BioXcel Therapeutics Announces Promising Topline Results from Part 1 of Pivotal SERENITY III Trial of BXCL501 for At-Home Use in Acute Treatment of Agitation in Bipolar Disorders or Schizophrenia

May 25, 2023

Clinically meaningful efficacy results observed with half (60mcg) of the approved dose of IGALMI™

Greater than 50% PEC response rate attained; proportionally consistent with dose response when compared to rates seen in SERENITY I and II

BXCL501 was well tolerated and demonstrated favorable safety results supporting potential for at-home use

SERENITY III Part 2 planned as an adaptive trial design with 60mcg and 80mcg to potentially address agitation spectrum for patients at home

Company to hold conference today at 8 a.m. ET

NEW HAVEN, Conn., May 25, 2023 (GLOBE NEWSWIRE) -- BioXcel Therapeutics, Inc. (Nasdaq: BTAI), a biopharmaceutical company utilizing artificial intelligence approaches to develop transformative medicines in neuroscience and immuno-oncology, today announced promising results for BXCL501, the Company's proprietary, orally dissolving film of dexmedetomidine under investigation for the treatment of agitation, in Part 1 of its Phase 3 SERENITY III trial conducted in institutional settings for acute treatment of bipolar disorders- or schizophrenia-associated agitation. These results are expected to enable the initiation of Part 2 for at-home use. BXCL501 would represent the first-ever FDA approved therapy for at-home use in this indication, if approved.

SERENITY III is a two-part, double-blinded, placebo-controlled pivotal study designed to evaluate BXCL501 in acutely agitated adult patients with bipolar disorders or schizophrenia for at-home use. Part 1 was similar to SERENITY I and II in design and assessed the efficacy and safety of a 60mcg dose using the same primary and secondary endpoints with patients in a monitored medical setting, as surrogates for the home setting. Patients enrolled in Part I were expected to have a relatively higher level of agitation than the home-based patient population expected to be enrolled in Part 2. Patients in Part 1 were evaluated with half (60mcg) of the already-approved 120mcg dose (IGALMI™) to enhance safety for the targeted at-home setting.

"We are pleased with the outcome and progression of our land-and-expand strategy, which we believe moves us closer to addressing up to an additional 23 million annual agitation episodes in bipolar disorder and schizophrenia patients in the at-home setting. This would potentially more than double our current market opportunity, if approved. Treatment in the early stages of agitation at home could significantly benefit patients, caregivers, and hospital systems by reducing the need for emergency room visits and associated treatment costs," said Vimal Mehta, CEO of BioXcel Therapeutics. "We believe the entirety of BXCL501's clinical dataset generated, along with our upcoming Alzheimer's-related agitation milestones, could transform the agitation landscape for a broad spectrum of neuropsychiatric patients."

Clinically meaningful efficacy results were observed with half (60mcg) of the lowest approved dose of IGALMI. In addition, greater than 50% PEC response rate was achieved, with responder rate dose-proportionally consistent with those observed in SERENITY I and II trials. Although the primary efficacy endpoint was not statistically significant at 2 hours (p=0.077), BXCL501 separated from placebo at 4 hours (p=0.049).

The study results suggested a broad safety margin with no reported serious adverse events (SAEs). The principal finding relates to the favorable safety results relative to those observed in studies evaluating the higher approved doses (120mcg and 180mcg). These data provide a clear path for initiating SERENITY III Part 2, to pursue approval in the at-home setting. Alignment has been obtained with the FDA for 60mcg and repeat dosing for Part 2.

"Overall, the 60mcg dose appears to be well-tolerated with safety results comparable to placebo, which is favorable for testing in the at-home setting. In the real world, physicians adapt their treatment approach based on both the patient and the underlying situation," said Dr. John Krystal, M.D., the Robert L. McNeil, Jr. Professor of Translational Research and Chair of the Department of Psychiatry at Yale School of Medicine. "Therefore, I believe the strategy for Part 2 of the trial is well-suited to evaluate the value of BXCL501 for treating the continuum of agitation occurring at home."

Summary of Topline Results from Part 1 of SERENITY III

- **Efficacy Results:** For the primary endpoint, at 2 hours post-dose, the change in PEC differed from that with placebo, but did not reach statistical significance, with a p-value of 0.077. At 4 hours post-dose, the p-value was 0.049. 52% were PEC responders by 2 hours post-dose (p = 0.019 versus placebo). The proportion responding was greater than with placebo as early as 1 hour (p = 0.035) and remained so through 4 hours. The proportion responding by CGI-I assessment (achieving a score of 1 or 2, 'Very much improved' or 'Much improved', respectively) was greater than with placebo at 2 hours post dose (p = 0.039).

- **Safety and Tolerability Results:** The 60mcg dose was well tolerated and there were no reported serious adverse events. All adverse events were reported as mild to moderate, with none of severe intensity. No adverse events required medical intervention or monitoring. The most commonly reported adverse event was somnolence, defined as feeling drowsy, sleepy, fatigued, or sluggish, which occurred in 13% of the 60mcg arm as opposed to 7% in the placebo group. Other

adverse events reported in order of incidence for 60mcg and greater than with placebo were oral paresthesia or oral hypoesthesia (6% vs 4% placebo), dry mouth (5% vs 3% for placebo) and dizziness (3% vs 1% for placebo). Cardiovascular-related adverse events in the 60mcg group entailed 1 report of hypotension (0 in placebo), 1 of orthostatic hypotension (0 in placebo), and no reports of bradycardia or other cardiovascular adverse events in either group.

SERENITY III Part 1 Efficacy Results:

Data	SERENITY III Part 1		SERENITY I and II		
Effect at 120 minutes (Primary Endpoint)	**Placebo (n=100)**	**BXCL501 60 mcg (n=101)**	**IGALMI™ 120 mcg (SERENITY I n=129)[3] (SERENITY II n=126)[4]**	**IGALMI™ 180 mcg (SERENITY I n=125)[3] (SERENITY II n=126)[4]**	**Placebo (SERENITY I n = 126)[3] (SERENITY II n = 126)[4]**
Reduction in PEC Score vs. Baseline LSM (SE)	-3.8 (0.4) 2 hours -4.3 (0.4) 4 hours	-4.8 (0.4) (p = 0.077) 2 hours -5.4 (0.4) (p = 0.049) 4 hours	SERENITY I: -8.5 (0.4) SERENITY II: -9.1 (0.4)	SERENITY I: -10.3 (0.4) SERENITY II: -10.4 (0.4)	SERENITY I: -4.8 (0.4) SERENITY II: -5.0 (0.4)
PEC Response Rate[1]	36%	52% (p = 0.019)	SERENITY I: 81% SERENITY II: 79%	SERENITY I: 90% SERENITY II: 92%	SERENITY I: 48% SERENITY II: 48%
CGI-I Response Rate[2]	26%	39% (p = 0.039)	SERENITY I: 66% SERENITY II: 70%	SERENITY I: 86% SERENITY II: 87%	SERENITY I: 36% SERENITY II: 38%

[1] PEC Response Rate: % of patients achieving ≥40% reduction in PEC scores by 2 hours

[2] CGI-I Response Rate: % of patients assessed as 'Very Much Improved, or 'Much Improved' by CGI-I at 2 hours

[3] All comparisons p < 0.0001 in agitated patients with Schizophrenia (SERENITY 1), IGALMI™Package insert, data on file and Citrome L, Preskorn SH, Lauriello J, et al. Sublingual Dexmedetomidine for the Treatment of Acute Agitation in Adults With Schizophrenia or Schizoaffective Disorder: A Randomized Placebo-Controlled Trial. J Clin Psychiatry. 2022;83(6). doi:10.4088/JCP.22m14447.

[4] All comparisons p < 0.0001 in agitated patients with Bipolar I or II Disorders (SERENITY 2), IGALMI™Package insert, data on file and Preskorn SH, Zeller S, Citrome L, et al. Effect of Sublingual Dexmedetomidine vs Placebo on Acute Agitation Associated With Bipolar Disorder: A Randomized Clinical Trial. JAMA. 2022;327(8):727-736. doi:10.1001/jama.2022.0799

Adverse Events Reported in SERENITY III Part 1 and in SERENITY I and II:

Adverse Event	SERENITY III Part 1		SERENITY I and II		
	BXCL501 60mcg N = 101	**Placebo N = 100**	**IGALMI™ 120mcg[3] N = 255**	**IGALMI™ 180mcg[3] N = 252**	**Placebo N = 252[3]**
Somnolence[1]	13 (13)	7 (7)	56 (22)	57 (23)	16 (6)
Oral paresthesia or oral hypoesthesia	6 (6)	4 (4)	14 (5)	18 (7)	2 (1)
Dizziness	3 (3)	1 (1)	10 (4)	15 (6)	2 (1)
Hypotension	1 (1)	0	14 (5)	13 (5)	0
Orthostatic hypotension	1 (1)	0	7 (3)	13 (5)	1 (0)
Dry mouth	5 (5)	3 (3)	19 (7)	11 (4)	3 (1)
Nausea	2 (2)	1 (1)	6 (2)	7 (3)	4 (2)
Bradycardia	0	0	5 (2)	5 (2)	0
Abdominal discomfort[2]	0	0	0 (0)	6 (2)	1 (0)

[1] Somnolence includes the terms feeling drowsy, feeling sleepy, fatigue and sluggishness

[2] Abdominal discomfort includes dyspepsia, gastroesophageal reflux disease

[3] IGALMI ™(dexmedetomidine) USPI, July 2022

No SAEs observed

The adverse events (AEs) listed correspond to those in the label for IGALMI. No other AEs were observed that would fulfill the criteria for inclusion in the AE table (at least 2% and greater than with placebo).

"We chose half of the lowest approved IGALMI dose, 60mcg, with the goal of increasing the margin of safety while supporting efficacy for at-home use," said Robert Risinger, M.D., Chief Medical Officer, Neuroscience, of BioXcel Therapeutics. "We believe these results have opened the therapeutic window for BXCL501's potential use at home for bipolar- and schizophrenia-related agitation. This is essential in the journey of dexmedetomidine. It was originally sequestered in the surgical unit as an anesthetic, then approved by the FDA as IGALMI to treat agitation in adult patients with schizophrenia or bipolar disorders in medical settings, before being investigated now for at-home use. These results support our SERENITY III Part 2 development path for use at home, where agitation typically originates and escalates prior to requiring emergency care."

At-Home Agitation Market Insights[1-4]

There are approximately 39 million annual episodes of agitation associated with bipolar disorders or schizophrenia in adults that occur in the U.S. Of these, an estimated 23 million (~60%) episodes occur outside of a medical institution.

- Patients report feeling out of control and helpless when agitation episodes occur at home.

- Episodes may occur three times a month on average, with the majority of them escalating to moderate or severe.
- Physicians underdiagnose and undertreat these episodes in a community setting, with only a third of patients receiving prescription drugs, which are off-label and often suboptimal, for their agitation symptoms.
- In a market survey, patients indicated they would take BXCL501 for 80% of their agitation episodes.
    - 90% of those patients indicated they would take BXCL501 when they feel an episode coming on or when an episode begins.

The Company plans to proceed with SERENITY III Part 2 using an adaptive trial design with 60mcg or greater dose, such as 80mcg, which has demonstrated statistical significance in the Company's prior Phase 1b trial. The design may include potential repeat dosing as required to address the entire agitation spectrum for patients at home.

Conference Call
BioXcel Therapeutics will host an investor conference call and webcast May 25, 2023 at 8 a.m. ET to discuss the pivotal Phase 3 SERENITY III Part 1 trial results. To access the call, please dial 877-407-5795 (domestic) or 201-689-8722 (international). A live webcast will be available on the Investors section of the company's website, www.bioxceltherapeutics.com, and a replay will be available through at least August 25, 2023. In addition, a slide presentation of the SERENITY III Part 1 top-line results and key market insights has been posted on the Events and Presentations page of the company's website.

BioXcel Therapeutics may use its website as a distribution channel of material information about the Company. Financial and other important information regarding the Company is routinely posted on and accessible through the Investors sections of its website at www.bioxceltherapeutics.com. In addition, you may automatically receive email alerts and other information about the Company when you enroll your email address by visiting the "Email Alerts" option under the News/Events menu of the Investors & Media section of its website.

***About the PEC (PANSS-EC or the Positive and Negative Syndrome Scale-Excitatory Component) Score for Agitation**
The PEC total score is a validated regulatory endpoint for measuring acute agitation in schizophrenia and bipolar patients. This scale is used in clinical research to quantify the severity of a patient's acute agitation. The PEC rating evaluates 5 elements associated with agitation: poor impulse control, tension, hostility, uncooperativeness, and excitement; each scored 1 (minimum) to 7 (maximum). The PEC total score is the sum of these 5 elements and thus ranges from 5 to 35.

About BXCL501
BXCL501 is an investigational proprietary, orally dissolving film formulation of dexmedetomidine, a selective alpha-2 adrenergic receptor agonist. BioXcel Therapeutics believes that BXCL501 potentially targets an important mediator of agitation, and the Company has observed anti-agitation results in multiple clinical studies across several neuropsychiatric disorders. BXCL501 is under investigation for the acute treatment of agitation associated with bipolar I or II disorder or schizophrenia in the at-home setting, for the acute treatment of Alzheimer's-related agitation, and as an adjunctive treatment for Major Depressive Disorder. The safety and efficacy of BXCL501 for these investigational uses have not been established. BXCL501 has been granted Breakthrough Therapy designation for the acute treatment of agitation associated with dementia and Fast Track designation for the acute treatment of agitation associated with schizophrenia, bipolar disorders, and dementia.

About IGALMI™ (dexmedetomidine) sublingual film

INDICATION

IGALMI™ (dexmedetomidine) sublingual film is a prescription medicine, administered under the supervision of a health care provider, that is placed under the tongue or behind the lower lip and is used for the acute treatment of agitation associated with schizophrenia and bipolar disorder I or II in adults. The safety and effectiveness of IGALMI has not been studied beyond 24 hours from the first dose. It is not known if IGALMI is safe and effective in children.

IMPORTANT SAFETY INFORMATION

IGALMI can cause serious side effects, including:

- **Decreased blood pressure, low blood pressure upon standing, and slower than normal heart rate, which may be more likely in patients with low** blood volume, diabetes, chronic high blood pressure, and older patients. IGALMI is taken under the supervision of a healthcare provider who will monitor vital signs (like blood pressure and heart rate) and alertness after IGALMI is administered to help prevent falling or fainting. Patients should be adequately hydrated and sit or lie down after taking IGALMI and instructed to tell their healthcare provider if they feel dizzy, lightheaded, or faint.
- **Heart rhythm changes (QT interval prolongation).** IGALMI should not be given to patients with an abnormal heart rhythm, a history of an irregular heartbeat, slow heart rate, low potassium, low magnesium, or taking other drugs that could affect heart rhythm. Taking IGALMI with a history of abnormal heart rhythm can increase the risk of torsades de pointes and sudden death. Patients should be instructed to tell their healthcare provider immediately if they feel faint or have heart palpitations.
- **Sleepiness/drowsiness**. Patients should not perform activities requiring mental alertness, such as driving or operating hazardous machinery, for at least 8 hours after taking IGALMI.
- **Withdrawal reactions, tolerance, and decreased response/efficacy**. IGALMI was not studied for longer than 24 hours after the first dose. Physical dependence, withdrawal symptoms (e.g., nausea, vomiting, agitation), and decreased response to IGALMI may occur if IGALMI is used longer than 24 hours.

The most common side effects of IGALMI in clinical studies were sleepiness or drowsiness, a prickling or tingling sensation or numbness of the mouth, dizziness, dry mouth, low blood pressure, and low blood pressure upon standing.

These are not all the possible side effects of IGALMI. Patients should speak with their healthcare provider for medical advice about side effects.

Patients should tell their healthcare provider about their medical history, including if they suffer from any known heart problems, low potassium, low magnesium, low blood pressure, low heart rate, diabetes, high blood pressure, history of fainting, or liver impairment. They should also tell their healthcare provider if they are pregnant or breastfeeding or take any medicines, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Patients should especially tell their healthcare provider if they take any drugs that lower blood pressure, change heart rate, or take anesthetics, sedatives, hypnotics, and opioids.

Everyone is encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088. You can also contact BioXcel Therapeutics, Inc. at 1-833-201-1088 or medinfo@bioxceltherapeutics.com.

Please see full Prescribing Information at igalmi.com.

About Agitation Associated with Schizophrenia and Bipolar Disorder

Agitation is a common and difficult-to-manage symptom associated with bipolar I or II or schizophrenia. Early identification and prompt intervention to relieve agitation are essential to avoid symptomatic escalation and the emergence of aggression. Expert consensus best-practice guidelines have recommended that agitation should be treated by a combination of behavioral calming techniques, verbal de-escalation, and medications that are voluntarily accepted by patients without coercion. The goal of using medication is to calm the patient so that he or she can be more accurately assessed by clinicians. Medication used in this manner is consistent with current guidelines, which state that the proper endpoint of medication administration is calming without inducing sleep. This approach may help avoid the costly and traumatic use of coercive techniques like physical restraint and seclusion, which may result in admission and prolonged hospitalization.[1]

About BioXcel Therapeutics, Inc.
BioXcel Therapeutics, Inc. is a biopharmaceutical company utilizing artificial intelligence approaches to develop transformative medicines in neuroscience and immuno-oncology. The Company's drug re-innovation approach leverages existing approved drugs and/or clinically validated product candidates together with big data and proprietary machine learning algorithms to identify new therapeutic indications. The Company's commercial product, IGALMI™ (developed as BXCL501), is a proprietary, sublingual film formulation of dexmedetomidine approved for the acute treatment of agitation associated with schizophrenia or bipolar I or II disorder in adults. The safety and effectiveness of IGALMI have not been established beyond 24 hours from the first dose. For more information, please visit igalmi.com and also see the IGALMI full Prescribing Information. BXCL501 is under evaluation for at-home use for the acute treatment of agitation in bipolar and schizophrenia patients, for acute treatment of agitation associated with probable Alzheimer's disease, and as an adjunctive treatment for major depressive disorder. The safety and efficacy of BXCL501 for these uses have not been established. The Company is also developing BXCL502 as a potential therapy for chronic agitation in dementia. Under its subsidiary, OnkosXcel Therapeutics, the Company is developing BXCL701, an investigational, oral systemic innate immune activator for the treatment of aggressive forms of prostate cancer and other solid and liquid tumors. The safety and efficacy of BXCL502 and BXCL701 have not been established. For more information, please visit bioxceltherapeutics.com.

Forward-Looking Statements
This press release includes "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. We intend such forward-looking statements to be covered by the safe harbor provisions for forward-looking statements contained in Section 27A of the Securities Act of 1933, as amended (the "Securities Act") and Section 21E of the Securities Exchange Act of 1934, as amended (the "Exchange Act"). All statements contained in this press release other than statements of historical fact should be considered forward-looking statements, including, without limitation, the Company's expected timing of, trial design and data results from, future clinical trials of BXCL501, in particular for the SERENITY III Part 2 trial, potential safety and tolerability features of BXCL501, the potential addressable market for BXCL501 and the potential benefits from treatment with BXCL501. When used herein, words including "anticipate," "believe," "can," "continue," "could," "designed," "estimate," "expect," "forecast," "goal," "intend," "may," "might," "plan," "possible," "potential," "predict," "project," "should," "target," "will," "would" and similar expressions are intended to identify forward-looking statements, though not all forward-looking statements use these words or expressions. In addition, any statements or information that refer to expectations, beliefs, plans, projections, objectives, performance or other characterizations of future events or circumstances, including any underlying assumptions, are forward-looking. All forward-looking statements are based upon the Company's current expectations and various assumptions. The Company believes there is a reasonable basis for its expectations and beliefs, but they are inherently uncertain. The Company may not realize its expectations, and its beliefs may not prove correct. Actual results could differ materially from those described or implied by such forward-looking statements as a result of various important factors, including, without limitation, its limited experience in drug discovery and drug development; its dependence on the success and commercialization of IGALMI™, BXCL501, BXCL502 and BXCL701 and other product candidates; its limited experience in marketing and selling drug products; the failure of preliminary data from its clinical studies to predict final study results; failure of its early clinical studies or preclinical studies to predict future clinical studies; its ability to receive regulatory approval for its product candidates; its ability to enroll patients in its clinical trials; undesirable side effects caused by the Company's product candidates; and the other important factors discussed under the caption "Risk Factors" in its Quarterly Report on Form 10-Q for the quarterly period ended March 31, 2023, as such factors may be updated from time to time in its other filings with the SEC, which are accessible on the SEC's website at www.sec.gov. These and other important factors could cause actual results to differ materially from those indicated by the forward-looking statements made in this press release. Any such forward-looking statements represent management's estimates as of the date of this press release. While the Company may elect to update such forward-looking statements at some point in the future, except as required by law, it disclaims any obligation to do so, even if subsequent events cause our views to change. These forward-looking statements should not be relied upon as representing the Company's views as of any date subsequent to the date of this press release.

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Source: BioXcel Therapeutics, Inc.

References

1. Data on file. BioXcel Therapeutics, Inc. New Haven, CT December 2020.
2. Wu EQ, Shi L, Birnbaum H, et al. Annual prevalence of diagnosed schizophrenia in the USA: a claims data analysis approach. Psychol Med. 2006;36(11):1535-1540.
3. National Institute of Mental Health. Prevalence of bipolar disorder in adults. November 2017. Accessed December 16, 2022. https://www.nimh.nih.gov/health/statistics/bipolar-disorder.
4. InVibe Feb 2023