Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

Methods

The study protocol and statistical analysis plan are available in Supplements 1 and 2.

Results – Exploratory Endpoints

At 2 hours postdose, mean Positive and Negative Syndrome Scale-Excited Component (PEC) response (≥40% reduction from baseline) rates were 90.5% and 77.0% with sublingual dexmedetomidine 180 µg and 120 µg compared with 46.0% with placebo (eFigure 1).

On the Clinical Global Impression-Improvement (CGI-I) scale, improvements in agitation (ie, lower CGI-I scores) relative to baseline were observed at 30 minutes postdose, with mean (standard deviation [SD]) scores of 3.0 (1.1) in both sublingual dexmedetomidine treatment groups and 3.4 (1.0) in the placebo group (eFigure 3). Agitation was much improved at 1 hour postdose, as shown by mean (SD) CGI-I scores of 2.0 (1.1) for sublingual dexmedetomidine 180 µg and 2.2 (1.1) for sublingual dexmedetomidine 120 µg, and it remained much improved at 2 hours postdose (mean [SD] scores of 1.6 [0.9] for 180 µg and 1.9 [1.1] for 120 µg) and 4 hours postdose (mean [SD] scores of 1.5 [0.8] for 180 µg and 1.8 [0.9] for 120 µg). The least squares mean (standard error [SE]) differences from placebo at 30 minutes, 1, 2, and 4 hours were −0.4 (0.1), -1.0 (0.1), -1.3 (0.1), and -1.1 (0.1) with sublingual dexmedetomidine 180 µg and −0.3 (0.1), -0.8 (0.1), -0.9 (0.1), and -0.8 (0.1) with sublingual dexmedetomidine 120 µg.

At 2 hours postdose, Agitation-Calmness Evaluation Scale (ACES) differences from placebo were observed in the sublingual dexmedetomidine 180 µg and 120 µg groups (least squares mean [SE] difference: 2.4 [0.2] and 1.8 [0.2], respectively). At 2, 4, and 8 hours postdose, the

percentage of patients who had their agitation resolved (ACES score ≥4) was greater in the sublingual dexmedetomidine 180 μg and 120 μg groups than in the placebo group (eFigure 4).

ACES change from baseline line through 8 hours postdose are presented in eTable 4 and eFigure 5. The respective percentages of patients experiencing calmness (improvement in ACES of ≥1 vs baseline) at 2, 4, and 8 hours postdose were 92.1% (116/126), 99.2% (125/126), and 94.4% (119/126) in the 180 μg group, 83.3% (105/126) 92.1% (116/126) and 88.9% (112/126) in the 120 μg group, and 56.3% (71/126), 79.4% (100/126), and 73.8% (93/126) with placebo.

Patient-reported medication acceptability was 80.2% with sublingual dexmedetomidine 180 μg and 79.3% with sublingual dexmedetomidine 120 μg and placebo. Overall, 65.1% (82/126) of patients treated with sublingual dexmedetomidine 180 μg, 59.5% (75/126) of patients treated with sublingual dexmedetomidine 120 μg, and 63.5% (80/126) of those treated with placebo liked the flavor of the medication. More than 99% of the patients in all treatment groups judged sublingual dexmedetomidine to have no unpleasant aroma, and the majority of participants judged the study medication to have no unpleasant aftertaste (84.9%, 92.1%, and 94.4% in the sublingual dexmedetomidine 180 μg, 120 μg, and placebo groups; Table 2).

eTable 1. Concomitant medications

	Sublingual Dexmedetomidine			
	180 µg (n=126)	**120 µg (n=126)**	**Placebo (n=126)**	**Overall (N=378)**
Any concomitant medication, n (%)	97 (77.0)	104 (82.5)	95 (75.4)	296 (78.3)
Other antidepressants	37 (29.4)	36 (28.6)	26 (20.6)	99 (26.2)
Trazodone	18 (14.3)	15 (11.9)	10 (7.9)	43 (11.4)
Bupropion	10 (7.9)	8 (6.3)	9 (7.1)	27 (7.1)
Lamotrigine	7 (5.6)	7 (5.6)	3 (2.4)	17 (4.5)
Mirtazepine	5 (4.0)	4 (3.2)	3 (2.4)	12 (3.2)
Duloxetine	4 (3.2)	3 (2.4)	1 (.8)	8 (2.1)
Venlafaxine	2 (1.6)	2 (1.6)	4 (3.2)	8 (2.1)
Wellbutrin	1 (.8)	4 (3.2)	1 (.8)	6 (1.6)
Other antipsychotics	23 (18.3)	33 (26.2)	32 (25.4)	88 (23.3)
Divalproex sodium	10 (7.9)	9 (7.1)	9 (7.1)	28 (7.4)
Risperidone	3 (2.4)	6 (4.8)	10 (7.9)	19 (5.0)
Abilify	3 (2.4)	6 (4.8)	7 (5.6)	16 (4.2)
Aripiprazole	4 (3.2)	7 (5.6)	3 (2.4)	14 (3.7)
Diazepines, oxazepines, thiazepines, and oxepines	26 (20.6)	39 (31.0)	22 (17.5)	87 (23.0)
Quetiapine	21 (16.7)	28 (22.2)	19 (15.1)	68 (18.0)
Zyprexa	3 (2.4)	6 (4.8)	3 (2.4)	12 (3.2)
Olanzapine	2 (1.6)	5 (4.0)	0	7 (1.9)
Selective serotonin reuptake inhibitors	24 (19.0)	21 (16.7)	20 (15.9)	65 (17.2)
Sertraline	5 (4.0)	7 (5.6)	8 (6.3)	20 (5.3)
Escitalopram	8 (6.3)	4 (3.2)	2 (1.6)	14 (3.7)
Citalopram	4 (3.2)	2 (1.6)	5 (4.0)	11 (2.9)
Benzodiazepine derivatives	14 (11.1)	17 (13.5)	16 (12.7)	47 (12.4)
Lorazepam	9 (7.1)	6 (4.8)	6 (4.8)	21 (5.6)
Clonazepam	3 (2.4)	5 (4.0)	4 (3.2)	12 (3.2)
Temazepam	2 (1.6)	5 (4.0)	4 (3.2)	11 (2.9)
Other analgesics and antipyretics	14 (11.1)	19 (15.1)	9 (7.1)	42 (11.1)
Gabapentin	14 (11.1)	19 (15.1)	9 (7.1)	42 (11.1)
Propionic acid derivatives	16 (12.7)	11 (8.7)	8 (6.3)	35 (9.3)
Ibuprofen	15 (11.9)	5 (4.0)	6 (4.8)	26 (6.9)
Naproxen	1 (.8)	5 (4.0)	2 (1.6)	8 (2.1)
Proton pump inhibitors	8 (6.3)	14 (11.1)	9 (7.1)	31 (8.2)
Omeprazole	4 (3.2)	7 (5.6)	4 (3.2)	15 (4.0)
Pantoprazole	2 (1.6)	2 (1.6)	4 (3.2)	8 (2.1)
Lithium	13 (10.3)	7 (5.6)	9 (7.1)	29 (7.7)
Lithium	9 (7.1)	3 (2.4)	8 (6.3)	20 (5.3)

	Sublingual Dexmedetomidine			
	180 µg (n=126)	120 µg (n=126)	Placebo (n=126)	Overall (N=378)
Lithium carbonate	4 (3.2)	4 (3.2)	1 (.8)	4 (1.1)
Selective beta-2-adrenoreceptor agonists	11 (8.7)	8 (6.3)	10 (7.9)	29 (7.7)
Albuterol	6 (4.8)	5 (4.0)	6 (4.8)	17 (4.5)
Indole derivatives	12 (9.5)	9 (7.1)	7 (5.6)	28 (7.4)
Lurasidone	7 (5.6)	5 (4.0)	7 (5.6)	19 (5.0)
Ziprasidone	4 (3.2)	3 (2.4)	1 (.8)	8 (2.1)
Angiotensin-converting enzyme inhibitors, plain	10 (7.9)	14 (11.1)	3 (2.4)	27 (7.1)
Lisinopril	8 (6.3)	11 (8.7)	3 (2.4)	22 (5.8)
Diphenylmethane derivatives	8 (6.3)	12 (9.5)	6 (4.8)	26 (6.9)
Hydroxyzine	8 (6.3)	12 (9.5)	6 (4.8)	26 (6.9)
Dihydropyridine derivatives	8 (6.3)	10 (7.9)	8 (6.3)	26 (6.9)
Amlodipine	8 (6.3)	8 (6.3)	7 (5.6)	23 (6.1)
HMG CoA reductase inhibitors	7 (5.6)	10 (7.9)	8 (6.3)	25 (6.6)
Atorvastatin	5 (4.0)	8 (6.3)	3 (2.4)	16 (4.2)
Simvastatin	0	0	4 (3.2)	4 (1.1)
Anilides	8 (6.3)	9 (7.1)	4 (3.2)	21 (5.6)
Paracetamol	8 (6.3)	8 (6.3)	4 (3.2)	20 (5.3)
Azaspirodecanedione derivatives	7 (5.6)	8 (6.3)	3 (2.4)	18 (4.8)
Buspirone	7 (5.6)	7 (5.6)	3 (2.4)	17 (4.5)
Thiazides, plain	7 (5.6)	7 (5.6)	3 (2.4)	17 (4.5)
Hydrochlorothiazide	7 (5.6)	7 (5.6)	3 (2.4)	17 (4.5)
Biguanides	5 (4.0)	8 (6.3)	4 (3.2)	17 (4.5)
Metformin	5 (4.0)	8 (6.3)	4 (3.2)	17 (4.5)
Ethers of tropine or tropine derivatives	2 (1.6)	5 (4.0)	7 (5.6)	14 (3.7)
Benztropine	2 (1.6)	5 (4.0)	7 (5.6)	14 (3.7)
Other hypnotics and sedatives	3 (2.4)	5 (4.0)	2 (1.6)	10 (2.6)
Diphenhydramine	2 (1.6)	4 (3.2)	2 (1.6)	8 (2.1)
Other centrally acting agents	2 (1.6)	3 (2.4)	5 (4.0)	10 (2.6)
Tizanidine	1 (.8)	0	4 (3.2)	5 (1.3)
Thyroid hormones	1 (.8)	6 (4.8)	3 (2.4)	10 (2.6)
Levothyroxine	1 (.8)	6 (4.8)	3 (2.4)	10 (2.6)
Beta-blocking agents, nonselective	4 (3.2)	2 (1.6)	0	6 (1.6)
Propranolol	4 (3.2)	2 (1.6)	0	6 (1.6)

eTable 2. Enrollment by study site

Site	Location	Patients Randomized
Altea Research Institute	Las Vegas, NV	29
Carolina Clinical Trials	Charleston, SC	12
Center for Behavioral Health	Gaithersburg, MD	36
Collaborative Neuroscience Network	Long Beach, CA	35
Community Clinical Research	Austin, TX	3
Comprehensive Clinical Development	Cerritos, CA	15
Hassman Research Institute	Berlin, NJ	32
Hassman Research Institute	Marlton, NJ	40
InSite Clinical Research	DeSoto, TX	28
NRC Research Institute	Orange, CA	23
Pillar Clinical Research	Richardson, TX	43
ProScience Research Group	Culver City, CA	5
Segal Trials	Fort Lauderdale, FL	51
Uptown Research Institute	Chicago, IL	9
Woodland International Research Group	Little Rock, AK	19

eTable 3. Electrocardiogram Parameters Notable Abnormalities Criteria

ECG Parameter	Notable Abnormality Criteria
ECG Mean Heart Rate (BPM	Decrease in HR from baseline > 25% to a HR < 50 bpm or increase in HR from baseline > 25% to a HR > 100 bpm
PR Interval, Aggregate (msec)	Increase in PR from baseline >25 % to a PR > 200 msec
QRS Duration, Aggregate (msec)	Increase in QRS from baseline > 25% to a QRS >120 msec
QTcF Interval, Aggregate (msec)	QTcF ≤ 450 msec
	QTcF ≤ 450 msec
	QTcF ≤ 450 msec
	QTcF > 450 msec
	QTcF > 480 msec
	QTcF > 500 msec
	QTcF increase ≤ 30 msec
	QTcF increase > 30 msec to ≤ 60 msec
	QTcF increase > 60 msec

eTable 4. Exploratory efficacy endpoints: CGI-I and ACES

	Sublingual Dexmedetomidine				Placebo	
	180 µg		120 µg			
CGI-I	**Mean**	**95% Confidence Interval**	**Mean**	**95% Confidence Interval**	**Mean**	**95% Confidence Interval**
30 minutes	3.0	2.77, 3.15	3.0	2.85, 3.23	3.4	3.19, 3.53
1 hour	2.0	1.80, 2.20	2.2	2.03, 2.43	3.0	2.79, 3.18
2 hours	1.6	1.40, 1.71	1.9	1.73, 2.13	2.8	2.62, 3.04
4 hours	1.5	1.36, 1.65	1.8	1.60, 1.96	2.3	2.04, 2.57
ACES						
2 hours	5.6	5.34, 5.95	5.0	4.71, 5.39	3.3	3.05, 3.57
4 hours	5.5	5.18, 5.76	5.1	4.74, 5.37	3.9	3.52, 4.22
8 hours	4.6	4.37, 4.89	4.2	3.95, 4.50	3.6	3.30, 3.84

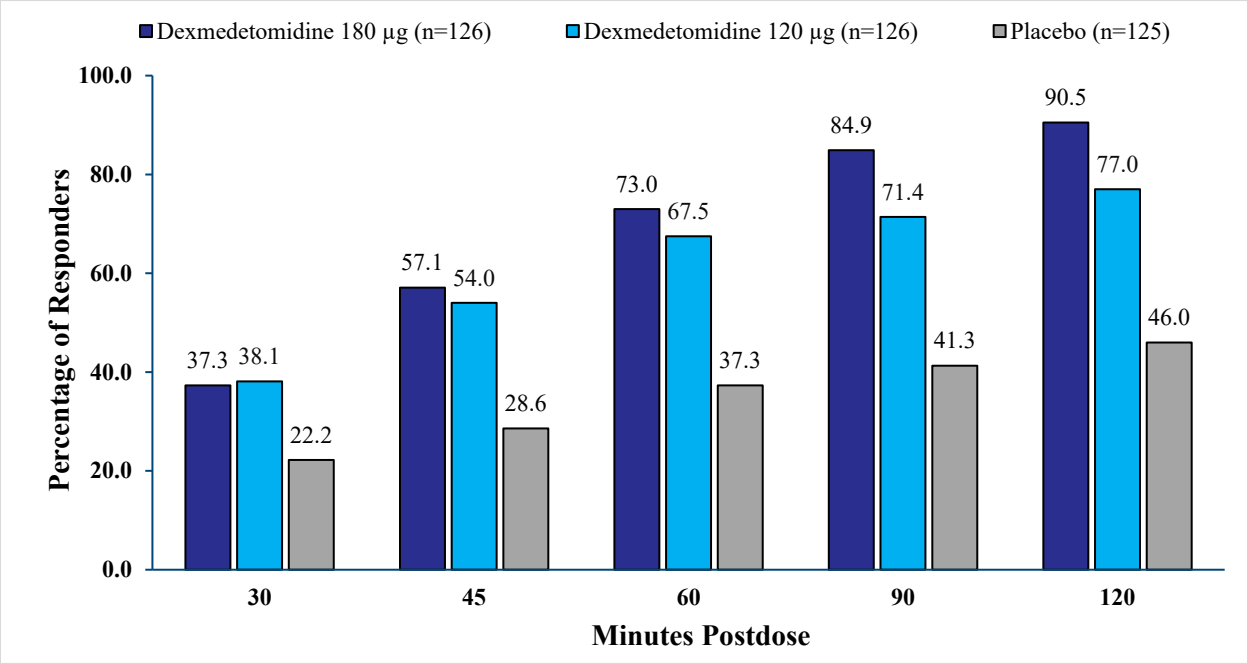
Abbreviations: CGI-I, Clinical Global Impressions – Improvement with possible scores ranging from 1 (very much improved) to 7 (very much worse); ACES, Agitation-Calmness Evaluation Scale, a single-item measure used to rate overall agitation and calmness where 1=marked agitation, 2=moderate agitation, 3=mild agitation 4=normal behavior, 5=mild calmness, 6=moderate calmness, 7=marked calmness, 8=deep sleep, and 9=unarousable.

eTable 5. Post hoc analysis of PEC change from baseline 20 minutes to 120 minutes postdose with site as random effect

Time Postdose	Sublingual Dexmedetomidine		Placebo
	180 µg	120 µg	
20 min, mean (95% CI)[a]	-3.1 (-3.85, -2.28)	-2.9 (-3.62, -2.27)	-1.9 (-2.40, -1.34)
LS Mean (SE)[b]	-3.0 (0.4)	-2.9 (0.4)	-1.9 (0.4)
Difference (97.5% CI)[c] P value[d]	-1.1 (-2.0, -0.2) .007	-1.0 (-1.9, -0.1) .01	
30 min mean (95% CI)[a]	-4.6 (-5.53, -3.74)	-4.3 (-5.18, -3.47)	-2.8 (-3.46, -2.11)
LS Mean (SE)[b]	-4.6 (0.5)	-4.3 (0.5)	-2.8 (0.5)
Difference (97.5% CI)[c] P value[d]	-1.7 (-2.9, -0.6) < .001	-1.5 (-2.6, -0.4) .003	
45 min, mean (95% CI)[a]	-6.7 (-7.59, -5.79)	-6.3 (-7.25, -5.38)	-3.6 (-4.36, -2.91)
LS Mean (SE)[b]	-6.6 (0.5)	-6.3 (0.5)	-3.7 (0.5)
Difference (97.5% CI)[c] P value[d]	-3.0 (-4.2, -1.7) < .001	-2.6 (-3.9, -1.4) < .001	
60 min, mean (95% CI)[a]	-8.4 (-9.27, -7.45)	-7.5 (-8.46, -6.62)	-4.4 (-5.17, -3.57)
LS Mean (SE)[b]	-8.3 (0.5)	-7.5 (0.5)	-4.4 (0.5)
Difference (97.5% CI)[c] P value[d]	-3.9 (-5.1, -2.6) < .001	-3.1 (-4.4, -1.9) < .001	
90 min, mean (95% CI)[a]	-9.7 (-10.60, -8.87)	-8.6 (-9.50, -7.64)	-4.7 (-5.46, -3.87)
LS Mean (SE)[b]	-9.7 (0.5)	-8.6 (0.5)	-4.7 (0.5)
Difference (97.5% CI)[c] P value[d]	-5.0 (-6.2, -3.7) < .001	-3.9 (-5.1, -2.6) < .001	
120 min, mean (95% CI)[a]	-10.4 (-11.21, -9.64)	-9.0 (-9.96, -8.10)	-4.9 (-5.73, -4.08)
LS Mean (SE)[b]	-10.4 (0.5)	-9.0 (0.5)	-4.9 (0.5)
Difference (97.5% CI)[c] P value[d]	-5.4 (-6.6, -4.2) < .001	-4.1 (-5.3, -2.9) < .001	

Abbreviations: PEC (The Positive and Negative Syndrome Scale - Excited Component is the sum of 5 subscales (poor impulse control, tension, hostility, uncooperativeness, and excitement) with each subscale ranging from 1 to 7 and total score ranging from 5 to 35. Observations after use of rescue medication are censored (set to missing).
Test statistics and estimates are from a restricted maximum likelihood repeated measures mixed model on change from baseline values. The covariates included in the models are: baseline PEC score, age stratum, timepoint (including all 7 timepoints from 10 minutes to 2 hours post-dose), treatment group, baseline PEC score by timepoint interaction term, and treatment group by timepoint interaction term. Study site is also included as a random effect with TYPE=VC (variance components) option (which models a different variance component for each random effect.
[a] Mean change from predose PEC total score
[b] Least square (LS) mean and standard error (SE) per treatment group
[c] Treatment Effect: Least square (LS) mean difference and 97.5% confidence intervals (CIs) between BXCL501 and Placebo
[d] p value comparing BXCL501 and Placebo

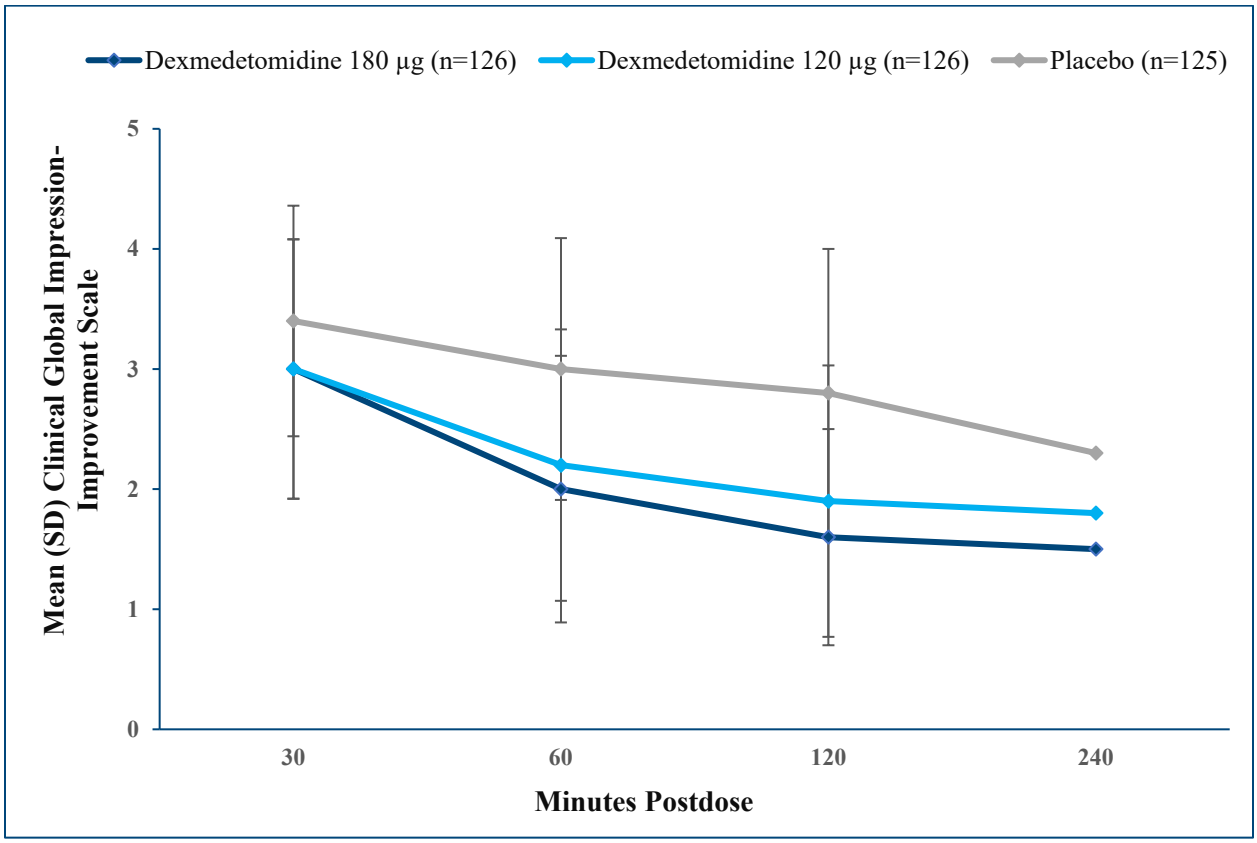
eFigure 1. Percentage of patients with a response[a] on the PEC total score



Abbreviations: PEC (Positive and Negative Syndrome Scale-Excited Component) comprised of 5 items with a total score range of 5 (absence of agitation) to 35 (extremely severe)

[a]Defined by ≥40% reduction from baseline on the PEC total score.

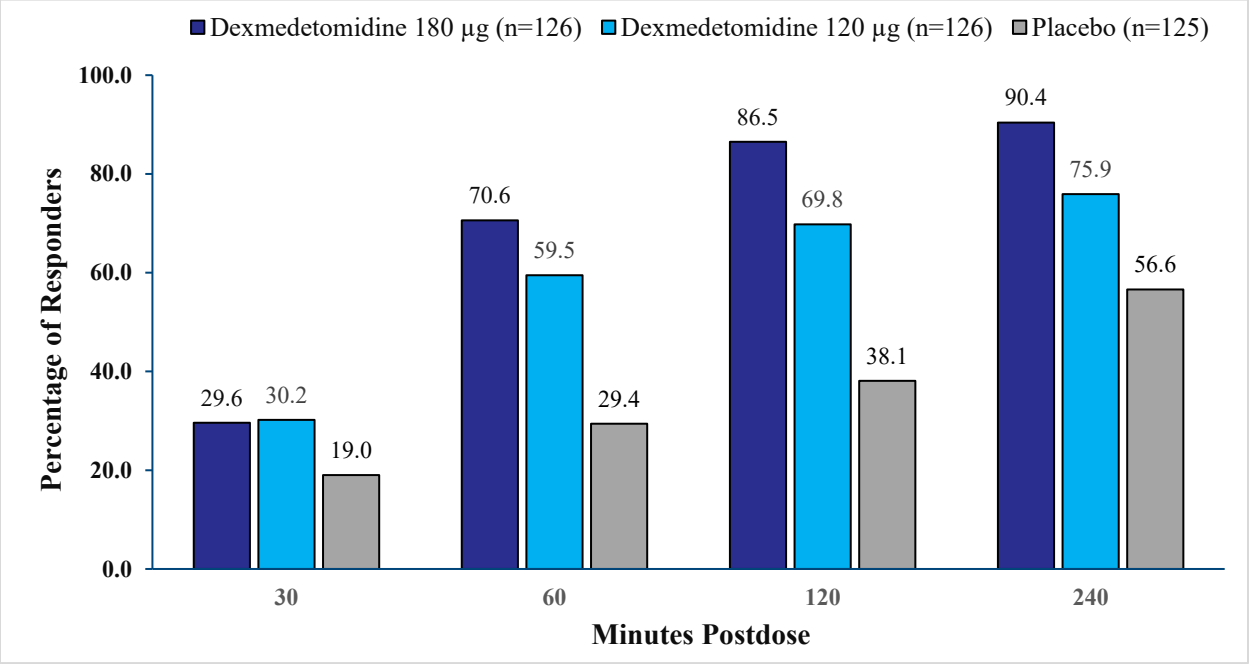
eFigure 2. Mean (standard deviation) on the Clinical Global Impression-Improvement scale



Abbreviations: SD (standard deviation)

Clinical Global Impression-Improvement evaluated drug response on agitation. Scores range from 1 to 7: 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, 7=very much worse

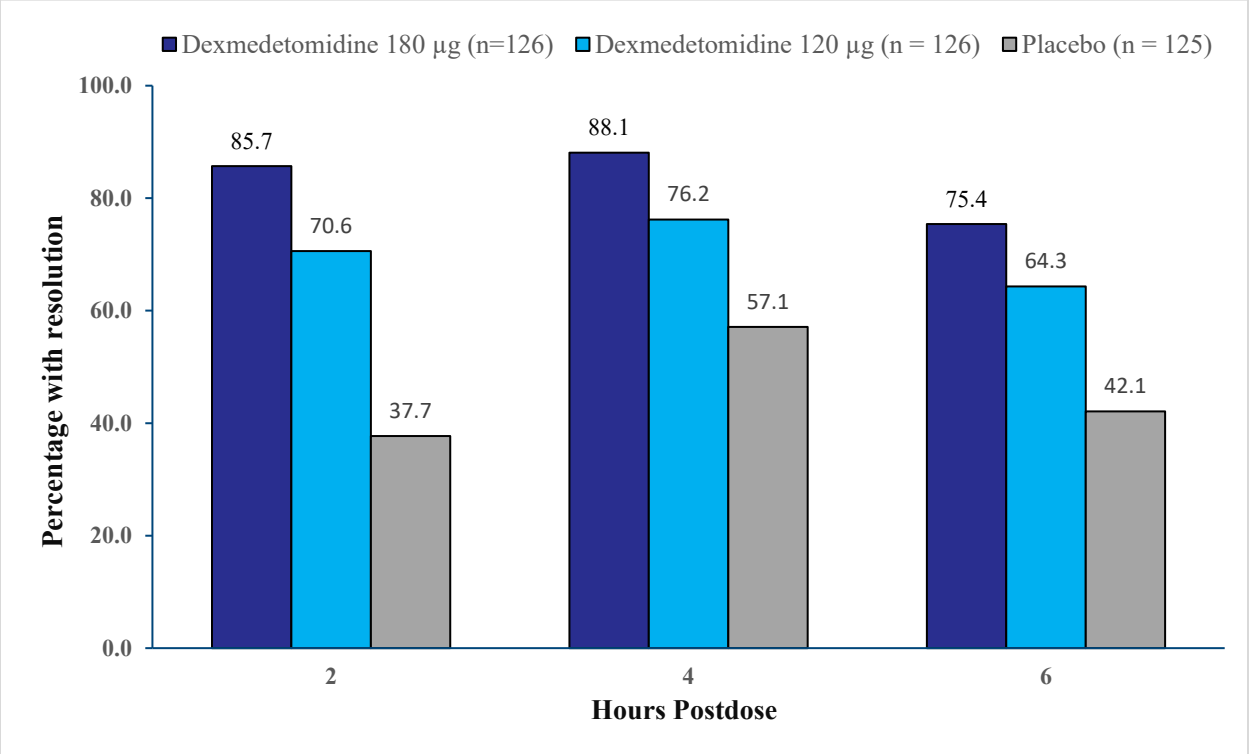
eFigure 3. Percentage of patients with a response[a] on the Clinical Global Impression-Improvement scale



[a]Defined by a score of 1 (very much improved) or 2 (much improved)

[b] Clinical Global Impression-Improvement evaluated drug response on agitation. Scores range from 1 to 7: 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, 7=very much worse

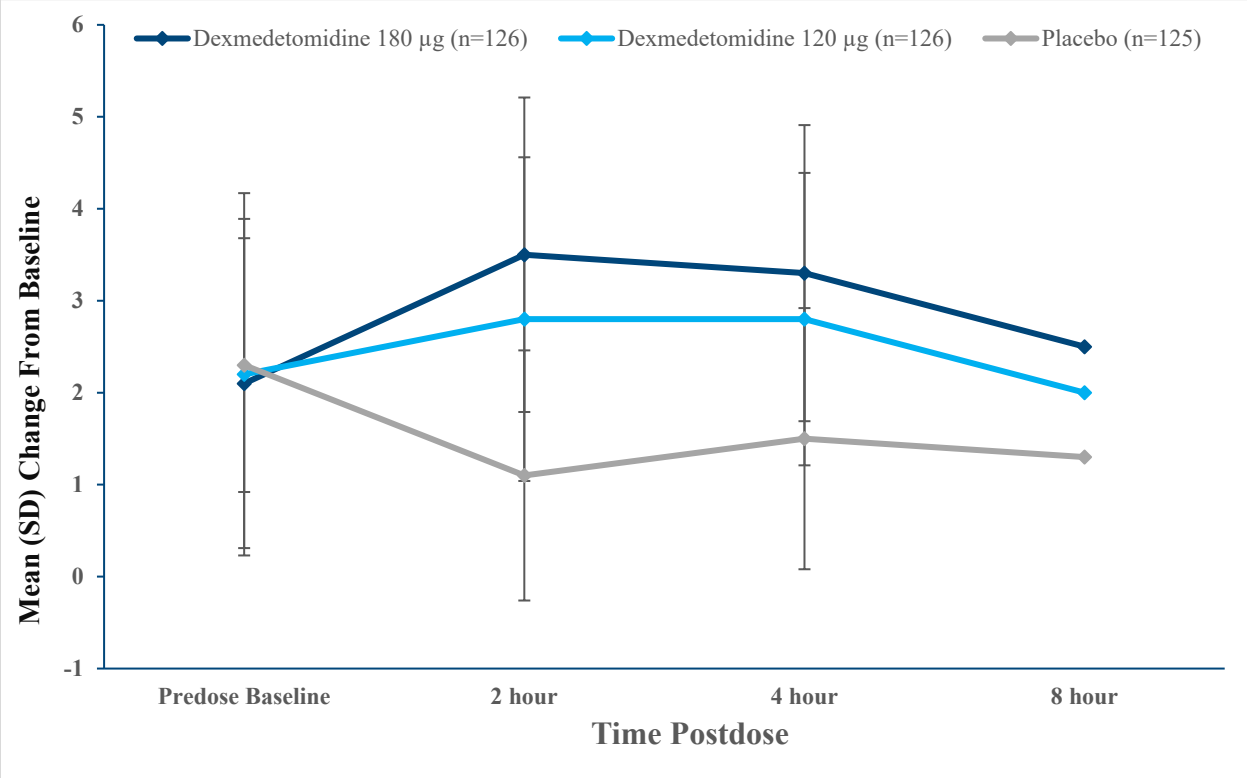
eFigure 4. Percentage of patients with resolution[a] of agitation on the Agitation-Calmness Evaluation Scale



[a]Defined by a score of ≥4 on the Agitation-Calmness Evaluation Scale

The Agitation-Calmness Evaluation Scale (ACES) is a single item measure used to rate overall agitation and calmness where 1=marked agitation, 2=moderate agitation, 3=mild agitation 4=normal behavior, 5=mild calmness, 6=moderate calmness, 7=marked calmness, 8=deep sleep, and 9=unarousable

eFigure 5. Mean (standard deviation) change from baseline on the Agitation-Calmness Evaluation Scale



The Agitation-Calmness Evaluation Scale (ACES) is a single item measure used to rate overall agitation and calmness, where 1=marked agitation, 2=moderate agitation, 3=mild agitation, 4=normal behavior, 5=mild calmness, 6=moderate calmness, 7=marked calmness, 8=deep sleep, and 9=unarousable