# Magdalena Biosciences

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## COMPANY OVERVIEW

**Purpose for the Joint Venture Named Magdalena Biosciences**

Filament Health (Filament) and Jaguar Health (Jaguar) wished to leverage their mutual expertise in benefit sharing with indigenous populations and rain forest communities, botanical drug development, plant sourcing and sustainable supply, scientific advisors, neuroscience, regulatory experience with FDA for botanical drug approval, clinical development, manufacturing, bioassay preparation and performance, and knowledge-based library of plants and extracts. The focus of Magdalena Biosciences, Inc. (Magdalena) will initially be development of a botanical drug under botanical guidance, targeting the initial indications of the treatment of attention deficit hyperactivity disorder (ADHD), social anxiety disorder, and depression. In addition, Magdalena will prepare a dossier of safety information from the human experience with plant extracts under consideration for ADHD and other indications to evaluate whether a clinical study might be initiated (preliminary look in humans) based on this dossier.

**Description of Drugs Approved under Botanical Guidance ("Botanical Drug")**

Botanical drugs are highly characterized, stabilized, and reproducible plant extracts formulated for delivery to humans. Frequently, the identification of the plant for sourcing such an extract is based on a many centuries' history of native and indigenous use of the plant by healers. Oral availability of the botanical extracts is known, and a large amount of safety information has been gathered over many years of study by Western scientists. Where a synthetic small molecule drug, frequently a metabolite of a precursor molecule, gives a single active compound, botanical drugs may have multiple active compounds. Botanical drugs are complex mixtures of different compounds. All the elements of their production as well as the source location of plants affect the final composition of the botanical drug. This includes the species and strains used, the growing and harvesting conditions, and the manufacturing methods. These are protected through patents or as trade secrets. In addition, novel use, formulation, and delivery patents may provide further protection.

**Initial Therapeutic Focus of the Joint Venture**

As mentioned above, the initial therapeutic focus of the joint venture will be ADHD, social anxiety disorder and depression — focused on a fast-acting anti-depressant.

**Attention-deficit/hyperactivity disorder (ADHD)**, a neurodevelopmental disorder characterized by the core symptoms of hyperactivity, inattentiveness, and impulsivity, is currently regarded as the most common neuropsychiatric disorder among children. Furthermore, while this disorder is most often diagnosed during childhood, it may also affect an individual throughout life. It is believed 11-12% of children and 3-5% of adults in the US suffer from ADHD and it remains the largest single psychiatric disorder in children. It is crucial to develop efficacious treatments for ADHD, given its serious academic, social, and familial consequences, along with the risk of incurring comorbid conditions and later substance abuse. ADHD has been associated with abnormalities in catecholaminergic function in the brain. The use of medications that increase levels of catecholamine in the brain received widespread support as these drugs have been demonstrated to alleviate ADHD symptoms. Drugs indicated in the management of ADHD are classified as stimulant and nonstimulant medications. The predominantly used or prescribed pharmacological interventions for ADHD are stimulant medications. Methylphenidate and dextroamphetamine are examples of these drugs, which are structurally like endogenous catecholamines and whose activity increases extracellular dopamine and norepinephrine levels, thereby correcting the underlying abnormalities in catecholaminergic functions and restoring neurotransmitter imbalance. Nonstimulant alternatives include atomoxetine and norepinephrine specific reuptake inhibitors and the antidepressants bupropion, imipramine, and phenelzine. Nonstimulant alternatives have also been reported to increase catecholamine levels in the brain resulting in behavioral improvement. However, nonstimulant medications have been found to be inferior to stimulant treatments on efficacy endpoints.

While pharmacological treatments generally improve ADHD symptoms for most children, 20-30% of affected individuals are nonresponders or are unable to tolerate adverse side effects of these drugs. Some of the side effects of stimulant medications include headache, insomnia, and decreased appetite, motor tics, nausea, and abdominal pain. Medications used to manage ADHD can lead to changes in diet and appetite and dry mouth, which can increase a patient's risk for cavities. Concerns over long-term exposure risks also discourage parents to medicate their children with stimulant drugs or for adults to take these medications. Furthermore, the high likelihood for dependence, diversion, and abuse, particular to drugs classified as schedule II (i.e., stimulants), limits the use of stimulant medications, as ADHD has been also associated with increased risk of substance use disorder.

There is a large unmet medical need to develop classes of stimulants that are naturally occurring and with a history of widespread and safe use in indigenous societies. Coca leaves are chewed in Columbia Peru, and Bolivia, for example, for treatment of altitude sickness, motion sickness, GI distress, hunger, and thirst, fast acting anti-depressant, and to assist in weight loss. In leaf form, coca does not produce dependence or any known toxicities. Coca leaves have been chewed by indigenous peoples for centuries.

**Social Anxiety Disorder:** Social anxiety disorder, sometimes referred to as social phobia, is a type of anxiety disorder that causes extreme fear in social settings. People with this disorder have trouble talking to people, meeting new people, and attending social gatherings. They fear being judged or scrutinized by others. Some people with the disorder do not have anxiety related to social interactions but have it

during performances instead. They feel symptoms of anxiety in situations such as giving a speech, competing in a sports game, or playing a musical instrument on stage. Social anxiety disorder usually starts during late childhood and may resemble extreme shyness or avoidance of situations or social interactions. It occurs more frequently in females than in males, and this gender difference is more pronounced in adolescents and young adults. Without treatment, social anxiety disorder can last for many years, or even a lifetime.

When having to perform in front of or be around others, people with social anxiety disorder may:

- Blush, sweat, or tremble
- Have a rapid heart rate
- Feel their "mind going blank," or feel sick to their stomach
- Have a rigid body posture, or speak with an overly soft voice
- Find it difficult to make eye contact, be around people they don't know, or talk to people in social situations, even when they want to
- Feel self-consciousness or fear that people will judge them negatively
- Avoid places where there are other people

Social anxiety disorder (SAD) is generally treated with psychotherapy (sometimes called "talk therapy"), medication, or both. Cognitive behavioral therapy (CBT), a research-supported type of psychotherapy, is commonly used to treat social anxiety disorder. CBT teaches you different ways of thinking, behaving, and reacting to situations to help you feel less anxious and fearful. CBT also can help you learn and practice social skills, which is very important for treating social anxiety disorder. CBT has been well studied and is the gold standard for psychotherapy.

Health care providers may prescribe medication to treat SAD. Different types of medication can be effective in treating this disorder, including:

- Antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs)
- Beta-blockers
- Anti-anxiety medications, such as benzodiazepines

SSRI and SNRI antidepressants are commonly used to treat depression, but they also can help treat the symptoms of SAD. They may take several weeks to start working. Antidepressants may also cause side effects, such as headaches, nausea, or difficulty sleeping. These side effects are usually not severe, especially if the dose starts off low and is increased slowly over time.

Beta-blockers can help control some of the physical symptoms of SAD, such as rapid heart rate, sweating, and tremors. Beta-blockers are commonly the medication of choice for the "performance anxiety" type of social anxiety disorder although rate of onset is about 1-2 hours. It can be difficult to time the drug administration prior to a performance.

Benzodiazepines, which are anti-anxiety sedative medications, are powerful and begin working right away to reduce anxious feelings. These medications can be very effective in rapidly decreasing anxiety, but some people build up a tolerance to them and need higher and higher doses to get the same effect. Some people even become dependent on them.

There are several unmet needs in the treatment of anxiety disorders including the need for more effective, rapidly acting, and better tolerated medications; early identification of nonresponse; effective treatments for refractory disorders; prevention of relapse; and promotion of resilience and long-lasting response[4]. With a high global prevalence of anxiety disorders, including SAD, and alarming increases in dependency, addiction and even deaths associated with misuse of benzodiazepines, the urgency for a new non-addictive, non-sedating, fast-acting, as-needed treatment for SAD and other anxiety disorders is more important now than ever before.

Magdalena is in the process of developing botanical drugs for the treatment of ADHD, social anxiety, and depression.

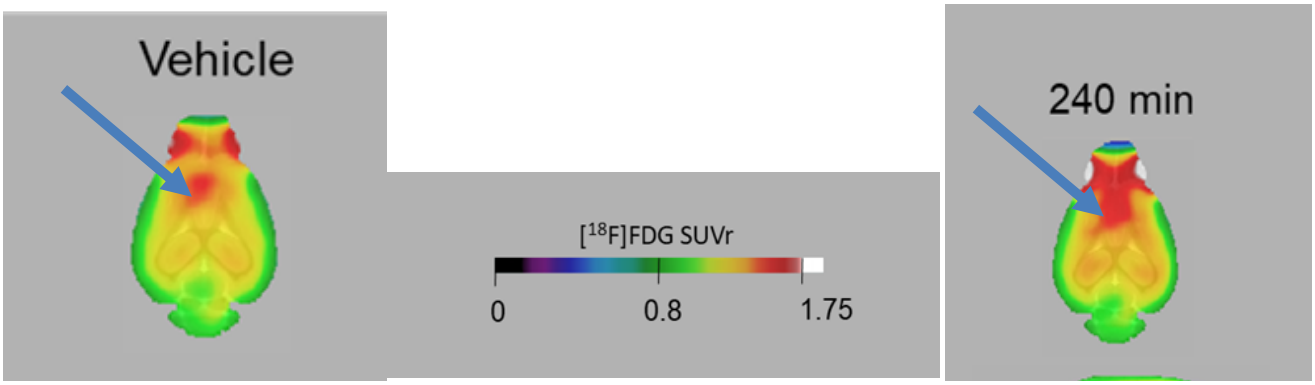
## PRELIMINARY DATA

Magdalena has recently embarked on a preclinical study to evaluate a specific plant extract in mice, using fluorodeoxyglucose positron emission tomography (PET) scans to look for changes in neuronal metabolism as a measure of neuronal activity. We hoped to see increased synaptic activity in specific brain regions relevant for a range of mental disorders that would be consistent with reports from indigenous people who have used this plant for medicinal purposes – and we indeed see very encouraging data. The PET scans identified effects that the team conducting this preclinical study do not frequently see – even with small molecule compounds they test for big pharmaceutical companies –a significant increase in neuronal metabolism at several brain areas. Importantly, the connectivity analysis shows that the extract not only lights up the brain in relevant areas, but also induces an impressive reshape at the network level.

Given this result, Magdalena aims to enter the clinic in 2025 with a botanical drug candidate after an IND (Investigational New Drug) application to the U.S. Food and Drug Administration (FDA) under FDA Botanical Guidance. Following activation of this IND by the FDA, Magdalena may be able to go directly into a Phase II clinical trial for the extract, with no need for a Phase I trial. Dossiers of safe use in humans will likely preclude the need for initial animal toxicology testing as well.

So many companies evaluating plant-derived drugs for mental health disorders are chasing the same seven compounds or plants. Magdalena is focused on identifying the next generation of psychoactive botanical drugs to treat mental health disorders, leveraging Jaguar's proprietary library of 2,300 highly characterized medicinal plants and 3,500 plant extracts, the team's extensive ethnobotanical expertise, and looking specifically at plants that have centuries of history of medicinal use in man by indigenous groups.

At Magdalena, rather than focus on psychedelics (controlled substances typically taken as single doses in a controlled environment), our goal is to identify effective, plant-based psychoactive drugs that are safe, can be taken at home, and can be used on a long-term basis.




Standardized uptake value from [18F]FDG-micro PETs (fluorodeoxyglucose positron emission tomography)

The frontal cortex is the area of the brain correlated with neuronal activity for many therapeutic indications including ADHD. As seen from these scans (vehicle has only the solution used to solubilize the plant extracts), comparisons with vehicle show stimulation of metabolism in the frontal cortex of the mouse brain.