BioXcel Therapeutics Announces Positive Top-Line Data from Repeat Dosing of BXCL501 in Phase 1b Multiple Ascending Dose Trial in Healthy Volunteers for Major Depressive Disorder (MDD) Program

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BXCL501 was well tolerated across a broad dose range from 30mcg to 140mcg administered chronically

Planning Phase 2 human proof-of-concept study to evaluate BXCL501 as a potential adjunctive treatment in MDD

Data further supportive of ongoing clinical programs evaluating BXCL501 for potential at-home use for agitation associated with schizophrenia or bipolar disorders (SERENITY III) and agitation associated with Alzheimer's disease (TRANQUILITY II and III)

NEW HAVEN, Conn., May 16, 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 positive top-line data from its Phase 1b multiple ascending dose (MAD) trial of BXCL501 (dexmedetomidine) sublingual film. BXCL501 is the Company's proprietary, orally dissolving film under investigation for the treatment of agitation associated with neuropsychiatric disorders and as a potential adjunctive treatment in Major Depressive Disorder (MDD).

The trial was designed to evaluate the safety and tolerability of repeat dosing of BXCL501 in healthy volunteers as a single agent and in combination with antidepressant duloxetine. These results support dose selection for a Phase 2 proof-of-concept (POC) trial to evaluate BXCL501 in combination with selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitor (SNRIs) to potentially accelerate antidepressant activity in patients with MDD.

"This positive outcome supports the potential market expansion opportunity for our lead asset, BXCL501, into chronic neuropsychiatric disorders," said Vimal Mehta, CEO of BioXcel Therapeutics. "Our focus has been on developing innovative treatments for the millions of patients who are impacted by agitation episodes, including Alzheimer's disease. Our first drug, IGALMI™, is approved for the acute treatment of agitation associated with schizophrenia or bipolar I or II disorder in adults. We believe these new data present a transformative opportunity beyond acute treatment for the BXCL501 program, including treatment for MDD. This drug candidate has a pipeline-within-a-product potential across a broad range of neuropsychiatric conditions."

The study was a double-blind, placebo-controlled evaluation of BXCL501 for once- and twice-daily administration over seven days in ascending dose groups. The study's primary objectives were to assess the safety, tolerability, and pharmacokinetics of BXCL501 in healthy volunteers in multiple ascending doses. The trial successfully met the primary endpoints.

BXCL501 is designed to activate human presynaptic alpha-2 adrenergic receptors, mediating the 'fight-or-flight' reflex that underlies the generation of anxiety and agitation. The Company believes this mechanism has the potential to treat depression where a patient's insomnia, agitation and anxiety symptoms, core items in the Hamilton Depression Rating Scale (HAM-D), are slow to respond or worsen with current first-line SSRI/SNRI treatments.

"We are pleased with the safety and tolerability results observed across a broad range of BXCL501 in our first-ever chronic dosing trial in healthy volunteers and are encouraged that a maximum tolerated dose (MTD) was not attained," said Robert Risinger, M.D., Chief Medical Officer, Neuroscience, of BioXcel Therapeutics. "We believe the results support further evaluation of this novel mechanism in combination with first-line standard of care SSRIs and SNRIs to potentially accelerate antidepressant effects, particularly in response to symptoms inadequately addressed by current agents. The data also support the ongoing pivotal SERENITY III and TRANQUILITY II and III trials in agitation."

Summary of Top-line BXCL501 Phase 1 Study Results

- **Multiple Ascending Dose (MAD) Study:** 125 healthy adult volunteers were enrolled across seven different cohorts in a 2:1 randomization to BXCL501 or placebo film dosed for seven days. Four distinct cohorts received 30mcg, 60mcg, 80mcg, or 120mcg doses of BXCL501 or placebo once daily. Two additional dosing cohorts received twice-daily (BID) BXCL501 at either 30mcg in the morning and 60mcg in the evening, or 40mcg in the morning and 80mcg in the evening. The final escalation cohort evaluated BXCL501 at 60mcg in the morning and 80mcg in the evening in combination with 30mg of duloxetine BID.
- **Safety and Tolerability Results:** BXCL501 was well tolerated across all dosing cohorts. MTD was not reached, based on pre-specified stopping criteria. All adverse events were reported as mild or moderate. The most common adverse events reported were orthostatic hypotension, somnolence, headache, dizziness, and hypotension. The highest dose tested was acceptably tolerated in combination with duloxetine. No serious adverse events were reported and there were no adverse event-related dropouts in any cohort. Twice-daily dosing improved daytime tolerability versus comparable once-daily dosing in the morning.
- **Pharmacokinetics:** The profile of BXCL501 exhibited consistency between doses evaluated, proportional increases with dose, and no accumulation with once- or twice-daily dosing, consistent with the half-life of BXCL501. The pharmacokinetics

of BXCL501 were similar with or without duloxetine coadministration.

BioXcel Therapeutics plans to present results from the Phase 1b MAD study at an upcoming medical conference.

The Company is developing a Phase 2 human POC trial design to investigate BXCL501 as an adjunctive treatment and its potential accelerant effect in combination with first-line SSRIs and SNRIs.

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 Major Depressive Disorder (MDD)
Major depression is the most common mental disorder in the U.S.[1] and is the strongest risk factor for suicide behavior.[2–4] From 2015 to 2019, there were widespread increases in depression without commensurate increases in treatment, and in 2020, past 12-month depression was prevalent among nearly 1 in 10 Americans.[5] Over 300 million antidepressant prescriptions are filled annually in the U.S.,[6] and current treatments are limited by slow onset of action and incomplete responses.

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, potential safety and tolerability features of BXCL501, the potential benefits from treatment with BXCL501, other indications of potential use of BXCL501 and the Company's plans to present results from the Phase 1b MAD study at an upcoming medical conference. 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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