.5-17.6 in the schizophrenia trial and 17.9-18.0 in the bipolar trial

Table 1. PEC Response, Absolute Risk Reduction, & Number Needed to Treat in the Population of Participants with Schizophrenia or Bipolar Disorder

	PEC Response[a] n (%)				Absolute Risk Reduction[b] %, (95% CI)			Number Needed to Treat n (95% CI)		
	Dexmedetomidine ODF			Placebo	Dexmedetomidine ODF			Dexmedetomidine ODF		
Time postdose	180 mcg n=251	120 mcg n=255	120 or 180 mcg n=506	n=252	180 mcg n=251	120 mcg n=255	120 or 180 mcg n=506	180 mcg n=251	120 mcg n=255	120 or 180 mcg n=506
10 minutes	30 (12.0)*	22 (8.6)	52 (10.3)*	14 (5.6)	6.4 (1.5, 11.3)	3.1 (−1.4, 7.5)	4.7 (.8, 8.6)	16 (9, 68)	33 (−73, 14)[c]	22 (12, 118)
20 minutes*	72 (28.7)	53 (20.8)	125 (24.7)	33 (13.1)	15.6 (8.6, 22.6)	7.7 (1.2, 14.2)	11.6 (6.0, 17.2)	7 (5, 12)	14 (8, 84)	9 (6, 17)
30 minutes*	106 (42.2)	94 (36.9)	200 (39.5)	64 (25.4)	16.8 (8.7, 25.0)	11.5 (3.5, 19.5)	14.1 (7.3, 21.0)	6 (5, 12)	9 (6, 29)	8 (5, 14)
45 minutes*	152 (60.6)	131 (51.4)	283 (55.9)	83 (32.9)	27.6 (19.2, 36.0)	18.4 (10.0, 26.9)	23.0 (15.8, 30.2)	4 (3, 6)	6 (4, 11)	5 (4, 7)
1 hour*	186 (74.1)	170 (66.7)	356 (70.4)	95 (37.7)	36.4 (28.3, 44.5)	29.0 (20.6, 37.3)	32.7 (25.5, 39.8)	3 (3, 4)	4 (3, 5)	4 (3, 4)
1.5 hours*	217 (86.5)	187 (73.3)	404 (79.8)	99 (39.3)	47.2 (39.8, 54.5)	34.0 (25.9, 42.2)	40.6 (33.6, 47.5)	3 (2, 3)	3 (3, 4)	3 (3, 3)
2 hours*	**225 (89.6)**	**199 (78.0)**	**424 (83.8)**	**109 (43.3)**	**46.4 (39.2, 53.6)**	**34.8 (26.8, 42.7)**	**40.5 (33.6, 47.4)**	**3 (2, 3)**	**3 (3, 4)**	**3 (3, 3)**
4 hours*	219 (87.3)	178 (69.8)	397 (78.5)	100 (39.7)	47.6 (40.3, 54.9)	30.1 (21.9, 38.4)	38.8 (31.8, 45.8)	3 (2, 3)	4 (3, 5)	3 (3, 4)
6 hours*	221 (88.0)	187 (73.3)	408 (80.6)	112 (44.4)	43.6 (36.3, 50.9)	28.9 (20.7, 37.1)	36.2 (29.2, 43.2)	3 (2, 3)	4 (3, 5)	3 (3, 4)
8 hours*	223 (88.8)	185 (72.5)	408 (80.6)	131 (52.0)	36.9 (29.6, 44.2)	20.6 (12.3, 28.8)	28.6 (21.6, 35.7)	3 (3, 4)	5 (4, 9)	4 (3, 5)
24 hours*	147 (58.6)	135 (52.9)	282 (55.7)	86 (34.1)	24.4 (16.0, 32.9)	18.8 (10.3, 27.3)	21.6 (14.3, 28.9)	5 (4, 7)	6 (4, 10)	5 (4, 7)

ODF, orally dissolving film; PEC, Positive and Negative Syndrome Scale-Excited Component; CI, confidence interval.
*Nominal P<.05 in the main studies, indicating treatment response rates significantly different from placebo, based on Fisher's exact test. [a]Defined as a ≥40% reduction from baseline as measured by the 5-item Positive and Negative Syndrome Scale-Excited Component; [b]dexmedetomidine ODF vs placebo; [c]not statistically significant.

Table 2. Adverse Events[a] and Number Needed to Harm in Participants With Schizophrenia or Bipolar Disorder

	Bipolar Disorder					Schizophrenia				
	Incidence n (%)			Number Needed to Harm[b] n (95% CI)		Incidence n (%)			Number Needed to Harm[b] n (95% CI)	
	Dexmedetomidine ODF		Placebo	Dexmedetomidine ODF		Dexmedetomidine ODF		Placebo	Dexmedetomidine ODF	
	180 mcg n=126	120 mcg n=126	n=126	180 mcg n=126	120 mcg n=126	180 mcg n=126	120 mcg n=129	n=126	180 mcg n=126	120 mcg n=129
Events of special interest										
Cardiac/vascular disorder	6 (4.8)	4 (3.2)	3 (2.4)	42 (−46, 15)[e]	126 (−31, 21)[e]	7 (5.6)	6 (4.7)	0	18 (11, 65)	22 (13, 99)
Hypotension/bradycardia(s)	6 (4.8)	4 (3.2)	0	21 (12, 96)	32 (17, 883)	5 (4.0)	6 (4.7)	0	26 (14, 179)	22 (13, 99)
Bradycardia(s)	2 (1.6)	1 (.8)	0	63 (−169, 27)[e]	126 (−133, 43)[e]	0	2 (1.6)	0	ND	65 (−172, 28)[e]
Hypotension	5 (4.0)	3 (2.4)	0	26 (14, 179)	42 (−356, 20)[e]	5 (4.0)	4 (3.1)	0	26 (14, 179)	33 (17, 914)
Event[d]										
Somnolence	26 (20.6)	25 (19.8)	5 (4.0)	6 (5, 12)	7 (5, 13)	25 (19.8)	26 (20.2)	9 (7.1)	8 (5, 23)	8 (5, 22)
Dry mouth	4 (3.2)	8 (6.3)	1 (.8)	42 (−96, 18)[e]	18 (10, 98)	5 (4.0)	9 (7.0)	1 (.8)	32 (−176, 15)[e]	17 (10, 66)
Dizziness	4 (3.2)	4 (3.2)	1 (.8)	42 (−96, 18)[e]	42 (−96, 18)[e]	6 (4.8)	2 (1.6)	1 (.8)	26 (−1664, 13)[e]	133 (−54, 30)[e]
Hypoesthesia oral	5 (4.0)	2 (1.6)	1 (.8)	32 (−176, 15)[e]	126 (−54, 29)[e]	7 (5.6)	5 (3.9)	0	18 (11, 65)	26 (14, 184)
Paresthesia oral	-	-	-	-	-	3 (2.4)	5 (3.9)	1 (.8)	63 (−67, 22)[e]	33 (−170, 15)[e]
Headache	1 (.8)	4 (3.2)	3 (2.4)	−63 (−22, 67)[e]	126 (−31, 21)[e]	1 (.8)	1 (.8)	3 (2.4)	−63 (−22, 67)[e]	−62 (−22, 69)[e]
Nausea	2 (1.6)	1 (.8)	3 (2.4)	−126 (−24, 38)[e]	−63 (−22, 67)[e]	-	-	-	-	-
Orthostatic hypotension	1 (.8)	1 (.8)	0	126 (−133, 43)[e]	126 (−133, 43)[e]	1 (.8)	0	0	126 (−133, 43)[e]	ND

ODF, orally dissolving film; CI, confidence interval; NNH, number needed to harm; ND, no difference.
[a]Occurring within the first 2 hours postdose. [b]A negative NNH denotes an advantage for dexmedetomidine ODF relative to placebo and is not interpretable as a harm. [c]Using NNT for response at 2 hours postdose (refer to Table 1). [d]Reported by at least 2% of participants in the safety population (all participants who received a dose of study drug). [e]Not statistically significant.

RESULTS

PEC Response, ARR, and NNT

- **Schizophrenia**: PEC 2-hour response rates with dexmedetomidine ODF 180 mcg and 120 mcg were significantly higher than with placebo (88.8% and 79.1%, respectively, vs 40.5%; P<.0001 vs placebo for both doses)
  - NNT (95% CI) versus placebo for response at 2 hours postdose was 3 (2, 3) for the dexmedetomidine ODF 180 mcg group and 3 (3, 4) for the 120 mcg group (Table 1)
- **Bipolar**: PEC 2-hour response rates with dexmedetomidine ODF 180 mcg and 120 mcg groups were significantly higher than with placebo (90.5% and 77.0%, respectively, vs 46.0%; P<.0001 vs placebo for both doses)
  - NNT (95% CI) versus placebo for response at 2 hours postdose was 3 (2, 3) for the dexmedetomidine ODF 180 mcg group and 4 (3, 6) for the 120 mcg group
- **Pooled:** For dexmedetomidine ODF efficacy data from both studies (N=506), the NNT (95% CI) versus placebo for response at 2 hours postdose was 3 (2, 3) for the 180 mcg group and 3 (3, 4) for the 120 mcg group (Table 1)

Adverse Events and NNH

- **Schizophrenia**: The NNH versus placebo was >10 for both doses of dexmedetomidine ODF for all acute AEs of special interest, except for somnolence (Table 2), which was 8 for both active treatment groups; the NNH for other AEs of interest was 17-33
- **Bipolar**: The NNH versus placebo was >10 for all for acute AEs of special interest, except for somnolence (Table 2), which was 6 (5, 12) for dexmedetomidine ODF 180 mcg and 7 (5, 13) for dexmedetomidine ODF 120 mcg; the NNH for other AEs of special interest was 18-26

KEY FINDINGS

In a post hoc analysis of data from 2 randomized, double-blind, placebo-controlled Phase 3 clinical trials of dexmedetomidine ODF, an investigational orally-absorbed formulation of an α_{2A} adrenergic agonist being developed for the treatment of agitation associated with schizophrenia or bipolar disorder in adults:

- NNT values were consistent with a potent beneficial effect
- NNH values indicated that dexmedetomidine ODF was reasonably tolerable
- Therapeutic response was encountered more frequently than any adverse event

References: 1. *Ther Clin Risk Manag*. 2013;9:235-245; 2. *Health Qual Life Outcomes*. 2011;9:18; 3. https://www.psychiatry.org/File%20Library/Psychiatrists/Meetings/Annual-Meeting/2021/2021-APA-Annual-Meeting-Poster-Proceedings.pdf (no. 69); 4.https://www.psychiatry.org/File%20Library/Psychiatrists/Meetings/Annual-Meeting/2021/2021-APA-Annual-Meeting-Poster-Proceedings.pdf (no 95).

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