



**Amarantus  
BioScience**

**Amarantus BioScience Holdings, Inc.**

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Ticker (Exchange)	AMBS (OTC)
Recent Price (09/05/2014)	\$0.11
52-week Range	\$0.04 – \$0.20
Shares Outstanding	~756.7 million
Market Capitalization	~\$83.2 million
Average 3-month Volume	10,188,400
Insider Ownership >5%	4.74%
Institutional Ownership	7.97%
EPS (Qtr. ended 06/30/2014)	(\$0.01)
Employees*	22

\* Includes 16 employees and 6 full-time consultants

**AMBS One-Year Stock Chart**



DEVELOPMENT PIPELINE		
DIAGNOSTIC DIVISION		
LymPro	Alzheimer's Disease	Phase 2b
NuroPro	Parkinson's Disease	Phase 2a
LymPro	TBI / CTE	Preclinical
THERAPEUTIC DIVISION		
Eltoprazine	Parkinson's LID	Phase 2b
Eltoprazine	ADHD	Phase 2b
MANF	Retinitis Pigmentosa	IND
MANF	Parkinson's Disease	IND
MANF	TBI / CTE	Preclinical

Source: Amarantus BioScience Holdings, Inc.

**Company Description**

Amarantus BioScience Holdings, Inc. (or "the Company") is a clinical-stage biopharmaceutical company developing diagnostic and therapeutic products to treat diseases related to **neurodegeneration†** and abnormal **apoptosis** (cell death). The Company's initial focus is on **Alzheimer's disease (AD)** and **Parkinson's disease (PD)**. Its pipeline includes an exclusive worldwide license to the Lymphocyte Proliferation Test (the LymPro Test®), a diagnostic blood platform for AD that could be the first of its kind to reach the market. In PD, the Company aims to enable earlier and better diagnoses using its blood-based NuroPro test. As well, Amarantus holds a license to Eltoprazine, a Phase 2b-ready therapeutic to treat the debilitating side effects of existing Parkinson's treatments, known as **Levodopa-Induced Dyskinesia (PD-LID)**. Eltoprazine's clinical data to date may also position it to treat **Adult Attention Deficit Hyperactivity Disorder (Adult ADHD)**. Amarantus is further building a global intellectual property position around Mesencephalic-Astrocyte-derived Neurotrophic Factor (MANF), a therapeutic protein with potential in **orphan diseases** that, today, lead to incurable blindness in patients, in addition to potential for other indications. The Company is located at Janssen Labs @QB3, a subsidiary of Johnson & Johnson that acts as an incubator for companies of interest to J&J's core positions.

**Key Points**

- Alzheimer's disease (AD) is a major field for healthcare research, with nearly 130 AD trials ongoing or recently completed in the U.S. alone. This is likely due to the disease's considerable unmet needs: it is the only one of the top 10 causes of deaths in the U.S. that cannot yet be prevented, cured, or slowed.
- Amarantus aims to launch the LymPro Test® for AD in the U.S. in the fourth quarter of 2014 as a **Laboratory Developed Test (LDT)**. By distinguishing between an AD patient and a patient with another form of **dementia**, the Company's assay could become a valuable tool used by clinical researchers. AD trials have a history of patient recruitment errors stemming from inaccurate dementia diagnoses.
- During 2014, the Company plans to commence a Phase 2b trial of Eltoprazine for PD-LID patients, and is preparing to file an Orphan Drug Designation and subsequent **Investigational New Drug (IND)** application with the FDA for MANF.
- Amarantus has recently strengthened its management team, hiring individuals who can position the Company's products within the competitive landscape and help build a global biotechnology holding company to bring assets through the development process.
- The Company is also a Founding Member of the **Coalition for Concussion Treatment (#C4CT)**, a program initiated in collaboration with Brewer Sports International to raise awareness of treatments in development for concussions and nervous system disorders.
- At June 30, 2014, Amarantus had cash and cash equivalents of approximately \$1.4 million, as well as access to an additional \$19.6 million of equity capital under a financing facility.



## Table of Contents

Investor Highlights .....	3
Executive Overview .....	5
Milestones .....	10
Intellectual Property.....	12
Licenses Agreements and Partnerships.....	13
Leadership .....	17
Core Story .....	23
Diagnostics .....	24
Therapeutics.....	33
Potential Competition .....	47
Financial Highlights.....	51
Historical Financial Results .....	52
Recent Events .....	56
Risks and Disclosures .....	60
Glossary .....	68



## Investor Highlights

- Amarantus BioScience Holdings, Inc. is a clinical-stage diagnostics and therapeutics company focused on diseases associated with neurodegeneration and **protein misfolding-related apoptosis**. The Company is building a portfolio across multiple indications and sectors in order to mitigate risk while still leaving significant potential upside in any one or all of its product candidates.
- The Company's lead and most advanced program is a blood diagnostic test for Alzheimer's disease (AD), called the Lymphocyte Proliferation Test (the LymPro Test®). Being able to differentiate AD early on in individuals with dementia—specifically AD versus those with another type of dementia, for example **frontotemporal dementia (FTD)**, Parkinson's disease (PD) dementia, **vascular dementia**, etc.—is a critical component in the diagnostic process. Amarantus believes that it can add significant value in this area, initially and specifically, within the context of patient selection for clinical trials. To date, data has been published in peer-reviewed publications on the LymPro Test®, demonstrating an overall 95% accuracy rating in 160 patients.
  - The Company is currently looking at a retrospective, prognostic patient record clinical study, where data that was produced in 2005 is now being examined. Patients are being evaluated at the present time in order to study how they have progressed over a nine-year period—data the Company believes could prove to be valuable in positioning the LymPro Test® going forward.
  - Amarantus anticipates being able to bring the LymPro Test® to market as a Laboratory Developed Test (LDT) under the **Clinical Laboratory Improvement Amendments (CLIA)** in the U.S. within the fourth quarter of 2014. The assay could have considerable utility in AD clinical trials due to a well-documented history of patient recruitment errors stemming from inaccurate AD diagnoses using earlier methods. The ultimate goal is to gain approval as a companion diagnostic paired with a therapeutic in treating AD. On September 2, 2014, the Company announced the initiation of CLIA-enabling studies at ICON Central Laboratories, a CLIA-certified laboratory that will serve as the facility that carries out the LymPro assay for CLIA launch. As well, the LymPro Test® is in preclinical development for **traumatic brain injury (TBI)/chronic traumatic encephalopathy (CTE)**.
  - The Company continues to make progress regarding the reimbursement strategy for broad-scale use, which could bring greater leverage for future potential partnership discussions. Amarantus believes that it has identified **Current Procedural Terminology (CPT)** codes relating to cell cycle dysfunction and AD that could facilitate reimbursement under CLIA or commercial sale—potentially providing a major competitive advantage.
  - Roughly 5.4 million U.S. individuals suffer from AD and over 500,000 are newly diagnosed each year (one in eight older Americans), with the disease being the third leading cause of death in the U.S. Costs for AD are likely to exceed \$1.4 trillion by 2050. Between 2000 and 2010, deaths from AD increased 66% while deaths from other major diseases decreased, with it being the only cause of death among the top 10 in the U.S. that cannot be prevented, cured, or slowed. Amarantus believes the market opportunity for an effective blood diagnostic for AD, such as its LymPro Test®, could surpass \$500 million per year in the U.S.
- Eltoprazine, a Phase 2b-ready **5-HT1a/1b partial agonist**, was in-licensed from PGI Drug Discovery LLC (formerly PsychoGenics Inc.) in January 2014. The lead indications under development for this compound are Parkinson's disease Levodopa-Induced Dyskinesia (PD-LID), a condition linked to the PD medication levodopa, as well as for Adult Attention Deficit Hyperactivity Disorder (ADHD). To date, over 700 patients have been dosed with Eltoprazine at varying doses as high as 30mg, noting that the active dose in both PD-LID and Adult ADHD is 5mg. Primary and secondary endpoints have been met in Phase 2 trials for both PD-LID and Adult ADHD. Amarantus is now sourcing contract manufacturers for clinical-grade material and establishing study designs with the European Medicines Agency (EMA) and with the U.S. FDA for the initiation of Amarantus' next clinical studies, for which Phase 2b is expected to begin in 2014.



- In 2012, the Michael J. Fox Foundation (MJFF) funded human clinical proof-of-concept studies with Eltoprazine. As well, the National Institutes of Mental Health (NIMH) in Cognitive Impairment Associated with Schizophrenia (CIAS) funded work on Eltoprazine. Statistically significant effects were seen in clinical data from Adult ADHD patients.
- Mesencephalic-Astrocyte-derived Neurotrophic Factor (MANF), a preclinical program, is a therapeutic protein being developed for **Retinitis Pigmentosa (RP)** and other orphan diseases, as well as PD, Alzheimer's disease, **Wolfram's Syndrome**, diabetes, and ischemic heart disease. Amarantus is currently working toward filing an Investigational New Drug (IND) Application with the FDA for MANF. Functional experiments are ongoing at the University of Miami Bascom Palmer Eye Institute, which has been *U.S. News & World Report's* top-ranking hospital in ophthalmology for over a decade.
  - Amarantus is preparing to engage with the FDA's Office for Orphan Products Development to initially develop the compound as a disease-modifying treatment for RP—an inherited, degenerative eye disease that causes severe vision impairment and often blindness by age 40. The Company has made a strategic decision to focus development in orphan indications and is leveraging data assembled internally by a number of contract research organizations (CROs), and by academic collaborators, such as the Buck Institute for Research on Aging, the University of Massachusetts Medical School, and the University of Miami.
- During 2014, the Company considerably expanded its management team and Board of Advisors. In February 2014, the Company appointed Mr. Kerry Segal as head of business development and Ms. Tiffini Clark as head of regulatory affairs. In March 2014, Dr. Louis Kirby, a board-certified neurologist and a specialist in developing drugs, medical devices, and laboratory developed diagnostics, joined the Board of Advisors, assisting Amarantus' LymPro Test® efforts. In April 2014, Amarantus hired Dr. Charlotte Keywood as chief medical officer (CMO) of the therapeutics division, bringing her experience in developing drugs for PD-LID, as well as brought on Mr. Robert Farrell as chief financial officer (CFO), prior CFO of Titan Pharmaceuticals Inc., Sanovas Inc., One World Health, and Fresenius USA. Biographies for these individuals, and the remaining executive management team and Board of Directors at Amarantus, are provided on pages 17-22.
- For the next 12 months, Amarantus intends to focus primarily on the following goals: (1) the commercialization of the LymPro Test®; (2) further clinical development of Eltoprazine; and (3) preclinical development of MANF. The Company has worked to improve its cash position, access to capital, and balance sheet with a goal of listing to a national exchange. At June 30, 2014, the Company had cash and cash equivalents of approximately \$1.4 million and access to an additional \$19.6 million of equity capital available under a financing facility with Lincoln Park Capital Fund, LLC.

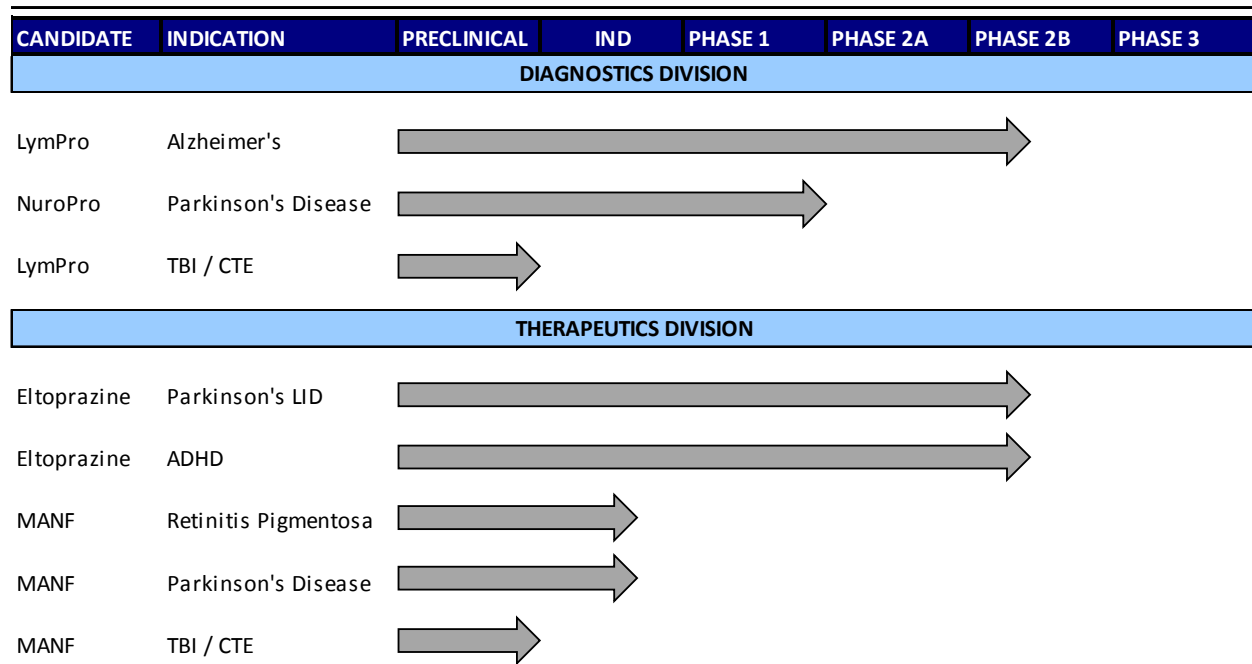


## Executive Overview

Amarantus BioScience Holdings, Inc. (“Amarantus” or “the Company”) is a San Francisco-based biopharmaceutical company developing intellectual property and proprietary technologies to create product candidates that treat human disease linked to neurodegeneration and abnormal apoptosis (programmed cell death). The Company owns or has exclusive licenses in multiple disease areas, with an initial focus on Alzheimer’s disease (AD), Parkinson’s disease Levodopa-Induced Dyskinesia (PD-LID), Adult Attention Deficit Hyperactivity Disorder (Adult ADHD), Retinitis Pigmentosa (RP), Wolfram’s Syndrome, and other conditions largely connected to the nervous system. The Company seeks to develop its product candidates through key milestones (such as those outlined under Milestones, page 10-11), then seek partnerships with biopharmaceutical companies, diagnostic companies, private foundations, and other respective key participants in specific sub-sectors of the healthcare industry to achieve regulatory approval in key jurisdictions, and subsequently market and distribute these products.

The Company’s most advanced development candidate, the Lymphocyte Proliferation Test (the LymPro Test®), is a unique blood diagnostic test for AD, which is expected to launch in the U.S. in the fourth quarter of 2014 as a Laboratory Developed Test (LDT) under the Clinical Laboratory Improvement Amendments (CLIA). Early diagnosis and differentiation of AD versus other types of dementia is critical to diagnosing the disease, especially when selecting patients for clinical trials. Eltoprazine, a Phase 2b-ready candidate, is targeting PD-LID, a form of dyskinesia associated with a well-known marketed PD drug, levodopa. Eltoprazine is also in development for Adult ADHD—a mental health condition characterized by difficulty maintaining attention as well as hyperactivity and impulsive behavior. The Mesencephalic-Astrocyte-derived Neurotrophic Factor (MANF) is in development to treat disorders like Retinitis Pigmentosa (RP), Parkinson’s disease (PD), and traumatic brain injury (TBI)/chronic traumatic encephalopathy (CTE), among other conditions. Each of the diagnostic and therapeutic development programs underway at Amarantus (summarized in Figure 1) are described in brief in accompanying section, with greater details provided within the Core Story (pages 23-46), followed by key specifics of the respective disease or condition being addressed.

Figure 1  
DEVELOPMENT PIPELINE



Source: Amarantus BioScience Holdings, Inc.

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## DIAGNOSTICS

### The LymPro Test®

The Lymphocyte Proliferation Test (the LymPro Test®) is a diagnostic blood test for mild-to-moderate AD. Being able to diagnose patients early on in their disease and differentiate among those individuals who have dementia (the AD type) versus people who have other types of dementia is a critical component in the diagnostic process, and is specifically where Amarantus believes it could provide significant value. To this end, there is a well-documented history of clinical trials for AD that have suffered due to errors in patient recruitment caused by not being able to adequately distinguish AD patients from patients with other forms of dementia. Amarantus' LymPro Test® could change this dynamic by offering researchers a better diagnostic option for their AD trials.

The scientific basis for the LymPro Test® is that AD patients have dysfunctional cellular machinery that incorrectly allows mature neurons in the brain to go into the **mitotic process** (cell division/cell cycle)—with neurons beginning the cell division process but not being able to complete it. Consequently, a number of **cytokines** and other genes are upregulated, ultimately leading to cell death via apoptosis. This incorrect cell division activation process is also present in the lymphocytes of AD patients, as lymphocytes share similar cellular division machinery with brain neurons. The LymPro Test® measures the integrity of this cellular division machinery process by calculating **CD69** upregulation in response to the **mitogenic stimulation**. If CD69 is upregulated, it means that the cellular division machinery process is correct and AD is not present. If CD69 is not upregulated, it means there is a dysfunctional cellular division machinery process and AD is more likely. Data has been published in peer-reviewed publications on the LymPro Test® with 160 patients, with an overall accuracy rating of 95%.

The Company intends to commercialize the LymPro Test® in the U.S. under the CLIA in the fourth quarter of 2014. On September 2, 2014, the Company announced the initiation of CLIA-enabling studies at ICON Central Laboratories, a CLIA-certified laboratory that will serve as the facility that carries out the LymPro assay for CLIA launch. Amarantus expects to assess its possibilities with respect to ex-U.S. commercialization of the LymPro Test® as well as ultimate FDA approval and marketing in the U.S., with the assay currently being developed at Becton, Dickinson, and Co. Amarantus is actively looking for the appropriate partner to develop this assay commercially for use as it works toward establishing a commercial supply chain following commercialization. Of note is that the LymPro Test® is also in preclinical development for traumatic brain injury (TBI)/chronic traumatic encephalopathy (CTE).

### *Alzheimer's Disease (AD)*

AD is the most common form of dementia—a general term for memory loss and loss of other intellectual abilities serious enough to interfere with an individual's daily life—causing problems with memory, thinking, and behavior. In its early stages, memory loss is mild; however, late-stage AD patients lose their ability to carry on a conversation and respond to their environment. While not a normal part of aging, the greatest known risk factor for AD is increasing age. The majority of individuals with AD are aged 65 and older and live an average of eight years after symptoms become noticeable to others. Survival can range from 4 to 20 years, depending on age and other health conditions.

Worldwide, more than 35 million people have AD or similar dementia. In the U.S., about 5.4 million individuals (one in eight people) over the age of 65 currently live with the disease—with about 500,000 new diagnoses occurring each year—and only half of these people having an actual physician diagnosis. With no cure, there are only treatments for the symptoms of AD, and while treatments cannot stop the disease from progressing, they can temporarily slow the worsening of dementia symptoms and improve quality of life. Development efforts are focused on discovering better ways to treat the disease, delay its onset, and prevent its progression.

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## NuroPro and PhenoGuard

Amarantus is also developing the NuroPro blood test, which entails a diagnostic platform for the early detection of neurodegenerative diseases. The test is being developed as a tool to help physicians more precisely diagnose disease and monitor progression. The diagnostic platform involves monitoring the concentration of 57 protein markers in blood serum linked to neurodegeneration in order to accurately detect and distinguish between AD, **ALS (Lou Gehrig's disease)**, and PD. The Company's license is also focused on developing a subset of 21 of these protein markers specifically targeting early diagnosis and ongoing monitoring of PD.

Amarantus additionally expects to begin exploring its PhenoGuard platform for **neurotrophic factor** discovery and to evaluate additional external in-licensure or acquisition drug candidates. PhenoGuard may enable Amarantus' scientists to rapidly discover novel secreted human proteins with biological activity for specific indications using the PhenoGuard cell line library and highly sensitive target validation cell culture systems, which are designed to provide accurate results and could enable scientists to make more informed decisions.

## THERAPEUTICS

### Eltoprazine

Eltoprazine is being developed to treat the primary side effects from Parkinson's Levodopa-Induced Dyskinesia (PD-LID), a condition linked to PD medication levodopa, as well as Adult ADHD. A small molecule drug candidate, Eltoprazine is a **selective partial agonist** on the 5-HT<sub>1a/1b</sub> receptors of the **serotonergic system** in the brain (with the serotonergic system linked to a wide range of motor and behavioral disorders, including aggression, cognition, attention, and control). Over 700 patients to date have been given Eltoprazine at varying doses as high as 30mg, with the active dose in both PD-LID and Adult ADHD being 5mg. Primary and secondary endpoints have been met in Phase 2 trials for both PD-LID and Adult ADHD, with the drug being well tolerated during the study and no serious adverse events reported. The Company intends to initiate Phase 2 or Phase 3 clinical studies for Eltoprazine in the areas of PD-LID and Adult ADHD in 2014, is sourcing contract manufacturers for clinical-grade material, and is establishing study designs to begin the next clinical studies. As well, Amarantus has put in place the necessary vendors to comply with global regulatory standards.

#### *PD-LID*

PD treatment was revolutionized in the 1960s by the introduction of levodopa. Following its discovery, however, patients undergoing continuous treatment reported complications seen in the emergence of **choreoathetoid movements** and off episodes. Levodopa-Induced Dyskinesia (LID) is characterized by a variety of **hyperkinetic movements**, and while **chorea** (abnormal involuntary movement) and **dystonia** (involuntary muscle contractions) are the most common, **stereotypies**, tics, **myoclonus**, or **ballism** may also occur. LID typically begins in the lower extremity **ipsilateral** (occurring on the same side of the body) to the side first affected by PD. In the beginning, patients may not notice subtle hyperkinetic movements; though, as it progresses, LID may interfere with activities, leading to functional impairment, disability, and poor quality of life. The risk for developing LID has been linked to the disease's severity, younger age of onset, female sex, duration of levodopa treatment, and total levodopa exposure. A literature survey of more than 2,000 publications identified LID in roughly 40% of PD patients treated with levodopa for four to six years. An alternative review found a prevalence of LID in up to 85% of patients with PD (noting that different methods to recognize LID have resulted in disparities in its frequency rate [as reported in literature]).

The current standard of care for LID is amantadine, which is believed to work reasonably well but carries a number of side effect profile issues as well as **pharmacokinetic** issues—thus, it is not ideal. Amantadine extended release, sold by Adamas Pharmaceuticals (profiled on page 47), has achieved improved pharmacokinetics though it still carries significant side effects. As a result, there remains a significant unmet medical need with an extended release amantadine, which Amarantus believes that its development candidate, Eltoprazine, may satisfy.



## ADHD

ADHD is a psychiatric disorder of the **neurodevelopmental** type (impairments of the growth and development of the brain or central nervous system), where there are significant problems of attention, hyperactivity, or acting impulsively that are not appropriate based on a person's age. Symptoms of ADHD include difficulty staying focused and paying attention, difficulty controlling behavior, and hyperactivity (over-activity). As one of the most common childhood disorders, ADHD can continue through adolescence and adulthood with roughly 7.8% of all U.S. school-age children, or about 4.4 million children aged 4 to 17 years, diagnosed at some point in their lives (Source: U.S. Centers for Disease Control and Prevention [CDC]). In addition, over eight million U.S. adults have exhibited symptoms of ADHD, with only about 600,000 receiving treatment. Adult ADHD is marked by difficulty maintaining attention, as well as hyperactivity and impulsive behavior, which can lead to a number of problems, including unstable relationships, poor work or school performance, and low self-esteem.

While there is no cure, treatments for ADHD can relieve many of the symptoms and improve functionality via medications, various types of psychotherapy, education or training, or a combination of these. More effective treatments and interventions are being developed as well as new tools such as brain imaging that can better understand or help discover better ways to treat or perhaps one day prevent ADHD. That said, with roughly 35 million prescriptions written annually and a market valued at over \$3.5 billion for ADHD treatments (expected to reach \$6.26 billion by 2018), there is a tremendous need for more effective non-stimulant therapies (Source: CompaniesandMarkets.com, June 2013).

## MANF

Discovered by the Company's chief scientific officer Dr. John Commissiong (biography on page 18), Mesencephalic Astrocyte-derived Neurotrophic Factor (MANF) is in preclinical development to treat several apoptosis (cell death)-related disorders, including Retinitis Pigmentosa (RP) as well as PD, Wolfram's Syndrome, diabetes, ischemic heart disease, and TBI/CTE. As an endogenous, highly conserved, widely expressed, and highly potent secreted human growth factor up-regulated in the adaptive pathway of the unfolded protein response, MANF has been able to mediate this critical biological process and thus may prove effective in treating these poorly served medical conditions. As a new family of neurotrophic factors, MANF's mechanisms of action are fundamentally differentiated from its predecessors.

Initially, orphan indications such as RP could provide Amarantus with an opportunity to reach the market in a more expeditious timeframe. Of note is that while Amarantus is not currently developing MANF for AD, it is possible that cost-effective definitive identification of earlier-stage patients could create an opportunity for the Company to evaluate its MANF program as a disease-modifying treatment for this therapeutic indication as well. The Company is currently implementing plans for the IND and expects to have information on this in the near term.

## Founding Member of the Coalition for Concussion Treatment (#C4CT) (Brewer Sports International)

Amarantus is a Founding Member of the Coalition for Concussion Treatment (#C4CT), a movement initiated in collaboration with Brewer Sports International (BSI) seeking to raise awareness of new treatments in development for concussions and nervous-system disorders. The companies to date have hosted three conferences—most recently this past July 2014 at the United Nations in New York—to bring key stakeholders in the field of TBI together to discuss important issues.

Brewer Sports International is a multi-faceted global sports advisory firm within The Brewer Group Companies, focused within sports, wellness, and media for professional athletes, sports agencies, public and private corporations, international organizations, governments, and non-governmental agencies (NGOs). Brewer Sports International was founded by Jack Brewer, a five-year National Football League (NFL) veteran and former team captain on three NFL teams. As well, Brewer Sports has created a unique financial services platform that is offered to professional athletes and sports agencies, and high net worth individuals as well as to businesses touching professional sports.



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## **Employees, Headquarters, Facilities, and Infrastructure**

In August 2014, the Company relocated its principal offices to larger space at 655 Montgomery Street in San Francisco, California. The Company is leasing approximately 5,700 square feet of office space at this location. In addition, Amarantus is continuing to lease office and laboratory space from Janssen Labs @QB3, a San Francisco-based subsidiary of Johnson & Johnson, located at 953 Indiana Street in San Francisco. The Company anticipates leasing additional space at this location as it increases the number of its personnel engaged in research and development activities.

As well, in June 2014, the Company announced that it had opened an office in Geneva, Switzerland, in preparation for the establishment of a Swiss affiliate. This office positions the Company near Swiss neuroscience- and life science-focused programs and initiatives, such as the Human Brain Project (HBP) and Campus Biotech. HBP is part of the Future and Emerging Technologies Flagship Program, a new program launched by the European Commission, and it was recently announced that the HBP research expects were to move to the Campus Biotech site in Geneva. As of August 2014, the Company had six employees and full-time consultants in its Geneva office, and anticipates expanding its management team and support staff at this location over the next 12 months.

## **Warrant Solicitation and Access to Capital**

On March 10, 2014, Amarantus announced that it had closed a previously announced Warrant Solicitation, which the Company elected to increase in size to \$3.6 million from \$3 million due to oversubscriptions. The total proceeds from the transaction were received by the Company in the first quarter of 2014. As well, on March 7, 2014, the Company signed a \$20 million purchase agreement with Lincoln Park Capital Fund, LLC (LPC), under which LPC agreed to purchase 4,000,000 shares of Amarantus' common stock for \$400,000 as an initial purchase. Amarantus has the right over a 30-month period to sell up to an additional \$19.6 million of its common stock to LPC in amounts of up to \$500,000 per sale, depending on certain conditions as set forth in the purchase agreement. The capital raised through this Warrant Solicitation and the access to capital from LPC offers Amarantus tremendous flexibility to be able to achieve a number of key milestones, including the commercialization of the LymPro Test<sup>®</sup> for AD, advancing the clinical testing of Eltoprazine into late-stage development, and filing one or more IND applications to the FDA for MANF in orphan indications.

## **Current Capitalization Structure**

As of June 30, 2014, the Company had approximately 757 million common shares outstanding. During the quarter, Amarantus issued additional common shares, primarily upon the exercise of warrants, that raised approximately \$1.2 million, and may issue up to 45 million additional common shares upon the exercise of warrants that are priced at \$0.12 (which the Company can force under certain equity conditions), and which could raise approximately \$5.4 million to fund ongoing operations. Amarantus may issue up to 76 million additional shares under its equity funding facility with LPC, under which Amarantus could raise a maximum of \$19.6 million of additional capital to fund ongoing operations, subject to certain conditions. With the warrants and the LPC equity funding facility, Amarantus has approximately \$25 million in additional funding available, which the Company believes could fund operations into 2016 (noting there is no assurance that the warrants will be exercised or that the Company will be able to fully draw from the LPC facility).



## Milestones

Amarantus is focused on formulating and advancing preclinical and clinical programs for product candidates through successive milestones with a goal of minimizing risk and maximizing commercial potential. The Company is also focused on creating attractive partnering targets among product-development-focused biotechnology, pharmaceutical, medical device, and diagnostic companies for its development candidates. Below outlines some of the recent corporate and product milestones that have been achieved, followed by those which the Company expects it could achieve over the upcoming year.

### Recent Milestones

#### *Corporate*

Amarantus has experienced significant transformation and growth during the first half of 2014 in a number of important areas, as highlighted below.

- Expanded its management team, as the Company continues to build a global biotechnology holding company with the ability to strategically bring assets through the development process (biographies on pages 17-22)
- Improved its cash position, access to capital, and balance sheet as the Company positions itself to list its common stock on a national exchange
- Completed warrant solicitation of \$3.6 million
- Entered into a \$20 million purchase agreement with Lincoln Park Capital (LPC) Fund
- Attended the 3<sup>rd</sup> #C4CT Alzheimer's-Focused Concussion Awareness Summit in July 2014, with international participation from Key Opinion Leading (KOLs) scientists, policy makers, caregivers, family offices, and others to share ideas, promote policy changes, and foster cross-border collaborations in seeking to create better outcomes for those affected by injuries and diseases of the brain

#### *Product Development*

##### The LymPro Test<sup>®</sup>

- Established a LymPro research collaboration with the Boston University School of Medicine
- Announced positive interim clinical performance data showing that Amarantus had replicated two earlier peer-reviewed publications, which was the primary objective of the study
- Announced the initiation of CLIA-enabling studies at ICON Central Laboratories, a CLIA-certified laboratory that will serve as the facility that carries out the LymPro assay for CLIA launch

##### Eltoprazine

- In-licensed Eltoprazine for Parkinson's Levodopa-Induced Dyskinesia (PD-LID)
- Announced positive Phase 2a data for Eltoprazine in PD-LID
- Announced positive Phase 2a data for Eltoprazine in Adult ADHD



## MANF

- Acquired an exclusive option to license intellectual property for use of MANF and conserved dopamine neurotrophic factor (CDNF)—two newly identified growth factors that are naturally produced by the brain—to treat antibiotic-induced ototoxicity
- Entered a research collaboration with the Buck Institute for Research on Aging for MANF development

## **Potential Milestones**

Amarantus is focused on achieving the following key milestones and delivering value from its current asset pipeline. The Company is opportunistic as it relates to strategically adding to its pipeline stemming from its current relationships, as detailed under License Agreements and Partnerships on pages 13-16.

### *Corporate*

- Listing its common shares on a national stock exchange (e.g., NASDAQ or NYSE)
- Working to establish appropriate channels for scientific and clinical development, and for financial partnerships that could provide near- and long-term value creation across multiple fronts

### *Product Development*

#### The LymPro Test®

- Clinical performance data (3Q-14)
- Clinical performance studies to support CLIA registration (2H-14)
- Analytical performance package to support CLIA launch (4Q-14)
- CLIA submission (4Q-14)
- CLIA launch (4Q-14)
- Potential partnership agreement after the completion of the LP-002 study, where the Company is weighing strategic options, including a potential spin-off of the diagnostics division

#### Etoprozine

- Initiate Phase 2b clinical trial for PD-L1D (4Q-14)

## MANF

- Functional genetic mouse model for Retinitis Pigmentosa (RP) (2H-14)
- Filing of **Orphan Drug Designation (ODD)** in RP (4Q-14)
- Wolfram's Syndrome Retinal Data (4Q-14)
- **Convection enhanced delivery (CED)** data with Renishaw plc (a global company with core skills in measurement, motion control, spectroscopy, and precision machining, as described on page 45) in PD (4Q-14)
- Preliminary systemic toxicology (4Q-14)
- Initiation of Good Manufacturing Practices (GMP) manufacturing to prepare for first-in-man studies (4Q-14)

## Intellectual Property

Amarantus employs a combination of licenses, patents, trade secrets, and confidentiality agreements to protect its assets. Where information has been made available, these are described below, and are highlighted in Figure 2.

### Patents

Amarantus seeks to build a competitive advantage in MANF intellectual property, such that other scientists from around the world (who are also currently working on MANF development) would be attracted to collaborate with the Company on broader clinical and commercial opportunities. Importantly, the Company successfully defended its key composition of matter patents for MANF in Europe during 2012. Amarantus also holds method of use patents for MANF in neurology as well as exclusive license options to intellectual property for MANF and CDFN in the following additional therapeutic areas: (1) retinal degeneration; (2) beta cell degeneration-related disorders (including diabetes and Wolfram's Syndrome); and (3) beta cell degeneration biomarker identification. Figure 2 summarizes the global jurisdictions where Amarantus pursues intellectual property protections through national-level patents as well as under the Patent Cooperation Treaty (PCT).

Figure 2  
 INTELLECTUAL PROPERTY SNAPSHOT

COUNTRY	APPLICATION NUMBER	FILING DATE	PATENT NUMBER	ISSUE DATE
<b>DOPAMINERGIC NEURONAL SURVIVAL-PROMOTING FACTORS AND USES THEREOF</b>				
Patent Cooperation Treaty (PCT)	CA2002/00373	20-Mar-2002		
Belgium	02706572.1	20-Mar-2002	1373502	20-Oct-2010
Denmark	02706572.1	20-Mar-2002	1373502	20-Oct-2010
European (EP)	02706572.1	20-Mar-2002	1373502	20-Oct-2010
Finland	02706572.1	20-Mar-2002	1373502	20-Oct-2010
France	02706572.1	20-Mar-2002	1373502	20-Oct-2010
Germany	02706572.1	20-Mar-2002	60238038.3	20-Oct-2010
Ireland	02706572.1	20-Mar-2002	1373502	20-Oct-2010
Italy	02706572.1	20-Mar-2002	47601BE2011	20-Oct-2010
Netherlands	02706572.1	20-Mar-2002	1373502	20-Oct-2010
Spain	02706572.1	20-Mar-2002	1373502	20-Oct-2010
Sweden	02706572.1	20-Mar-2002	1373502	20-Oct-2010
Switzerland	02706572.1	20-Mar-2002	1373502	20-Oct-2010
United Kingdom	02706572.1	20-Mar-2002	1373502	20-Oct-2010
U.S.	12/535,029	04-Aug-2009	8,084,425	27-Dec-2011
U.S.	13/305,025	28-Nov-2011		
<b>NEURODEGENERATIVE DISORDERS</b>				
Brazil	PI0909221-8	25-Mar-2009		
Canada	2,719,582	25-Mar-2009		
China (People's Republic)	200980116306.0	25-Mar-2009		
European Patent Convention	09724166.5	25-Mar-2009		
India	7434/DELNP/2010	25-Mar-2009		
Japan	2011-502031	25-Mar-2009		
U.S.	12/934,454	14-Mar-2011		
<b>BRAIN TARGETS FOR NEUROTROPHIC FACTORS TO TREAT NEURODEGENERATIVE DISEASE</b>				
PCT	PCT/US2013/066688	24-Oct-2013		

Source: Amarantus BioScience Holdings, Inc.



## Licenses Agreements and Partnerships

Amarantus is developing technologies that it believes could have application across multiple therapeutic categories and provide for unique development opportunities. In an effort to maximize such opportunities, the Company has either partnered, or has plans to partner, for product development with leading academic institutions, research institutes, hospitals, clinics, and small- to large-scale biotechnology, pharmaceutical, diagnostic, and device companies. Specifically, Amarantus is focused on creating partnerships that would allow for the development of adjunct products for diseases caused by poorly served biological pathways. Details of these license agreements and partnerships, where information has been made publically available, are provided below.

### **ICON Central Laboratories**

On September 2, 2014, Amarantus announced that it had entered into a Master Services Agreement with ICON Central Laboratories, a division of ICON PLC, for global therapeutic and diagnostic clinical development services. The Company has submitted an initial work order to ICON for delivery of the Fit for Purpose Flow Cytometry Assay Validation of the LymPro Test<sup>®</sup> at ICON's CLIA-certified central laboratory facility in Farmingdale, New York. ICON offers central laboratory testing and biomarker services to the biopharmaceutical industry and has central laboratories and support staff in the U.S., Ireland, Singapore, China, and India. With this agreement, Amarantus can prepare the LymPro Test<sup>®</sup> for launch with a commercial development organization, since there is now the required CLIA capabilities as the backbone for launch in the U.S. and abroad. The Fit for Purpose Flow Cytometry Assay Validation is the Analytical Performance Package (APP) that could prove to be the critical set of experiments demonstrating that the LymPro Test<sup>®</sup> is a reproducible commercial-grade test.

Under this arrangement, Amarantus maintains all intellectual property rights to current and future versions of the LymPro Test<sup>®</sup> at the current time and sets the foundation for the CLIA process as the ongoing LP-002 clinical study progresses, as well as positions ICON in a subcontractor relationship with the LymPro Test<sup>®</sup>. ICON is to provide central laboratory services to Amarantus in a fee-for-service arrangement (ICON's primary business model). The agreement extends over four years and covers the central laboratory requirements for the LymPro Test<sup>®</sup> under CLIA (as under CLIA, only one laboratory facility can run a Laboratory Developed Test). As well, the agreement is to provide for consulting support for further clinical development for Eltoprazine and MANF. Importantly, under the ICON agreement, Amarantus further gains access to a global distribution network for the LymPro Test<sup>®</sup>, including central laboratories in Europe, Singapore, India, and China, which could allow the LymPro Test<sup>®</sup> to enter these new markets via an established distribution framework.

### **Memory Dx, LLC (MDx)**

In December 2012, Amarantus entered into an exclusive license agreement with Memory Dx, LLC (MDx), under which MDx granted to the Company an exclusive worldwide license to develop, manufacture, market, sell, and import medical devices under MDx's intellectual property pertaining to AD diagnosis. As consideration for the license, in March 2013, Amarantus issued two million shares of its common stock at \$0.0395 per share to MDx and is to pay MDx a royalty equal to 9% of the net proceeds of all sales stemming from the license. Moreover, MDx, alongside Amarantus, is expected to complete a validation study of a blood test to detect AD.

In 2013, Amarantus paid MDx \$50,000 to prepare the laboratory for this study. Amarantus may sell, sub-license, or assign the license agreement, with an option to terminate upon 30 days written notice if MDx is unable to meet its obligations of the validation study. In April 2014, this agreement was modified to include an additional payment of 1.5 million shares and \$150,000 in cash for the acquisition of Version 2 (V2) of the LymPro Test<sup>®</sup> and a contingent payment of 6.5 million shares in exchange for cancellation of all obligations due to MDx by Amarantus upon a direct license being executed between Amarantus and the University of Leipzig (provided Amarantus can enter into a direct license for the LymPro assets itself from the University of Leipzig). The University of Leipzig had previously licensed the LymPro technology to Memory Dx. As a result, financial terms on this asset are still a work in progress.

On August 1, 2014, Amarantus announced that it had entered into an exclusive option to license the intellectual property surrounding the therapeutic concepts of Dr. Thomas Arendt from the University of Leipzig, where Amarantus will have 12 months to analyze preclinical data from Dr. Arendt's lab, and potentially negotiate a licensing agreement.

#### **PsychoGenics Inc. (PGI Drug Discovery, LLC)**

In January 2014, Amarantus entered a License Agreement with PGI Drug Discovery, LLC (PsychoGenics Inc.), in which the Company was granted an exclusive license (with a right to sublicense) to utilize certain licensed compounds and licensed products of closely-held PsychoGenics, including certain intellectual property covering the use of Eltoprazine and certain of its related compounds in all therapeutic indications. Under this Agreement, Amarantus paid PsychoGenics \$100,000 in cash for the license; agreed to pay PsychoGenics up to an aggregate of \$4 million in development milestones through NDA submission; pay a research support payment to PsychoGenics as partial reimbursement for costs incurred for earlier research and management of CIAS, ADHD, and LID clinical trials totaling up to \$650,000 (to be paid in a mixture of cash and stock); and reimburse PsychoGenics for the Eltoprazine clinical supply inventory up to \$500,000, payable upon the earlier of the initiation of a Phase 2b clinical study or six months after the date of the license agreement.

As well, Amarantus is to pay a single-digit royalty to PsychoGenics of the annual worldwide aggregate net sales. In conjunction, Amarantus and PsychoGenics entered a services agreement where PsychoGenics is to provide certain services to Amarantus related to PsychoGenics's proprietary analytical systems (set forth in certain study plans). Amarantus agreed to a payment commitment of \$450,000 at a minimum annual rate of \$150,000 for each of three years. As partial consideration of the research support payment, Amarantus entered into a Securities Purchase Agreement with PsychoGenics, in which PsychoGenics subscribed to four million shares of Amarantus' common stock (with Amarantus granting PsychoGenics certain piggy-back registration rights).

PsychoGenics is a closely held, preclinical CNS service provider, whose employees (including approximately 30 Ph.D.'s) have expertise in the fields of psychopharmacology, behavior, molecular biology, and informatics. The company has over 160 repeat pharmaceutical, biotechnology, and not-for-profit, domestic and international clients, offering over 80 different behavioral tests to phenotype rodent disease models and test drug candidates in the areas of psychiatric and neurodegenerative disorders, pain and inflammation, and spinal cord and TBI. PsychoGenics' other capabilities include electrophysiology, molecular biology, neurogenesis, microdialysis, and a variety of in-licensed transgenic mouse models. This knowledge in preclinical neuropharmacology combined with the use of Amarantus' testing platforms has created a novel and powerful approach in discovering and developing product candidates.

#### **University of Massachusetts (UMass)**

In December 2013, Amarantus entered into a series of exclusive license agreements with the University of Massachusetts (UMass), providing the Company with certain technology and related patent rights and materials associated with MANF-based therapeutics as both a biomarker and treatment for beta cell degenerating disorders, including Wolframs syndrome, Type 1-, and Type 2 diabetes. Under the terms of the agreements, Amarantus pays license fees and specified development costs, and is required to pay royalties of 2% of net sales of products stemming from the licensed technologies, with the ability to terminate the agreement upon 90 days written notice.

In March 2014, the Company announced that it had entered into an exclusive option agreement with UMass to license the University's method of use intellectual property surrounding the use of MANF and conserved dopamine neurotrophic factor (CDNF) to treat antibiotic-induced ototoxicity. The option agreement includes all intellectual property covering the use of the MANF-family of proteins (MANF and CDFN) for antibiotic-induced ototoxicity and certain other ear disorders. Amarantus owns composition of matter patents and various composition and method of use patent applications for MANF and derivative sequences for protein therapeutic, gene therapy, and certain cell therapy applications. Antibiotic-induced ototoxicity has been associated with at least 18 marketed drugs to date, particularly **aminoglycosides**, where the incidence of ototoxicity is believed to be approximately 25% among users.



### **University of Miami**

In December 2013, Amarantus announced that it had entered into an exclusive option agreement with the University of Miami to license the Bascom Palmer Eye Institute's method of use intellectual property surrounding the use of MANF and CDFN in treating retinal diseases. The option agreement includes all intellectual property covering the use of the MANF-family of proteins (MANF and CDFN) for retinal diseases, including age-related macular degeneration, glaucoma, inherited retinal disorders (including RP), sporadic retinal disorders, other degenerative retinal disorders, and retinal injuries.

This option agreement follows previously announced positive data for MANF in the S334ter Type 3 genetic mouse model of RP. The Company owns composition of matter patents and various composition and method of use patent applications for MANF and derivative sequences for protein therapeutic, gene therapy, and certain cell therapy applications. In reprioritizing the Company's MANF pipeline towards orphan diseases, this agreement enables the Company to gain worldwide control of the patent prosecution process for both MANF and CDFN in this key set of indications. Data generated from this set of experiments using a highly relevant genetic mouse model of RP reproducibly demonstrates the neuroprotective activity of intravitreal MANF injection in protecting cellular degeneration—a key unmet need.

The Bascom Palmer Eye Institute at the University of Miami has been ranked No. 1 nationally in ophthalmology in *U.S. News & World Report's* annual "Best Hospitals" for 10 consecutive years. As the largest ophthalmic care, research and educational facility in the southeastern U.S., Bascom Palmer treats over 250,000 patients and performs over 13,000 surgeries annually. Its physicians and scientists are internationally recognized for specific expertise in every eye disorder, including glaucoma, macular degeneration, diabetic retinopathy, cataracts, dry eye, eye cancers, and eye diseases in children.

### **Provista Diagnostics, Inc.**

On May 1, 2014, Amarantus entered into an asset purchase agreement with Provista Diagnostics, Inc., in which Amarantus purchased certain assets of Provista related to a fluorescently activated cell sorter (FACS), including all right, title, and interest in the certain assets, equipment, software, and technology related to FACS, in exchange for a one-time cash payment of \$20,000 to Provista.

### **Power3 Medical License and Subsequent Asset Purchase for NuroPro and BC-SeraPro**

In 2012, Amarantus acquired a license and the intellectual property rights to two diagnostic blood test platforms, NuroPro and BC-SeraPro, from Power3 Medical Products, Inc. NuroPro is a neurodegenerative disease diagnostic platform (described on pages 31-32) with a lead application in PD. BC SeraPro is an oncology diagnostic platform with a lead application in breast cancer. In December 2012, Amarantus acquired all of the assets from the bankruptcy estate of Power3 Medical Products, Inc.

### **Banyan Biomarkers, Inc.**

Amarantus and Banyan Biomarkers are collaborating to evaluate the potential for MANF as a disease-modifying agent in treating traumatic brain injury (TBI). Banyan Biomarkers is believed to be a leader in developing *in vitro* diagnostic products to address unmet clinical needs for detecting TBI, such as developing a simple point-of-care blood test that could be used by physicians to detect the presence and severity of brain trauma and improve the medical management of head injured patients. Banyan Biomarkers has a licensing agreement with the University of Florida for exclusive global use of technology related to this product.



## **Brewer Sports International**

Amarantus and Brewer Sports International (BSI) are working together to advance the Coalition for Concussion Treatment (#C4CT). To date, the companies have hosted three conferences to bring key stakeholders in the field of TBI together to discuss important issues. BSI is a multi-faceted global sports advisory firm within The Brewer Group Companies, focused within sports, wellness, and media for professional athletes, sports agencies, public and private corporations, and various partners, such as international organizations, governments, and non-governmental agencies (NGOs).

Most recently, on July 31, 2014, Amarantus and Brewer Sports International held an Alzheimer's-focused summit as part of the #C4CT Concussion Awareness Summit at the United Nations in New York City. As part of the conference, Amarantus presented interim findings from a clinical trial, where two versions of the LymPro test were studied—an older version (V1), which was licensed from Provista Life Science, and a newer version (V2). Amarantus is currently looking to enroll 72 patients and to “bridge” the V1 and V2 data, as the AAIC and #C4CT data was from V1. Data from V2 may be available by the end of the third quarter.





## Leadership

In recent months, Amarantus has appointed skilled and experienced team members who are believed to possess the ability to properly position the Company's products (both diagnostic and therapeutic) among other companies within the competitive landscape. Specifically, Amarantus has added a new chief financial officer, a new chief medical officer, a head of business development, and head of regulatory affairs. Biographies of the key members of Amarantus' management team are included in the accompanying section, followed by the Company's Board of Directors and Board of Advisors. Worth noting is that two of the Company's officers and directors, Dr. John Commissiong and Mr. Gerald Commissiong, are father and son. To date, there are no other family relationships between or among the directors, executive officers, or persons nominated or chosen by the Company to become directors or executive officers.

## Management

Figure 3  
EXECUTIVE MANAGEMENT

Gerald E. Commissiong	President and Chief Executive Officer (CEO)
Robert Farrell, J.D.	Chief Financial Officer
Charlotte Keywood, M.D.	Chief Medical Officer, Therapeutics Division
John W. Commissiong, Ph.D.	Chief Scientific Officer
Marc E. Faerber	Corporate Controller and Vice President of Financial Operations
Kerry Segal	Head of Business Development
Tiffini Clark	Head of Operations and Regulatory Affairs
F. Randall Grimes	Head of Sponsored Research
Paul Jorgensen	Head of Diagnostics Product Development
Mark Wakefield	Head of Clinical Development

*Source: Amarantus BioScience Holdings, Inc.*

### *Gerald E. Commissiong, President and Chief Executive Officer (CEO)*

Mr. Commissiong is president, CEO, and a member of the Board of Directors of Amarantus, which he co-founded with Dr. John Commissiong, Ph.D. in 2008. From the inception of the Company, Mr. Commissiong attracted seed capital, acquired the intellectual property rights to MANF, and recruited scientific and executive talent to allow for the further development of the Company's technologies. Prior to his position as CEO in October 2011, Mr. Commissiong was the chief operating officer (COO), where he was responsible for strategic transactions, licensing, research collaborations, mergers and acquisitions, and fundraising. From August 2009 until March 2011, he served as chief business officer, where he was responsible for business and corporate development. Prior to co-founding Amarantus, Mr. Commissiong played professional football for the Calgary Stampeders of the Canadian Football League. Mr. Commissiong received a B.Sc. in management science and engineering with a focus on financial decisions from Stanford University.

### *Robert Farrell, J.D., Chief Financial Officer (CFO)*

Mr. Farrell is currently CFO for Amarantus, having served as CFO of Titan Pharmaceuticals from 1996 to 2008, and as president and CEO from 2008 to 2010. During his tenure at Titan, Mr. Farrell was responsible for all SEC filings, fundraising, financial and tax planning strategies, mergers and acquisitions (M&A), corporate partnerships, licensing transactions, and financial operations, where he raised over \$390 million via public equity and non-dilutive financings, including seven corporate partnerships. Mr. Farrell most recently served as CFO at Sanovas, Inc. He previously served as CFO, corporate group vice president and general counsel at Fresenius USA and Fresenius Medical Care, where he completed six corporate partnership and M&A transactions totaling over \$4 billion. Mr.



Farrell also previously served as the CFO for the Institute for One World Health in San Francisco and currently serves on the Board of Directors of Prime Genomics, Inc. Mr. Farrell holds a J.D. from the University of California's Hastings School of Law.

*Charlotte Keywood, M.D., Chief Medical Officer, Therapeutics Division*

Dr. Keywood's experience in the pharmaceutical industry includes running European and U.S. pre- and post-registration clinical development programs across a broad range of therapeutic areas, as well as medical marketing and pharmacovigilance activities. Most recently, she was CMO at Addex Pharma for 10 years, overseeing clinical development of the company's allosteric modulator programs. Dr. Keywood served from 2001 to 2003 as medical director for Axovan, a Swiss biotech company that was acquired by Actelion in 2003. From 1996 to 2001, she was medical director at Vernalis, where she helped bring a new migraine drug, Frova (Frovatriptan Succinate), to the market. From 1991 to 1996, she was medical director of the European subsidiary of U.S. biotechnology company Genesia. Dr. Keywood is a cardiologist who completed post-graduate training at St Thomas' Hospital, London.

*John W. Commissiong, Ph.D., Chief Scientific Officer (CSO)*

Dr. Commissiong has served as the CSO and a director of Amarantus since co-founding the company in 2008. Prior to Amarantus, Dr. Commissiong served as the CSO of Neurotophics, Inc. and Prescient Neuropharma, Inc. Throughout his career, Dr. Commissiong has been focused on the discovery of novel neurotrophic factors for the treatment of neurodegenerative diseases as well as understanding the fundamental underlying biology of protoplasmic type-1 astrocytes that secrete neurotrophic factors. He was chief of the Neural Transplantation Unit, NINDS-NIH, from 1989 to 1994 where his research focused on identifying therapeutic approaches to spinal cord injury. Dr. Commissiong was head of the Neurotrophic Factors Group, NINDS-NIH from 1994 to 1997, where he focused on developing technologies to systematically identify novel neurotrophic factors with applications for specific CNS disorders. He co-founded Prescient Neuropharma in 1999, and discovered MANF in 2003. The work pioneered by Dr. Commissiong has led to significant advancements in the field of astrocyte-neuron biology. Dr. Commissiong believes that a fundamental understanding of astrocyte-neuron interactions in the CNS may lead to a new generation of therapies to treat brain-related disorders. Dr. Commissiong did his postdoctoral work in the Lab Preclin Pharmac, NIMH-NIH, concentrating on the application of quadrupole mass spectrometry in the analysis of neurotransmitters. He holds a Ph.D. in neurophysiology from the University of Southampton, an M.Sc. in biochemical pharmacology from the University of Southampton, and a B.S. in biology and chemistry from the University of the West Indies.

*Marc E. Faerber, Corporate Controller and Vice President of Financial Operations*

Mr. Faerber has over 30 years of experience, nearly two-thirds of which was in life sciences. During the past 10 years, he has been providing financial, business, and advisory services to a broad base of start-up companies—primarily in the fields of cardiology, gastroenterology, orthopedics, diagnostics, and biotechnology. Mr. Faerber has extensive experience managing transactions, including the establishment of international organizations throughout Europe and parts of Asia, international technology licensing and distribution, M&A, and numerous funding transactions, including an initial public offering, as well as other international business structural issues. Mr. Faerber has also held various positions in finance and corporate management, including CFO, CEO, and director. He began his career at KPMG as a certified public accountant, and has a B.S. in business administration from Providence College.

*Kerry Segal, Head of Business Development*

Mr. Segal heads up business development (both buy-side and sell-side) and M&A for Amarantus. Specifically, he is responsible for in-licensing and out-licensing activities, as well as M&A opportunities across therapeutics and diagnostics areas. Mr. Segal is a 30-year veteran of the biopharmaceutical industry, including Johnson & Johnson, Cephalon, Valeant, Impax, and two start-ups. Mr. Segal has 22 years of front-line transactional experience, during which time he has identified and closed transactions valued in excess of \$2.6 billion and generated non-dilutive capital through partnerships in excess of \$270 million.

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*Tiffini Clark, Head of Operations and Regulatory Affairs*

Ms. Clark brings over 20 years of experience to Amarantus, with over 10 years of professional multidisciplinary biotechnology and pharmaceutical experience, primarily in regulatory activities, research, and development. Ms. Clark is responsible for overseeing all regulatory activities, including support of business development activities. She recently served as regulatory affairs specialist, project management and regulatory operations at Pharmacyclics. Previously, she served as drug safety coordinator and senior archivist at Johnson & Johnson Pharmaceutical Research and Development. At Pharmacyclics, she was a team member that brought IBRUTINIB from discovery, IND, and into Phase 3 clinical development and was an integral member of the business development team that executed a \$975 million transaction with Janssen Biotech, Inc. Ms. Clark was also an integral member of business development team that completed transactions with Novo Nordisk for the Factor VIIa inhibitor, PCI-27483, and the pan-HDAC deal with Les Laboratoires Servier. Ms. Clark has prepared, submitted, and maintained seven INDs, one NDA, several orphan drug applications, FDA meeting packages, and Fast Track designations.

*F. Randall Grimes, Head of Sponsored Research*

Mr. Grimes has more than 20 years of marketing, business development, financial, and R&D leadership experience in early-stage life science companies. He founded The Randall Group in 2001 to help small- to medium-sized technology companies raise funds using state and federal competitive grants. He has garnered over \$25 million in non-dilutive capital for clients and employers, including more than \$1.5 million for LymPro Test® development. Mr. Grimes previously served as the vice president of technology development at Provista Diagnostics, Inc., vice president of operations at RCP Diagnostics, Biomarker Technologies LLC, and GW Medical Technologies LLC. Mr. Grimes authored eight issued patents and has published articles in major technical and trade journals. He holds a B.S. from the University of Arizona in material sciences and engineering and an MBA from University of Michigan Business School with an emphasis in new product development and operations management.

*Paul Jorgensen, Head of Diagnostics Product Development*

Mr. Jorgensen is a biotechnology executive with over 20 years of experience in the areas of *in vitro* diagnostics development, validation, and manufacturing. He has worked at a number of large biotechnology and diagnostic firms, including Boehringer-Mannheim, Chiron Corporation, and the diagnostics division of Bio-Rad Laboratories. In 2000, he helped found and served as director, operations for AcroMetrix Corporation, which manufactured products for molecular diagnostics and was a pioneer in standardizing viral load assays. The company was sold to Life Technologies in 2009. Most recently, Mr. Jorgensen was director of development and laboratory operations for Tethys Bioscience, where he established Tethys' CLIA clinical lab and was responsible for the launch of the company's PreDx Diabetes Risk Score product. Mr. Jorgensen has a degree in biochemistry and biophysics from the University of California at Davis.

*Mark Wakefield, Head of Clinical Development*

Mr. Wakefield brings over 15 years of experience to Amarantus across large pharmaceutical, vaccines, and biotechnology—of which the last eight-plus years were focused on establishing and implementing development strategies, as head of clinical development operations at Addex Pharma SA (Switzerland), where he was responsible for the execution of multinational (U.S. and EU) trials. Between 2000 and 2005, he coordinated the public-private partnering between Chiron Vaccines (Italy), Norwegian Institute for Public Health, and the New Zealand Ministry of Health and was responsible for the operational execution of the clinical development program, which led to the successful development and roll-out of MeNZBTM vaccine. From 1998 to 2000, he was involved in running a large Phase 3b cardiovascular study for Astra in the Netherlands. Mr. Wakefield graduated from the University of Amsterdam, where he studied chemistry, with a specialization in biochemistry in the section Medical Enzymology and Metabolism, E.C. Slater Institute for Biochemical Research, under Prof. J.M. Tager, with an emphasis on the routing of newly synthesized molecules and organelle formation. His Ph.D. research on neurotrophic factors during brain development was done under Dr. R. Balázs at the Netherlands Institute for Brain Research (now NINS).



## **Board of Directors**

### *David A. Lowe, Ph.D., Independent Director*

Dr. Lowe is president and CEO of NeuroAssets, Sarl, a Swiss-based neuroscience-focused consulting firm, providing advisory services to pharmaceutical, venture capital, and biotechnology companies throughout the world. NeuroAssets Sarl, which has development expertise within the areas of neurology, endocrinology, and ophthalmology, is overseeing the translational development of MANF through first-in-man clinical studies, as well as is advising on the development of the LymPro Test<sup>®</sup> blood diagnostic for AD, PhenoGuard Protein Discovery Engine, and potential additions to the Amarantus portfolio. With over 35 years of experience in CNS drug discovery and development within the biopharmaceutical industry, Dr. Lowe previously served as the CSO of PsychoGenics, Inc. and prior thereto, as director and CSO of Memory Pharmaceuticals, Inc., a biotechnology company pursuing treatments for AD and schizophrenia. Prior to Memory Pharmaceuticals, Dr. Lowe served as the executive vice president and CSO at Fidelity Biosciences Group, Fidelity Investments in Boston, Massachusetts. Dr. Lowe also served as president, CEO, and director of Envivo Pharmaceuticals, a Fidelity-funded pharmaceutical company pursuing new treatments for AD now in Phase 3 development. Dr. Lowe also served as vice president and therapeutic area head, central nervous system, at Roche Pharmaceuticals, vice president and global therapeutic area head of central nervous system research at Bayer AG, and head of CNS biology and deputy head of CNS Research at Sandoz Ltd (now Novartis). Dr. Lowe received a Ph.D. in neurobiology from the University of Leeds, UK.

### *Donald D. Huffman, Chair of Audit Committee*

Mr. Huffman currently serves as a director of Dance Biopharm Inc., a diabetes company entering Phase 3 clinical development with an inhaled insulin program. Previously, Mr. Huffman served as the CFO of WaferGen Biosystems Inc., an emerging genomic analysis company and was its co-president from September 2011 to March 2012. Before that, Mr. Huffman served as the CFO of Asante Solutions, Inc., a medical device company with an approved wearable insulin pump. Mr. Huffman also served as CFO of Guava Technologies, Inc., a life science instrumentation company acquired by Millipore Corporation and then Merck & Co., Inc. Previous to that he served as CFO and principal of Sanderling Ventures, a biomedical venture capital firm. Mr. Huffman has also served as the CFO of three other public companies: Volcano Corporation (formerly known as EndoSonics Corporation), Microcide Pharmaceuticals, Inc., and Celtrix Pharmaceuticals, Inc., which was acquired by Insmed Incorporated in 2000. Mr. Huffman earned a B.S. in mineral economics from Pennsylvania State University and an MBA from the State University of New York at Buffalo. He completed the Financial Management Program at the Stanford University Graduate School of Business.

### *Robert L. Harris, J.D., Independent Director and Compliance Officer*

Mr. Harris has served as a member of the Board of Directors of Amarantus since December 2010. He is a retired vice president of Environmental, Health, Safety, Technical and Land Services at Pacific Gas and Electric Company, where he worked from September 1972 to January 2007. In 1985, he became the first and only lawyer in PG&E's history to argue and win a case for it in the U.S. Supreme Court. In so doing, he became the first lawyer in the nation to convince the Supreme Court that a corporation, like an individual, has negative First Amendment rights. He graduated from San Francisco State University in 1965 and received a J.D. from the University of California School of Law at Berkeley (Boalt Hall) in 1972. He was admitted to the California State Bar in December 1972 and argued and won a case in the U.S. Supreme Court in 1985. Harris also completed the Harvard Graduate School of Business Advanced Management Program and the Management Development Program at Duke University's School of Business.



*Mark Benedyk, Ph.D., Independent Director*

Dr. Benedyk is currently a managing partner at Rila Partners LLC, a business and corporate development consultancy. In this role, he serves on the Strategic Advisory Board of KemPharm, Inc., is a director at the Center for Drug Research and Development Ventures, Inc., and is a member of the Translational Medicine Advisory Board of the CNS Regenerative Medicine Foundation. Previously, he was head of The Pfizer Incubator (TPI), where his duties included membership on the TPI Board of Directors, board positions with TPI portfolio companies, oversight of the TPI operations team, and reviewing investment opportunities in multiple technologies. Dr. Benedyk has held executive business development roles at Ascenta Therapeutics, Optimer Pharmaceuticals, Aurora Biosciences (acquired by Vertex Pharmaceuticals), and Elan Pharmaceuticals, where he led partnering efforts for several key clinical-stage products for the treatment of AD, migraine, and other neurological indications. He received a Ph.D. in developmental and molecular genetics from The Rockefeller University, and a B.S. in microbiology and botany from the University of Michigan.

*Iain Ross, Independent Director*

Mr. Ross is currently chairman of the Board of Ark Therapeutics Group PLC and Biomer Technology Ltd, and is also a non-executive director of Benitec Biopharma Limited, Novogen Limited, and Tissue Therapies Ltd, each of which is traded on the Australian Securities Exchange. He is a Qualified Chartered Director of the UK Institute of Directors and Vice Chairman of the Council of Royal Holloway, University of London. Following a career with multi-national companies including Sandoz, Fisons plc, and Hoffman La Roche, Mr. Ross joined the Board of Celltech Group plc in 1991 and was responsible for building Celltech Biologics, the contract manufacturing division which was later sold to Alusuisse Lonza. For the past 18 years, he has undertaken a number of start-ups and development-stage companies as a board member on behalf of private equity groups and banks, including Quadrant Healthcare plc, Allergy Therapeutics Ltd, Eden Biodesign Ltd, Phadia AB, and Silence Therapeutics plc.

*Gerald E. Commissiong, President and CEO*

Biography on page 17.

*John W. Commissiong, Ph.D., Chief Scientific Officer*

Biography on page 18.

**Board of Advisors**

*Dr. Joseph Rubinfeld, Corporate Advisor*

Dr. Rubinfeld is one of the four original co-founders of Amgen. Dr. Rubinfeld co-founded Amgen after a 23-year career in a variety of senior scientific and operational positions at Bristol-Myers Squibb Company. Dr. Rubinfeld served as a senior director at Cetus Corporation from 1987 to 1990 until he co-founded SuperGen in 1991, and served as its president and CEO through 2003. Dr. Rubinfeld is credited with inventing Amoxicillin, biodegradable detergent, and polaroid film. Dr. Rubinfeld received a Ph.D. in chemistry from Columbia University.

*Dr. Adam J. Simon, Corporate Advisor*

Dr. Simon is the founder and president of AJ Simon Enterprises, LLC, a consulting firm serving pharmaceutical and biotechnology clients, including Bristol-Myers Squibb. He is also the founder and CEO of Cerora, Inc., a healthcare information technology company focused on developing medical devices and services to assess brain health, including TBI. Earlier in his career, he spent more than 13 years at Merck Research Laboratories, where he served as a senior research fellow in integrative systems neuroscience and biomarkers and in AD research. He has also been a visiting scientist at Princeton University. Dr. Simon received bachelor's degrees in physics and mathematics from the University of Rochester. He received a doctorate in physics from the University of Chicago. He holds four patents related to medical research, and has published more than 60 articles in scientific and medical journals.

*Dr. Owen Garrick, Corporate Advisor*

Dr. Garrick brings over 20 years of pharmaceutical and biotechnology experience to Amarantus. He currently serves as the chief operating officer at Bridge Clinical Research and is president of the American Medical Association Foundation. Prior to that, he was director of corporate strategy and business development at McKesson Corporation. Dr. Garrick was executive director and co-head of mergers and acquisitions at Novartis Pharmaceuticals, where he oversaw company acquisitions, hybrid equity/license rights deals, mature product divestments, and venture investments in biotechnology companies. Prior to Novartis, Dr. Garrick was an associate at Goldman Sachs in New York. Dr. Garrick received an M.D. from Yale School of Medicine and earned an MBA from Wharton School of Business. He holds an AB from Princeton University, where he has served on the national fundraising board.

*Dr. Colin Bier, Corporate Advisor*

Dr. Bier is managing and scientific director of ABA BioResearch, an independent bioregulatory consulting company providing expertise for technology assessment, fairness evaluation, due diligence, and technical representation. Dr. Bier has extensive regulatory experience in the strategic management and development of pharmaceuticals, biopharmaceuticals, medical devices, and diagnostics. Dr. Bier received a doctorate in experimental pathology from Colorado State University in 1978 and pursued additional training as a Medical Research Council Postdoctoral Fellow and the Dr. Douglas James Fellow in the Department of Pathology, McGill University. Dr. Bier has extensive management experience in the biomedical sector, having held senior scientific and executive management positions in the contract research industry as well as private industry and is a senior advisor to several venture funds and global biopharmaceutical companies. Dr. Bier is chairman of the Advisory Committee for Technology Transfer of the Jewish General Hospital in Montréal, Canada, is on the Scientific Advisory Board of three companies and serves as a director of two private companies, and is a member of the Board of Trustees of Mount Sinai Hospital in Montréal. Dr. Bier is working closely with Dr. Adam Simon, another member of the Company's Corporate Advisory Board (biography on page 21), to finalize and implement the Company's commercialization strategy for the LymPro Test® to both maximize potential revenue and position the assay as a potential companion diagnostic for therapeutic AD programs.

*Dr. Louis Kirby, Corporate Advisor*

Dr. Kirby is a board-certified neurologist and is a specialist in the development of drugs, medical devices, and laboratory developed diagnostics over the course of his career in the pharmaceutical and medical device industry. He previously founded Pivotal Research Centers, which became one of the nation's largest free-standing private clinical research operations, before being sold in 2005 to a public company. Dr. Kirby currently consults for various biotechnology and large pharmaceutical companies. Dr. Kirby previously worked as chief medical officer at Provista Life Sciences, developing blood-based biomarkers for breast cancer and AD. Dr. Kirby also previously served as director and co-chair at the Critical Path Institute, working with AD and PD biomarkers in the regulatory arena, working as a liaison between academia, industry and the FDA/EMA (EMA), where he assembled international expert panels and managed their deliberations. Currently, Dr. Kirby is co-founder of ZettaScience (ZettaScience.com), a mission-based science infrastructure company offering a global scientific data search engine for researchers at universities, government, and industry that promotes deeper scientific collaboration on pressing global challenges. Dr. Kirby sits on the Board of Directors of the Southwest Autism Research and Resource Center (SARRC) and chairs its Medical Research committee. Dr. Kirby is also an author, writing science-based thrillers including *Shadow of Eden*, a medical and political thriller that currently is an Amazon bestseller. Dr. Kirby received a undergraduate degree in honors liberal arts at University of Texas (Austin) and a medical degree from the University of Texas (Galveston).

## Core Story

Amarantus BioScience Holdings, Inc. (“Amarantus” or “the Company”) is a development-stage biopharmaceutical company developing intellectual property and proprietary technologies into products to treat human disease. The Company owns or has exclusive licenses to various candidates in the biopharmaceutical and diagnostic areas, with a particular focus in the areas of Alzheimer’s disease (AD), Parkinson’s disease (PD), retinal degenerative disorders, and other ailments of the human body (specializing in conditions affecting the nervous system). Amarantus develops its product candidates, listed in Figure 4, through certain milestones and then pursues strategic partnerships within each product candidate’s market sector to achieve regulatory approval and subsequent marketing and distribution of these products. Greater details on each candidate are furnished within each respective section—Diagnostics (the LymPro Test® and NuroPro/PhenoGuard) and Therapeutics (Eltoprazine and MANF)—on pages 24-46.

Figure 4  
 DEVELOPMENT PIPELINE

CANDIDATE	INDICATION	STAGE	DESCRIPTION
<b>DIAGNOSTICS DIVISION</b>			
LymPro	Alzheimer's Disease (AD)	Phase 2b	Blood-based diagnostic test to differentiate AD from other forms of dementia in patients
NuroPro	Parkinson's Disease (PD)	Phase 2a	Blood-based diagnostic platform for early detection of neurodegenerative diseases
LymPro	Traumatic Brain Injury (TBI) / Chronic Traumatic Encephalopathy (CTE)	Preclinical	Blood-based test to identify TBI/CTE patients early on before complications from their injuries progress
<b>THERAPEUTICS DIVISION</b>			
Eltoprazine	Parkinson's Levodopa-Induced Dyskinesia (PD-LID)	Phase 2b	Drug to treat PD-LID side effects of Levodopa treatment; potential to reduce future dyskinesia onset
Eltoprazine	Adult ADHD	Phase 2b	Drug to reduce symptoms of ADHD in adults
MANF	Retinitis Pigmentosa (RP)	IND	Disease-modifying treatment for RP; reduce and prevent apoptosis in response to injury or disease
MANF	PD	IND	Disease-modifying treatment for PD; reduce and prevent apoptosis in response to injury or disease
MANF	TBI / CTE	Preclinical	Drug to reduce and prevent apoptosis from TBI / CTE

Source: Amarantus BioScience Holdings, Inc.

## MANUFACTURING, DISTRIBUTION, AND MARKETING

Since Amarantus does not have any in-house manufacturing capabilities, the Company intends to outsource the manufacturing of its products to third-party contractors, who have capabilities to manufacture chemical drugs, *in vitro* diagnostics, and biologic candidates for submission and clinical testing under FDA guidelines. The Company has stated that after it has developed its product candidates through successive milestones toward regulatory approval, it will employ its industry connections to either seek marketing approval of its product candidates or assemble partnering transactions with biopharmaceutical companies seeking to fortify pipelines and fund the costly later-stage clinical development required to achieve successful commercialization. Because of this, the Company does not expect to go directly into the marketplace; however, it retains the right to do so depending on market conditions. Amarantus seeks to find a distribution and marketing partner for future commercialization.



## Diagnostics

The LymPro Test® .....	24
Using a Blood Test to Measure the Brain.....	25
Development Status.....	27
Market Opportunities .....	28
Alzheimer’s Disease (AD) .....	29
Traumatic Brain Injury (TBI) and Chronic Traumatic Encephalopathy (CTE).....	31
The NuroPro Blood Test .....	31
Phenoguard .....	32

### THE LYMPRO TEST®

Amarantus licensed the Lymphocyte Proliferation Test (the LymPro Test®), an Alzheimer’s disease (AD) diagnostic blood test from Memory Dx, LLC (MDx) (formerly called as Provista Life Sciences, Inc. [detailed on page 13]) in December 2012. Developed as a tool to diagnose AD in its mild to moderate stage, the LymPro Test® works by identifying immune-based biomarkers in the blood of AD patients, thus being able to diagnose AD and enable physicians to conclusively distinguish AD from other forms of dementia. A key element in treating AD is to be able to identify and initiate therapeutic intervention as early as possible. Such patient-specific identification could be particularly useful in clinical trials of AD patients, as there has been a well-documented history of patient recruitment errors caused by an inaccurate diagnosis of the disease.

It is hypothesized that certain diseases are the result of compromised cellular machinery, which leads to aberrant cell cycle re-entry by neurons. The inventive step for the LymPro Test® that makes it unique is the use of **peripheral blood lymphocytes (PBLs)** as a surrogate for neuronal cell function—suggesting a common immune-based relationship between PBLs and neurons in the brain. The need for objective, non-invasive, and reliable AD biomarkers has never been greater as confirmed by the FDA’s recent decision to approve a third amyloid imaging agent for adjunctive aid in diagnosing AD—attesting to the value given to incremental improvements in the diagnostic paradigm for AD.

Ultimately, the LymPro Test® may provide physicians with a low cost, minimally-invasive tool for intervention and reduce the need for brain imaging scans. In addition, the LymPro Test® is being evaluated as a diagnostic blood test for traumatic brain injury (TBI)/chronic traumatic encephalopathy (CTE) (as announced in January 2014 via a collaboration with the Boston University School of Medicine, described on pages 27-28). Created at the University of Leipzig in Germany, the LymPro Test® has received over \$3 million to date in research grants from the National Institutes of Health (NIH).



## Using a Blood Test to Measure the Brain

Establishing a blood test for AD is difficult due to the blood-brain barrier—where the challenge stems from establishing a diagnostic measure in the blood that can measure what is occurring in the brain. Amarantus has achieved this by stimulating PBLs via mitogenic stimulation, which initiates the cell division cycle, where mitosis equals cell division and thus mitogenic compounds cause cell division. In healthy cells, a biomarker called CD69 increases to shut down what is known as “premature mitosis.” In AD patients, however, CD69 is not increased and the PBLs enter the cell cycle inappropriately—which is not the case with other types of dementia and is the reason that AD specifically can be targeted using the unique diagnostic method.

In October 2013, Amarantus reported positive analytical performance data for the LymPro Test<sup>®</sup>. Produced by the Custom Technology Team at Becton, Dickinson and Company (BD), data demonstrated that CD69 was a valid biomarker for diagnosis in the blood as it increased in response to mitogenic stimulation with both **pokeweed mitogen (PWM)** and **phytohaemagglutinin (PHA)** across all control samples. Importantly, the primary tool for AD diagnosis today is a lumbar puncture in order to take a sample of the patient’s **cerebrospinal fluid (CSF)**, which is painful and troubling to most patients, although an MRI may also be used in some situations. As well, over time, the standard for AD diagnosis has been an autopsy, which limits data validation while a patient is still alive.

*"The scientific community and the FDA believe that it is critical to identify and study patients with very early Alzheimer's disease before there is too much irreversible injury to the brain....It is in this population that most researchers believe that new drugs have the best chance of providing meaningful benefit to patients."*

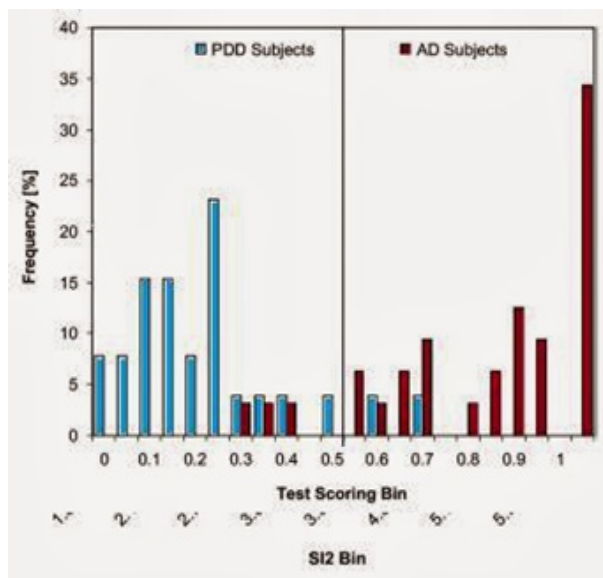
- Russell Katz, MD, Director of the Division of Neurology Products in the FDA's Center for Drug Evaluation and Research

### Phase 1 Study

Phase 1 study results of 88 patients demonstrated that the scoring model was able to differentiate between AD subjects and other demented (OD) subjects (e.g., those having Parkinson’s disease dementia [PDD] or mild cognitive impairment [MCI]) with co-positivity (sensitivity) of up to 91% and co-negativity (specificity) of up to 92% relative to the clinical diagnosis of AD. This indicates the test was able to correctly identify 91% of patients who did have AD, as having AD, and correctly identify 92% of patients who had other dementia, as having other dementia.

Figure 5

#### SEPARATION BETWEEN ALZHEIMER'S DISEASE AND OTHER DEMENTIA



Source: Stieler et al; *Neurobiology of Aging* 33 (2012) 234–241.

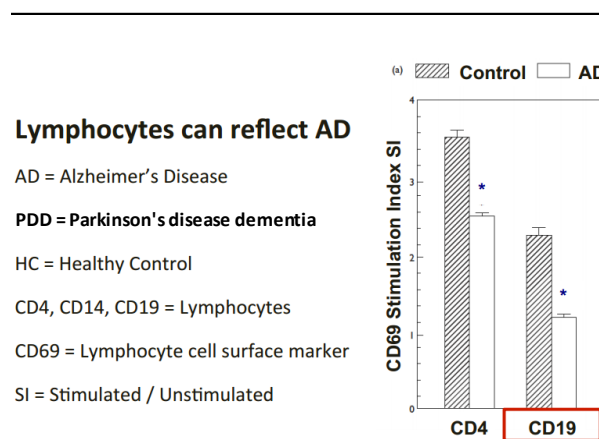
The results were independent of the severity of the dementia caused by AD. Between AD subjects and non-AD subjects, a co-positivity of 88% and a co-negativity of 82% was reported. The separation between AD and OD was particularly apparent (Figure 5 [page 25], where the dark bars represent patients likely having AD and the light bars represent patients with another form of dementia, which in this case is PDD). Investigators further found a 95.6% correlation in area under the curve (AUC) relative to clinically diagnosed AD compared to OD (Source: Stieler et al., *Neurobiology of Aging* 33 [2012] 234–241).

Data from the Phase 1 study has been compared to the physician’s diagnosis. The 88-patient Phase 1 study was conducted in subjects with mild-to-moderate dementia previously diagnosed as probably having AD (n=32) or PDD (n=26) versus a healthy control (n=30). In between the initial physician’s diagnosis and autopsy (patient death) are follow-up examinations. The LymPro Test® compared well to the physician’s initial diagnosis, showing an overall accuracy rate of 95%.

*Positive Top-Line Interim Clinical Data (August 2014)*

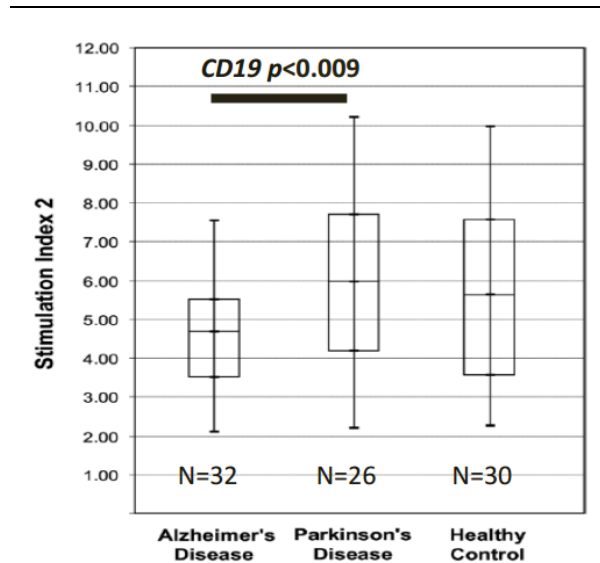
In August 2014, Amarantus announced positive interim clinical performance data for the LymPro Test®. The interim analysis was based on 44 subjects (34 healthy controls and 10 AD patients) from LP-002 (a projected 72-patient clinical performance study). It was conducted with the primary objective of identifying whether the Company could replicate data published in two peer-reviewed publications (Stieler, et al 2001, and Stieler, et al 2012). Results in Amarantus’ trial to date showed that the expression of the marker CD69 on the surface of lymphocyte subpopulations CD14 (p=0.037) and CD19 (p=0.010) was statistically significantly different between AD and healthy controls. As well, initial predictive models correctly classified AD subjects with an overall accuracy of 80% from a single lymphocyte sub-population (CD19+, unadjusted for training and test sample sets). The Company is currently completing enrollment and expects to report full data sets by the end of the third quarter of 2014.

Figure 6  
 MEASURING THE BRAIN IN BLOOD:  
 AD VERSUS HEALTHY CONTROL



Source: Amarantus BioScience Holdings, Inc.; Stieler, JT, and Arendt, T., et al *Neuroreport* 2001 12(18).

Figure 7  
 REPLICATION OF THE 2001 FINDINGS



Source: Amarantus BioScience Holdings, Inc.; Stieler et al, *Neurobiology of Aging* 33 (2012) 234-341.

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## Development Status

The LymPro Test<sup>®</sup> has completed two Phase 1 clinical studies in over 80 patients, demonstrating 98% sensitivity and 96% specificity for AD diagnosis. The Company is in the process of conducting a seven-year follow-up analysis of the patients studied in the Phase 1 trial, which could prove critical for longitudinal analysis in validating the test. The LymPro Test<sup>®</sup> is now moving into a Phase 2 validation study. If successful, it could begin generating revenue as a Laboratory Developed Test (LDT) within 18 months of study initiation, with sales to commercial entities and sales to companies performing AD clinical research.

### *Potential CLIA Launch*

Amarantus anticipates being able to bring the LymPro Test<sup>®</sup> to market as a Laboratory Developed Test (LDT) under the Clinical Laboratory Improvement Amendments (CLIA) in the U.S. within the fourth quarter of 2014. The assay could have considerable utility in AD clinical trials due to a well-documented history of patient recruitment errors stemming from inaccurate AD diagnoses using earlier methods. The ultimate goal is to gain approval as a companion diagnostic paired with a therapeutic in treating AD. On September 2, 2014, the Company announced the initiation of CLIA-enabling studies at ICON Central Laboratories, a CLIA-certified laboratory that will serve as the facility that carries out the LymPro assay for CLIA launch.

The Company then expects to evaluate its options with respect to ex-U.S. commercialization as well as FDA approval and marketing in the U.S. and is working on establishing its commercial supply chain. Furthermore, the Company continues to make progress regarding the reimbursement strategy for broad-scale use, which could bring greater leverage for future potential partnership discussions. Amarantus believes that it has identified Current Procedural Terminology (CPT) codes relating to cell cycle dysfunction and AD that might facilitate reimbursement for the LymPro Test<sup>®</sup> under CLIA or commercial sale, which could provide a material advantage to the Company.

### *Partnership Agreement with Memory Dx*

Regarding Amarantus' agreement with Memory Dx for the LymPro Test<sup>®</sup>, Amarantus has agreed to issue two million shares of restricted common stock to Memory Dx, pay a development milestone upon successful completion of the Phase 2 validation study, and pay a 9% royalty on sales. As well, Amarantus has agreed to allow Memory Dx to perform the necessary validation study to gain CLIA certification. In the future, the two companies may look to expand their relationships with large pharmaceutical companies as well as pursue greater grant funding to further develop the test. As well, Amarantus may assign or sub-license the LymPro Test<sup>®</sup> at any time to a third party of its choice.

In May 2014, Amarantus announced that it had acquired additional rights from Memory Dx for the LymPro Test<sup>®</sup> related to certain improvements that were sought out for the LymPro assay following the completion of work published in 2012 in the scientific journal *Neurobiology of Aging*. Memory Dx and Amarantus identified that these data sets fall outside the purview of Memory Dx' license agreement with the University of Leipzig, thereby allowing Memory Dx to sell the rights outright to Amarantus (without related milestones and royalties). This agreement positions Amarantus to have exclusivity over the LymPro Test<sup>®</sup> for the foreseeable future both in the U.S. and internationally as the Company continues negotiations with its CLIA partners. Moreover, as Amarantus continues to build out its diagnostics division, these additional rights coupled with plans to re-launch development for the NuroPro diagnostic blood test for PD (described on pages 31-32), could bolster the diagnostic division as a stand-alone corporate entity in the future.

### *Collaboration with Boston University School of Medicine (BUSM)*

In January 2014, Amarantus announced the establishment of a research collaboration with the Boston University School of Medicine (BUSM), where Amarantus is working with BUSM Professor of Neurology and Neurosurgery, Dr. Robert Stern, to evaluate the feasibility of using the LymPro Test<sup>®</sup> as a blood-based test to identify patients early in the disease process of the neurodegenerative diseases, chronic traumatic encephalopathy (CTE), and AD.

There is a scientific basis for believing that the cell cycle dysregulation that the LymPro Test<sup>®</sup> measures in AD patients may have relevance to TBI and CTE. Dr. Stern, who is the Clinical Core Director at the BU Alzheimer's Disease Center, has grant funding from the National Institutes of Health (NIH) to fund his work on developing methods of detecting and diagnosing CTE during life. As part of the study, Dr. Stern and his colleagues have examined over 70 former NFL players and 20 same age elite non-contact sport athletes to date. TBI is a clear risk factor that could accelerate an already-present predisposition for AD. Current and former athletes as well as soldiers who have been exposed to multiple concussions and sub-concussive events should be on high alert for symptomatology of early AD.

#### *Alzheimer's Association International Conference (AAIC)*

The Company had three posters accepted for presentation (analytical performance, LP-001 and LP001 retrospective seven-year patient record clinical performance data) at the Alzheimer's Association International Conference (AAIC) during July 2014 in Copenhagen, Denmark, under the direction of Dr. Louis Kirby and Paul Jorgensen (biographies on pages 22 and 19, respectively). The primary focus was the data of the LP001 retrospective patient record study underway with Amarantus' collaborator's facility at Banner Sun Health Research Institute in Phoenix, Arizona. The data demonstrated that LymPro successfully improved the diagnostic paradigm when a refined diagnosis was obtained with additional clinical assessments over time.

#### **Market Opportunities**

The market for a diagnostic product for AD, such as the LymPro Test<sup>®</sup>, could prove significant. The ability to distinguish between patients with AD and other degenerative dementias, such as Parkinson's disease dementia (PDD) or psychosis, and mild cognitive impairment (MCI) or age-related memory loss (AAMI), using a simple and inexpensive test that could accurately and reliably stratify patients would have a number of benefits, including the following:

- Significantly accelerating diagnosis, which would enable earlier treatment within a primary practice setting;
- Simplifying the diagnosis process, which would allow for financial savings to the healthcare system;
- Improving outcomes by enabling for a more focused treatment built off of the correct type of cognitive impairment and;
- Correctly differentiating between patients while they are alive (versus through an autopsy—the current standard for AD diagnosis) for participation in clinical trials and therapeutic development.

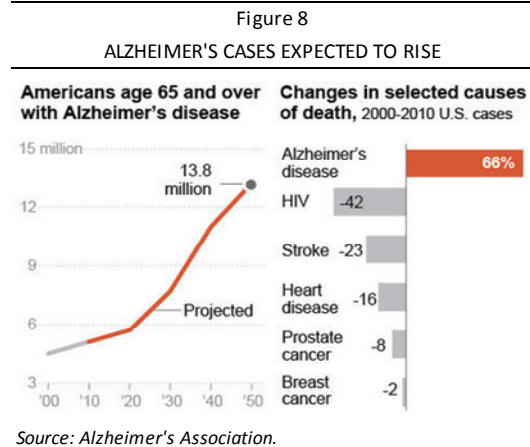
The last point is particularly relevant for Amarantus, which believes the LymPro Test<sup>®</sup> could become a much-needed tool for improving AD clinical trial research. To this end, according to the Alzheimer's Association, there are over 130 clinical trials ongoing, both pharmaceutical (drug) and non-pharmacological (non-drug), at nearly 500 trial sites across the country.

The ultimate goal for Amarantus via the LymPro Test<sup>®</sup> is to gain approval as a companion diagnostic paired with a therapeutic in treating AD. It is worth noting that therapeutic developments for the treatment of AD are the rate-limiting step. The Company believes the LymPro Test<sup>®</sup> is the most advanced blood test related to cell cycle regulation, with Amarantus already putting this in validation for commercial preparation (whereas much of its competition is still in academic laboratories). Thus, pursuing CLIA approval could prove to be the appropriate strategy for the Company. Amarantus believes that the market opportunity for an effective AD diagnostic could reach in the hundreds of millions of dollars.

## Alzheimer's Disease (AD)

Alzheimer's disease (AD) is the most common form of dementia—a general term for memory loss and other intellectual abilities serious enough to interfere with an individual's daily life—causing problems with memory, thinking, and behavior. As a progressive disease, AD worsens over time. In its early stages, memory loss is mild; however, late-stage AD patients lose their ability to carry on a conversation and respond to their environment. While not a normal part of aging, the greatest known risk factor for AD is increasing age, with the majority of affected individuals age 65 and older. Individuals with AD live, on average, eight years after symptoms become noticeable to others; however, they can survive from 4 to 20 years depending on age and other health conditions.

Worldwide, more than 35 million people have AD or similar dementia. In the U.S., about 5.2 million individuals (one in eight people) over the age of 65 currently live with the disease—with about 500,000 new diagnoses occurring each year—and only half of these people having an actual physician diagnosis. Up to 5% (or approximately 200,000) people with the disease have early onset AD (also known as younger-onset), which appears when people are in their 40s and 50s. As the baby boomer generation ages, the number of Americans with AD and other dementias will undoubtedly escalate, so much so that, by 2050, the number of people age 65 and older with the disease may more than triple—from 5 million to 16 million—without a medical breakthrough to prevent or slow the disease (as illustrated in Figure 8).



Being the sixth leading cause of death in the U.S. and the fifth leading cause of death for those age 65 and older (noting that it may cause even more deaths than official sources recognize), AD is responsible for a greater number of deaths than prostate cancer and breast cancer combined (shown in Figure 8). Between 2000 and 2010, deaths from AD increased 66% while deaths from other major diseases decreased, with it being the only cause of death among the top 10 in America that cannot be prevented, cured, or slowed. Unfortunately, compared to cardiovascular disease, stroke, prostate and breast cancers, AD is the only cause of death increasing, and is doing so at a very rapid rate (Source: Alzheimer's Association).

With no cure, there are only treatments for the symptoms of AD, and while treatments cannot stop the disease from progressing, they can temporarily slow the worsening of symptoms and improve quality of life. For patients with AD and other dementia, U.S. biopharmaceutical research companies have 93 medicines in clinical trials or awaiting FDA approval (which include 81 for AD, 11 for cognition disorders, and 2 for dementias) (Source: PhRMA.org). Today's development efforts are focused on discovering better ways to treat the disease, delay its onset, and prevent its progression. Such is the goal of the LymPro Test®—a tool to be able to identify and diagnose AD in its mild to moderate stage.

### *Cause and Progression of AD*

Neither the cause nor the progression of AD is well understood among the medical community. Research indicates that the disease is associated with amyloid plaques and tangles within the brain, with current treatments only able to address symptoms but nothing yet to stop or reverse AD progression. Mental stimulation, exercise, and a balanced diet are suggested to have an impact on delaying cognitive symptoms (though not brain pathology) in healthy older individuals; however, there is no conclusive evidence which supports this belief. With no known cure and the disease being degenerative, those afflicted must rely on others for assistance, where the role of the main caregiver typically falls on either a spouse or relative—dramatically affecting both individuals' lives.



*Costs of Living with and Treating AD*

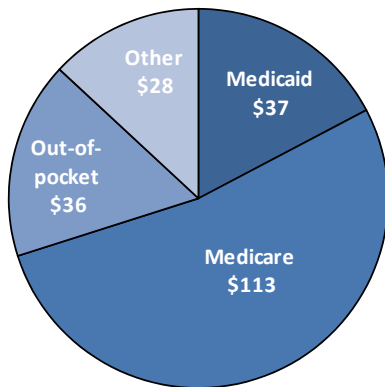
AD is the most costly condition in the nation, with direct costs to American society of caring for those with the disease estimated at \$214 billion (Figure 9), including \$150 billion in costs to Medicare and Medicaid, according to the Alzheimer’s Association. As well, there are another \$200 billion in indirect costs, which could reach \$1.2 trillion to the U.S. economy by 2050 (in today’s dollars).

Approximately one in every five dollars spent by Medicare is on individuals with AD or another dementia, with the average per-person Medicare spending for those with AD and other dementias three times higher than for those without these conditions. For seniors with AD and other dementias, the average per-person Medicaid spending is 19 times higher than average per-person Medicaid spending for all other seniors. Total Medicaid spending for people with AD is \$37 billion and out-of-pocket spending for individuals with AD and other dementias is estimated at \$36 billion. According to the Alzheimer’s Disease Foundation, the incidence of AD could double in the next 20 years driven by the increasing trend toward a longer lifespan coupled with the baby boomer population approaching retirement.

*Women and Alzheimer’s*

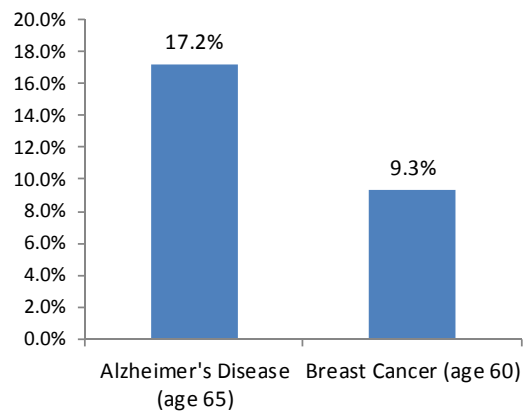
It is noteworthy that approximately two-thirds of U.S. seniors living with AD are women, where of the five million people age 65 and older with Alzheimer’s, 3.2 million are women and 1.8 million are men. Women are almost twice as likely to develop the disease as men, with an estimated lifetime risk at age 65 being 1 in 6 versus nearly 1 in 11 for a man. To put this into perspective, women in their 60s are about twice as likely to develop AD during the rest of their lives as they are to develop breast cancer (Figure 10).

Figure 9  
2014 COSTS OF ALZHEIMER’S DISEASE (IN BILLIONS)  
Total Costs of AD Care = \$214 billion



Source: Alzheimer's Association.

Figure 10  
REMAINING LIFETIME RISK OF WOMEN DEVELOPING ALZHEIMER’S DISEASE AND BREAST CANCER



Source: Alzheimer's Association.



## Traumatic Brain Injury (TBI) and Chronic Traumatic Encephalopathy (CTE)

As announced in January 2014, Amarantus and the Boston University School of Medicine (BUSM) are working to evaluate the feasibility of using the LymPro Test® as a blood-based test to identify patients early in the disease process of the neurodegenerative diseases, traumatic brain injury (TBI)/chronic traumatic encephalopathy (CTE) and AD, believing that since the LymPro Test® can measure AD in patients, it may have relevance in these areas as well. TBI, also known as **intracranial injury**, occurs when an external force traumatically injures the brain, and is classified according to severity, mechanism (closed or penetrating head injury), and other features. Head injury and concussions typically refer to TBI, but is a broader category since it can involve damage to structures other than the brain like the scalp and skull. As a leading cause of death and disability worldwide—specifically among children and young adults, TBI can be caused by falls, vehicle accidents, and violence. Beyond the damage caused at the moment of injury, brain trauma causes secondary injury, which results in a variety of events and processes that take place in the minutes and days following the injury, including alterations in cerebral blood flow and the pressure within the skull, which contribute substantially to the damage from the initial injury.

TBI can lead to a multitude of physical, cognitive, social, emotional, and behavioral effects, where the outcome can range from complete recovery to permanent disability or death. Critical developments in diagnosing and treating TBI patients have decreased death rates and improved outcomes. Such developments include current imaging techniques used for diagnosis and treatment, such as **computed tomography (CT)** scans and **magnetic resonance imaging (MRIs)**. Treatment depends on the injury and may be minimal or may include interventions, including medications or surgery. Further rehabilitation may come in the form of physical therapy, speech therapy, recreation therapy, and occupational therapy.

Chronic traumatic encephalopathy (CTE), a brain disorder caused by multiple TBIs, is a neurological degenerative disease found in individuals who have been subjected to repetitive TBIs by means of the acceleration of the head on impact and the subsequent damage to **axons**. Though repetitive brain trauma is believed to be needed to cause CTE, it is not sufficient—such that not everyone experiencing repetitive brain trauma will develop the disease. Additional risk factors are possible though have yet to be reported as the donated brains in the brain bank at the Boston University School of Medicine and elsewhere consist mostly of the brains of athletes with a history of professional participation in contact sports.

Professional athletes are the leading population to suffer from CTE stemming from frequent concussions during their time playing a contact-sport. These contact sports include American football, ice hockey, rugby, boxing, and wrestling. Others diagnosed with CTE have been involved in military service, had a previous history of chronic seizures, were victims of domestic abuse, or were involved in activities resulting in repetitive head collisions. Reports of CTE have steadily increased among younger athletes, likely due to either greater awareness of the issue and/or due to athletes becoming bigger and stronger, producing greater degrees of force on impact.

### THE NUROPRO BLOOD TEST

Amarantus' diagnostic platform for the early detection of neurodegenerative diseases, the NuroPro Blood Test, is being developed as a tool to assist physicians in more accurately diagnosing and monitoring diseases and disease progression. The platform involves monitoring the concentration of 57 protein markers in blood serum identified to be linked to neurodegeneration in order to accurately detect and distinguish between AD, ALS (Lou Gehrig's disease), and PD. Amarantus' license is focused on further developing a subset of 21 of these protein markers specifically targeting early diagnosis and ongoing monitoring of PD. Because the amount of time it takes to accurately diagnose PD and the relatively high early misdiagnosis rates, a blood-based biomarker test could generate significant interest among neurologists and primary care physicians as it would allow physicians the ability to intervene at an earlier stage in disease progression.



The PD application of the NuroPro Blood Test has completed proof-of-concept and Phase 1 clinical validation studies and Amarantus is preparing the Phase 2 validation study required to gain CLIA certification. Upon CLIA certification, the Company intends to begin the commercial sale of the NuroPro Parkinson's Disease Blood Test. The ability to advance NuroPro to simultaneously generate revenue while bolstering the Company's MANF program (described on pages 42-46)—by allowing its clinical researchers to more efficiently select and monitor PD patients in the Company's therapeutic program—could represent a material opportunity for Amarantus.

## **PHENOGUARD**

Amarantus has developed a discovery platform, PhenoGuard Protein Discovery Engine, which allows Company scientists to rapidly discover novel secreted human proteins with biological activity for specific indications. The Platform consists of the Company's PhenoGuard Cell Line Library and highly sensitive Target Validation cell culture systems, which can provide accurate results and enable Company scientists to make more informed decisions.

The first application of the Protein Discovery Engine was in the discovery of MANF from astrocytes. In April 2014, the Company presented preliminary data on PhenoGuard at the "Astrocytes in Health and Neurodegenerative Disease: A joint Biochemical Society/British Neuroscience Association Focused Meeting" conference in London, England. The abstract titled "Protoplasmic type-1 astrocytes are sources of drug candidates for neurodegenerative diseases" focuses on the Company's progress in identifying new neurotrophic factors from a library of 88 PhenoGuard astrocyte cell lines. To date, two neurotrophic factors, MANF and CDFN, have been discovered as a result of this work.





**Therapeutics**

Etoprazine (PD-LID)..... 33

    Market Introduction..... 34

    Data Summary..... 34

    Etoprazine’s Development Status ..... 35

    Current Treatment Options for PD-LID ..... 35

    Potential Benefits of Etoprazine versus Current Options ..... 36

    Parkinson’s Disease (PD) ..... 36

    Parkinson’s Disease Levodopa-Induced Dyskinesia (PD-LID) ..... 37

Etoprazine (ADHD)..... 39

    Attention Deficit Hyperactivity Disorder (Adult ADHD) ..... 40

MANF (Mesencephalic-Astrocyte-derived Neurotrophic Factor)..... 42

    Key Issued Composition of Matter Patents..... 42

    Potential for Orphan Drug Designation ..... 42

    Publication of Positive Independent Peer-Reviewed Data ..... 43

    Development Status..... 43

    Potential Market Opportunity ..... 45

**ELTOPRAZINE (PD-LID)**

Etoprazine is in Phase 2a for the treatment of Parkinson’s disease Levodopa-Induced Dyskinesia (PD-LID). PD-LID refers to side effects that occur in Parkinson’s disease (PD) patients as they take the PD medication levodopa. PD-LID leads to an emergence of involuntary, abnormal movements and “off episodes,” which is when a patient’s symptoms reappear despite being on the levodopa medication.

Etoprazine is a small molecule drug candidate that functions as a selective 5-HT1a/1b receptor partial agonist. It was originally developed by Solvay, S.A. (now AbbVie Inc.) and has demonstrated favorable human clinical data in a Phase 2a trial for treating PD-LID. As well, Etoprazine, which has been evaluated in a number of neurology-focused indications, has an established safety profile, having been administered to over 700 patients in 12 clinical trials to date. Amarantus expects to move Etoprazine forward in a Phase 2b clinical study during the fourth quarter of 2014 for PD-LID. In addition, due to the drug candidate’s strong neuroactivity in the earlier PD-LID trial, the Company is also targeting it toward a second indication: Adult Attention Deficit Hyperactivity Disorder (Adult ADHD), and may also pursue schizophrenia, among other indications.

## Market Introduction

At least four million people worldwide have PD, with 35% exhibiting symptoms of LID after three or more years of treatment with levodopa. In addition to LID, 35% to 50% of PD patients exhibit cognitive dysfunction and 60% exhibit psychiatric disorders, including depression. According to an August 2012 report released by the Michael J. Fox Foundation, the potential market opportunity for a drug that could treat PD-LID may exceed \$750 million annually in the U.S. alone. Furthermore, the globally aging population could create an increase in PD diagnoses, as the average age of diagnosis for this disease is between 58 and 62 years. It is estimated that PD market growth could be roughly 2% to 3% per year.

Adequately addressing PD-LID in this patient population could represent an important improvement to the standard of care for patients worldwide and thus could become a significant commercial opportunity upon reaching the market. The current standard of care for PD-LID treatment, amantadine, is believed to work reasonably well though it still carries a number of unwanted side effects as well as pharmacokinetic issues.

## Data Summary

### *PsychoGenics' Clinical Study of Eltoprazine in PD-LID*

In June 2012, PsychoGenics (now PGI Drug Discovery, described on page 35) reported positive results from a clinical study of Eltoprazine in PD-LID, where Eltoprazine met the primary objective of the study by exhibiting a statistically significant reduction in LID at the 5mg dose ( $p=0.0007$ ) and the 7.5mg dose ( $p=0.0467$ ), without adversely affecting levodopa efficacy. The study was conducted at two sites in Sweden, where 22 patients were given single doses of Eltoprazine and placebo along with a challenge dose of levodopa at each of the five treatment visits. Patients were then assessed for symptoms of PD and dyskinesia over a period of three hours post-treatment. The assessments were videotaped and scored by two independent raters who did not know which product (Eltoprazine or placebo) the participants had received. Primary efficacy was measured using the **Clinical Dyskinesia Rating Scale (CDRS)** and the **Unified Parkinson's Disease Rating Scale (UPDRS)**. Secondary endpoints included the **Rush Dyskinesia Rating Scale** and an assessment of patients' mood using the **Hospital Anxiety & Depression Score (HADS)** and **Montgomery-Asberg Depression Rating Scale (MADRS)**. Eltoprazine was well tolerated in this study and there were no serious adverse events.

### *Michael J. Fox Foundation (MJFF)*

In 2012, the Michael J. Fox Foundation (MJFF) funded human clinical proof-of-concept studies with Eltoprazine. The National Institutes of Mental Health (NIMH) in Cognitive Impairment Associated with Schizophrenia (CIAS) also funded work on Eltoprazine. Clinical data showed statistically significant effects in Adult ADHD patients. The MJFF has further worked to repurpose drugs to treat PD, one of which includes Eltoprazine. The MJFF has funded additional work testing a combination of Eltoprazine with other candidates for PD-LID, including amantadine. An advantage for Eltoprazine is the drug's secondary benefits, which include potential improvements in cognitive function as seen in PsychoGenics' Phase 2a study. The drug also seems to reduce the onset of future dyskinesia. Eltoprazine has been studied in **general anxiety disorder (GAD)**, depression, and aggression. Given the unmet medical need in the PD-LID space (with Eltoprazine showing promise in this disease), Amaranthus expects to be able continue to work with MJFF to advance this program.

## Eltoprazine's Development Status

Amarantus expects to enter a Phase 2b clinical trial with Eltoprazine during the fourth quarter of 2014. With a history and interest by the MJFF, it is possible that the Company may pursue grant funding to help offset study development costs. Investigational New Drug (IND) applications have already been filed in ADHD and schizophrenia, with a clinical trial agreement (CTA) and medical products agency (MPA) agreement filed in Sweden for PD-LID. Of note is that Amarantus has recently hired Dr. Charlotte Keywood (biography on page 18), who previously oversaw development of **dipraglurant** in PD-LID at Addex Therapeutics, which is likely to be key in helping Amarantus shape its development strategy with Eltoprazine—whether for PD-LID, ADHD, generalized anxiety disorder (GAD), or other potential indication(s).

### *Agreement with PGI Drug Discovery LLC (formerly PsychoGenics Inc.)*

Amarantus announced that it had completed the in-licensure of Eltoprazine from PGI Drug Discovery LLC (formerly PsychoGenics Inc.) in January 2014, with Amarantus gaining rights to Eltoprazine worldwide, excluding Asian territories. Eltoprazine was previously studied for the alleviation of involuntary movements, including dyskinesias, in PD patients who experienced side effects from their levodopa medication. Under this agreement with PGI, Amarantus intends to push Eltoprazine forward in a Phase 2b clinical study during the fourth quarter of 2014 for the treatment of LID. This acquisition was based on a relationship with former PGI chief scientific officer and current Amarantus Board member, David A. Lowe, Ph.D. (biography on page 20).

Under the terms of the license agreement, Amarantus agreed to pay PGI \$100,000 in cash for the license; pay PGI up to an aggregate of \$4 million in development milestones through New Drug Application (NDA) submission; pay a research support payment to PGI as partial reimbursement for costs incurred for earlier research and management of CIAS, ADHD, and LID clinical trials totaling up to \$650,000—to be paid in a mixture of cash and stock; and reimburse PGI for the Eltoprazine clinical supply inventory up to \$500,000 payable upon the earlier of the initiation of a Phase 2b clinical study or six months after the date of the license agreement. As well, Amarantus is to pay a single-digit royalty to PGI of the annual worldwide net sales by the Company.

Concurrent with this license agreement, Amarantus and PGI entered into a services agreement, in which PGI agreed to provide certain services to Amarantus related to PGI's proprietary analytical systems. Amarantus agreed to a payment commitment of \$450,000 at a minimum annual rate of \$150,000 for each of three years. The services agreement is for a term of the later of three years or the completion of any study plan accepted by the parties under the services agreement. As partial consideration of the research support payment by the Company to PGI, Amarantus entered into a Securities Purchase Agreement with PGI, pursuant to which PGI subscribed to four million shares of the Company's common stock and the Company granted PGI certain piggy-back registration rights.

## Current Treatment Options for PD-LID

### *Existing Product: Amantadine*

Amantadine is a generic antiviral used off-label to treat LID. Its use in treating LID has been studied in a series of small clinical trials (most open-label or lacking a control arm). A randomized double-blind trial of 18 LID patients concluded that amantadine reduced the duration of dyskinesia episodes by 60% and improved quality of life. A second study found that amantadine reduced dyskinesia symptoms by 45% (noting that the duration of the effect was only eight months, where a rebound of symptoms took place when therapy was stopped). Amantadine's use in treating LID likely stems from its activity as an **NMDA antagonist**.

Amantadine is supplied by Endo Pharmaceuticals Inc. (profiled on page 49). Adamas Pharmaceuticals also recently completed an 80-subject Phase 2/3 trial of an extended-release amantadine, ADS-5102 (amantadine HCl) ER, a high-dose, controlled-release version of the medication given once daily at bedtime. As announced in June 2013, the trial met its primary endpoint of reducing LID (measured by the MDS-Unified Parkinson's Disease Rating Scale [MDS-UPDRS]). Greater details of ADS-5102 are provided under Potential Competition (page 47).

*In Development: Dipraglurant*

Dipraglurant by Addex Therapeutics is an oral negative allosteric modulator (NAM) of the metabotropic glutamate receptor 5 (mGluR5), being developed for the treatment of PD-LID. Dipraglurant was examined in a randomized, double-blind, placebo-controlled Phase 2a trial in 83 subjects with moderate-to-severe PD, with results showing the drug to be safe and well tolerated (noting side effects of vertigo, blurred vision, and a drunk feeling, though none of these were severe). Results on the modified **Abnormal Involuntary Movement Scale (AIMS)** scale showed statistically significant improvement on days 1 and 14, with clinically relevant reductions in the dipraglurant group on all three periods tested (days 1, 14, and 28). However, it is noteworthy that in April 2014, another product in development for PD-LID that also targeted the mGluR5 receptor, called mavoglurant from Novartis AG, was discontinued due to a lack of efficacy in clinical trials. Addex has reportedly been seeking to out-license or partner dipraglurant since 2012.

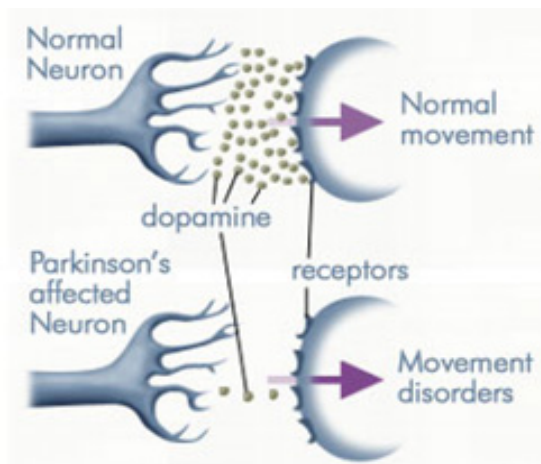
**Potential Benefits of Eltoprazine versus Current Options**

A potential benefit for Eltoprazine over amantadine and dipraglurant could prove to be Eltoprazine’s possible improvements in cognitive function as seen in PGI’s Phase 2a study, with the potential to further reduce future dyskinesia onset. Eltoprazine has also been studied in general anxiety disorder, depression, and aggression. The mechanism of action is well understood for Eltoprazine, and should its secondary improvements in severely ill PD patients be confirmed, this could create substantial value with additional potential stemming from expanding development into ADHD or cognition, where a non-stimulate/non-scheduled product could show material benefits over generic methylphenidate.

**Parkinson’s Disease (PD)**

Parkinson’s disease (PD), named after English doctor James Parkinson who published the first description of the brain disease in an essay in 1817, is a severe neurological disorder characterized by tremor, muscle rigidity, and an inability to walk with a steady gait. PD is primarily associated with the degeneration of a specific set of **dopaminergic (DA) neurons** in the human brain (Figure 11). According to the National Institutes of Health (NIH), symptoms begin to appear when 60% to 80% of these DA neurons have become dysfunctional or have died.

Figure 11  
 PARKINSON'S DISEASE: DOPAMINE LEVELS IN A NORMAL VS. A PARKINSON'S AFFECTED NEURON



Source: AGING SCIENCES – Anti-Aging Firewalls.

Figure 12  
 PARKINSON'S DISEASE: SYMPTOMS



Source: Medicscientist.com.



### *Symptoms*

Symptoms and signs vary between patients, and mild early signs may go unnoticed. Beginning on one side of the body, symptoms typically stay worse on that side, even after they begin to affect both sides. Such symptoms may include tremors, which usually begins in a limb—often hand or fingers. A back-and-forth rubbing of the thumb and forefinger (pill-rolling tremor) may also occur. People with PD may also see a tremor of the hand when relaxed (at rest). Over time, PD may hinder the ability to move and slow movement, making simple tasks difficult and time consuming. Steps may become shorter or it may become difficult to get out of a chair. A person may drag his feet as he walks and muscle stiffness may occur in any part of the body, which can limit range of motion and be painful. Furthermore, a person's posture may become stooped, or there may be balance problems. Individuals with PD may also have a decreased ability to perform unconscious movements, such as blinking, smiling, or swinging of the arms when walking. As well, a person may no longer be able to gesture when talking, and may experience speech problems, where a person may speak softly, quickly, slur, or hesitate before speaking, or speech may be more of a monotone versus with the typical inflections. Writing may also appear small and become difficult for patients.

### *Risk Factors and Cause*

While its cause is unknown, several factors appear to play a role in PD, including genes. Researchers have identified specific genetic mutations that can cause the disease (however, these are not common except in rare cases when many family members are affected by PD) as well as have discovered certain gene variations and environmental triggers, where exposure to certain toxins or other factors may increase the risk of later PD (though the risk is relatively small). With those factors having the potential to trigger PD, more research is necessary to identify the main causes of the disease. Risk factors for developing PD include age, as the disease typically begins in middle or later in life. Most people developing PD are roughly age 60 or older, and risk increases with age. Other risk factors include heredity, where having a close relative with PD increases the chances of developing the disease (though risk remains small unless there are multiple relatives with PD); sex (men are more likely to develop PD than women); and exposure to toxins (ongoing exposure to herbicides and pesticides may increase an individuals' risk for PD).

### *Diagnosis*

There is no approved blood or laboratory test proven to help diagnose sporadic PD. A diagnosis is based on medical history and a neurological examination has been the standard to date. The disease can be difficult to diagnose accurately; thus, physicians may opt to have brain scans or laboratory tests conducted so as to rule out other diseases or conditions.

### *Medications*

In PD, certain nerve cells (neurons) in the brain gradually break down or die, and many of the symptoms result from a loss of neurons that produce a chemical messenger in the brain called dopamine. Medications are able to reduce many of the symptoms of PD, since they can increase or substitute for dopamine. When dopamine levels decrease, abnormal brain activity occurs and results in signs and symptoms of PD.

### **Parkinson's Disease Levodopa-Induced Dyskinesia (PD-LID)**

In the 1960s, treatment of PD was revolutionized by the introduction of levodopa. Following its discovery, however, it was reported that continuous treatment was leading to an emergence of hyperkinetic or abnormally heightened, and sometimes uncontrollable, muscle movements as well as off episodes where patients are symptomatic despite taking medication. While levodopa therapy remains an effective symptomatic treatment to date for PD, its effectiveness is limited by these motor complications, which leads to a decline in quality of life. Levodopa-induced dyskinesia (LID) is the primary side effect linked to levodopa and includes chorea (abnormal involuntary movement), dystonia (sustained muscle contraction, abnormal posture), and athetosis (involuntary convoluted movements).



LID typically starts in the lower extremity ipsilateral to the side first affected by PD (normally the most affected side), and in the beginning stages of LID, patients may not notice subtle hyperkinetic movements; however, as it progresses, LID often interferes with activities, leading to functional impairment, disability, and poor quality of life.

#### *PD and Dyskinesia*

In the context of PD, dyskinesia is often the result of chronic levodopa therapy. These motor fluctuations occur in more than half of PD patients after 5 to 10 years of treatment (with the percentage of affected patients increasing over time). Based on the relationship with levodopa dosing, dyskinesia most commonly occurs at the time of peak levodopa plasma concentrations and is referred to as **peak-dose dyskinesia (PDD)**. As patients advance, they may experience **diphasic dyskinesia (DD)**, which occurs when the drug concentration rises or falls. If dyskinesia becomes too severe or impairs an individual's quality of life, a reduction in levodopa might be necessary, though this reduction may be accompanied by a worsening of motor performance. Consequently, once established, LID can prove quite difficult to treat.

#### *Risks*

Risks of developing LID have been linked to PD severity, younger age at onset, female sex, duration of levodopa treatment, and total levodopa exposure. A literature survey of more than 2,000 publications identified LID in almost 40% of patients with PD treated with levodopa for four to six years. An alternative review found a prevalence of LID in up to 85% of patients with PD, noting that the use of different methods to recognize LID has resulted in variations in the frequency rate reported in the literature.

#### *Market Size*

Roughly four million individuals worldwide are living with PD, including 500,000 individuals in the U.S. Between 40% to 85% of these patients are thought to be exhibiting symptoms of LID after four or more years of treatment with levodopa. Amarantus estimates the potential market opportunity for a drug that could treat LID in the U.S. alone could surpass \$750 million annually. The NIH estimates that the total cost to the U.S. exceeds \$6 billion annually, with the risk of PD increasing with age—thus the financial and public health impact of this disease is likely to increase as the population gets older (Source: National Institute of Neurological Disorders and Stroke).

## ELTOPRAZINE (Adult ADHD)

In February 2014, Amaranthus announced positive Phase 2a data for Eltoprazine in Adult ADHD. Results from the study demonstrated statistically significant improvements of both doses of 5mg and 10mg versus placebo in a range of ADHD clinical measures. The primary objective was to compare the effects of two doses of Eltoprazine (5mg and 10mg) with placebo on symptoms of ADHD in adults. The primary efficacy parameter was **ADHD Rating Scale-IV (AHDH-RS-IV)**. The secondary efficacy parameters compared two doses of Eltoprazine (5mg and 10mg) versus the **Conner's Continuous Performance Test (CPT)**, the Investigator's **Clinical Global Impression-Improvement (CGI-I)** scale, the safety/tolerability of multiple doses of Eltoprazine, and the safety after discontinuation. Data demonstrated that at both 5mg and 10 mg, the study met its primary endpoint as measured by change from baseline in ADHD-RS-IV score in 5mg ( $p=0.003$ ) and 10mg ( $p=0.037$ ) doses, which were statistically significantly superior to placebo with approximately 25% greater efficacy compared to placebo. Total ADHD-RS-IV scores improved by 13.6, 17.9, and 17.4 points from baseline for placebo, 5mg, and 10mg of Eltoprazine, respectively.

Inattention, hyperactivity, and impulsivity ADHD-RS-IV subscales were also analyzed. For the inattention subscale, both 5mg and 10mg groups showed a statistically significant benefit over placebo (0.003 and 0.039, respectively). For the hyperactivity subscale, the 5mg dose showed a statistically significant benefit in favor of Eltoprazine versus placebo ( $p=0.008$ ). The 10mg dose was superior to placebo; however, the difference was not statistically significant ( $p=0.130$ ). For the Impulsivity subscale, no significant benefit was observed for either drug dose compared to placebo. Both 5mg and 10mg demonstrated significantly greater improvement over placebo for CGI-I scores ( $p=0.023$  and 0.004, respectively). The percentage of subjects who were considered improved by the investigator was 57.9% for placebo, 68.4% for 5mg, and 81.1% for 10mg. The percentage difference was significant between 10mg and placebo (0.029), but it was not between 5mg and placebo ( $p=0.342$ ).

Results indicate the overall positive outcomes reported on the ADHD-RS-IV were largely driven by the inattention and hyperactivity subscales—an outcome which was expected as most enrolled subjects had primary deficit in inattention at baseline. Benefits of the active treatments were also observed for secondary efficacy variables, **Profile of Mood States (POMS)**, where the 5mg dose was statistically significantly better than placebo for POMS total score ( $p=0.006$ ). Both the 5mg and 10mg groups were statistically significantly better than placebo for anger-hostility score ( $p<0.001$  and  $p=0.036$ , respectively); and the 5mg group was also statistically significantly better than placebo for tension anxiety score ( $p=0.046$ ).

As well, **Barnes Akathisia Scale (BAS)** had both 5mg and 10mg groups showing a reduction in restlessness that was statistically significantly better than placebo for BAS ( $p=0.029$  and  $p=0.007$ , respectively); both 5mg and 10mg groups were statistically significantly better than placebo for Awareness of Restlessness subscore ( $p=0.003$  and  $p<0.001$ , respectively); and the 10mg group was also statistically significantly better than placebo for Distress Related Restlessness subscore ( $p=0.047$ ). For the Abnormal Involuntary Movement Scale (AIMS), 10mg showed a significantly greater reduction in abnormal movements than placebo ( $p<0.001$ ). There were no serious adverse events (SAEs), and most adverse events were mild of moderate in severity, with only two severe treatment-related adverse events with the 5mg/day (hypnagogic hallucination and constipation) and one severe treatment-related adverse event with the 10mg/day (fatigue).



## **Attention Deficit Hyperactivity Disorder (ADHD)**

ADHD is a psychiatric disorder of the neurodevelopmental type in which there are significant problems of attention, hyperactivity, or acting impulsively, which are not appropriate based on a person's age. As one of the most common childhood disorders, ADHD can continue through adolescence and adulthood. Its symptoms include difficulty staying focused and paying attention, difficulty controlling behavior, and hyperactivity (over-activity).

### *Causes, Signs, and Symptoms*

The cause of ADHD is uncertain though many studies suggest that genes play a large role. Similarly to many other illnesses, ADHD likely results from a combination of factors. Beyond genetics, researchers are exploring possible environmental factors, and studying how brain injuries, nutrition, and the social environment may also play a role. Key behaviors of ADHD include inattention, hyperactivity, and impulsivity, noting that while it is normal for all children to be inattentive, hyperactive, or impulsive at times, children with ADHD experience these behaviors more often and in a more severe manner. ADHD is one of the most common childhood disorders, with the average age of onset about seven years old, though the disorder can sometimes follow a child through adolescence and into adulthood. ADHD affects approximately 4.1% U.S. adults age 18 and older in a given year and 9% of U.S. children age 13 to 18, where boys are at four times greater risk than girls. It has been shown in studies that the number of children diagnosed with ADHD is increasing though the reason for this trend remains unknown. No single test can diagnose ADHD, but rather a licensed health professional must gather information about an individual and his or her behavior and environment.

### *Market Size*

ADHD is one of the most common psychiatric disorders in children and adolescents, with approximately 7.8% of all U.S. school-age children, or about 4.4 million children aged 4 to 17 years, having been diagnosed with ADHD at some point in their lives (Source: U.S. Centers for Disease Control and Prevention [CDC]). As well, over eight million adults in the U.S. also exhibit the symptoms of ADHD (see accompanying section, while only an estimated 600,000 are actually treated). The ADHD market is valued at over \$3.5 billion dollars, with approximately 35 million prescriptions written annually.

### *ADHD in Adults*

Similar to children, adults who may have ADHD should be evaluated by a licensed mental health professional, noting that a professional may need to consider a wider range of symptoms when assessing adults for ADHD as such symptoms may be more varied and possibly not as clear-cut as those exhibited in children. To be diagnosed, an adult must have ADHD symptoms that began in childhood and continued throughout adulthood. Certain rating scales are used to determine if an adult meets the diagnostic criteria for ADHD. A mental health professional may also look at an individual's history of childhood behavior and school experiences, and may interview spouses or partners, parents, close friends, and other associates. As well, a physical exam and various psychological tests are performed.

### *Treatments*

Current treatments, which focus on reducing symptoms of ADHD and improving functionality, may include medication, various types of psychotherapy, education or training, or a combination of these. While there is no cure, treatments may be able to relieve many of the disorder's symptoms. In fact, with treatment, the majority of people with ADHD can be successful and lead productive lives. More effective treatments and interventions are being developed as well as new tools, such as brain imaging, to better understand and discover more effective ways to treat or even prevent ADHD.





## Medications

In children, medications are only recommended as a first-line treatment for individuals with severe symptoms and may be considered for those with moderate symptoms who either refuse or fail to improve with counseling since long-term effects of medications are not clear (noting that medications are not recommended for preschool-aged children). Medications used most commonly for treating ADHD are called “stimulants.” While it may seem counterintuitive at the thought of treating ADHD with a medication considered a stimulant, it actually has a calming effect on some, with different types of such medications available. Other ADHD medications, which are non-stimulants, work differently.

Many children benefit from ADHD medications as they reduce hyperactivity and impulsivity and improve their ability to focus, work, and learn. As well, medication may also improve physical coordination. That said, a one-size-fits-all approach does not work for all children affected by ADHD, where what works for one person might not work for another and might actually produce side effects while others may not be affected. From time to time, several different medications or dosages must be tested in order to find one that works, noting that medications must be closely and carefully monitored by caregivers and physicians. Treatment for Adult ADHD is similar to treatment for childhood ADHD, and at present, includes stimulant drugs or other medications and psychological counseling.

Stimulant medications come in different forms—pills, capsules, liquids, or patches. Some medications also come in short-acting, long-acting, or extended-release varieties, noting that while the active ingredient remains the same, the drug is released differently in the body. Long-acting or extended-release forms often allow a child to take the medication just once a day before school. That said, with no medical cure yet available for this persistent and chronic condition, there is a large and unmet need for new non-stimulant therapies for ADHD, with Amaranthus’ Eltoprazine reporting positive Phase 2a data in Adult ADHD, including demonstrating statistically significant improvements of both doses of 5mg and 10mg versus placebo in a range of ADHD clinical measures.



### **MANF (Mesencephalic-Astrocyte-derived Neurotrophic Factor)**

Amarantus' MANF product candidate is a highly potent, neurotrophic factor with mechanisms of action differentiated from its predecessors. It is believed to have broad potential as it is a naturally occurring protein produced by the body for the purpose of reducing and preventing apoptosis (cell death) in response to injury or disease via the unfolded protein response of the endoplasmic reticulum (where MANF has been able to mediate this critical biological process). By manufacturing MANF and administering it to the body, the Company is seeking to use a regenerative medicine approach to assist the body with higher quantities of MANF when needed.

As the front-runner and primary holder of intellectual property (IP) around MANF, the Company is initially focused on developing MANF-based protein therapeutics, with the lead indication being Retinitis Pigmentosa (RP). A genetic degenerative disorder of the eye that starts in adolescence, RP makes people blind by the time they reach age 40. There are about 100,000 patients in the U.S. and a comparable number in the EU affected by RP, which qualifies it as an orphan indication, though Amarantus believes there to be a large enough population in which to make meaningful revenues. A list of some well-known individuals with RP, including business mogul Steve Wynn, is provided at the following link: <http://retinitispigmentosatreatment.com/celebrities-who-have-retinitis-pigmentosa/>.

Other applications that the Company may consider to pursue with MANF could include PD and Wolfram's Syndrome (a rare disorder stemming from pituitary gland dysfunction and a shortage of insulin in the body), as well as TBI/CTE, myocardial infarction, antibiotic-induced ototoxicity, and certain other rare orphan diseases.

### **Key Issued Composition of Matter Patents**

Importantly, Amarantus owns key issued composition of matter patents for MANF, and has successfully defended these patents from a patent challenge in Europe in 2012. The Company also owns method of use patents for MANF in the area of neurology, and has acquired exclusive options and licenses to additional intellectual property covering the therapeutic use of MANF and CDFN in the area of retinal degeneration, the therapeutic use of MANF in beta cell degeneration-related disorders (including diabetes and Wolfram's Syndrome), and the use of MANF in the area of beta cell degeneration biomarker identification. Furthermore, the Company is pursuing a broader intellectual property strategy for MANF intended to attract key scientists working on MANF to collaborate with the Company in order to build the world's leading MANF-based collaborative effort that would inform clinical development and commercial opportunities for MANF.

### **Potential for Orphan Drug Designation**

In August 2013, Amarantus announced positive data on MANF in RP, with the study concluding that intravitreal (into the eye) injection of recombinant human MANF protein protects against retinal degeneration in an animal model of RP. Simultaneously, the Company is assembling the necessary orphan regulatory expertise to apply to the FDA for an Orphan Drug Designation (ODD) for MANF.

ODD could represent an opportunity for Amarantus to reach the market at reduced development costs, with preclinical data in RP showing promise. In 2012, an abstract was presented from the University of Miami's Bascom Palmer Eye Institute at the Association for Research in Vision and Ophthalmology annual conference, with results showing that recombinant human MANF significantly protected rod and cone photoreceptors from degeneration. MANF's mechanism of action, protection of the endoplasmic reticulum, facilitation of protein folding, and reduction of cell apoptosis indicated to be well-matched for RP or other eye diseases. Amarantus believes that the Company could file an Orphan Drug application for RP in the fourth quarter of 2014, and that an IND could follow thereafter.



### Publication of Positive Independent Peer-Reviewed Data

In May 2014, Amarantus announced the publication of positive independent peer-reviewed data on MANF in the areas of AD and diabetes, as well as additional studies that further support its critical role in proper cellular function. The studies further corroborate the role of MANF in reducing misfolded protein concentration and improving proper overall endoplasmic reticulum function. A study entitled “MANF Inhibits Tau Hyperphosphorylation in Cultured Neuronal Cells” published in the journal *Chinese Pharmacological Bulletin*, discusses how MANF had a pronounced effect in reducing tau hyperphosphorylation, reducing cell death, and improving overall cellular health in a preclinical models. Misfolded tau is a significant part of the pathophysiology of AD and CTE. The data in the study demonstrated the following:

- Pretreatment with recombinant MANF can inhibit **okadaic acid (OA)**-induced tau hyperphosphorylation in N2a cells;
- Transfection of N2a cell with MANF cDNA also inhibits OA-induced tau hyperphosphorylation and supports cell viability; and
- Downregulation of MANF with siRNA promotes OA-induced toxicity.

Further, a study entitled “MANF Is Indispensable for the Proliferation and Survival of Pancreatic  $\beta$  Cells” published in the journal *Cell*, MANF demonstrated to be essential for the protection and proliferation of pancreatic beta islet cells (where beta islet cells degenerate via apoptosis in Type 1 Diabetes, Type 2 Diabetes, and Wolfram’s Syndrome). According to this study, the data demonstrate the following:

- MANF-deficient mice show growth retardation and a diabetic phenotype;
- Beta cell mass is significantly reduced in MANF knock-out mice, caused by decreased proliferation and increased apoptosis; and
- Recombinant MANF significantly increases beta cell proliferation *in vitro*, while overexpression of MANF in the pancreas of diabetic mice enhances beta cell regeneration.

The Company believes that these published papers continue to demonstrate the emerging evidence for overlap in mechanisms involved in AD and diabetes, and further support for the Company’s work, while increasing the scale for future clinical development efforts, together with RP and PD.

### Development Status

Amarantus believes that the biology underlying its MANF program is innovative—addressing misfolded and unfolded proteins using endogenous proteins that are resident in the area specifically unregulated to protect against protein misfolding. The Company believes that MANF is the first and only molecule that acts both inside and outside the cell, with available literature increasing dramatically, from approximately three papers five years ago to well over 50 today.

Under the direction of Dr. David Lowe (president and CEO of NeuroAssets, Sarl, a Swiss-based neuroscience-focused consulting firm who is overseeing the translational development of MANF through first-in-man clinical studies [biography on page 20]), experiments are underway at multiple CROs, as well as a collaboration agreement being moved forward with the University of Miami’s Bascom Palmer Eye Institute (described on page 44), to evaluate the safety and efficacy of MANF in multiple models of RP. Amarantus owns the exclusive option for the method of use patents using MANF in RP as well as the composition of matter on the actual protein.



#### *Buck Institute for Research on Aging Research Collaboration*

Amarantus announced in August 2014 that it had entered into a research collaboration with the Buck Institute for Research on Aging for the development of MANF in undisclosed therapeutic indications. Under the terms of the agreement, Amarantus has agreed to fund research by Henri Jasper, Ph.D., professor at the Buck Institute for Research on Aging, and his Buck faculty colleague Deepak Lamba, Ph.D., and Postdoctoral Fellow Joanna Neves, Ph.D., to further their scientific insights and generate intellectual property regarding the therapeutic potential of MANF. As well, Amarantus has acquired an exclusive option to license this intellectual property. The Company has further received a right to use certain undisclosed scientific findings for the purpose of regulatory submissions and grant applications to obtain further funding for its programs.

#### *University of Massachusetts Medical School License Agreement*

Amarantus also entered into an exclusive worldwide license agreement in December 2013 with the University of Massachusetts Medical School for intellectual property surrounding the use of MANF as both a biomarker and a treatment for beta cell-degenerating disorders, where the license agreement includes all intellectual property covering the use of MANF as a biomarker and treatment for beta cell degeneration disorders, including Wolfram's syndrome, Type 1 diabetes, and Type 2 diabetes. Along with this announcement, the Company reported positive data for MANF in treating degenerating beta cells in various cellular models of beta cell degeneration. Generated by the laboratory of former University of Massachusetts Medical School researcher, Fumihiko Urano, M.D., Ph.D., this data demonstrated that MANF has a potent activity in preserving beta cell viability in response to endoplasmic reticulum stress (ER Stress) that mimic Wolfram's Syndrome and diabetes *in vitro*. As well, MANF is selectively secreted by beta cells in response to ER stress.

As well, in February 2014, Amarantus entered into an Option Agreement with the University of Massachusetts in which the Company was granted an option to obtain an exclusive license (with the right to sublicense) to the patent applications to be filed based upon UMA 14-006 titled "MANF as a Therapeutic Agent for the production of Mammalian Sensory Cells." Terms of the option are 18 months, which may be extended by the Company for an additional six months upon demonstration to University of Massachusetts of continued progress evaluating the business opportunity with respect to the patent rights and payment of a fee to the University of Massachusetts. In consideration for the grant of the option, the Company paid an option fee of \$1,000 and is to pay a retainer fee of \$15,000 to cover initial patent expenses to be incurred in connection with obtaining the patent rights.

#### *University of Miami Option Agreement*

In August 2014, the Company announced that it had exercised an exclusive option to license intellectual property related to MANF's utility in treating retinal disorders from the University of Miami's Bascom Palmer Eye Institute, and has entered into an exclusive license for this intellectual property. The Bascom Palmer Eye Institute at the University of Miami Miller School of Medicine has been ranked No. 1 nationally in ophthalmology in *U.S. News & World Report's* annual "Best Hospitals" rankings for 11 consecutive years.

Under the terms of the agreement, Amarantus has been granted a perpetual, exclusive worldwide license to intellectual property covering the use of MANF for treating retinal disorders, including RP. The option agreement includes all intellectual property covering the use of the MANF family of proteins (MANF and CDFN) for retinal diseases, including age-related macular degeneration, glaucoma, inherited retinal disorders (including RP), sporadic retinal disorders, other degenerative retinal disorders, and retinal injuries. This option agreement follows previously announced positive data for MANF in the S334ter Type 3 genetic mouse model of RP.

### *Renishaw plc*

Concurrently, the Company has been working with Renishaw plc (a global company with core skills in measurement, motion control, spectroscopy, and precision machining) to complete experiments evaluating the feasibility of using Renishaw’s delivery system, including the neuromate® stereotactic robot, neuroinspire™ surgical planning software, and neuroinfuse™-intraparenchymal delivery system for the delivery of MANF in PD and other neurological conditions. The companies have stated their plan to collaborate to conduct certain feasibility studies to ensure the long-term viability of delivering MANF using Renishaw’s product line to key brain structures, where upon achieving success in doing so, could then enter into a definitive agreement to support human clinical studies and commercial use. In October 2013, Amarantus entered into a letter of intent with Renishaw to use Renishaw’s proprietary implantable neurosurgical products and systems for MANF in PD.

### *Strategic Expansion into Additional Indications and Geographic Areas*

MANF may be applicable not only to areas of neurology and ophthalmology like RP but also in metabolic disorders like diabetes. The Company has also been seeking a research collaborator for MANF’s development in Wolfram’s syndrome, where Amarantus has been successful in establishing strong relationships with key researchers—important for the future development of this indication. Wolfram’s Syndrome is a rare disorder stemming from pituitary gland dysfunction and a shortage of insulin in the body. Also called **DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, and Deafness)**, Wolfram’s Syndrome causes diabetes mellitus, optic atrophy, and deafness, as well as various other possible disorders. Amarantus believes that conducting small clinical studies and generating proof-of-concept data in an orphan designation like Wolfram’s Syndrome may facilitate partnering opportunities for Type 1 diabetes.

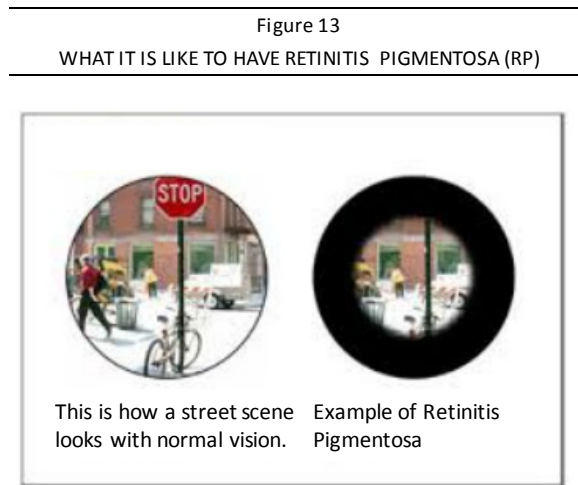
Collaborating with leading academic groups who hold specialties in the various areas pertaining to MANF’s fundamental biology may prove critical in developing this compound. In particular, the Company may seek out possible collaborators who have established operations in the Far East, specifically in developing the compound for diabetes and cardiovascular disease, as Amarantus may be able to leverage its academic network and the emerging scientific critical mass in China to further its interests around the world.

### **Potential Market Opportunity**

#### *Retinitis Pigmentosa (RP)*

RP refers to a group of inherited diseases causing retinal degeneration that affects approximately 100,000 individuals in the U.S. (qualifying it for an orphan disease under FDA guidelines). It is a disease of the retina in the eye. The retina lines the back wall of the eye and is responsible for capturing images from the visual field. Individuals with RP experience a gradual decline in their vision stemming from the death of photoreceptor cells, as illustrated in Figure 13. Scientists believe this is due to significant endoplasmic reticulum stress and protein misfolding.

While night blindness is one of the earliest and most frequent symptoms of RP, other symptoms include a progressive degeneration of peripheral and night vision as well as the degeneration in color perception and central vision. The condition is typically diagnosed in adolescents and young adults, with the rate of progression and degree of visual loss differing from person to person. The majority of people with RP are legally blind by the time they reach age 40. Amarantus estimates that there could be a multi-billion market opportunity for RP based on a U.S. market of 100,000 patients, an EU market of 100,000 patients, and a Japanese market for 50,000 patients—with assumed pricing of \$300,000 (\$150,000/eye).



*Source: Amarantus BioScience Holdings, Inc.*



### *Parkinson's Disease (PD)*

Refer to pages 36-37 for a complete description.

### *Wolfram's Syndrome*

Wolfram's syndrome, also called DIDMOAD, is a rare genetic disorder that causes diabetes mellitus, optic atrophy, and deafness as well as various other possible disorders. First described in four siblings in 1938 by Don J. Wolfram, M.D., the disease affects the brain and central nervous system, and is believed to be caused by both a malfunction of the **mitochondria** and of **myelination** (the latter in effect similar to multiple sclerosis [MS]). There are approximately 20,000 patients worldwide with Wolfram's syndrome. The first symptom is typically diabetes mellitus, usually diagnosed around age six. The next symptom is often optic atrophy, the wasting of optic nerves, about age 11, where the first signs are loss of color vision and peripheral vision. This disease typically worsens over time, and those with optic atrophy are most often blind within eight years of the first symptoms. People suffering from this syndrome have a life expectancy of about 30 years. The diabetes aspect of Wolfram's Syndrome is typically managed using insulin and other diabetes medications, and the retinal and otology impacts often go untreated. Amarantus estimates that there could be a multi-billion market opportunity for Wolfram's Syndrome based on a market of 20,000 patients and assuming pricing of \$100,000 per treatment.

### *Diabetes*

Known simply as diabetes, diabetes mellitus is a group of three metabolic diseases—Type 1, Type 2, and gestational diabetes—and occurs when an individual has abnormally high levels of glucose in the circulating blood caused by either a failure of the body's pancreas to produce insulin and/or an inability to respond sufficiently to circulating insulin. Diabetes is considered an autoimmune disease since the body's immune system attacks and destroys insulin-producing beta cells in the pancreas. When not adequately controlled, diabetes can lead to a number of complications including stroke, blindness, amputation, kidney failure, and heart attack, among others, which can ultimately be fatal, calling attention to the importance of managing and treating this metabolic disease. Diabetes is the seventh leading cause of death among the U.S. population.

According to Standard & Poor's, the diabetes drug market is estimated at \$35 billion and is on pace to exceed \$58 billion by 2018. GBI Research (a publisher of in-depth strategic intelligence reports in a broad range of professional industries) forecasts the market, specifically for Type 2 diabetes, could grow from \$20.4 billion in 2012 to \$38.8 billion in 2019, with a compound annual growth rate (CAGR) of 10.2%.

### *Ischemic Heart Disease*

A potential future indication for MANF, ischemic heart disease is characterized by a reduction of blood supply to the heart muscle, typically caused by atherosclerosis of the coronary arteries. Symptoms of stable IHD include angina and decreased exercise tolerance, though unstable IHD presents itself as chest pain or other symptoms at rest. Risk of IHD increases with age, smoking, high cholesterol levels, diabetes, and hypertension, and is seen more often in men as well as those individuals with family history. Furthermore, IHD is the most common cause of death in most Western countries, and a leading cause for hospital admissions. Myocardial infarctions (heart attacks) are one of the leading causes of death for both men and women globally, where important risk factors include previous cardiovascular disease, older age, tobacco smoking, high blood levels of certain lipids and low levels of high density lipoprotein, diabetes, high blood pressure, obesity, chronic kidney disease, excessive alcohol consumption, and chronic high stress levels. Many forms of IHD, including myocardial infarction, have been characterized as having a pathway of apoptosis-related cell death associated with reperfusion-related injuries. Amarantus' development candidate, MANF, has been shown to be upregulated and to protect heart muscle in reperfusion models of cardiac ischemia.



## Potential Competition

Amarantus may compete with a wide range of companies, both large and small, as it advances the development of its therapeutic compounds targeting diverse medical conditions: Parkinson's disease Levodopa-induced dyskinesia (PD-LID), Adult ADHD, Retinitis Pigmentosa (RP), and more. The Company's diagnostic efforts with its LymPro Test<sup>®</sup> and NuroPro test could also encounter competitive products in the form of new diagnostic tests and assays as well as older, less formal techniques for identifying the onset of Alzheimer's disease (AD) and Parkinson's disease (PD), such as tests of patients' cognitive abilities. The primary tool for AD diagnosis today is a lumbar puncture in order to take a sample of the patient's cerebrospinal fluid (CSF), which is painful and troubling to most patients, although an MRI may also be used in some situations. Beyond pharmaceutical and biotechnology firms, there are also academic organizations, research centers, and government agencies working to investigate the causes of and new treatment modalities for debilitating, degenerative conditions like AD and PD.

For some of Amarantus' target indications, such as ADHD, there already exist on the market prescription and generic products that could pose a barrier to adoption of new treatments, such as those in development by Amarantus, even though the Company believes its technologies and product development can lead to improved options for many patients. Examples of approved ADHD medicines include but are not limited to the following: (1) Shire Pharmaceuticals' Adderall XR (an amphetamine also used to treat narcolepsy); (2) a milder amphetamine known as methylphenidate that is offered both as a brand name and a generic under the brands Ritalin from Novartis AG, Concerta from Janssen Pharmaceuticals, Inc. (part of JNJ), and Daytrana from Noven Therapeutics, LLC, among many other brands/companies; (3) dexamethylphenidate, which is also a CNS stimulant both branded and sold as a generic under the product name Focalin from Novartis, Attenade from Celgene Corp., and Dexamethylphenidate HCl Tablets CII from Teva Pharmaceutical Industries Ltd., among others; and (4) Strattera, a selective norepinephrine reuptake inhibitor (NRI), from Eli Lilly and Co.

Several of Amarantus' product candidates may ultimately penetrate a market where there are other marketed products but the Company is well versed in its target indications' existing and potential competition and believes that its products can represent an improved option for diagnosing and treating complex diseases like AD, PD-LID, ADHD, RP, traumatic brain injury (TBI), and more. The following summaries are not intended to be an exhaustive collection of potential competitors to Amarantus; however, they are believed to be representative of the type of competition the Company may encounter as it seeks to further commercialize its product candidates.

### **Adamas Pharmaceuticals, Inc. (ADMS-NASDAQ)**

<http://adamaspharma.com>

California-based Adamas is a specialty pharmaceutical company focused on developing CNS products, with its lead product candidate being ADS-5102 (amantadine HCl), a potential treatment for PD-LID. Adamas intends for ADS-5102 to resolve limitations of immediate-release amantadine. ADS-5102 is a once-daily, extended-release product candidate taken before bed that has been designed to give patients roughly twice the amount of amantadine in the morning and afternoon as the immediate-release version, offering LID symptom relief to patients during the day. At night, ADS-5102 concentrations are lower, potentially reducing the negative impact of amantadine on sleep. The medicine can be swallowed or opened and sprinkled on food for easier ingestion. In a Phase 2/3 clinical trial, this candidate showed a 43% reduction in LID. It is now under review in an ongoing Phase 3 study that began in June 2014, and Adamas hopes to pursue an NDA filing with the FDA in 2016. The Phase 3 study (EASE LID) is enrolling 130 patients in a 26-week multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy of ADS-5102.

Beyond LID, ADS-5102 is being studied for its effect remedying chronic behavioral symptoms associated with traumatic brain injury (TBI). Additional potential indications where Adamas may commence clinical trials for ADS-5102 could also include ADHD, post-concussive syndrome, multiple sclerosis (MS) fatigue, depression, hyperkinetic movement disorders, and antipsychotic-induced weight gain. Adamas' portfolio also includes MDX-8704, which is a daily fixed-dose combination of Namenda XR<sup>®</sup> and donepezil for treating moderate to severe dementia associated with AD. This product is being co-developed with Forest Laboratories, Inc. and has an NDA on file with the FDA.



### **Addex Therapeutics (ADXN-SIX Swiss Exchange)**

<http://www.addextherapeutics.com>

Swiss company Addex Therapeutics is focused on developing a particular type of oral small-molecule drugs known as allosteric modulators. Addex believes allosteric modulators can offer greater selectivity and better control at the site of disease-mediating receptors in the body. In contrast to many existing small-molecule drugs, which bind receptors at the same location as the body's own endogenous ligands (and which therefore have to compete with the ligands for the binding site), allosteric modulators bind to a different site on the receptor and do not have to compete. They instead are thought to work synergistically with natural ligands and to offer more control over receptor activation/deactivation/function than currently marketed products. Using this technology, Addex has created ADX48621 (dipraglurant), which is an mGluR5 negative allosteric modulator (NAM) for potential treatment of PD-LID. ADX48621 is at the Phase 2a stage and may be used in combination with levodopa or dopamine agonists for Parkinson's disease (PD) treatment. Addex has been pursuing a partnering agreement for the development of this candidate based on successful early preclinical and clinical studies. However, in April 2014, another product in development for LID that also targeted the mGluR5 receptor, called mavoglurant from Novartis AG, was discontinued due to a lack of efficacy in clinical trials.

Addex's pipeline also includes a positive allosteric modulator (PAM), called ADX71149, which is in Phase 2a development in partnership with Janssen Pharmaceuticals Inc. to treat schizophrenia and anxiety, as well as a number of preclinical PAM and NAM candidates for overactive bladder; PD, MS, and other diseases; Type 2 diabetes; AD; depression; and inflammation like rheumatoid arthritis, among other diseases.

### **Eli Lilly and Company (LLY-NYSE)**

<http://www.lilly.com>

Global pharmaceutical company Eli Lilly and Co. produces medicines for the areas of oncology, cardiovascular disease, diabetes, critical care, neuroscience, men's health, musculoskeletal fields, and animal health. In addition to its marketed products in each of these divisions, Lilly has approximately 60 product candidates in varying stages of clinical development and regulatory review. The company's research and development (R&D) pipeline includes a Phase 3 product candidate called solanezumab (LY2062430), which has shown to bind to soluble monomeric forms of amyloid  $\beta$  (Ab) and thus may represent another potential treatment for slowing the progression of AD. Solanezumab attaches to amyloid proteins to make them visible for attack by the body's own immune system. The candidate has so far shown success in Phase 3 trials of safety and efficacy at slowing disease progression for mild cases of AD. Solanezumab, however, did not appear to slow disease progression in moderate or advanced cases of the condition. Lilly is conducting three other Phase 3 trials of the product candidate: (1) solanezumab versus placebo on the progress of mild AD (trial called "Expedition 3"); (2) solanezumab for older individuals who may be at risk for memory loss due to evidence of amyloid plaque build-up in their brains but who have not yet shown symptoms of AD (the "A4 Study"); and (3) solanezumab and another product gantenerumab versus placebo in patients who have a genetic mutation for placing them at increased risk for early onset AD.

Lilly has also recently introduced one of the first options in a new class of products for AD diagnosis. The company's Amyvid (Florbetapir F 18 Injection) was approved by the FDA in April 2012 for use in patients being evaluated for AD and other causes of cognitive decline. Amyvid is a radioactive diagnostic agent for PET imaging that binds to beta-amyloid plaques in the brain and is detected using PET scans. Amyvid is intended for use in combination with other evaluations, including medical history and clinical cognitive impairment exams. This agent is distributed at imaging centers, which must administer the drug to patients within several hours of receiving it from a radiopharmacy because it loses more than half of its radioactivity every two hours. It is also expensive, at roughly \$1,600 per patient. Including the PET scan and office visit to conduct the Alzheimer's test, Amyvid can cost up to \$3,000 (Source: NPR's "Should Medicare Pay For Alzheimer's Scans?," January 31, 2013).





**Endo Pharmaceuticals Inc.**

<http://www.endo.com>

As described on page 47, Adamas Pharmaceuticals is working toward developing an extended-release version of an existing medication, amantadine. Amantadine is currently marketed by Pennsylvania-based Endo Pharmaceuticals Inc., part of global specialty healthcare company Endo International plc. It is sold as Symmetrel, which was initially developed to treat influenza in the 1960s and has since also been identified as a treatment for PD-LID. It is available as a capsule, liquid, and tablet form, and is believed to be the only product available today for treating LID, though it is not often used for mild or early stage PD-LID.

**GE Healthcare Ltd.**

[http://www3.gehealthcare.com/en/products/categories/nuclear\\_imaging\\_agents/vizamyl](http://www3.gehealthcare.com/en/products/categories/nuclear_imaging_agents/vizamyl)

Part of the General Electric Company, GE Healthcare has expertise in medical imaging and diagnostics, among other fields such as patient monitoring systems, drug discovery, biopharmaceutical manufacturing technologies, performance improvement, and performance solutions services. GE Healthcare is headquartered in the United Kingdom but operates in over 100 countries around the world. In October 2013, the FDA approved the second F 18 injection product in the U.S. (following Lilly's Amyvid [described on page 48]), which was GE Healthcare's Vizamyl (flutemetamol F 18 injection), a radioactive diagnostic drug used in PET brain imaging for adults being evaluated for AD or dementia. Like other approved F 18 molecules used in brain scans for AD, Vizamyl is intended for use in conjunction with other diagnostic measures of cognitive decline and, alone, does not establish an AD diagnosis. A positive Vizamyl brain scan indicates a moderate or greater amount of amyloid present in the patient's brain, which could suggest AD. A negative scan indicates there is little or no amyloid accumulation, and thus the patient's dementia is likely not due to AD.

GE Healthcare began commercial distribution of Vizamyl in the second quarter of 2014. The initial U.S. imaging centers to receive the drug for patient use during the second quarter were located in East Rutherford, NJ, Woburn, MA, Beltsville, MD, East Lansing, MI, Dallas, TX, Phoenix, AZ, and Colton, CA. GE Healthcare has also developed a program for training physicians on how to interpret the images returned by a Vizamyl scan, noting that images should only be interpreted by readers who have completed this program.

**Laboratory Corp. of America Holdings (LH-NYSE)**

[www.labcorp.com](http://www.labcorp.com)

Laboratory Corp. of America Holdings (LabCorp) is a global provider of laboratory testing services on behalf of physicians, hospitals, managed care organizations, and biotechnology/pharmaceutical companies. The company estimates that it processes tests on 470,000 specimens daily, which range from general laboratory tests for allergies, anatomic pathology, cardiology, coagulation, dermatology, endocrinology, gastroenterology, genetics, infectious diseases, obstetrics/gynecology, oncology, pain management, pharmacogenetics, and urology to specialized tests in areas such as bone marrow and stem cell transplant monitoring, DNA tests, drug tests, forensics services, and more. In April 2012, LabCorp licensed intellectual property for the development and commercialization of an AD diagnostic test from OPKO Health Inc. The test is designed to detect elevated levels of antibodies that appear to be unique to AD, as discovered using OPKO's proprietary molecular diagnostics platform. LabCorp licensed the exclusive rights for North America and the United Arab Emirates (UAE).



### **MedGenesis Therapeutix Inc.**

<http://www.medgenesis.com>

Closely-held Canadian company MedGenesis is a biopharmaceutical company focused on treating neurologic diseases using convection enhanced delivery (CED). CED is a minimally invasive technique designed to enable targeted, local treatment of CNS disorders by delivering the therapeutic agent to a target within the blood-brain barrier. MedGenesis' lead indications are PD and brain cancer. In PD, the company is studying GDNF, a neurotrophic factor for dopamine neurons that impacts several other relevant neurotransmitter systems. MedGenesis believes that GDNF can have disease-modifying efficacy in PD, including neuroprotection, axonal sprouting, and improved motor function, based on preclinical study results in animal models. The company has also conducted two Phase 1 trials in 15 patients that reportedly had positive results sustained beyond the end of treatment, according to MedGenesis' website. However, in a Phase 2 study of GDNF versus placebo in 34 patients, the company was unable to confirm efficacy of the treatment but believes that this may be due to inexperience with the CED approach and limited available CED technology, causing poor delivery of the product candidate to the target tissue.

### **Neurotech Pharmaceuticals**

<http://www.neurotechusa.com/index.html>

Rhode Island-based Neurotech Pharmaceuticals is a biotechnology company focused on retinal diseases. It has developed a patented technology platform known as Encapsulated Cell Technology (ECT), which entails a genetically engineered implant capable of continuously treating diseased retinas for over two years. The implant delivers protein drugs directly to the vitreous (the back) of the eye, while avoiding the need for monthly medicine injections into the eye. Neurotech has two primary product candidates: (1) the NT-501 (Renexus<sup>®</sup>) ECT implant system in studies to treat geographic atrophy (GA) associated with RP as well as other eye diseases like dry AMD and macular telangiectasia; and (2) NT-503, a VEGF-antagonist for wet AMD. The company believes the ECT system is a platform technology that could enable a number of future indications as well, due to its ability to produce many biotherapeutic drugs from peptides and hormones to monoclonal antibodies (MAbs) and scaffolds.

NT-501, or Renexus, delivers a constant dose of ciliary neurotrophic factor (CNTF) to the back of the eye. CNTF is a human growth factor that stimulates and protects neural cells, including those that detect light in the retina. In clinical trials of over 50 months for some patients, Renexus has shown a favorable safety profile. The product candidate holds orphan drug designation and fast track status from the FDA for RP, and is in clinical studies at the University of California. Previous Phase 2 trials of the device for this condition found a statistically significant, dose-dependent increase in retinal thickness of the photoreceptor layers, though the study durations were not long enough to monitor multi-year effects of visual benefit in retinitis pigmentosa patients. The current study aims to monitor photoreceptor preservation and disease progression.

### **Piramal Imaging SA**

[www.piramal.com/imaging/](http://www.piramal.com/imaging/)

Piramal Imaging operates in the field of developing PET tracers for molecular imaging. The company is part of The Piramal Group's Piramal Enterprises, Ltd. (500302-BOM) subsidiary, which was formed in 2012 in India out of Piramal's acquisition of Bayer Pharma AG's molecular imaging R&D portfolio. Today, Piramal Imaging has R&D facilities in Berlin, Germany, and a U.S. commercial subsidiary in Boston, Massachusetts. Both the FDA and the European Commission approved Piramal's Neuraceq (florbetaben F 18 injection) in early 2014 as a PET tracer for estimating the beta-amyloid neuritic plaque density in adults being tested for a potential AD diagnosis. Neuraceq is the third F 18 injection for PET brain scans to be approved by the FDA (on the heels of Lilly's Amyvid and GE Healthcare's Vizamyil [described on pages 48 and 49, respectively]). Neuraceq is not on its own a confirmation of an AD or other cognitive decline diagnosis, but rather is intended for use as an adjunct to other diagnostic evaluations. Neuraceq is a very new treatment; the first center in the U.S. to perform commercial scans with Neuraceq was WVU Healthcare in West Virginia in August 2014.



## Financial Highlights

Amarantus has focused over the past year on gaining the necessary financial strength and flexibility to drive its pipeline forward. The recent transactions, as highlighted below, have positioned the Company for future clinical endeavors over the next 12 to 24 months.

- In August 2013, raised \$1.17 million through issuance of a Series D 8% Convertible Preferred Stock financing with Dominion Capital, LLC. The shares are convertible at \$0.03 per common share and were issued at a 10% original issue discount.
- In September 2013, raised \$1.39 million through issuance of a Senior Convertible Debenture. The shares are convertible at \$0.04 per common share and were issued at an 8% original issue discount.
- In October 2013, raised \$1.61 million through issuance of a second tranche of the Senior Convertible Debentures issued in September 2013.
- In March 2014, raised \$3.35 million through closing a previously announced warrant solicitation. In aggregate, 60 million warrants were exchanged into common stock at an exercise price of \$0.06 per share. New warrants were issued to investors participating in the exchange for 45 million warrants at \$0.12 per share (callable if the stock exceeds \$0.18 per share for over 20 consecutive trading days).
- In March 2014, raised \$400,000 million through the first transaction of an agreed upon \$20 million total securities purchase agreement with Lincoln Park Capital (LPC). Amarantus sold four million shares to LPC at \$0.10 per share. The agreement allows for the sale of up to an additional \$19.6 million in stock to LPC over the ensuing 30 months, with maximum amounts totaling \$500,000 million per day.

## Historical Financial Results

Figures 14, 15, and 16 summarize Amarantus' key historical financial statements: the Condensed Consolidated Statements of Operations, Balance Sheets, and Statements of Cash Flows, as presented in the Company's Form 10-Q filed with the U.S. Securities and Exchange Commission (SEC) on August 15, 2014.

Figure 14

### CONDENSED CONSOLIDATED STATEMENTS OF OPERATIONS

(Unaudited) (in thousands, except share and per share data)

	Three Months Ended June 30, 2014	Three Months Ended June 30, 2013 (Restated)	Six Months Ended June 30, 2014	Six Months Ended June 30, 2013 (Restated)
<b>Net sales</b>	\$ —	\$ —	\$ —	\$ —
<b>Operating expense:</b>				
Research and development	1,640	474	2,157	1,138
General and administrative	2,101	830	3,220	2,051
	<u>3,741</u>	<u>1,304</u>	<u>5,377</u>	<u>3,189</u>
Loss from operations	<u>(3,741)</u>	<u>(1,304)</u>	<u>(5,377)</u>	<u>(3,189)</u>
<b>Other income (expense):</b>				
Interest Expense	(71)	(268)	(709)	(1,141)
Loss on issuance of common stock	—	—	(67)	—
Loss on issuance of warrants	—	—	(3,867)	—
Other Income (Expense)	(20)	—	(20)	—
Change in fair value of warrant and derivative liabilities	<u>(193)</u>	<u>375</u>	<u>473</u>	<u>(1,505)</u>
Total other income (expense)	<u>(284)</u>	<u>107</u>	<u>(4,190)</u>	<u>(2,646)</u>
Net Loss	<u>\$ (4,025)</u>	<u>\$ (1,197)</u>	<u>\$ (9,567)</u>	<u>\$ (5,835)</u>
Preferred stock dividend	26	—	52	—
Net loss attributable to common stockholders	(4,051)	(1,197)	(9,619)	(5,835)
Basic and diluted net (loss) per common share	<u>\$ (0.01)</u>	<u>\$ (0.00)</u>	<u>\$ (0.01)</u>	<u>\$ (0.02)</u>
Basic and diluted weighted average common shares outstanding	<u>734,023,717</u>	<u>397,175,440</u>	<u>682,657,535</u>	<u>380,084,393</u>

Source: Amarantus BioScience Holdings, Inc.

Figure 15

## CONDENSED CONSOLIDATED BALANCE SHEETS

(Unaudited) (in thousands, except share and per share data)

<u>ASSETS</u>	<u>June 30, 2014</u>	<u>Dec. 31, 2013</u>
<b>Current assets:</b>		
Cash and cash equivalents	\$ 1,402	\$ 1,033
Receivable from sale of stock	146	—
Deferred funding fees, net	3	109
Prepaid expenses and other current assets	250	106
<b>Total current assets</b>	<b>1,801</b>	<b>1,248</b>
Property and equipment, net	50	—
Intangible assets, net	1,561	611
<b>Total assets</b>	<b>\$ 3,412</b>	<b>\$ 1,859</b>
 <b><u>LIABILITIES AND STOCKHOLDERS' EQUITY (DEFICIT)</u></b>		
<b>Current liabilities:</b>		
Accounts payable (includes related parties \$390 and \$490 as of June 30, 2014 and December 31, 2013, respectively)	2,006	972
Related party liabilities and accrued interest	250	248
Accrued expenses	257	292
Accrued interest	52	112
Demand promissory note	500	—
8% Senior convertible debentures, net of discount	124	932
Convertible promissory notes	85	124
Derivative liability	325	5,859
<b>Total current liabilities</b>	<b>3,599</b>	<b>8,539</b>
<b>Total liabilities</b>	<b>3,599</b>	<b>8,539</b>
Commitments and contingencies	—	—
Series D convertible preferred stock, \$1,000 stated value; 1,300 shares designated; 1,299.327 issued and outstanding as of and December 31, 2013	—	839
<b>Stockholders' equity (deficit)</b>		
Convertible preferred stock, \$0.001 par value — 10,000,000 shares authorized:		
Series A, \$0.001 par value, 250,000 shares designated, -0- shares issued and outstanding as of June 30, 2014 and December 31, 2013	—	—
Series B, \$0.001 par value, 3,000,000 shares designated, -0- shares issued and outstanding as of June 30, 2014 and December 31, 2013	—	—
Series C, \$0.001 par value, 750,000 shares designated, 750,000 shares issued and outstanding as of June 30, 2014 and December 31, 2013	1	1
Series D, \$1,000 stated value; 1,300 shares designated; 1,299.327 issued and outstanding as of June 30, 2014	839	—
Common stock, \$0.001 par value — 1,000,000,000 shares authorized; 746,569,263 and 574,171,945 shares issued and outstanding at June 30, 2014 and December 31, 2013, respectively	747	574
Additional paid-in capital	34,877	18,938
Accumulated deficit	(36,651)	(27,032)
<b>Total stockholders' equity (deficit)</b>	<b>(187)</b>	<b>(7,519)</b>
<b>Total liabilities and stockholders' equity (deficit)</b>	<b>\$ 3,412</b>	<b>\$ 1,859</b>

Source: Amaranthus BioScience Holdings, Inc.



Figure 16

CONDENSED CONSOLIDATED STATEMENTS OF CASH FLOWS

(Unaudited) (in thousands)

	<b>Six Months Ended June 30,</b>	
	<b>2014</b>	<b>2013 (Restated)</b>
<b>Cash flows from operating activities</b>		
Net loss	\$ (9,567)	\$ (5,835)
Adjustments to reconcile net loss to net cash used in operating activities		
Depreciation and amortization	6	—
Amortization of debt discount	572	596
Amortization of deferred financing fees	106	133
Amortization of intangibles	53	—
Stock issued for services	595	65
Write-off of clinical trial material	500	—
Loss on stock issuance	67	—
Loss on warrant issuance	3,867	—
Non-cash interest expense related to warrants and derivative	32	—
Change in fair value of warrants and derivative liability	(473)	1,505
Stock-based compensation expense	475	598
Changes in assets and liabilities:		
Clinical trial material	(500)	—
Receivable for sale of common stock	(146)	—
Deferred funding fees	116	—
Prepaid expenses and other current assets	(144)	(27)
Accounts payable	824	954
Related party liabilities and accrued interest	2	24
Accrued expenses and accrued interest	(18)	341
Net cash used in operating activities	<u>(3,633)</u>	<u>(1,646)</u>
<b>Cash flows from investing activities</b>		
Acquisition of property and equipment	(56)	—
Acquisition of intangible assets	(600)	(34)
Net cash used by investing activities	<u>(656)</u>	<u>(34)</u>
<b>Cash flows from financing activities</b>		
Proceeds from demand and convertible notes	500	1,733
Repayment of convertible promissory notes	(9)	(143)
Proceeds from issuance of common stock	400	—
Proceeds from exercise of warrants	3,767	—
Net cash provided by financing activities	<u>4,658</u>	<u>1,590</u>
Net increase (decrease) in cash and cash equivalents	369	(90)
<b>Cash and cash equivalents</b>		
Beginning of period	1,033	157
End of period	<u>\$ 1,402</u>	<u>\$ 67</u>

Source: Amarantus BioScience Holdings, Inc.

Figure 16 (continued)  
 CONDENSED CONSOLIDATED STATEMENTS OF CASH FLOWS  
 (Unaudited) (in thousands)

	<b>Six Months Ended June 30,</b>	
	<b>2014</b>	<b>2013 (Restated)</b>
<b>Supplemental schedule of non-cash activities:</b>		
Convertible debentures converted and associated reclassification of derivative liabilities	\$ 8,238	\$ —
Debt discount written off - associated with convertible promissory notes	\$ (1,787)	\$ —
Convertible promissory notes issued for payables and accrued liabilities	\$ 2	\$ 161
Convertible notes payable issued for accounts payables	\$ —	\$ 188
Stock issued for deferred funding fees	\$ 518	\$ —
Stock subscription	\$ 146	\$ —
Intangible asset	\$ (50)	\$ —
Deferred funding fees charged to equity upon sale of common stock	\$ (518)	\$ —
Stock issued to acquire intangible assets	\$ 103	\$ 79
Reclass of Series D Preferred from mezzanine to equity	\$ 839	\$ —
Stock issued to satisfy accounts payable and accrued expenses	\$ 22	\$ 770
Stock issued for notes payable	\$ —	\$ 600
Stock issued for warrant obligations	\$ —	\$ 78
Debt discount for derivative conversion feature	\$ —	\$ 645
Stock issued for convertible debt	\$ 11	\$ 563
<b>Supplemental cash flow information</b>		
Interest payments	\$ 1	\$ —

*Source: Amarantus BioScience Holdings, Inc.*



## Recent Events

**09/04/2014**—Amarantus announced that Gerald E. Commissiong, President and CEO, is scheduled to present at the 14<sup>th</sup> Annual Biotech in Europe Forum at the Congress Center in Basel, Switzerland. The presentation is scheduled for Wednesday, October 1st at 11:45 AM in the Darwin Room.

**9/02/2014**—Amarantus announced that it has entered into a Master Services Agreement with ICON for global therapeutic and diagnostic clinical development services. The Company has submitted an initial work order to ICON for delivery of the Fit for Purpose Flow Cytometry Assay Validation of the LymPro Test<sup>®</sup> at ICON's CLIA-certified Central Laboratory facility in Farmingdale, New York.

**08/29/2014**—Announced the appointment of Mr. Iain Ross to the Company's Board of Directors. Mr. Ross brings over 30 years of biopharmaceutical industry experience to Amarantus across executive management, investment, and directorship roles.

**08/19/2014**—Amarantus announced that Mr. Gerald Commissiong, president and CEO, is scheduled to present to investors at the 16<sup>th</sup> Annual Rodman & Renshaw Healthcare Conference to be held September 8-10, 2014, at the New York Palace Hotel in New York City. The presentation is scheduled for Tuesday, September 9<sup>th</sup> at 2:30 PM ET and will be webcast live. Mr. Commissiong is also scheduled to present at the Aegis Capital Healthcare and Technology Conference to be held at the Wynn Las Vegas on September 10-13, 2014. His presentation will take place on Thursday, September 11<sup>th</sup> at 2:30 PM PT. Amarantus also participated in the First Annual Zacks Healthcare Meetup on Monday, September 8, 2014.

**08/15/2014**—Amarantus announced that it exercised its exclusive option to license intellectual property related to MANF's utility in treating retinal disorders from the University of Miami's Bascom Palmer Eye Institute, and has entered into an exclusive license for said intellectual property. Under the terms of the agreement, the Company has been granted a perpetual, exclusive worldwide license to intellectual property, covering the use of MANF for the treatment of retinal disorders, including Retinitis Pigmentosa (RP).

**08/11/2014**—Announced that it has entered into a research collaboration with the Buck Institute for Research on Aging for the development of Mesencephalic-Astrocyte-derived Neurotrophic Factor (MANF) in undisclosed therapeutic indications. MANF is a targeted therapeutic that addresses the underlying programmed cell death (apoptosis) associated with a wide range of human disorders, including orphan indications such as Retinitis Pigmentosa.

**08/04/2014**—Brewer Sports International (BSI) and Amarantus reported that a cross-section of researchers, clinicians, policy-makers, patient groups, and athletes presented at the 3<sup>rd</sup> Alzheimer's focused #C4CT (Coalition for Concussion Treatment) Concussion Awareness Summit, powered by MDM Worldwide on Thursday, July 31, 2014, at the United Nations in New York City, New York. Participants reached a general consensus that repeated sub-concussive hits to the head can lead to memory and cognitive issues, and may possibly be implicated in subsequent neurodegenerative conditions, such as chronic traumatic encephalopathy (CTE) and potentially Alzheimer's disease (AD). Furthermore, such head hits appear to be more dangerous for children under the age of approximately 12, even when they do not involve concussion, in part because children's brains are bigger relative to their overall size, and their necks are weaker. In addition, with women now participating in greater numbers in contact sports, there are greater concussion rates among women athletes.

**08/01/2014**—Announced positive interim clinical performance data for the Company's proprietary cell cycle dysregulation diagnostic blood assay LymPro Test<sup>®</sup>, currently under development for AD diagnosis. In an interim analysis of 44 subjects (34 healthy controls and 10 Alzheimer's patients) from LP-002, a projected 72-patient clinical performance study, the Company announced it achieved replication of the two earlier peer-reviewed publications, the primary objective of the study.





**08/01/2014**—Announced that the Company has acquired an exclusive option to license the intellectual property surrounding the therapeutic concepts of Dr. Thomas Arendt from the University of Leipzig that were presented at the 3<sup>rd</sup> Alzheimer’s focused Coalition for Concussion Treatment Summit. Under the terms of the agreement, the Company and the University of Leipzig have 12 months to negotiate a definitive license agreement, and the Company is working with Dr. Arendt to establish a Sponsored Research Agreement to outline the advancement of the therapeutic strategies into human clinical development.

**07/31/2014**—Announced that Brewer Sports International and Amarantus were hosting the 3<sup>rd</sup> Alzheimer’s-focused #C4CT Summit powered by MDM Worldwide at the United Nations. The Summit focused on the current state of concussions and the potential link between traumatic brain injury (TBI) and neurodegenerative diseases like Alzheimer’s. A diverse working group of clinicians, medical researchers, policy makers, international diplomats, athletes, celebrities, and philanthropic organizations were assembled to raise awareness, advance clinical research, and develop public policy in order to address this major unmet medical need and public health issue.

**07/30/2014**—Announced that it amended the clinical protocol for its LP-002 AD bridging diagnostic study of the LymPro Test<sup>®</sup> in order to perform an interim analysis of 44 subjects recruited from a single clinical site, from an originally planned 72 subjects across four clinical sites.

**07/30/2014**—Brewer Sports International and Amarantus announced that due to overwhelming registration for the upcoming #C4CT Summit to be held at the United Nations on July 31, 2014, the Coalition for Concussion Treatment is reluctantly unable to accept any new registrants. This summit was among the largest to date with hundreds of confirmed guests including doctors and medical researchers specializing in the treatment of neurodegenerative diseases, policy makers, international ambassadors, athletes, and victims of traumatic brain injury (TBI). The summit covered Alzheimer’s disease and other neurodegenerative diseases and the emerging link between TBI and neurological conditions.

**07/28/2014**—Announced the appointment of Donald D. Huffman to the Company’s Board of Directors, where he chairs the newly-formed Audit Committee. Mr. Huffman brings over 20 years of biopharmaceutical industry experience in various financial and audit roles, with specific expertise in mergers and acquisitions.

**07/23/2014**—Brewer Sports International and Amarantus announced a presentation by Dr. Thomas Arendt, Professor at University of Leipzig, at the 3<sup>rd</sup> Alzheimer’s-focused #C4CT (Coalition for Concussion Treatment) Concussion Awareness Summit, powered by MDM Worldwide on Thursday, July 31, 2014 at the United Nations in New York City, New York. Dr. Arendt summarized his scientific hypotheses regarding the evolutionary context of AD and an emerging therapeutic target in a 30-minute presentation in the afternoon session.

**07/22/2014**—Brewer Sports International and Amarantus announced the Honorable Jim Greenwood, President and CEO of the Biotechnology Industry Organization (BIO), as a panelist for the 3<sup>rd</sup> Alzheimer’s focused #C4CT Concussion Awareness Summit.

**07/18/2014**—Announced that it has updated its MANF publications list with eight previously undisclosed independent peer-reviewed research papers. The scientific articles include several Chinese publications as well as new publications that have been released since the beginning of 2014.

**07/17/2014**—Brewer Sports International and Amarantus announced their continued support of One Mind at the 3<sup>rd</sup> Alzheimer’s-focused #C4CT Concussion Awareness Summit.

**07/15/2014**—Announced positive clinical performance data for Version 2 of the Company’s proprietary cell cycle dysregulation diagnostic blood assay LymPro Test<sup>®</sup>. The LymPro Test<sup>®</sup> clinical data package assessed was produced in 2008 at Provista Life Sciences. The seven-year longitudinal patient record clinical progression assessment data was conducted by Dr. Marwan Sabbagh at the Banner Sun Health Research Institute who originally enrolled the 44 patients involved in the Provista clinical trial, and analyzed by Dr. Louis Kirby, the Company’s chief medical officer. The LymPro Test<sup>®</sup> differentially diagnosed AD versus age-matched other dementias and cognitively intact controls in statistically significant manner.



**07/14/2014**—Announced positive analytical performance data for the LymPro Test®. The analytical data package, produced at the Company’s contract laboratory Becton Dickinson, provides the basis for reproducible clinical performance assessment of the LymPro Test®. The Company presented pilot clinical performance data, and an up-to six year longitudinal assessment of the patients’ clinical diagnosis change over time, in two complementary poster presentations on Tuesday, July 15, 2014, at AAIC 2014 in Copenhagen, Denmark (Poster position 117 and 118).

**07/07/2014**—Announced that analytical performance, clinical performance, and six-year longitudinal data related to the Company’s LymPro Test® were presented at the Alzheimer’s Association International Conference (AAIC), held at the Bella Center in Copenhagen, Denmark, July 12-17, 2014.

**07/02/2014**—Announced positive interim toxicology data for MANF in an ocular safety animal model, relevant to MANF development in RP. The data produced at an ophthalmology contract research laboratory using slit-lamp observations in rabbits demonstrated that an intravitreal injection with MANF was safe and well tolerated in the eye.

**07/01/2014**—Announced that it independently confirmed MANF’s activity in mitigating tau hyperphosphorylation in preclinical models of AD. The studies commissioned by Amarantus independently confirm data published in 2012 in the Chinese Pharmacological Bulletin entitled “MANF Inhibits Tau Hyperphosphorylation in Cultured Neuronal Cells” in which the authors demonstrated that MANF had a pronounced effect in reducing tau hyperphosphorylation, reducing cell death, and improving overall cellular health in *in vitro* models of AD.

**06/25/2014**—Amarantus and Brewer Sports International (BSI), announced that Congressman Chaka Fattah will be delivering the morning keynote address at the #C4CT Concussion Awareness Summit focused on Traumatic Brain Injury-induced AD at the United Nations on July 31, 2014. Congressman Fattah addressed the Summit regarding policy initiatives currently underway to improve funding for brain research.

**06/23/2014**—Announced that Amarantus’ president and CEO, Mr. Gerald Commissiong, would be presenting at the 2014 BIO International Convention on Thursday, June 26. The presentation took place in the Mission Beach Room. Hosted by the Biotechnology Industry Organization (BIO), the conference took place on June 23-26, 2014, at the San Diego Convention Center in San Diego, California.

**06/20/2014**—Announced that it has entered into a research collaboration with the Washington University School of Medicine in St. Louis to evaluate the efficacy of MANF to treat Wolfram-Syndrome-induced blindness in animals. Dr. Fumihiko Urano, a researcher at the Washington University School of Medicine, is leading the research. The project initially focuses on evaluating MANF treatment efficacy in retinal cells that are produced from induced pluripotent stem cells, which were derived from Wolfram’s patients. Dr. Urano has developed his models of retinal damage with funding from the Jack and JT Snow Foundation.

**06/11/2014**—Amarantus and Brewer Sports International announced the addition of Cavendish Global as partner at the 3<sup>rd</sup> #C4CT Concussion Awareness Summit.

**05/21/2014**—Reported financial results for the first quarter ended March 31, 2014. At March 31, 2014, the Company had cash and cash equivalents totaling approximately \$3.8 million and an additional \$19.6 million of equity capital available under a financing facility with Lincoln Park Capital Fund, LLC. For the first quarter of 2014, the Company reported a net loss of approximately \$5.5 million, or (\$0.01) per share, compared with a net loss of approximately \$4.6 million, or (\$0.01) per share, for the first quarter of 2013. The Company is now focused on the execution of its business plan to transform Amarantus into a commercial-stage company.



**05/07/2014**—Brewer Sports International and Amarantus announced their 3<sup>rd</sup> #C4CT Concussion Awareness Summit, on Thursday, July 31, 2014, at the United Nations in New York City. The 3<sup>rd</sup> #C4CT Summit focuses on important scientific, medical translational, and prevention-related topics of Traumatic Brain Injury (TBI) and the link to AD and PD. The summit brings together high-level executives and business leaders, renowned researchers, international diplomats, major media outlets, and professional athletes to discuss a variety of topics surrounding TBI induced Alzheimer's and other neurodegenerative diseases on a global platform.

**05/06/2014**—Announced that it opened an office in Geneva, Switzerland, in preparation for the establishment of a Swiss affiliate. The main purpose of this office is to facilitate interaction with the European biotechnology, pharmaceutical research and development, and investment communities. Opening an office in Switzerland positions the Company in proximity to innovation, as evidenced by neuroscience- and life science-focused programs and initiatives such as the Human Brain Project (HBP) and Campus Biotech. HBP is part of the Future and Emerging Technologies Flagship Program, a new initiative launched by the European Commission, and it was recently announced that the HBP research will move to the Campus Biotech site in Geneva. The mission of Campus Biotech is to become a center of excellence and focal point for scientists and entrepreneurs in the life science sector.

**05/05/2015**—Announced that it acquired additional rights for its flagship Alzheimer's blood diagnostic, LymPro Test<sup>®</sup>, from Memory Dx, LLC. The rights acquired by Amarantus are related to certain improvements that were sought out for the LymPro assay following the completion of work published in 2012 in the scientific journal *Neurobiology of Aging*. Memory Dx and Amarantus identified that these data sets fall outside the purview of Memory Dx's license agreement with the University of Leipzig, thereby allowing Memory Dx to sell the rights outright to Amarantus, without related milestones and royalties.

**05/01/2014**—Announced the publication of positive independent peer-reviewed data on MANF in the areas of AD and diabetes, as well as additional studies further supporting its critical role in proper cellular function. The studies further corroborate the role of MANF's critical importance in reducing misfolded protein concentration and improving proper overall endoplasmic reticulum function. In a study entitled "MANF Inhibits Tau Hyperphosphorylation in Cultured Neuronal Cells" published in the journal *Chinese Pharmacological Bulletin*, the authors demonstrated that MANF had a pronounced effect in reducing tau hyperphosphorylation, reducing cell death, and improving overall cellular health in a preclinical models.



## Risks and Disclosures

This Executive Informational Overview® (EIO) has been prepared by Amarantus BioScience Holdings, Inc. (“Amarantus” or “the Company”) with the assistance of Crystal Research Associates, LLC (“CRA”) based upon information provided by the Company. CRA has not independently verified such information. Some of the information in this EIO relates to future events or future business and financial performance. Such statements constitute forward-looking information within the meaning of the Private Securities Litigation Act of 1995. Such statements can only be predictions and the actual events or results may differ from those discussed due to the risks described in Amarantus’ statements on Forms 10-K, 10-Q, and 8-K, as well as other forms filed from time to time.

The content of this report with respect to Amarantus has been compiled primarily from information available to the public released by the Company through news releases, Annual Reports, and U.S. Securities and Exchange Commission (SEC) filings. Amarantus is solely responsible for the accuracy of this information. Information as to other companies has been prepared from publicly available information and has not been independently verified by Amarantus or CRA. Certain summaries of activities and outcomes have been condensed to aid the reader in gaining a general understanding. CRA assumes no responsibility to update the information contained in this report. In addition, CRA’s compensation is a cash amount of thirty-seven thousand, five hundred U.S. dollars for its services in creating this report and for updates. For more complete information about the risks involved in an investment in the Company, please see Amarantus’ most recently filed Annual Report on Form 10-K for the year ended December 31, 2013. Investors should carefully consider risks and information about Amarantus’ business. Investors should not interpret the order in which considerations are presented in this or other filings as an indication of their relative importance. Additional risks and uncertainties not presently known to Amarantus or that it currently believes to be immaterial may also adversely affect its business. If any of such risks and uncertainties develops into an actual event, Amarantus’ business, financial condition, and results of operations could be materially adversely affected, and the trading price of the Company’s shares could decline.

This report is published solely for information purposes and is not to be construed as an offer to sell or the solicitation of an offer to buy any security in any state. Past performance does not guarantee future performance. Additional information about Amarantus and its public filings, as well as copies of this report, can be obtained by calling (408) 737-2734.

### **Risks Related to Product Candidates and Operations**

*Amarantus is largely dependent on the success of its lead product candidates, the LymPro Test®, Eltoprazine, and MANF, and may not be able to successfully commercialize these products.*

The Company has incurred and will continue to incur significant costs relating to the development of its lead product candidates, the LymPro Test®, Eltoprazine, and MANF. Amarantus has not obtained approval to commercialize these candidates in any jurisdiction and may never be able to obtain approval or, if approvals are obtained, to commercialize the LymPro Test®, Eltoprazine, and MANF successfully. If the Company fails to successfully commercialize its products, it may be unable to generate sufficient revenue to sustain and grow its business, and the business, financial condition, and results of operations will be adversely affected.

*If the Company fails to obtain U.S. regulatory approval of the LymPro Test®, Eltoprazine, MANF, or any of its other current or future product candidates, Amarantus will be unable to commercialize these potential products in the U.S.*

The development, testing, manufacturing, and marketing of the Company’s product candidates are subject to extensive regulation by governmental authorities in the U.S. In particular, the process of obtaining FDA approval is costly and time consuming, and the time required for such approval is uncertain. Amarantus’ product candidates must undergo rigorous preclinical and clinical testing and an extensive regulatory approval process mandated by the FDA. Such regulatory review includes the determination of manufacturing capability and product performance. Generally, only a small percentage of pharmaceutical products are ultimately approved for commercial sale.



The Company can give no assurance that its current or future product candidates will be approved by the FDA or any other governmental body. In addition, there can be no assurance that all necessary approvals will be granted for future product candidates or that FDA review or actions will not involve delays caused by requests for additional information or testing that could adversely affect the time to market for and sale of its product candidates. Furthermore, failure to comply with applicable regulatory requirements may result in the suspension of regulatory approval as well as possible civil and criminal sanctions.

*The Company's proprietary rights may not adequately protect its intellectual property and product candidates and if Amarantus cannot obtain adequate protection for its intellectual property and product candidates, the Company may not be able to successfully market its product candidates.*

Commercial success will depend, in part, on obtaining and maintaining intellectual property protection for Amarantus' technologies and product candidates. The Company will only be able to protect its technologies and product candidates from unauthorized use by third parties to the extent that valid and enforceable patents cover them, or that other market exclusionary rights apply.

While the Company has issued enforceable patents covering its product candidates, the patent positions of life sciences companies, like Amarantus, can be highly uncertain and involve complex legal and factual questions for which important legal principles remain unresolved. No consistent policy regarding the breadth of claims allowed in such companies' patents has emerged to date in the U.S. The general patent environment outside the U.S. also involves significant uncertainty. Accordingly, the Company cannot predict the breadth of claims that may be allowed or that the scope of these patent rights would provide a sufficient degree of future protection that would permit Amarantus to gain or keep its competitive advantage with respect to these products and technology.

The Company's issued patents may be subject to challenge and possibly invalidated by third parties. Changes in either the patent laws or in the interpretations of patent laws in the U.S. or other countries may diminish the market exclusionary ability of Amarantus' intellectual property. In addition, others may independently develop similar or alternative compounds and technologies that may be outside the scope of the Company's intellectual property. Should third parties obtain patent rights to similar compounds or radiolabeling technology, this may have an adverse effect on Amarantus' business.

To the extent that consultants or key employees apply technological information independently developed by them or by others to Amarantus' product candidates, disputes may arise as to the proprietary rights of the information, which may not be resolved in the Company's favor. Consultants and key employees that work with Amarantus' confidential and proprietary technologies are required to assign all intellectual property rights in their discoveries to the Company.

However, these consultants or key employees may terminate their relationship with Amarantus, and the Company cannot preclude them indefinitely from dealing with its competitors. If Company trade secrets become known to competitors with greater experience and financial resources, the competitors may copy or use Amarantus' trade secrets and other proprietary information in the advancement of their products, methods, or technologies. If the Company were to prosecute a claim that a third party had illegally obtained and was using Company trade secrets, it would be costly and time consuming and the outcome would be unpredictable. In addition, courts outside the U.S. are sometimes less willing to protect trade secrets than courts in the U.S. Moreover, if Company competitors independently develop equivalent knowledge, Amarantus would lack any contractual claim to this information, and its business could be harmed.

*If the Company's product candidates, including the LymPro Test<sup>®</sup>, Eltoprazine, and MANF do not gain market acceptance among physicians, patients, and the medical community, Amarantus will be unable to generate significant revenue, if any.*

The products that the Company develops may not achieve market acceptance among physicians, patients, third-party payers, and others in the medical community. If Amarantus, or any of its partners, receive the regulatory approvals necessary for commercialization, the degree of market acceptance will depend upon a number of factors, including the following:



- limited indications of regulatory approvals;
- the establishment and demonstration in the medical community of the clinical efficacy and safety of the Company's product candidates and their potential advantages over existing diagnostic compounds;
- the prevalence and severity of any side effects;
- the Company's ability to offer its product candidates at an acceptable price;
- the relative convenience and ease of administration of its products;
- the strength of marketing and distribution support; and
- sufficient third-party coverage or reimbursement.

The market may not accept the LymPro Test<sup>®</sup>, Eltoprazine, or MANF-based products based on any number of the above factors. The market may choose to continue utilizing the existing products for any number of reasons, including familiarity with or pricing of these existing products. The failure of any of Amarantus' product candidates to gain market acceptance could impair its ability to generate revenue, which could have a material adverse effect on the Company's future business and prevent it from obtaining the necessary partnerships to further its business strategy.

#### **Risks Associated with the Company's Financial Condition**

*The Company's independent registered public accounting firm has expressed substantial doubt about its ability to continue as a going concern, which may hinder Amarantus' ability to obtain future financing.*

Amarantus' consolidated financial statements as of December 31, 2013, were prepared under the assumption that the Company will continue as a going concern for the next 12 months. Its independent, registered public accounting firm has issued a report that included an explanatory paragraph referring to its projected future losses along with recurring losses from operations and expressing substantial doubt in Amarantus' ability to continue as a going concern without additional capital becoming available. The ability to continue as a going concern is dependent upon the Company's ability to obtain additional equity or debt financing, attain further operating efficiencies, reduce expenditures, and, ultimately, generate revenue. The financial statements do not include any adjustments that might result from the outcome of this uncertainty.

*Amarantus is at an early stage of development as a company and currently has no source of revenue and may never become profitable.*

The Company is a development-stage biopharmaceutical company. Currently, it has no products approved for commercial sale and, to date, has not generated any revenue. Amarantus' ability to generate revenue depends heavily on the items listed below:

- demonstration in future clinical trials that the Company's product candidate, MANF for the treatment of PD, is safe and effective;
- the Company's ability to seek and obtain regulatory approvals, including with respect to the indications Amarantus is seeking;
- successful manufacture and commercialization of the Company's product candidates; and
- market acceptance of its products.



All of the Company's existing product candidates are in various stages of development and will require extensive additional preclinical and clinical evaluation, regulatory review and approval, significant marketing efforts and substantial investment before they could provide the Company with any revenue. As a result, if Amarantus does not successfully develop, achieve regulatory approval, and commercialize the LymPro Test<sup>®</sup>, Eltoprazine, and/or MANF, it will be unable to generate any revenue for many years, if at all. The Company does not anticipate that it will generate revenue for several years, at the earliest, or that it will achieve profitability for at least several years after generating material revenue, if at all. If the Company is unable to generate revenue, Amarantus will not become profitable, and may be unable to continue its operations.

*The Company does not have any products that are approved for commercial sale and therefore does not expect to generate any revenues from product sales in the foreseeable future, if ever.*

Amarantus currently does not have any products that are approved for commercial sale. To date, the Company has funded its operations primarily from grants and sales of its securities. The Company has not received, and does not expect to receive for at least the next several years, in the case of Eltoprazine and MANF and until the fourth quarter of 2014 in the case of the LymPro Test<sup>®</sup>, if at all, any revenues from the commercialization of its product candidates. To obtain revenues from sales of the Company's product candidates, Amarantus must succeed, either alone or with third parties, in developing, obtaining regulatory approval for, manufacturing, and marketing drugs with commercial potential. The Company may never succeed in these activities, and may not generate sufficient revenues to continue its business operations or achieve profitability.

*Amarantus has incurred significant losses since inception and anticipates that the Company will incur continued losses for the foreseeable future.*

As of December 31, 2013, the Company had an accumulated deficit of approximately \$26.3 million. Amarantus expects to incur significant and increasing operating losses for the next several years as it expands its research and development, advances product candidates into clinical development, completes clinical trials, seeks regulatory approvals and, if the Company receives FDA approval, commercializes its products.

Because of the numerous risks and uncertainties associated with product development efforts, Amarantus is unable to predict the extent of any future losses or when it will become profitable, if at all. If unable to achieve and then maintain profitability, the market value of the Company's common stock will likely decline.

*The Company will need to raise substantial additional capital to fund its operations, and failure to obtain funding when needed may force Amarantus to delay, reduce, or eliminate certain product development programs.*

Amarantus expects to continue to spend substantial amounts to accomplish the following:

- continue development of the Company's product candidates;
- finance its general and administrative expenses;
- license or acquire additional technologies;
- manufacture product for clinical trials;
- launch and commercialize the Company's product candidates, if any such product candidates receive regulatory approval; and
- develop and implement sales, marketing, and distribution capabilities.

Amarantus will be required to raise additional capital to complete the development and commercialization of its product candidates and to continue to fund operations at the current cash expenditure levels. Future funding requirements will depend on many factors, including, but not limited to the following:



- the rate of progress and cost of the Company's clinical trials and other development activities;
- any future decisions Amarantus may make about the scope and prioritization of the programs it pursues;
- the costs of filing, prosecuting, defending, and enforcing any patent claims and other intellectual property rights;
- the costs of manufacturing product;
- the costs and timing of regulatory approval;
- the costs of establishing sales, marketing, and distribution capabilities;
- the effect of competing technological and market developments;
- the terms and timing of any collaborative, licensing, and other arrangements that Amarantus may establish; and
- general market conditions for offerings from biopharmaceutical companies.

Worldwide economic conditions and the international equity and credit markets have recently significantly deteriorated and may remain depressed for the foreseeable future. These developments could make it more difficult for Amarantus to obtain additional equity or credit financing, when needed.

The Company cannot be certain that funding will be available on acceptable terms, or at all. To the extent that the Company raises additional funds by issuing equity securities, its stockholders may experience significant dilution. Any debt financing, if available, may involve restrictive covenants that impact Amarantus' ability to conduct its business. If unable to raise additional capital when required or on acceptable terms, the Company may have to significantly delay, scale back, or discontinue the development and/or commercialization of one or more of its product candidates. Amarantus may also be required to do the following:

- seek collaborators for its product candidates at an earlier stage than otherwise would be desirable and on terms that are less favorable than might otherwise be available; and/or
- relinquish license or otherwise dispose of rights to technologies, product candidates, or products that the Company would otherwise seek to develop or commercialize itself on unfavorable terms.

### **Risks Associated with Management**

*If the Company is unable to hire and retain key personnel, it may not be able to implement its business plan.*

Due to the specified nature of Amarantus' business, having certain key personnel is essential to the development and marketing of the products the Company plans to sell and thus to the entire business itself. Consequently, the loss of any of those individuals may have a substantial effect on Amarantus' future success or failure. The Company may have to recruit qualified personnel with competitive compensation packages, equity participation, and other benefits that may affect the working capital available for operations. Management may seek to obtain outside independent professionals to assist in assessing the merits and risks of any business proposals as well as in the development and operation of many projects. No assurance can be given that the Company will be able to obtain such needed assistance on terms acceptable. Failure to attract additional qualified employees or to retain the services of key personnel could have a material adverse effect on operating results and financial condition.





## **Risks Related to the Company's Common Stock**

*Amarantus' stock price may be volatile.*

The stock market, particularly in recent years, has experienced significant volatility particularly with respect to pharmaceutical, biotechnology, and other life sciences company stocks. The volatility often does not relate to the operating performance of the companies represented by the stock. Factors that could cause this volatility in the market price of the Company's common stock include the following:

- results from and any delays in the Company's clinical trials;
- failure or delays in entering additional product candidates into clinical trials;
- failure or discontinuation of any of the Company's research programs;
- research publications that are unfavorable;
- delays in establishing new strategic relationships;
- delays in the development or commercialization of the Company's potential products;
- market conditions in the pharmaceutical and biotechnology sectors and issuance of new or changed securities analysts' reports or recommendations;
- actual and anticipated fluctuations in the Company's financial and operating results;
- developments or disputes concerning the Company's intellectual property or other proprietary rights;
- introduction of technological innovations or new commercial products by the Company or its competitors;
- issues in manufacturing the Company's potential products;
- market acceptance of the Company's potential products;
- third-party healthcare reimbursement policies;
- FDA or other domestic or foreign regulatory actions affecting the Company or its industry;
- litigation or public concern about the safety of the Company's product candidates; and
- additions or departures of key personnel.

These and other external factors may cause the market price and demand for the Company's common stock to fluctuate substantially, which may limit or prevent investors from readily selling their shares of common stock and may otherwise negatively affect the liquidity of Amarantus' common stock. In the past, when the market price of a stock has been volatile, holders of that stock have instituted securities class action litigation against the company that issued the stock. If any of the Company's stockholders brought a lawsuit against it, Amarantus could incur substantial costs defending the lawsuit. Such a lawsuit could also divert the time and attention of the Company's management.

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*The Company has not and does not anticipate paying any dividends on its common stock.*

The Company has paid no dividends on its common stock to date and it is not anticipated that any dividends will be paid to holders of its common stock in the foreseeable future. While the future dividend policy will be based on the operating results and capital needs of the business, it is currently anticipated that any earnings will be retained to finance Amarantus' future expansion and for the implementation of its business plan. Investors should take note of the fact that a lack of a dividend can further affect the market value of its stock, and could significantly affect the value of any investment in the Company.

*Amarantus has a potential issuance of additional common shares from the conversion of its promissory note.*

The promissory note dated March 5, 2008, can be converted at the option of the Company based upon the fair market value of common stock as of the date of issuance at the closing price quoted on the exchange on which the Company's common stock is listed. The conversion price as at December was \$0.0798, and would convert to 3,107,356 shares.

*If the Company fails to establish and maintain an effective system of internal control, it may not be able to report its financial results accurately or to prevent fraud. Any inability to report and file financial results accurately and timely could harm Amarantus' reputation and adversely impact the trading price of its common stock.*

Effective internal control is necessary for the Company to provide reliable financial reports and prevent fraud. If the Company is not able to provide reliable financial reports or prevent fraud, it may not be able to manage its business as effectively as it would if an effective control environment existed, and its business and reputation with investors may be harmed. As a result, the Company's small size and any current internal control deficiencies may adversely affect its financial condition, results of operation, and access to capital. Amarantus has not performed an in-depth analysis to determine if historical undiscovered failures of internal controls exist, and may in the future discover areas of its internal control that need improvement.

*Amarantus' common stock is currently deemed a "penny stock," which makes it more difficult for its investors to sell their shares.*

The Company's common stock is subject to the "penny stock" rules adopted under Section 15(g) of the Exchange Act. The penny stock rules generally apply to companies whose common stock is not listed on The Nasdaq Stock Market or other national securities exchange and trades at less than \$4.00 per share, other than companies that have had average revenue of at least \$6 million for the last three years or that have tangible net worth of at least \$5 million (\$2 million if the company has been operating for three or more years). These rules require, among other things, that brokers who trade penny stock to persons other than "established customers" complete certain documentation, make suitability inquiries of investors, and provide investors with certain information concerning trading in the security, including a risk disclosure document and quote information under certain circumstances.

Many brokers have decided not to trade penny stocks because of the requirements of the penny stock rules and, as a result, the number of broker-dealers willing to act as market makers in such securities is limited. If the Company remains subject to the penny stock rules for any significant period, it could have an adverse effect on the market, if any, for Amarantus' securities. If Company securities are subject to the penny stock rules, investors will find it more difficult to dispose of these securities.

*Offers or availability for sale of a substantial number of shares of Amarantus' common stock may cause the price of the Company's common stock to decline.*

If Company stockholders sell substantial amounts of common stock into the public market upon the expiration of any statutory holding period, under Rule 144, or issued upon the exercise of outstanding options or warrants, it could create a circumstance commonly referred to as an "overhang" and in anticipation of which the market price of the Company's common stock could fall. The existence of an overhang, whether or not sales have occurred or are occurring, also could make it more difficult for the Company to raise additional financing through the sale of equity or equity-related securities in the future at a time and price that is deemed reasonable or appropriate.



*The Company's certificate of incorporation allows for its Board to create a new series of preferred stock without further approval by Company stockholders, which could adversely affect the rights of the holders of the Company's common stock.*

Amarantus' Board of Directors has the authority to fix and determine the relative rights and preferences of preferred stock and has designated 250,000 preferred shares as Series A Convertible Preferred Stock, 2,500,000 as Series B Convertible Preferred Stock, 750,000 as Series C Convertible Preferred Stock, and 1,300 as Series D Convertible Preferred Stock. The Company's Board of Directors also has the authority to issue additional shares of preferred stock without further stockholder approval. As a result, the Company's Board of Directors could authorize the issuance of a series of preferred stock that would grant to holders preferred right to its assets upon liquidation, the right to receive dividend payments prior to dividends distributed to the holders of common stock, and the right to the redemption of the shares, together with a premium, prior to the redemption of the Company's common stock. In addition, Amarantus' Board of Directors could authorize the issuance of a series of preferred stock that has greater voting power than its common stock or that is convertible into Company common stock, which could decrease the relative voting power of its common stock or result in dilution to existing stockholders.

*Amarantus improperly classified certain unpaid bonuses to senior management and may need to restate Form 10-K for the year ended December 31, 2012, and Forms 10-Q for the quarters ended March 31, 2013, June 30, 2013, and September 30, 2013.*

Unpaid bonuses to Gerald E. Commissiong, president and chief executive officer, and Dr. John W. Commissiong, chief scientific officer earned in fiscal years 2012 and 2013, were improperly reflected as prepaid expenses and other current assets in Form 10-K filed with the SEC on April 17, 2013, and forms 10-Q filed with the SEC on May 12, 2013, August 19, 2013, and November 14, 2013. This improper classification was not in conformity with the financial policies of the Company. A total bonus of \$443,874 was paid in 2014, \$230,222 for Gerald E. Commissiong, and \$213,763 for Dr. John W. Commissiong. The Company is continuing its review of this improper classification and may determine that a restatement of its Form 10-K for the year ended December 31, 2012, and Forms 10-Q for the quarters ended March 31, 2013, June 30, 2013, and September 30, 2013 is necessary.

### **Going Concern**

Amarantus is a development-stage company engaged in biotechnology research and development. The Company has suffered recurring losses from operations since inception, and has generated negative cash flows from operations. For these reasons, in its report dated April 21, 2014, its auditors have raised a substantial doubt about its ability to continue as a going concern. Company financial statements have been prepared assuming that it will continue as a going concern, which contemplates the realization of assets and satisfaction of liabilities in the normal course of business. The Company expects to incur further losses in the development of its business and has been dependent on funding operations through the issuance of convertible debt and private sale of equity securities. These conditions raise substantial doubt about the ability to continue as a going concern. Management's plans include continuing to finance operations through the private or public placement of debt and/or equity securities and the acquisition of non-dilutive forms of financing including grants. However, no assurance can be given at this time as to whether Amarantus will be able to achieve these objectives. The financial statements do not include any adjustment relating to the recoverability and classification of recorded asset amounts or the amounts and classification of liabilities that might be necessary should the Company become unable to continue as a going concern.



## Glossary

**5-HT1a/1b Partial Agonist**—A family of therapeutic agents that binds and triggers a response from specific 5-hydroxytryptamine (5-HT) serotonin receptors. 5-HT receptors are found in the central and peripheral nervous systems and mediate both excitatory and inhibitory neurotransmission. 5-HT1a/1b agonists are used as analgesic, antidepressant, and antipsychotic therapeutic agents.

**Abnormal Involuntary Movement Scale (AIMS)**—A testing instrument used to evaluate the severity of symptoms of tardive dyskinesia, which are divided into abnormal movements of the face and mouth, extremities, trunk, global judgment by an examiner, and dental status.

**ADHD Rating Scale-IV (AHDH-RS-IV)**—A method used in clinical trials to measure the efficacy and quantify a subject's response to ADHD treatments in children and adolescents.

**Adult Attention Deficit Hyperactivity Disorder (Adult ADHD)**—A mental health condition exhibited by difficulty maintaining attention, as well as hyperactivity and impulsive behavior. Adult ADHD symptoms can lead to a number of problems, including unstable relationships, poor work or school performance, and low self-esteem.

**ALS (Lou Gehrig's Disease)**—Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a progressive neurodegenerative disease of the nerve cells in the brain and spinal cord that control voluntary muscle movement. It is characterized by muscle spasticity progressive weakness due to muscle atrophy, and difficulty in speaking (dysarthria), swallowing (dysphagia), and breathing (dyspnea).

**Alzheimer's Disease (AD)**—Progressive mental degenerative disorder that attacks the brain's nerve cells or neurons, resulting in loss of memory, thinking, and language skills, and behavioral changes. It is the most common cause of premature senility.

**Aminoglycosides**—A group of broad-spectrum antibacterial therapeutic agents that inhibit protein synthesis and are used primarily against aerobic gram-negative bacteria.

**Apoptosis**—A natural process of cells' self-destruction or death that occurs as a normal and controlled part of an organism's growth or development. Apoptosis can be initiated by a stimulus or by removal of a repressor agent. Also called programmed cell death.

**Axons**—A thin and elongated extension of a neuron that conducts impulses away from the cell body.

**Ballism**—A type of involuntary violent movement of the limbs, manifested in jerking, flinging movements of the extremity, usually affecting only one side of the body. Also known as ballismus.

**Barnes Akathisia Scale (BAS)**—A testing device, range of 0 to 14, with higher scores indicating greater severity, used to evaluate restlessness related to drug therapy.

**CD69 (Cluster of Differentiation 69)**—A type of transmembrane protein encoded by the CD69 gene present on platelets, activated lymphocytes, and activated T or natural killer cells that functions as a signal transducer, enhancing cell activation and platelet aggregation.

**Cerebrospinal Fluid**—A watery fluid that is continuously produced and absorbed and that flows in the ventricles within the brain and around the surface of the brain and spinal cord.

**Chorea**—A neurological disorder characterized by jerky involuntary movements affecting especially the shoulders, hips, and face.



**Choreoathetoid Movements**—Choreoathetosis is the occurrence of involuntary movements in a combination of chorea (irregular migrating contractions) and athetosis (twisting and writhing).

**Chronic Traumatic Encephalopathy (CTE)**—A progressive degenerative disease of the brain found in athletes (and others) with a history of repetitive brain trauma, including symptomatic concussions as well as asymptomatic sub-concussive hits to the head. The brain degeneration is associated with memory loss, confusion, impaired judgment, impulse control problems, aggression, depression, and, eventually, progressive dementia.

**Clinical Dyskinesia Rating Scale (CDRS)**—A testing scale developed to evaluate involuntary movements often associated with treated Parkinson’s disease (PD).

**Clinical Global Impression-Improvement (CGI-I)**—A 7-point scale that requires the clinician to assess how much the patient’s illness has improved or worsened relative to the beginning baseline state before treatment. Ratings are as follows: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; or 7, very much worse.

**Clinical Laboratory Improvement Amendments (CLIA)**—A U.S. federal regulatory standard applicable to all U.S. clinical laboratory facilities or sites that test human specimens for health assessment or to diagnose, prevent, or treat disease.

**Coalition for Concussion Treatment (#C4CT)**—Campaign that serves as a platform to spread awareness about Alzheimer’s disease (AD), Parkinson’s disease, and the severe effects of traumatic brain injury (TBI), and other ailments affecting the brain.

**Computed Tomography (CT)**—An imaging method that combines a series of X-ray views taken from many different angles and computer processing to create three-dimensional cross-sectional images of a body structure. CT scans can reveal some soft tissue and other structures that cannot be seen in conventional X-rays.

**Conner’s Continuous Performance Test (CPT)**—Test used to aid the process of diagnosing Attention-Deficit/Hyperactive Disorder (ADHD) and other neurological conditions related to attention, by indexing the respondent’s performance in areas of inattentiveness, impulsivity, sustained attention, and vigilance.

**Convection Enhanced Delivery**—An approach for delivering drugs into brain tissue that entails the continuous injection of a therapeutic fluid under positive pressure.

**Current Procedural Terminology (CPT)**—A code set used to report medical procedures and services to entities such as physicians, health insurance companies, and accreditation organizations.

**Cytokines**—Regulatory proteins that are produced by immune system cells and act on other cells to stimulate or inhibit their function. Cytokines are intercellular mediators in the modulation of immune response.

**Dementia**—A general term for a decline in mental ability severe enough to interfere with daily life. Dementia describes a group of symptoms that indicate a chronic or persistent disorder of the mental processes affecting memory, thinking, language, judgment, and behavior.

**DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, and Deafness)**—A rare genetic disorder, causing diabetes insipidus (inability to concentrate the urine), diabetes mellitus, optic atrophy (degeneration of the nerve to the eye), and deafness, as well as various other possible disorders. Also known as Wolfram’s syndrome.

**Diphasic Dyskinesia (DD)**—An impairment in the ability to control movements, characterized by spasmodic or repetitive motions or lack of coordination, and caused by or related to medication and treatments used for PD.

**Dipraglurant**—An mGlu5 negative allosteric modulator (NAM) being developed by Addex Therapeutics to treat Parkinson’s disease levodopa-induced dyskinesia (PD-LID) and rare forms of dystonia.



**Dopaminergic (DA) Neurons**—Neurons that produce or use dopamine as their primary neurotransmitter. Dopamine is a chemical that is responsible for transmitting signals in between the nerve cells (neurons) of the brain. Very few neurons actually make dopamine. PD has been related to the loss of dopaminergic neurons in the midbrain area called the substantia nigra.

**Dystonia**—A state of abnormal muscle tone resulting in muscular spasm and abnormal posture, typically due to neurological disease or a side effect of drug therapy.

**Frontotemporal Dementia**—A group of disorders caused by progressive cell degeneration in the brain's frontal lobes (behind the forehead) or its temporal lobes (behind the ears).

**General Anxiety Disorder (GAD)**—A mental health condition in which a person is often worried or anxious about many things and finds it hard to control this anxiety.

**Hospital Anxiety and Depression Score (HADS)**—A test commonly used by doctors to determine the levels of anxiety and depression that a patient is experiencing.

**Hyperkinetic**—Pertaining to or marked by hyperactivity (hyperkinesia).

**Intracranial Injury**—Brain injury caused by physical trauma or external force, not degenerative or congenital. Also known as traumatic brain injury (TBI).

**Investigational New Drug (IND)**—A drug that has not been approved for general use by the FDA but is under investigation in clinical trials regarding its safety and efficacy first by clinical investigators and then by practicing physicians using subjects who have given informed consent to participate.

**Ipsilateral**—Belonging to or occurring on the same side of the body.

**Laboratory Developed Test (LDT)**—A term used to refer to a certain class of in vitro diagnostics (IVDs). While most LDTs qualify as medical devices, FDA allows these products to enter the market without prior approval. On July 31, 2014, the FDA announced that it will start regulating some LDTs.

**Levodopa-Induced Dyskinesia (PD-LID)**—A form of dyskinesia associated with levodopa used to treat Parkinson's disease (PD).

**Magnetic Resonance Imaging (MRIs)**—A technique that uses a magnetic field and radio waves to create detailed images of the organs and tissues within the body.

**Mitochondria**—An organelle found in large numbers in most cells, in which the biochemical processes of respiration and energy production occur.

**Mitogenic Stimulation**—The induction (triggering) of mitosis, typically via a mitogen; a chemical substance that encourages a cell to commence cell division.

**Mitotic Process**—The entire process of cell division, including division of the nucleus and the cytoplasm, normally resulting in two new nuclei genetically identical to each other and to their parent cell.

**Montgomery-Asberg Depression Rating Scale (MADRS)**—A diagnostic questionnaire used to measure the severity of depressive episodes in patients with mood disorders.

**Myelination**—The process of forming a myelin sheath around a nerve to allow nerve impulses to move more quickly.

**Myoclonus**—Spasmodic jerky contraction of groups of muscles.



**Neurodegeneration**—Umbrella term for the progressive loss of structure or function of neurons, including death of neurons. Many neurodegenerative diseases including ALS, PD, AD, and Huntington’s occur as a result of neurodegenerative processes.

**Neurodevelopmental**—The processes that generate, shape, and reshape the nervous system, from the earliest stages of embryogenesis to the final years of life.

**Neurotrophic Factor**—Belongs to a family of proteins that are responsible for the growth and survival of developing neurons and the maintenance of mature neurons.

**NMDA Antagonist**—A class of anesthetics that work to antagonize, or inhibit, the action of the N-Methyl-D-aspartate (NMDA) receptor. These agents can protect against brain damage in neurologic disorders, but have psychotomimetic effects and can damage neurons in the cerebral cortex.

**Okadaic Acid (OA)**—A toxin that accumulates in some mollusks and causes diarrheal shellfish poisoning.

**Orphan Diseases**—Any disease that affects a small percentage of the population. Also referred to as a rare disease. In the U.S., the Rare Diseases Act of 2002 defines rare disease as “any disease or condition that affects less than 200,000 people in the United States.”

**Orphan Drug Designation (ODD)**—A pharmaceutical agent that has been developed specifically to treat a rare medical condition, the condition itself being referred to as an orphan disease. The designation, given in the U.S. by the FDA, makes it easier to obtain approval, as well as other financial incentives, such as extended exclusivity periods, all intended to encourage the development of drugs which might otherwise lack a sufficient profit motive.

**Parkinson’s Disease (PD)**—A progressive disease of the nervous system marked by tremor, muscular rigidity, and slow, imprecise movement, primarily affecting middle-aged and elderly people. It is associated with degeneration of the basal ganglia of the brain and a deficiency of the neurotransmitter dopamine.

**Peak-Dose Dyskinesia (PDD)**—A type of dyskinesia that occurs when the dopamine in the brain is supposed to be at its peak. PDD results from too much dopamine in the system.

**Peripheral Blood Lymphocytes (PBLs)**—Mature lymphocytes (white blood cells) that circulate in the blood rather than are specific to particular organs.

**Pharmacokinetic**—Refers to the movement of a therapeutic agent into, through, and out of the body; in essence, the time course of its absorption, bioavailability, distribution, metabolism, and excretion.

**Phytohaemagglutinin (PHA)**—A toxic plant protein, especially extracted from the red kidney bean. It has important medical applications, especially in immunology, because it can induce mitosis and also causes red blood cells to clump together.

**Pokeweed Mitogen (PWM)**—A mitogen derived from *Phytolacca Americana* (pokeweed). It functions as a lectin that stimulates growth and proliferation of B lymphocytes.

**Profile of Mood States (POMS)**—A psychological rating scale used to assess transient, distinct mood states.

**Protein Misfolding-Related Apoptosis**—Death of cells due to protein misfolding (proteopathy), a class of diseases in which certain proteins become structurally abnormal, and thereby disrupt the function of cells, tissues, and organs of the body.

**Retinitis Pigmentosa (RP)**—A chronic hereditary eye disease characterized by black pigmentation and gradual degeneration of the retina.



**Rush Dyskinesia Rating Scale**—A scale of the International Parkinson and Movement Disorder Society used to evaluate movement disorders or dyskinesia.

**Selective Partial Agonist**—A partial agonist binds to and activates a given receptor but only has partial efficacy at the receptor relative to a full agonist. A selective agonist is selective for a specific type of receptor.

**Serotonergic System**—One of the oldest of the amine systems in the brain that appears to be involved in inhibition, both in terms of sensory input and in behavioral output.

**Stereotypies (Plural of Stereotypy)**—Repetitive body movement invariance that serves no social function. Stereotypies may be simple movements such as body rocking, or complex, such as self-caressing, crossing and uncrossing of legs, and marching in place.

**Traumatic Brain Injury (TBI)**—A nondegenerative, noncongenital insult to the brain from an external mechanical force, possibly leading to permanent or temporary impairment of cognitive, physical, and psychosocial functions with an associated diminished or altered state of consciousness.

**Unified Parkinson's Disease Rating Scale (UPDRS)**—The most commonly used rating scale for measuring the course of PD. The scale has five components that are evaluated by interview and clinical observation: (1) evaluation of mentation, behavior, and mood; (2) self-evaluation of the activities of daily life including speech, swallowing, handwriting, dressing, hygiene, falling, salivating, turning in bed, walking, cutting food; (3) clinician-scored monitored motor evaluation; (4) Hoehn and Yahr staging of severity of PD; and (5) Schwab and England activities of daily life scale.

**Vascular Dementia**—A common form of dementia caused by an impaired supply of blood to the brain, such as may be caused by a series of small strokes.

**Wolfram's Syndrome**—See *DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, and Deafness)*.





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a s s o c i a t e s

*Facts Without Fiction*

## EXECUTIVE INFORMATIONAL OVERVIEW®

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