Jaguar Health's Mental Health Entheogen Therapeutics Initiative Targets Plant-based Candidate Compound for Possible Schizophrenia and Psychoses Indications

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Neuropharmacological profile shows alstonine demonstrates antipsychotic activity and has a mechanism of action distinct from existing therapies

SAN FRANCISCO, CA / ACCESSWIRE / October 2, 2020 / Jaguar Health, Inc. (NASDAQ:JAGX) announced today that the company's recently launched mental health Entheogen Therapeutics Initiative (ETI), aimed at developing groundbreaking, novel and natural medicines derived from psychoactive plants, is targeting the plant-based compound alstonine for possible schizophrenia and psychoses indications and for development with potential corporate partners. Neuropsychopharmacology profile analysis of alstonine shows that the compound demonstrates antipsychotic activity and has a mechanism of action distinct from existing FDA-approved therapies for schizophrenia and other mental conditions that present psychotic symptoms.

Schizophrenia, the most serious form of psychosis, is a chronic, disabling mental illness that affects approximately one percent of the U.S. population.[1] It is estimated that up to 34% of patients with schizophrenia fail to respond to currently available treatments.[2] Psychotic symptoms can also be present in other mental illnesses, including depression, bipolar disorder, dementia, and borderline personality disorder.

Alstonine is a heteroyohimbine-type alkaloid that occurs naturally in a variety of plant species, including a species of West African plant contained in Jaguar's proprietary library of plants with medicinal properties and potential to treat mood disorders including depression, neuro-degenerative diseases, addiction, and other mental health disorders.

"There are around eight psychoactive and psychadelic compounds in various formulations and stages of development by other companies, such as psilocybin, MDMA, and ibogaine," said Lisa Conte, Jaguar's president and CEO. "Jaguar is focused on advancing plant-based innovation for patients and on identifying the next generation of plant-based first-in-class agents for treatment of mental health conditions, and alstonine may prove to be the first in a new class of plant-based antipsychotic compounds."

Thomas Carlson, M.D., M.S., who has documented the ethnobotanical uses of alstonine-bearing plant species during research expeditions to Nigeria in West Africa, is championing the development of alstonine for Jaguar. Dr. Carlson is a member of the ETI scientific strategy team (SST) and was a key architect of the ethnomedical field research process conducted by ethnobotanist and physician teams as part of the SST of Jaguar's predecessor company, Shaman Pharmaceuticals.

"I believe psychedelic and psychoactive compounds derived from plants may demonstrate significant potential for treating mood disorders and addressing other unmet mental health needs," said Dr. Carlson, who is an ethnobotanist, botanist, and physician, and a teaching professor of integrative biology at the University of California, Berkeley.

"We observed the administration of the plant-based alstonine treatment, referred to as ‘Heart of Man' in Igbo - a Nigerian language, by a traditional Nigerian healer in mentally ill patients, and the subsequent benefit to the patients. It is rewarding for me to participate in the demystification of traditional medicine and to credit Indigenous knowledge for potential contribution to western-world issues."

As with Dr. Carlson, ETI SST member Dr. Elaine Elisabetsky, a professor in the pharmacology and biochemistry departments of the Universidade Federal do Rio Grande do Sul in Brazil, was also a member of the Shaman Pharmaceuticals SST. She is a highly regarded ethnopharmacologist and the co-author of the book *Medicinal Resources of the Tropical Forest*. Dr. Elisabetsky is the guest editor of a special volume of the peer-reviewed, community-driven journal *Frontiers in Psychiatry* titled "Natural Products as Sources of Innovative Approaches in Psychiatry."

"My field research collaborations in the past yielded exciting new potential applications for alstonine, which has already demonstrated a novel mechanism of action and positive results in several published preclinical studies that replicate difficult to manage domains in conditions such as schizophrenia, as cognitive and social interaction deficits," said Dr. Elisabetsky. "Alstonine appears to offer a mechanism of action that is distinct from existing antipsychotic therapies such as clozapine and haloperidol, and it may therefore prove beneficial in the management of patient outcomes. For instance, alstonine does not demonstrate any direct dopamine interaction, which means the compound may cause fewer side effects than existing antipsychotic therapies, such as hormonal and nigrostriatal symptoms. Because of its interaction with specific serotonin receptors, it is also unlikely that alstonine will cause weight gain, an adverse effect that leads to poor adherence to second-generation antipsychotics such as clozapine. I am so pleased that this potentially exciting compound is gaining prioritization and attention for formal drug development activities. I worked with Dr. Carlson, Nigerian colleagues, and a Nigerian traditional psychiatrist to document the ethnobotanical uses of the plant, then subsequently worked for years to isolate alstonine as the chemical responsible for the behavior profile, and finally to characterize alstonine's antipsychotic activity in its mechanism of action through animal models and *ex vivo* and *in vitro* neurochemistry."

In a 2004 paper published in the monthly peer-reviewed journal *Pharmacology, Biochemistry, and Behavior*, Dr. Elisabetsky demonstrated that alstonine possesses anxiolytic properties in mice. A 2008 publication in the peer-reviewed academic journal *Progress in Neuro-Psychopharmacology & Biological Psychiatry* demonstrates that alstonine reverses social interaction withdrawal in mice. In a 2015 paper published in the monthly peer-reviewed medical journal *Phytomedicine,* Dr. Elisabetsky demonstrated that alstonine possesses antipsychotic properties in mice.

"While Jaguar remains steadfastly focused on the commercial success of our FDA-approved drug product, Mytesi® (crofelemer), and on the development of crofelemer follow-on indications in the area of GI health, we're thrilled to be leading this effort to potentially uncover a pipeline of novel psychoactive plant-based compounds, engage with recognized leaders in this space, and share our findings with potential corporate partners with the goal of developing plant-based compounds into possible medical breakthroughs," said Conte. "For decades, our team has recognized the unique and powerful knowledge traditional and Indigenous peoples have about plants, ecosystems, interrelationships, and healing compounds, and we continue to be extremely grateful to the traditional healers who have taught our team of field research scientists about medical applications of plants to treat and heal people in their communities and the world."

About Jaguar Health, Inc. and Napo Pharmaceuticals, Inc.

Jaguar Health, Inc. is a commercial stage pharmaceuticals company focused on developing novel, plant-based, non-opioid, and sustainably derived prescription medicines for people and animals with GI distress, specifically chronic, debilitating diarrhea. Our wholly owned subsidiary, Napo Pharmaceuticals, Inc., focuses on developing and commercializing proprietary plant-based human gastrointestinal pharmaceuticals from plants harvested responsibly from rainforest areas. Our Mytesi® (crofelemer) product is approved by the U.S. FDA for the symptomatic relief of noninfectious diarrhea in adults with HIV/AIDS on antiretroviral therapy and the only oral plant-based prescription medicine approved under FDA Botanical Guidance.

For more information about Jaguar, please visit https://jaguar.health. For more information about Napo, visit www.napopharma.com.

About Mytesi®

Mytesi (crofelemer) is an antidiarrheal indicated for the symptomatic relief of noninfectious diarrhea in adult patients with HIV/AIDS on antiretroviral therapy (ART). Mytesi is not indicated for the treatment of infectious diarrhea. Rule out infectious etiologies of diarrhea before starting Mytesi. If infectious etiologies are not considered, there is a risk that patients with infectious etiologies will not receive the appropriate therapy and their disease may worsen. In clinical studies, the most common adverse reactions occurring at a rate greater than placebo were upper respiratory tract infection (5.7%), bronchitis (3.9%), cough (3.5%), flatulence (3.1%), and increased bilirubin (3.1%).

See full Prescribing Information at Mytesi.com. Crofelemer, the active ingredient in Mytesi, is a botanical (plant-based) drug extracted and purified from the red bark sap of the medicinal *Croton lechleri* tree in the Amazon Rainforest. Napo has established a sustainable harvesting program for crofelemer to ensure a high degree of quality and ecological integrity.

Forward-Looking Statements

Certain statements in this press release constitute "forward-looking statements." These include statements related to Jaguar's plans to target the plant-based compound alstonine for possible schizophrenia and psychoses indications and for development with potential corporate partners, the belief that alstonine may prove to be the first in a new class of plant-based antipsychotic compounds, the belief that psychedelic and psychoactive compounds derived from plants may demonstrate significant potential for treating mood disorders and addressing other unmet mental health needs, the expectation that alstonine may cause fewer side effects than existing antipsychotic therapies, such as hormonal and nigrostriatal symptoms, and the expectation that it is unlikely that alstonine will cause weight gain. In some cases, you can identify forward-looking statements by terms such as "may," "will," "should," "expect," "plan," "aim," "anticipate," "could," "intend," "target," "project," "contemplate," "believe," "estimate," "predict," "potential" or "continue" or the negative of these terms or other similar expressions. The forward-looking statements in this release are only predictions. Jaguar has based these forward-looking statements largely on its current expectations and projections about future events. These forward-looking statements speak only as of the date of this release and are subject to several risks, uncertainties and assumptions, some of which cannot be predicted or quantified and some of which are beyond Jaguar's control. Except as required by applicable law, Jaguar does not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise.

[1]Bromet EJ, Dew MA, Eaton W. *Epidemiology of psychosis with special reference to schizophrenia*. In: Tsuang MT, Tohen M, Zahner GEP, eds. Textbook in psychiatric epidemiology. New York: John Wiley, 1996:283-300

[2]Demjaha, A. et al. *Antipsychotic treatment resistance in first-episode psychosis: prevalence, subtypes and predictors*. Psychol. Med 47, 1981-1989 (2017); Lally, J. et al. *Two distinct patterns of treatment resistance: clinical predictors of treatment resistance in first-episode schizophrenia spectrum psychoses*. Psychol. Med 46, 3231-3240 (2016); Meltzer, H. Y. et al. *Age at onset and gender of schizophrenic patients in relation to neuroleptic resistance*. Am. J. Psychiatry 154, 475-482 (1997).

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