Prana Biotechnology Ltd.

*PBT2, a Novel Approach to Treat Neurodegenerative Diseases, Now in Two Phase II Trials*

Recent failures of monoclonal antibodies targeting beta-amyloid for Alzheimer’s disease (AD) have shaken the confidence of this approach. Ever since beta-amyloid plaques were associated with dementia, pharmaceutical companies have searched for drugs that would induce and accelerate their removal. However, the pathogenesis of AD is complex, and it is now believed that beta-amyloid is not the only culprit. We now think an approach targeting upstream mechanisms that create conditions in synapses favorable for beta-amyloid deposition and hyperphosphorylation of tau protein have a much better chance of being effective. In the past several years, redistribution of certain transition metals in neurons have been implicated in several neurodegenerative diseases, leading to the Metals Dyshomeostasis Hypothesis. There is mounting evidence that compounds that can restore metal homeostasis in the neuron can stop and even reverse cognitive decline associated with neurodegenerative diseases. We think Prana’s PBT2 could be such a compound. In this report, we review PBT2’s development and evidence of efficacy. PBT2 is now being evaluated in two Phase II trials of AD and Huntington’s disease (HD).

- The transition metals zinc (Zn), copper (Cu), and iron (Fe) are implicated in multiple defects associated with neurodegenerative diseases. Zn precipitates beta-amyloid in synapses and can regulate the phosphorylation of tau. Yet it is also important for efficient neurotransmission. Evolution has found ways to quickly and efficiently remove Zn, Cu, and amyloid from the brain upon their release, largely preventing their interaction.

- With age, and with certain risk factors, the efficiency of this process is compromised. Beta-amyloid will bind Zn and precipitate, sequestering Zn in the synapse and causing its depletion from the neuron. The redistribution leads to hyperphosphorylation of tau and eventual formation of neurofibrillary tangles. The accumulation of these toxic aggregates induces an inflammatory response and oxidative stress that also contributes to neuronal cell death and cognitive dysfunction.

- Prana’s PBT2 has been evaluated in several Phase I and II clinical trials, with promising early results that must be confirmed in subsequent clinical trials. PBT2 was shown to be safe and well tolerated and to reduce beta-amyloid levels in the brain and improve executive function in patients with mild AD.

- Two new Phase II trials of PBT2 commenced this year, one in AD, the other in HD. Top-line results from both trials are expected toward the end of 2013. In our view, if these trials deliver favorable results, PBT2 could become one of very few effective drugs for the treatment of neurodegenerative diseases, but confirmatory Phase II or III trials would still be necessary.

- MLV maintains its BUY recommendation and $6.00 one-year price target for Prana Biotechnology Ltd.
Getting to the Root Cause of Alzheimer’s and Other Neurodegenerative Diseases: An Emerging Hypothesis

Alzheimer’s, Parkinson’s, and Huntington’s disease, and amyotrophic lateral sclerosis (ALS, or Lou Gehrig’s disease) are all neurodegenerative diseases characterized by neuronal cell death. Each of these diseases is progressive, meaning that motor and non-motor symptoms increase in severity until death ensues. The diseases are differentiated by the types and location of dying neurons, which translates into a different set of symptoms for each disease. Alzheimer’s disease (AD), for example, is characterized by progressive dementia, while loss of physical skills and movement abnormalities are the main symptoms of Parkinson’s disease (PD) and Huntington’s disease (HD).

Microscopic examination of the brains of patients who died from neurodegenerative disease provides clues as to possible causes. Notably, aggregates of protein are seen in these diseases: tau and beta-amyloid (Aβ) in AD (Exhibit 1), alpha (α)-synuclein in PD, and mutant Huntingtin protein (mHtt) in HD. Accumulation of these proteins is thought to interfere with neuronal function, principally neurotransmission, and to be cytotoxic, which ultimately leads to programmed cell death, or apoptosis, if the process cannot be stopped or the protein aggregates removed. While accumulation of protein aggregates in and of itself may not be sufficient to cause neurodegeneration and neuronal death, it may activate downstream mechanisms that do. Neuroinflammation, oxidative stress, mitochondrial dysfunction, changes in energy metabolism, cell cycle abnormalities, and cerebrovascular alterations have all been implicated in the pathogenesis leading to neuronal cell death in neurodegenerative diseases.¹,²

While there is general consensus that symptoms of neurodegenerative diseases are caused by accumulation of protein aggregates leading to neuronal cell death and loss of function, there is no consensus as to how abnormal aggregation of these proteins is stimulated and sustained, or even if there is a mechanism common to aggregation of proteins characteristic of each of the neurodegenerative diseases. Moreover, it is not clear how these protein aggregates affect neuronal function and neurotransmission. Consequently, biotech and pharmaceutical companies have focused their efforts on finding drugs to interfere with protein aggregation or to stimulate mechanisms to remove them, or to prevent or correct abnormal neurotransmission across synapses of affected nerves. Notably, drugs that have been successfully developed to

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treat neurodegenerative diseases, and many still in various stages of development, have been only palliative, providing some relief from symptoms. The clinical benefit, however, is only temporary, since the mechanism driving disease progression remains untreated. To date there is still no cure or, arguably, even disease-modifying drugs, for any of the neurodegenerative diseases.

Drugs that effectively treat symptoms of neurodegenerative disease are, of course, widely used and commercially successful. Clinical trials and post-marketing surveillance have conclusively demonstrated that symptomatic relief improves the quality of life and alleviates caregiver burden for these patients. Donezepil (Aricept®), for example, significantly improves and delays declines in AD patients’ scores on the cognitive subscale of the Alzheimer’s disease Assessment Scale (ADAS-cog) and delays nursing home placement.\(^3\) Tetrabenazine (Xanazine®), in another example, markedly reduces the Total Chorea Score (of the Unified Huntington’s Disease Rating Scale, or UHDRS) in HD patients, but has little effect on functional capacity or cognition.\(^5\)

**Disease Modification – The Holy Grail of Drug Development for Neurodegenerative Disease**

The Holy Grail of discovering and developing drugs for the treatment of neurodegenerative diseases is true disease modification, not palliation of symptoms. Disease-modifying drugs targeting the causes of disease would be expected to stop disease progression and, preferably, reverse it. We know, for example, that drugs like donepezil and memantine (Namenda®) target abnormal neurotransmission, but do not target mechanisms that cause abnormal neurotransmission in the first place. Similarly, the development of drugs targeting Aβ in order to reduce plaque burden in AD do not target mechanisms that lead to Aβ aggregation and the formation of plaques. In this regard, a great deal of time and resources have been directed at the development of monoclonal antibodies that bind to Aβ to induce its engulfment and removal by immune cells.

We are not saying that drugs of this type have no clinical utility, because the widespread use of those already approved and their commercial success clearly demonstrate that patients and physicians appreciate the benefits they provide, limited as they may be. In our view, a drug that targets the cause of AD and other neurodegenerative disease, or at least targets disease mechanisms upstream of the pathology that leads to symptoms, could be far more effective and deliver more durable, longer-lasting benefit. Here, we describe the efforts of a small Australian biotechnology
company, Prana Biotechnology, Ltd., along with its collaborators and advisors in the US and Europe, to develop small molecule, orally available drugs that target neurodegenerative disease-causing mechanisms, and not just symptoms. We think their leading drug candidate, PBT2, has demonstrated compelling evidence of efficacy in multiple preclinical studies and in early-stage clinical trials. PBT2 is now being evaluated in two ongoing Phase II clinical trials, one for the treatment of AD and the other for HD.

Prana’s drug candidates for the treatment of neurodegenerative diseases target a mechanism now thought to be upstream of Aβ aggregation and formation of intracellular neurofibrillary tangles in AD, and aggregation of Huntingtin in HD and α-synuclein in PD. The critical defect that leads to aggregation of these proteins is a loss of transition metal homeostasis and their trafficking during neurotransmission. The key transition metals, zinc (Zn), copper (Cu), and iron (Fe), all play important physiologic roles in neuronal function and neurotransmission, but their distribution between cell compartments and extracellular space must be well regulated by cells to avoid pathologic consequences. As we will describe in more detail below, PBT2 appears to restore transition metal homeostasis in AD and HD, leading to disaggregation of Aβ and improvement of cognitive function and memory in animal models of AD and early-stage clinical trials of patients with AD, and prevention of mHtt aggregation and brain atrophy while improving motor function in animal models of HD.

The emerging important early role of metals in the pathogenesis of AD and HD has been debated for several years,\(^6,7\) even though it has long been recognized that alteration in ionic homeostasis may play a role in neurodegeneration and neuronal cell death.\(^8\) In the next section, we set the stage with a brief review of the Amyloid Cascade, or Aβ, Hypothesis of the pathogenesis of AD, then discuss evidence supporting the Transition Metals Dyshomeostasis Hypothesis. We then review Prana’s preclinical and clinical experience with PBT2, which we think strongly supports this alternative view of the pathogenesis of neurodegenerative diseases, and its clinical development plan. Finally, we put PBT2 in the context of other drug candidates currently in development for the treatment of neurodegenerative diseases and describe why we think PBT2 has certain key advantages over its emerging competition.

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Amyloid Cascade or Aβ Hypothesis

Several important discoveries led to the focus on Aβ as a viable and attractive target for drug developers. In the late 1960s, plaque count in the brain was correlated with severity of dementia. Aβ was identified as the principal aggregated protein in plaques of brains of AD patients only in 1985. It was determined to be produced during normal cell metabolism in 1992, after its parent protein, amyloid precursor protein (APP), was cloned in 1987. Today, the processing of APP into its fragments by proteolytic enzymes is well understood, as well as mechanisms that remove it before it can aggregate and form plaques. The generation of Aβ and its accumulation into plaques is the central tenet of the Amyloid Cascade, or Aβ, Hypothesis.

APP is a widely distributed and ubiquitously expressed transmembrane glycoprotein that is highly expressed in the nervous system, where it plays a role in neuronal cell and synaptic adhesion and synaptogenesis and neurogenesis. It is processed in two different ways (Exhibit 2). In the so-called “amyloidogenic pathway,” APP is cleaved by β-secretase, also called β-APP site cleaving enzyme (BACE), at the amino terminus of Aβ, releasing a soluble protein called APPsβ, and then by γ-secretase, an intramembranous protease complex, to produce Aβ and APP intracellular domain (AICD) protein. In the “non-amyloidogenic pathway,” APP is cleaved by α-secretase within the Aβ domain of APP, releasing a soluble protein called APPsα and precluding the generation of any Aβ. The same γ-secretase then cleaves the remaining piece of APP, releasing AICD and a small peptide called p3. Each of these metabolites, including Aβ, are also likely to have physiologic roles that are important for normal neuronal function but are still to be definitively determined. For example, there is evidence that APPsα regulates neuronal progenitor cell proliferation, neuronal survival, and migration.

Under normal, non-pathologic conditions, the non-amyloidogenic pathway predominates in APP processing. Small amounts of Aβ produced normally by the amyloidogenic pathway are degraded by a number of peptidases (insulin-degrading enzyme, nepriylisin, and endothelin-converting enzyme) or cleared from the brain by low-density lipoprotein (LDL) receptor-related, protein-mediated efflux across the blood brain barrier (BBB). This is balanced, in part, by influx mediated by the receptor for advanced glycation end

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In this way, Aβ can appear both in the cerebrospinal fluid (CSF) and in the plasma, where it is being evaluated as a potential biomarker and diagnostic tool for AD. Two forms of Aβ are generated by γ-secretase, one of 40 and the other of 42 amino acids in length (Aβ_{40} and Aβ_{42}, respectively). While Aβ_{42} is more prone to aggregation than Aβ_{40}, the latter is normally produced in greater abundance.\(^{15}\)

The central importance of Aβ in AD pathogenesis and a clearer understanding of how Aβ is produced from APP led to the Aβ Hypothesis (Exhibit 3). It remains the prevailing dogma to this day. The triggering event is increased Aβ levels, but what is still not adequately explained, in our view, are the defects at the cellular level that stimulate Aβ to accumulation, aggregation, and formation of toxic plaques. As we described above, mechanisms to efficiently remove Aβ from the synapse exist, but what tips the balance away from Aβ clearance to Aβ production and accumulation is not explained. The reasons usually given are somewhat nebulous — genetic and environmental risk factors and, simply, aging.

**Exhibit 3: The Amyloid Cascade, or Aβ Hypothesis, for the Pathogenesis of AD**

Presumed cascade of events in the development of AD. Note that the first step in the cascade is an increase in Aβ levels, which is often attributed to mutations in the APP or presenilin* genes, which increase the proportion of Aβ_{42} produced, in familial AD and to genetic and environmental risk factors and aging in sporadic AD†. The principal genetic risk factor is the ApoE ε4 genotype, with possible minor contributions of other candidate genes.

Familial AD is an autosomal dominant disorder, with the onset of AD expected before the age of 65. With a prevalence is <0.1%, the vast majority of patients with AD have the sporadic form.

* Presenilin is a component of the intramembranous protease complex that is γ-secretase.
† “Sporadic” is a term used to describe AD that is not inherited, but associated with certain genetic risk factors.

Furthermore, the critical link between Aβ and neurofibrillary tangles, produced by hyperphosphorylation of tau protein inside neurons, is not adequately explained by the Aβ Hypothesis, in our view. As late as 2006, there was still no consensus as to whether

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**In our view, the Amyloid Cascade Hypothesis does not adequately explain mechanisms at the cellular level that trigger Aβ aggregation and accumulation**
tau hyperphosphorylation and tangle formation are a cause or consequence of AD,\textsuperscript{16} while the Aβ Hypothesis held that changes in tau and tangle formation were triggered by high and toxic levels of Aβ.\textsuperscript{17}

Tau is normally a soluble cytoplasmic protein distributed in the axons of neurons and in most other cells as well. It is a microtubule associated protein (MAP) that binds to microtubules to regulate their assembly and stability.\textsuperscript{18,19,20} Tau phosphorylation causes it to detach from microtubules, thereby enhancing microtubule disassembly and instability. Tau dephosphorylation increases binding to microtubules, accelerating microtubule growth and enhancing stabilization.

Tau phosphorylation is regulated by opposing activities of protein kinases (mainly GSK-3β, but other kinases as well) and protein phosphatases (PP-1, -2A, and -2B).\textsuperscript{21} Normally, tau has about 15 functionally important phosphorylation sites, of which an average of two to five are phosphorylated; however, in brains from AD patients, as many as 45 phosphorylation sites have been identified, with up to ten phosphorylated sites per tau molecule. If the balance between kinase and phosphatase activity is disturbed and tau becomes hyperphosphorylated, tau and other MAPs become sequestered, enabling them to aggregate into insoluble fibrils, forming “tangles” characteristic of AD. Diseases with dysfunctional, hyperphosphorylated tau are called “tauopathies.”

With unstable and dysfunctional microtubules, they become less able or unable to perform their principal function: regulating transport of organelles, neurotransmitters, and other proteins through the axon to and from a neuron’s cell body. Consequently, synapses are unable to function efficiently or at all, thereby disrupting neurotransmission and neuronal networks and eventually causing cell death.

Since both Aβ plaques and neurofibrillary tangles are both linked to dementia of AD, the obvious question is: Which comes first? According to the Aβ Hypothesis, the primary event is increased generation of Aβ, which then, by as yet undetermined mechanisms, disturbs the balance of kinase and phosphatase activity toward

\textsuperscript{16} Ibid.
\textsuperscript{21} CDK5, cyclin-dependent kinase-5; GSK3β, glycogen synthase kinase-3β; PP, protein phosphatase. PP-2B is also known as calcineurin.
Hyperphosphorylation. However, the precise mechanism and interactions have yet to be determined.\textsuperscript{22}

**Transition Metal Dyshomeostasis or Metal Hypothesis**

While the Aβ Hypothesis clearly establishes that the toxic effects of Aβ plaques and intracellular neurofibrillary tangles cause aberrant neurotransmission and neuronal cell death, leading to dementia and behavioral symptoms of AD, the Hypothesis does not, in our view, adequately explain biochemical changes that initiate the pathological cascade with respect to both Aβ and tau. We now draw attention to recent studies of possible precipitating events in neurodegenerative diseases that have implicated what was considered a downstream consequence of Aβ aggregation and plaque formation as one of the key initiating events. These studies point to aberrant trafficking and distribution of certain transition metals as one of the root causes of AD.

In the Aβ Hypothesis (refer to Exhibit 3, above), “altered neuronal homeostasis” is considered a downstream effect of Aβ deposition, plaque formation, and microglia activation leading to “progressive synaptic and neuritic injury” that finally “alters” neuronal homeostasis. Recent evidence suggests that the order of events is incorrect—that it is altered neuronal homeostasis, particularly with respect to regulation of the concentration, trafficking, and distribution of transition metals, that enables and promotes both Aβ aggregation and tau hyperphosphorylation. A Transition Metal Dyshomeostasis Hypothesis (or Metal Hypothesis) has been proposed to explain these findings.\textsuperscript{23,24} Notably, the Metal Hypothesis is not only relevant to AD, but also to other neurodegenerative diseases, including PD and HD, where abnormal protein aggregation and deposition are thought to be key drivers of disease progression.

Metal trafficking between cells, across membranes, and between compartments is highly regulated.\textsuperscript{25} Each metal has its own set of specific ion channels and protein transporters that shuttle specific ions across membranes, as well as binding proteins, chaperone proteins to shuttle ions within compartments, and storage organelles, in order to tightly control the intracellular concentration of free metal ions. This tight regulation, keeping free ion concentrations within certain limits, is referred to as “metal homeostasis.”

Notably, the free concentration of all essential metal ions is quite low. This is largely because metals are highly interactive and reactive, and can be toxic at higher concentration due to non-physiologic, so-called “adventitious” interactions with small molecules, peptides, and proteins that usually do not interact with metals. Many proteins or enzymes also require metals for their three-dimensional structure or activity (metalloproteins), and they are typically reliant on specific ions. Metals are involved in signal transduction whereby the activity of an enzyme or channel is turned on or off like a switch upon ion binding and release. Some metals, notably Cu and Fe, are redox active, or capable of accepting or donating electrons. These reactions can produce reactive oxygen species (ROS), such as oxygen ions and peroxides, which are known to have important physiologic roles in cell signaling, inflammation, and defense against microorganisms. However, oxidative stress can occur if too many ROS are produced, resulting in bystander damage to cellular proteins, lipids, membranes, and nucleic acids (DNA and RNA) that may cause dysfunction or cell death.

Certain metals, particularly Zn and Cu, play key roles in neurotransmission. Free Zn is released into the synapse along with glutamate, a neurotransmitter that stimulates the N-methyl-D-aspartate (NMDA) receptor on the post-synaptic side of the synapse of glutaminergic synapses. Zn appears to modulate the activity or levels of the NMDA receptor, as does Cu, which is also released into the synaptic cleft during neurotransmission, but from the post-synaptic side. Free Zn and Cu concentrations in the synaptic cleft during neurotransmission are estimated to reach about 300 and 15 μM, respectively. Notably, it appears as though the glutaminergic synapse during activation is the only place in the body where free, reactive Zn and Cu are present. Everywhere else, free Zn and Cu levels are so tightly controlled that their free concentration approaches zero.

The glutaminergic synapse is also where an interesting association between Zn and Aβ is observed. These types of synapses are located in the cortex and hippocampus of the brain, and it is here that Aβ deposits and plaques first appear. Cognition and memory are key functions of these regions, and cognitive dysfunction is one of the first symptoms of AD. Aβ deposits are linked to Zn and Cu because this protein is also released from post-synaptic neurons during neurotransmission, where it is also believed to modulate the

**Interestingly, the one place in the body where free Zn and Cu can interact with Aβ is in the synaptic cleft of glutaminergic neurons of the cortex and hippocampus, which is also the first place deposits of Aβ occur in early AD**

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26 Ibid.
29 Ibid.
When Zn, Cu, or Fe are added to soluble Aβ, it causes rapid aggregation and precipitation, and advanced, senile Aβ plaques contain large amounts of all these ions.

Tau normally undergoes cycles of phosphorylation and dephosphorylation by kinases and phosphatases, respectively, but in AD, with depleted intracellular Zn, the kinase activity predominates, leading to hyperphosphorylation of tau.

activity of the NMDA receptor. Importantly, Aβ is a metalloprotein that possesses selective low and high affinity binding sites for Zn and Cu. Studies have shown that soluble Aβ in the test tube rapidly aggregates and precipitates upon the addition of Zn, Cu, or Fe at concentrations of Zn and Cu that are achieved during neurotransmission at glutaminergic synapses. Thus, under physiologic conditions, Zn, Cu, and Aβ released together into the synaptic cleft could interact and cause Aβ to precipitate. In advanced AD, senile Aβ plaques have been found to contain large amounts of Cu, Zn, and Fe, equivalent to about 400 μM, 1 mM, and 1 mM, respectively.

In healthy synapses, however, mechanisms are in place to quickly remove free Zn, Cu, and Aβ from the synaptic cleft. Specific transporters—copper transporter-1 (CTR1) for Cu and Zrt and Irt-like proteins (ZIP) for Zn—rapidly transport Cu and Zn back into neurons, where another set of transporters and chaperones sequester them out of harm’s way with Zn- or Cu-specific metalloproteins. Aβ is cleared and removed from the synaptic cleft by proteases and LDL receptor-related, protein-mediated efflux across the BBB, as described above. Notably, if Zn (but not Cu) is bound to Aβ, then the Aβ:Zn complex assumes a conformation that makes Aβ resistant to proteolytic cleavage by matrix metalloprotease 2 (MMP2) and other proteases. Rapid removal of Aβ and Zn from the synaptic cleft before they can interact with each other to form protease resistant complexes is therefore of critical importance in preventing Aβ aggregation and deposition.

What about hyperphosphorylation of tau and the formation of neurofibrillary tangles? As mentioned above, the level of tau phosphorylation is mediated by activities of kinases and phosphatases. GSK3, which is thought to be the major and most efficient kinase responsible for phosphorylating tau, is itself regulated by phosphorylation at different sites. Phosphorylation on certain serine residues inhibits its activity, while phosphorylation on certain tyrosine residues stimulates its activity, and serine phosphorylation can override tyrosine phosphorylation. Calcineurin (PP-2B) and other phosphatases dephosphorylate GSK3 at its serine inhibitory site, thereby activating GSK3 and enabling it to phosphorylate tau. Calcineurin’s activity is, however, inhibited by an interaction with Zn. Consequently, in the presence of Zn, calcineurin’s activity is attenuated or inhibited, thereby keeping

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32 Ibid.
GSK3’s inhibitory serine site phosphorylated and preventing it from phosphorylating tau.

Taken together, the evidence suggests that if Zn homeostasis is disturbed by redistribution of Zn between extracellular and intracellular compartments such that Zn binds to and causes the accumulation of Aβ in the extracellular space, thereby depleting intracellular stores, then there will be serious pathologic consequences that lead to AD. In summary:

- The initiating events are inefficiencies in clearing Zn, Cu, and Aβ from the synaptic cleft during normal neurotransmission. The inefficiencies may arise from oxidative stress over many years that damages clearance mechanisms, coupled with genetic risk factors.
- This provides an opportunity for Zn to bind to Aβ, causing it to aggregate and precipitate. The more Zn that binds, the less likely the Aβ:Zn precipitate will be cleared by proteases or transported across the BBB.
- As post-synaptic neurons continue to release Aβ and Zn into their synaptic clefts, Aβ precipitates enlarge and sequester more and more Zn, causing redistribution of Zn from the intracellular space to the extracellular space.
- As Zn is depleted from the neuron, calcineurin is activated, causing dephosphorylation of GSK3, which, in turn, is also activated to phosphorylate tau.

In our view, Zn dyshomeostasis is kind of a “unifying” hypothesis that explains why Aβ forms deposits and plaques and how this leads to tau hyperphosphorylation, something the Aβ Hypothesis cannot satisfactorily explain. Moreover, there is now considerable preclinical experimental data, as is evident from the results of studies published in peer-reviewed journals and referenced in this research note, in support of this hypothesis.

Importantly, the evidence also points to a potential drug target, and this is to find a way to restore Zn homeostasis. The only way to prove or disprove this hypothesis is to discover a drug with this property and then test it in clinical trials to determine if it can stop or reverse AD progression. This result would be expected, since the evidence predicts that restoring Zn homeostasis would lead to dephosphorylation of tau with restoration of calcineurin’s inhibition of GSK3’s kinase activity and to disaggregation of Aβ as Zn is released from the Aβ deposits and redistributed back inside the neuron.

With this in mind, in 1997 several investigators in the field founded a company in Australia, called Prana Biotechnology Ltd., to discover and develop drugs that could restore metal homeostasis. The goal was to discover and develop small molecules capable of binding and

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transporting metals, but then releasing them in compartments where they should be. This requirement excluded the use of metal chelators, which would never release the metal. Molecules capable of metal exchange or acting as an ionophore were more likely to work. Prana identified clioquinol (CQ), a 8-hydroxyquinoline (8-HQ) derivative, as possessing these properties (Exhibit 4). CQ has been sporadically used as an antifungal and antiprotozoal drug since the 1960s. Further work led to the discovery of PBT2, another 8-HQ derivative with superior pharmacologic properties (PBT2’s structure is undisclosed). Preclinical studies with both compounds and early-stage clinical trials with PBT2 delivered results supportive of the Metal Dyshomeostasis Hypothesis. Prana has now advanced PBT2 into two Phase II clinical trials in patients with AD and HD.

**Prana’s PBT2: Already in Phase II for AD and HD**

Prana has conducted several promising preclinical studies and advanced CQ as far as a small pilot Phase II trial. However, further development was discontinued after a di-iodo contaminant was found during the manufacturing process. Meanwhile, Prana discovered and tested a second-generation 8-HQ derivative, PBT2, with better penetration across the BBB and, again, promising preclinical results. These studies indicated that the two drugs were having the intended effect of restoring metal homeostasis, with evidence of improved cognition as well.

- In transgenic mice that overexpress a mutant form of APP linked to early onset familial AD and develop amyloid plaques and progressive cognitive deficits (Tg2576 mice), a 49% reduction in cortical deposition of Aβ and an improvement in general health and weight were observed in CQ-treated mice compared to controls.

- Also in Tg2576 mice, radiolabeled \(^{125}\text{I}\)-CQ was shown to cross the BBB and bind to Aβ plaques, with enrichment in the neocortex. The Tg2576 mice also retained more of the tracer in their brains than normal mice. The investigators also demonstrated saturable binding of \(^{125}\text{I}\)-CQ to synthetic Aβ\(_{40}\) and Aβ\(_{42}\) that was precipitated by the addition of Zn. Adding back free Zn, Cu, or the metal chelator DTPA (diethylene triamine pentaacetic acid) released \(^{125}\text{I}\)-CQ from its bound state on Aβ.

- In two different amyloid-bearing transgenic mouse models of AD (Tg2576 and APP/PS1 mice), PBT2 and CQ decreased soluble brain Aβ within hours and improved cognitive performance in the Morris Water Maze test (Exhibit 5) to exceed that of their

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39 Ibid.


The investigators noted that the rapid effect and recovery of cognitive function indicated that deficits characteristic of these transgenic mice were reversible.

- In a study with a normal, widely-used mouse strain (C57BL/6), younger mice (12 months of age) were able to swim to the platform in the Morris Water Maze faster than older mice (18 months). As C57BL/6 mice age, they accumulate Aβ oligomers and hyperphosphorylated tau. An 11-day treatment with PBT2 improved the performance of the older mice to match that of the younger mice (Exhibit 6).

Exhibit 6: PBT2 Improves the Performance of Older Mice in the Morris Water Maze to Match That of Younger Mice

Morris Water Maze 18 month old C57BL/6 mice treated once daily with 30 mg/kg PBT2 by oral gavage for 11 days. “Young” and “Old” mice are 12 months and 18 months of age, respectively.

- In another strain of transgenic mice that develop AD (APP/PS1 mice), a 35-day treatment with PBT2 led to substantial declines in the phosphorylation of soluble and insoluble tau in their brains (Exhibit 7). We think the results of these studies, and other preclinical studies that are beyond the scope of this report to describe, support the basic premise of the Metal Dyshomeostasis Hypothesis. Prana calls molecules like CQ and PBT2 “metal-protein attenuation compounds,” or MPACs. They can easily form complexes with metals and cross biological membranes, including the BBB and neuronal cell membranes. Once they deliver their cargo to

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Exhibit 5: Morris Water Maze

The Morris Water Maze test is a behavioral test widely used in studies of rodent aging that involve learning and recall of spatial information (memory). Progressive impairment of this skill is an important dimension of age-related cognitive decline in both rodent and human aging.

The test involves placing a mouse into a white, circular polyethylene tank filled with water with a submerged platform (dark square, above) that the mouse is expected to find based on visual cues. When first placed into the tank, mice will find the platform by random swimming and should be able to remember where the platform is by visual cues around the tank and in the testing room. Mice are tested daily, and the time to find the platform and distance swam typically decreases with each day of testing.


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Ibid.
compartments depleted of the metal, they release the metal and then diffuse back out to do it again.

**Exhibit 7: PBT2 Reduce Levels of Tau Phosphorylation**

Levels of (A) insoluble phosphorylated tau and (B) soluble phosphorylated tau in the brains of APP/PS1 mice treated for 35 days with PBT2 (10 mg/kg/d) showing significant reductions with PBT2 treatment. Transgenic APP/PS1 mice overexpress APP bearing missense mutations that cause AD in humans and express human presenilin with a deletion mutation (dE9) that also causes AD. *p = 0.03, compared to control.

**Phase I and II Experience**

With these promising preclinical results, and Phase I trials showing that CQ and PBT2 were safe and well tolerated, Prana advanced CQ, and then PBT2, into clinical trials. The first Phase II trial was a small pilot trial enrolling 36 patients with moderately severe AD as determined by the AD Assessment Scale-Cognition (ADAS-cog) and Mini-Mental State Examination (MMSE). The ADAS-cog is a test that measures several cognitive domains, including identification of objects, memory, language, and execution of simple tasks (or praxis). It is the standard primary outcome neuropsychological measure for AD clinical trials. Total scores range from 0 to 70, with higher scores (≥18) indicating cognitive impairment. Typically, a four-point change at six months of treatment in a clinical trial is considered clinically important. The MMSE is a brief, 30-point questionnaire testing arithmetic, memory, and orientation problems that is scored on a 0- to 30-point scale, with a score of ≤9, 10-20, 21-24 points indicating severe, moderate, or mild cognitive impairment, respectively.

Patients in this Phase I trial were randomized into two treatment groups: placebo and dose titration of CQ (125 mg twice daily for 12 weeks, 250 mg twice daily for the next 12 weeks, and 375 mg twice daily for the last 12 weeks, for a total of 36 weeks). CQ was well tolerated and showed evidence of efficacy, but due to the trial’s small size it was not powered to show efficacy. Nevertheless, patients randomized to CQ showed a greater decline in their ADAS-cog scores than patients in the placebo group after 36 weeks of dosing. Interestingly, the beneficial effect of CQ was more

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pronounced in patients with severe AD (ADAS-cog ≥25 versus <25). During the treatment period, plasma levels of Aβ increased in the placebo group as they decreased in the CQ group. Patients in this trial had lower-than-normal levels of plasma Zn, and CQ significantly increased plasma levels while placebo had little effect.

In our view, results from this small Phase II trial were promising and suggested that CQ was having its intended effect. The increase in plasma levels of Aβ and Zn could be attributed to a decrease in Aβ deposition and associated sequestration of Zn, or possibly reduction in Aβ plaque burden with concomitant release of Zn.

As described above, Prana discontinued further development of CQ and moved forward with PBT2, an MPAC with superior pharmacokinetic and pharmacodynamic properties. Prana commenced its first Phase IIa trial of PBT2 in patients with early AD in December 2006 (Study PBT2-201).\(^{45}\) This was a randomized, double-blind, placebo-controlled trial of 80 patients 55 years of age or older with mild AD (at screening, the mean ADAS-cog score was 18.8, range: 7-35; the mean MMSE score was 22.9, range 16-29). Patients were randomized into three groups to receive 50 mg or 250 mg PBT2 (20 and 30 patients, respectively), or placebo (30 patients), for three months. The objective, and primary endpoint, of the trial was to demonstrate safety and tolerability of PBT2. The trial succeeded, in this regard, as there were no withdrawals due to adverse events and no reports of serious adverse events.

The secondary efficacy endpoint in this trial was a Neuropsychological Test Battery (NTB) of several validated cognitive tests used to assess changes in patients with mild AD. The NTB delivers nine outcome measures of memory and so-called “executive” function. These can be grouped using Z statistics to yield a composite Z score of all nine tests, a memory factor Z score of the four memory tests, and an executive function Z score of the five executive function tests. The results showed a dose-dependent trend of improving composite Z score and executive function Z score (Exhibit 8). The difference between the placebo and 250 mg PBT2 in the composite Z score was not significant (p=0.193), while the difference in the executive function Z score was statistically significant (p=0.042).\(^{46}\) There was essentially no change in the memory factor Z score in the three treatment groups.

Changes in key biomarkers were also measured as secondary endpoints in this trial. In the three-month period of treatment, the level of Aβ\(_{40}\) and Aβ\(_{42}\) in the cerebrospinal fluid (CSF) increased in

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the placebo group, but decreased in the 250 mg PBT2 group. The decrease was statistically significant for $\text{A}\beta_{42}$ ($p=0.023$), while trending toward significance for $\text{A}\beta_{40}$ ($p=0.09$). This finding is consistent with the observation of a decrease in the concentration of $\text{A}\beta$ in the interstitial fluid of the brains of transgenic APP/PS1 mice treated with PBT2.\textsuperscript{47} Plasma concentrations of $\text{A}\beta$ were unchanged with PBT2 treatment, suggesting to the investigators that PBT2 affects $\text{A}\beta$ clearance in the central nervous system, but not from the periphery where blood platelets may contain the principal depot. There were no significant differences between the levels of total tau and phosphorylated tau in the CSF, though there was a modest trend to lower levels in the 250 mg PBT2 group compared to placebo.

**Exhibit 8: PBT2 Improved the Executive Function Z Score in Mild AD Patients After 12 Weeks of Treatment**

A Neuropsychological Test Battery (NTB) of nine validated tests was used to assess cognition. Grouping of all nine tests using Z statistics generates a composite Z score, of the four memory tests generates a memory factor Z score, and of the five executive tests generates an executive factor Z score.

The difference between placebo and 250 mg PBT2 in the composite and memory factor Z scores was not significant.

The difference between placebo and 250 mg PBT2 in the executive function Z scores was significant ($p=0.042$).


We find the results of this Phase II trial to be very encouraging, but with several reservations. While we think the observed effects are consistent with PBT2 serving to restore metal homeostasis, we recognize that this was a small trial that was not powered to demonstrate efficacy. Nevertheless, while successfully demonstrating once again that PBT2 is safe and well tolerated, there were promising signs of efficacy. Moreover, the durability of any efficacy effect cannot be determined, as the treatment period was quite short, only three months. The results of this trial must be confirmed in larger clinical trials of longer duration, and additional biomarker studies to confirm that PBT2 is acting on its intended target would be very helpful.

\textbf{The results of this Phase II trial must be confirmed and extended in additional Phase II and III trials of PBT2 in AD}

Ongoing Phase II Trials in AD and HD

To this end, Prana initiated two additional Phase II trials of PBT2 earlier this year—one in AD and another in HD. The latter is the first trial of PBT2 in HD, and it signals a possible broader indication for the drug beyond the original AD indication. We will describe the rationale for the HD trial after we briefly describe the second Phase II trial of PBT2 in AD patients.

Safety and Tolerability of PBT2 in Patients with Mild AD

Prana reported treating the first patient in its randomized, double-blind, placebo-controlled Phase II safety and efficacy trial, called IMAGINE, on March 6, 2012. IMAGINE will be conducted entirely in Australia. The trial design is shown in Exhibit 9.

The objective of this 40-patient trial is to assess the effect of PBT2 on the distribution of Aβ in the brain after a year of treatment, or four times longer than the first Phase II trial. Previous preclinical and clinical studies strongly suggest that PBT2 releases Aβ from its aggregates and deposits in the brain. Patients with mild symptoms that signal impending onset of AD (prodromal) are being recruited in order to evaluate the effect of PBT2 at one of the earliest stages of the disease.

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<th>ACTRN: ACTRN12611001008910</th>
<th>Listed status: Currently recruiting</th>
<th>Last updated: June 26, 2012</th>
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<td>Official Title: A Randomised, Double-Blind, Placebo Controlled Study to Assess the Safety and Tolerability of PBT2, and its Effect on Amyloid Deposition in the Brains of Patients with Prodromal or Mild Alzheimer’s Disease.</td>
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<td>Acronym: IMAGINE (Study number: PBT2-204)</td>
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<tr>
<td>Study design: Randomized, parallel assignment, double blind, safety and efficacy study</td>
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<tr>
<td>Test compound: PBT2</td>
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<td>Phase: II</td>
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<td>Indication: Prodromal AD or mild AD</td>
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<td>Enrollment: 40</td>
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<td>Controls: Placebo</td>
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<tr>
<td>Groups (Arms): Two arms: PBT2 and placebo; randomized 2:1, PBT2:placebo</td>
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<tr>
<td>Key inclusion and exclusion criteria: Diagnosis of prodromal AD or mild AD, and 11C-PiB-PET positive (SUVR &gt;1.7) and MMSE ≥20; ≥55 years of age. Excluded if allergic to PBT2 or its excipients; diagnosed with other known primary neurodegenerative disorders associated with dementia.</td>
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<tr>
<td>Dosing schedule: Four-week screening period, then 250 mg PBT2 (immediate release capsules) or matching placebo by oral administration once per day for 52 weeks (1 year), and 4-week follow up.</td>
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<td>Stages: Single</td>
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<tr>
<td>Primary endpoint(s): Brain amyloid levels by 11C-PiB PET imaging, neocortical SUVR at baseline, and 26 and 52 weeks</td>
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<tr>
<td>Secondary endpoint(s): Safety and tolerability, brain metabolic activity (by 18F-FDG PET SUVR), total brain (cortical grey matter), hippocampal and ventricular volume (by MRI), cognition (by NTB and MMSE questionnaires), and functional abilities (by ADCS-ADL-23 questionnaire).</td>
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<td>Sites: 3 (5 planned)</td>
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<tr>
<td>Location: All in Melbourne, Australia</td>
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<tr>
<td>Principal investigator: Prof. Christopher Rowe, Director, Nuclear Medicine &amp; Centre for PET, Austin Hospital, Heidelberg, Victoria, Australia.</td>
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</table>

Abbreviations: ACTRN, Australian Clinical Trials Registry Number; AD, Alzheimer’s disease; ADCS-ADL-23, AD Cooperative Study-Activities of Daily Living-23; 11C-PiB, carbon 11-Pittsburgh imaging compound-B; 18F-FDG, fluorine 18-labelled fluorodeoxyglucose; MMSE, Mini-mental State Examination; MRI, magnetic resonance imaging; NTB, Neuropsychological Test Battery; PET, positron emission tomography; SUVR, standardized uptake value ratio.

Source: ClinicalTrials.gov, company reports and MLV research.
the disease, before there is considerable dysfunction and death of neurons and where effective therapy may deliver the greatest benefit. According to Prana, the strategic goal of IMAGINE is to provide additional clinical and safety data to support a major licensing partnership. Results are expected in 2H:13. Prana received a $700,000 award from the Alzheimer’s Drug Discovery Foundation (ADDF) of New York, NY, to help fund IMAGINE for two years.48

The primary endpoint of IMAGINE is a measure of the amount of Aβ in the brain with positron emission tomography (PET) using a 11C-labelled radiotracer called Pittsburgh Compound B (PiB) that localizes to Aβ plaques (Exhibit 10). Other measurements will include a measure of brain metabolic activity using 18F-FDG (fluorine 18-labelled fluorodeoxyglucose) PET and hippocampal and ventricular volumes by magnetic resonance imaging (MRI). FDG mimics glucose and accumulates in areas of high metabolic activity. Metabolic activity in the AD brain is markedly diminished as neurons die. In AD brain, hippocampal volumes decrease, while the ventricle enlarges.

**Exhibit 10: Phase II Trial of PBT2 in Patients with Prodromal or Mild Alzheimer’s Disease**

Comparison of PiB-PET images (top), MRI (middle), and FDG-PET images (bottom) from a cognitively normal person and a patient with mild AD. The normal individual was 71 years of age and had an MMSE score of 30, whereas the patient with AD was 69 years of age and had an MMSE of 21. The AD patient has marked PiB accumulation together with an FDG scan typical for the disease with temporoparietal and frontal hypometabolism. Scale bars indicate SUV for PiB and FDG. Note that the dynamic range of PiB is twice that of FDG. Scans are courtesy of University of Pittsburgh Amyloid Imaging Group.

**Abbreviations:** FDG, 18F-fluorodeoxyglucose; MMSE, mini-mental state exam; MRI, magnetic resonance imaging; PET, positron emission tomography; 11C-PiB, Pittsburgh Compound-B; SUV, standardized uptake values.


Cognition will be measured by an NTB, MMSE, and ADCS-ADL-23, or AD Cooperative Study Activities of Daily Living, questionnaire. Based on the results of the first Phase II trial, we would expect to see a clear decline in Aβ levels in the brain, with a concomitant increase in metabolic activity and restoration of more normal brain volumes, and in parallel with improving cognition scores. We note that since this trial is also small, we will not be surprised or disappointed if statistically significant differences in these parameters are not achieved. We view this as a confirmatory Phase II trial that, with favorable trends suggesting that PBT2 has a disease-modifying effect, will lead to the design and execution of a larger, pivotal Phase III trial.

By necessity, we think a pivotal Phase III trial will have to enroll one thousand or more AD patients, or about the same size as the Phase III trials of bapineuzumab, a monoclonal antibody directed against Aβ. Such a trial may also have to be of longer duration to definitively show a difference in cognitive function between placebo and drug-treated groups. The primary endpoint of the bapineuzumab trials is ADAS-cog and the Disability Assessment for Dementia (DAD) scale after 78 weeks, or 1.5 years, of treatment. We think a trial of this scope and magnitude is beyond the reach of a small biotechnology company like Prana. To this end, Prana has said publicly that it is seeking a large pharmaceutical company as a partner to complete development of PBT2. To strengthen its hand in negotiations, Prana needs to complete IMAGINE and deliver results that support the proposed mechanism of action of PBT2 in restoring metal homeostasis.

Safety and Tolerability of PBT2 in Early- to Mid-Stage HD

In our view, one of the more intriguing aspects of the Metals Dyshomeostasis Hypothesis is its potential applicability to other neurodegenerative diseases, including PD and HD, as mentioned in the beginning of this research report. It is becoming evident that these diseases may share a common pathogenesis: redistribution and loss of homeostasis of transition metals in specific neurons of the brain that lead to aggregation and precipitation of certain proteins and, ultimately, loss of function and death of neurons. Not only does this make PBT2 more attractive to potential partners—if it is indeed effective in other neurodegenerative diseases—but it also provides an opportunity for a small company like Prana to develop PBT2 farther into clinical development independently of a partner in order to reap the rewards of much more favorable terms when a partnership agreement is finally concluded.

Unlike AD, HD is an orphan disease, affecting about 30,000 people in the US, with prevalence rates of about 1 in every 10,000 people. Developing a drug for an orphan disease provides advantages, including faster development times, due to smaller trials, lower expenses (also due to smaller trials), and possibly higher clinical
success rates and probability of obtaining regulatory approval. If approved and commercialized, orphan drugs enjoy premium pricing, and, because of fewer patients, lower marketing costs.

There is emerging evidence of transition metals dyshomeostasis in brains of HD patients.\(^9\) In particular, Fe and Cu are implicated in causing oxidative stress, cross-linking, and oligomerization of the mutant Huntingtin protein, and, in post-mortem analysis, the metals appear to be elevated in areas of the brain associated with symptomatic and advanced HD. Zn and manganese (Mn) may also play a role. In preclinical studies, PBT2 protected glutaminergic neurons from the toxic effects of excess glutamate, and, in transgenic mice that contain the human HD gene (R6/2 mice) and develop symptoms of HD, PBT2 treatment for several weeks improved certain motor skills, including hind limb clasp duration and maintaining balance without falling on a slowly rotating rod (Rotarod test).\(^{50}\) Brain atrophy, as measured by lateral ventricular area, was prevented and overall survival in PBT2 treated R6/2 mice was also improved.

Earlier this year, on April 30, 2012, Prana enrolled the first patient in its randomized, double-blind, placebo-controlled Phase IIa safety and efficacy trial of PBT2 that is expected to enroll about 100 patients with early- to mid-stage HD at up to 20 sites in the US and Australia (Exhibit 11). The primary endpoint is safety and tolerability. Secondary endpoints include various established measures of motor, cognitive, and behavioral function, brain volume, and certain plasma and urine biomarkers. HD patients will be treated with 100 mg or 250 mg PBT2 for six months, with a four-week follow-up period. Results are expected in 2H:13.

With both Phase II trials underway, we outline projected milestones leading to completion of these trials in Exhibit 12. Both trials are expected to complete enrollment by early 2013, and Prana has guided to periodic reports from Data Safety and Monitoring Board reviews on trial safety. Top-line results are expected toward the end of 2013. We speculate that if the HD trial is executed smoothly and without any delays, Prana’s next HD trial, which the company said will likely be a single confirmatory, registrational trial, could commence in late 2013, but more likely in early 2014. On this rapid timetable, Prana could file an NDA for PBT2 in late 2014, with possible approval for the treatment of HD in 2016. Due to the larger size and longer duration of a pivotal Phase III trial of PBT2 in AD, we do not believe PBT2 could complete clinical development, obtain regulatory approval, and be launched before 2019.

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Exhibit 11: Phase II Trial of PBT2 in Patients with Early- to Mid-Stage Huntington’s Disease

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<th>NCT01590888</th>
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<th>Last updated:</th>
<th>July 16, 2012</th>
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<td>A Randomized, Double-blind, Placebo-controlled Study to Assess the Safety and Tolerability, and Efficacy of PBT2 in Patients With Early to Mid-stage Huntington Disease</td>
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<td>Reach2HD (Study number: PBT2-203)</td>
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<td>Study design:</td>
<td>Randomized, parallel assignment, double blind, safety and efficacy study</td>
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<td>Test compound:</td>
<td>PBT2</td>
<td></td>
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<tr>
<td>Indication:</td>
<td>Early to mid stage (specified criteria) Huntington's disease</td>
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<td>Enrollment:</td>
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<td>Start date:</td>
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<td>Controls:</td>
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<td>Groups (Arms):</td>
<td>Three arms: two doses but same dosing schedule of PBT2 and placebo</td>
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<td>Key inclusion and exclusion criteria:</td>
<td>Diagnosis of HD, with its clinical features, CAG repeat number ≥36, TFC scale score between 6 and 13 (inclusive), and cognitive impairment as demonstrated by a MoCA score of ≥12; ≥25 years of age; if taking tetrabenazine, then on stable dose for at least 3 months; if female and of childbearing potential, then in using adequate birth control, or not of reproductive potential; fluent in English for the administration of rating scales and have sufficient visual, hearing and motor skills to complete procedures; has a study partner fluent in the English who is willing to provide consent and spends on average of at least two hours a day for at least four days a week with patient and agrees to attend certain study visits and provide accurate information about the patient; and able to swallow oral capsules. Excluded if allergic to PBT2 or its excipients; diagnosed with other known primary neurodegenerative disorders associated with dementia, dementia syndromes due to non-primary CNS disease, another condition that may result in clinically significant cognitive impairment; or any clinically significant uncontrolled medical or psychiatric illness, including history of seizures; other pre-specified clinically significant non-CNS disease(s) or laboratory values.</td>
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<tr>
<td>Dosing schedule:</td>
<td>Four week screening period, then 100 or 250 mg PBT2 or matching placebo by oral administration once per day for 26 weeks (6 months), with a 4-week follow up.</td>
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<td>Stages:</td>
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<td>Primary endpoint(s):</td>
<td>Safety and tolerability by frequency of AE</td>
<td>Change in baseline in CTB, motor function, functional abilities, behavior, subject and investigator global assessments, plasma and urine biomarkers, and brain volume and function by MRI.</td>
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<td>Sites:</td>
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<td>Principal investigator:</td>
<td>Dr. E. Raymond Dorsey, Associate Professor of Neurology, Director, The Johns Hopkins Parkinson's Disease and Movement Disorders Center, The Johns Hopkins Hospital, Baltimore, MD.</td>
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<td>Milestones:</td>
<td>Jan. 4, 2012</td>
<td>FDA approval to commence trial (IND opened).</td>
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<tr>
<td></td>
<td>Apr. 30, 2012</td>
<td>First patient enrolled.</td>
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<tr>
<td>Abbreviations:</td>
<td>AE, adverse events;  CAG, cytosine-adenine-guanine;  CNS, central nervous system;  CTB, Cognitive Test Battery;  HD, Huntington’s disease;  MoCA, Montreal Cognitive Assessment;  MRI, magnetic resonance imaging;  TFC, Total Functional Capacity</td>
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Source: ClinicalTrials.gov, company reports and MLV research.

Exhibit 12: Prana’s Upcoming Milestones in the Next 12-18 Months

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<tr>
<th>Expected*</th>
<th>Milestone</th>
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<td>4Q:12</td>
<td>Complete patient enrollment of Phase II trial in patients with Alzheimer's disease.</td>
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<tr>
<td>1Q:13</td>
<td>Complete patient enrollment of Phase IIa trial in patients with Huntington's disease.</td>
</tr>
<tr>
<td>1H:13</td>
<td>Periodic announcements of DSMB review of both AD and HD Phase II trials.</td>
</tr>
<tr>
<td>2H:13</td>
<td>Announce top line results of Phase IIa trial in patients with HD.</td>
</tr>
<tr>
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<td>Announce top line results of Phase II trial in patients with AD.</td>
</tr>
<tr>
<td></td>
<td>Commence pivotal Phase III trial in HD (if Phase II results are positive).</td>
</tr>
</tbody>
</table>

* Expected in calendar half-year (H) or quarter (Q), not Prana’s fiscal calendar. The company’s fiscal year ends June 30.

Abbreviations: AD, Alzheimer's disease; DSMB, Data Safety Monitoring Board; HD, Huntington’s disease.

Source: Company reports and MLV projections.
**Prana’s Product Pipeline**

We note that PBT2 is not the only drug candidate under development by Prana. PBT434 is a small molecule drug candidate in preclinical development for the treatment of PD. It could prevent Fe-induced oxidative damage and neuronal injury and death, and decrease the toxic accumulation of α-synuclein that is characteristic of PD. Last year, Prana received a grant from the Michael J. Fox Foundation to help fund PBT434 development. Prana stated that the initial grant of about $200,000 will be used to fund preclinical toxicology testing ahead of an IND submission and human testing.

Prana is also exploring the utility of MPACs in the treatment of brain and other cancers, but this is still a very early-stage preclinical research program. Prana has identified PBT519 as a possible drug candidate for this indication.

We have updated Prana’s product pipeline in Exhibit 13, where we use calendar quarters and half-years, not Prana’s fiscal-year quarters (Prana’s FY ends on June 30).

**Exhibit 13: Prana Biotechnology’s Product Pipeline**

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<tr>
<th>Product</th>
<th>Alzheimer’s disease</th>
<th>Huntington’s disease</th>
<th>Parkinson’s disease</th>
<th>Brain cancer</th>
<th>Preclinical</th>
<th>IND</th>
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Notes: (1) Ongoing Phase II trial funded by a grant from the Alzheimer’s Drug Discovery Foundation (ADDF) of New York, NY. (2) Preclinical toxicology studies are funded by the Michael J. Fox Foundation.

Abbreviations:

Source: Company reports and MLV projections.

**CONCLUDING REMARKS**

Here we provide three additional pieces of evidence that, in our opinion, support the Metals Dyshomeostasis Hypothesis and add confidence that Prana’s PBT2 could be an effective drug in the treatment of AD and other neurodegenerative diseases:

- **First, we ask:** What might be the initial defect that causes metal dyshomeostasis? The usual answer is somewhat obfuscating—aging or oxidative stress that leads to accumulation of defects in proteins, membranes, and nucleic acids. We are intrigued by one study using Zn transporter-3 knock-out (ZnT3 KO) mice.\(^{51}\)
  Interestingly, ZnT3 KO mice develop age-dependent deficits in

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learning and memory, emerging at about six months of age and associated with changes in the expression levels of many different neuronal proteins. ZnT3 expression was also found to decrease with age in wild-type mice, healthy older humans, and, especially, AD patients. ZnT3 is a transporter protein that transports Zn into presynaptic vesicles. Inefficient reloading of synaptic vesicles with Zn could have two consequences: 1) with slower reuptake, free Zn could stay in the presynaptic cleft longer, providing a greater opportunity to interact with, and precipitate, Aβ, or 2) less Zn will be released into the synaptic cleft during neurotransmission, compromising signal transmission in the neuronal network, which could cause cognitive decline.

• Next, we note that an independent investigation screening for compounds that protect against toxic, misfolded proteins that are implicated in disease progression, including α-synuclein, Aβ, and TDP-43, a protein that aggregates in patients with certain types of frontotemporal lobar degeneration (FTD) and amyotrophic lateral sclerosis (ALS), discovered that 8-HQ derivatives, such as CQ and PBT2, are the most effective class of compounds in protecting against TDP-43 mediated toxicity in yeast. For rapid screening, a protocol was developed where compounds could be evaluated for their ability to reverse TDP-34 induced toxicity in yeast. The investigators concluded that “our unbiased identification of 8-HQs in a yeast TDP-43 toxicity model suggests that tailoring 8-HQ activity to a particular neurodegenerative disease may be a viable therapeutic strategy.” We consider this independent validation of Prana’s choice of an 8-HQ derivative as its leading drug candidate.

• Finally, we note a recent study showing that a specific gene mutation in APP of humans provides protection against AD. The investigators searched for low-frequency gene variants in APP and found a coding mutation (A673T) in APP that protects against AD and cognitive decline in the elderly. With this mutation, the formation of amyloidogenic peptides (Aβ) is reduced by 40%, strongly suggesting that preventing Aβ formation or accumulation, or inducing or accelerating its removal, is a valid target in developing drugs to treat AD. Here we note that the approach taken by developers of failed anti-Aβ monoclonal antibodies, such as bapineuzumab, was not necessarily misguided. Rather, it suggests to us that just targeting Aβ may not be sufficient, and that targeting multiple underlying mechanisms that not only reduce Aβ deposition and

accumulation, but also reverse hyperphosphorylation of tau, would be much more effective. In this regard, Prana’s PBT2 does both, and possibly more, in restoring the normal physiology and metal homeostasis of neurons in the brain that are associated with neurodegenerative diseases.

VALUATION

Based on our long-term revenue and expense projections, and if development of PBT2 and other drug candidates in Prana’s pipeline proceeds without any significant delays, unfavorable trial results, or other negative surprises, we think Prana could become profitable in 2016 based on regulatory approvals and launch of PBT2 for Huntington’s Disease in the US and EU, both in 2016. We use a discounted P/E model applied to our projected 2016 EPS to arrive at our current value of $4.50 per share and one-year price target of $6.00 per share. In our view, a 45% discount rate is appropriate for current uncertainties regarding the timing and outcome of ongoing clinical trials. We believe a 25x P/E multiple is appropriate for our projection of the company’s growth.

INVESTMENT RISK

Investment risks are typical of biotechnology companies in Prana’s peer group. These include, but are not limited to: (1) Prana may not successfully complete development, obtain regulatory approval, or commercialize their drug candidates; (2) superior products developed by competitors may be approved and marketed prior to Prana’s drug candidates; (3) Prana has had substantial losses and anticipates future losses, and may be unable to raise additional capital on favorable terms to sustain operations; and (4) Prana’s stock price is likely to be volatile, with stockholders benefiting only if its stock appreciates in value as the company does not plan to pay stock dividends. For a more detailed discussion of investment risks, please refer to our Prana Biotechnology Ltd. Initiation of Coverage report of October 4, 2011.
## APPENDICES

### Appendix A: Balance Sheet

**PRAN Balance Sheet***

<table>
<thead>
<tr>
<th>June Fiscal Year End</th>
<th>2009A</th>
<th>2010A</th>
<th>2011A</th>
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<tr>
<td>All units in $A'000, except per ADR</td>
<td>Jun-09</td>
<td>Dec-09</td>
<td>Jun-10</td>
</tr>
</tbody>
</table>

### ASSETS

#### Current assets:
- Cash and cash equivalents: 4,305, 8,372, 5,227, 2,882, 8,838, 6,747
- Trade and other receivables: 1, 11, 1, 1, 3, 692
- Other current assets: 185, 120, 1,480, 681, 91, 80

**TOTAL current assets:** 4,491, 8,503, 6,708, 3,563, 8,932, 7,519

#### Property and equipment, net
- 71, 75, 59, 56, 41, 33

#### Other non-current assets
- 35, 35, 35, 35, 38, 38

**TOTAL non-current assets:** 106, 110, 94, 91, 79, 70

**TOTAL Assets:** 4,597, 8,613, 6,801, 3,654, 9,011, 7,589

### LIABILITIES AND STOCKHOLDER'S EQUITY

#### Current liabilities:
- Trade and other payables: 604, 682, 1,244, 789, 1,400, 1,384
- Financial liabilities: -

**TOTAL current liabilities:** 799, 897, 1,500, 1,101, 2,075, 2,065

#### Provisions
- 195, 215, 256, 311, 320, 348

**TOTAL non-current liabilities:** 48, 65, 72, 4, 4, 6

**TOTAL liabilities:** 847, 963, 1,572, 1,105, 2,080, 2,072

**Net Assets:** 3,750, 7,650, 5,229, 2,549, 6,931, 5,517

### Equity

- Issued and unissued capital: 70,189, 75,115, 75,120, 76,441, 82,341, 84,268
- Reserves: 7,127, 8,318, 8,563, 8,414, 9,495, 9,523
- Accumulated deficit: (73,567), (75,782), (78,473), (82,307), (84,905), (88,274)

**TOTAL stockholders' equity (deficit):** 3,750, 7,650, 5,229, 2,549, 6,931, 5,517

**Total liabilities and stockholders' equity:** 4,597, 8,613, 6,801, 3,654, 9,011, 7,589

**Weighted average number of ADRs:** 20,236, 22,121, 22,753, 24,072, 24,758, 27,966

### SELECTED METRICS

- **Current ratio:** 5.62, 9.48, 4.47, 3.24, 4.30, 3.64
- **Working capital (in thousands):** $3,692, $7,606, $5,207, $2,462, $6,857, $5,453
- **Book value per ADR:** $0.19, $0.35, $0.23, $0.11, $0.28, $0.20
- **Cash, cash equivalents (A$: thousands):** $4,305, $8,372, $5,227, $2,882, $8,838, $6,747
- **Cash, cash equivalents/ADR:** $0.21, $0.38, $0.23, $0.12, $0.36, $0.24
- **Debt:** 0, 0, 0, 0, 356, 333
- **Debt to (stockholder's) equity ratio:** 0.00, 0.00, 0.00, 0.00, 0.05, 0.06

*Source: Company reports and MLV projections. * Australian Accounting Standards Board (AASB) presentation.*
## Appendix B: Income Statement – Semi-Annual, with Projections

### PRAN Income Statement*: Semi-Annual Profit and Loss, with Projections

<table>
<thead>
<tr>
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<tbody>
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<tr>
<td>Operating revenue</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Product sales - for HD</td>
<td>2,329</td>
<td>2,076</td>
<td>2,200</td>
<td>4,276</td>
<td>6,000</td>
<td>7,000</td>
<td>13,000</td>
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<tr>
<td>Research &amp; development (R&amp;D), net</td>
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<td></td>
<td></td>
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<tr>
<td>General &amp; administrative</td>
<td>4,110</td>
<td>2,199</td>
<td>2,226</td>
<td>4,424</td>
<td>2,389</td>
<td>2,389</td>
<td>4,778</td>
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<tr>
<td>TOTAL operating revenue</td>
<td>6,440</td>
<td>4,274</td>
<td>4,426</td>
<td>8,700</td>
<td>8,389</td>
<td>9,389</td>
<td>17,778</td>
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<tr>
<td>Other income (expense)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Net income (expense)</td>
<td>(6,440)</td>
<td>(4,274)</td>
<td>(4,426)</td>
<td>(8,700)</td>
<td>(8,389)</td>
<td>(9,389)</td>
<td>(17,778)</td>
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<tr>
<td>Income before tax</td>
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<td></td>
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<tr>
<td>Income tax expense</td>
<td>(2,215)</td>
<td>176</td>
<td>80</td>
<td>256</td>
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<td>Loss before income tax</td>
<td>(4,631)</td>
<td>(4,067)</td>
<td>(4,361)</td>
<td>(8,428)</td>
<td>(8,292)</td>
<td>(9,296)</td>
<td>(17,588)</td>
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<td>Income tax benefit (expense)</td>
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<td>9</td>
<td>-</td>
<td>9</td>
<td></td>
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<tr>
<td>OTHER INCOME (EXPENSE)</td>
<td></td>
<td>23</td>
<td>80</td>
<td>8</td>
<td>3</td>
<td>7</td>
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<tr>
<td>TOTAL other income (expense)</td>
<td>9</td>
<td>208</td>
<td>65</td>
<td>273</td>
<td>97</td>
<td>93</td>
<td>190</td>
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<tr>
<td>Net income (Loss)</td>
<td>(6,431)</td>
<td>(3,370)</td>
<td>(3,361)</td>
<td>(6,731)</td>
<td>(7,292)</td>
<td>(8,296)</td>
<td>(15,588)</td>
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### Appendix C: Income Statement – Annual, with Projections

### PRAN Income Statement*: Annual Profit and Loss, with Projections

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<tr>
<td>Operating revenue</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Product sales - for HD</td>
<td>-</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>Research &amp; development (R&amp;D), net</td>
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<td>2,329</td>
<td>4,276</td>
<td>13,000</td>
<td>14,000</td>
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<td>General &amp; administrative (G&amp;A)</td>
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<td>5,028</td>
<td>4,110</td>
<td>4,424</td>
<td>4,778</td>
<td>5,161</td>
<td>5,573</td>
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<tr>
<td>TOTAL Operating revenue</td>
<td>8,717</td>
<td>5,116</td>
<td>6,440</td>
<td>8,700</td>
<td>17,778</td>
<td>19,161</td>
<td>19,573</td>
<td>24,754</td>
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<tr>
<td>Operating expenses</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost of goods sold</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5,735</td>
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<tr>
<td>Research &amp; development (R&amp;D), net</td>
<td>428</td>
<td>215</td>
<td>163</td>
<td>256</td>
<td>200</td>
<td>200</td>
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<tr>
<td>General &amp; administrative (G&amp;A)</td>
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<td>8</td>
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<tr>
<td>TOTAL Operating expenses</td>
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<td>9</td>
<td>273</td>
<td>190</td>
<td>193</td>
<td>195</td>
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<tr>
<td>Net income (Loss)</td>
<td>(7,523)</td>
<td>(4,907)</td>
<td>(6,431)</td>
<td>(8,428)</td>
<td>(17,588)</td>
<td>(18,968)</td>
<td>(19,378)</td>
<td>32,795</td>
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</table>

### Source

Source: Company reports and MLV projections. * Australian Accounting Standards Board (AASB) presentation.
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Prana Biotechnology Ltd. (PRAN): Share Price (in USD) and Volume History as of 08-09-2012

MLV RATING ALLOCATION (as of August 09, 2012)

Buy: MLV projects that the subject company’s stock price will increase in value by 20% or more in the next 12 months.
Hold: MLV projects that the subject company’s stock price will trade in a range that is not more than 20% above or below its current price.
Sell: MLV projects that the subject company’s stock price will decrease in value by 20% or more in the next 12 months.

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<th>INVESTMENT BANKING SERVICE WITHIN 12 MONTHS</th>
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<td>Count</td>
<td>Percent</td>
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<tr>
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<td>79.45%</td>
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<td>HOLD</td>
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<td>SELL</td>
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