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TETRA DISCOVERY PARTNERS

Type 4D Phosphodiesterase (PDE4D) Modulator Currently in Clinical Trials Offering Hope in Treating Alzheimer's Disease, Depression and Brain Injury

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CEOCFO: ***Mr. Gurney, would you tell us about Tetra Discovery Partners?***
Mr. Gurney: I formed Tetra in 2011. Prior to that, I was an executive for Decode Genetics, based in Iceland. While I was with Decode, the company showed that genetic variation in the gene encoding phosphodiesterase 4D (PD4D) possibly was linked to risk for stroke. Therefore, we launched a drug discovery program at Decode. Our team was the first to crystallize the PDE4 enzyme with its regulatory domains intact, and we established ourselves as innovators in this area. Decode restructured in 2010, and I founded Tetra a year later. We have been able to continue working in this area, and now we have a drug, BPN14770, which is a negative allosteric modulator of PD4D. This compound has completed initial Phase 1 studies and given us an interesting and intriguing readout in terms of cognitive benefits in healthy elderly.

CEOCFO: ***Would you explain what the drug is and what it does?***
Mr. Gurney: The drug is a small molecule, so we synthesize it in a chemical reactor. It was developed in collaboration with an initiative at the National Institute of Health, known as the Blueprint Neurotherapeutics program. We were in discovery chemistry and chemical optimization for the first two years of that program, and we needed a year or so to scale up synthesis and conduct the safety studies required for filing an IND with the FDA. The compound resulting from these efforts is the drug that is now in human clinical trials.

CEOCFO: ***What happens when it goes in the body?***
Mr. Gurney: The way we store memories in our brain is by changing the connection between brain cells. Those connections are known as synapses. A variety of work in academic departments has shown that the basic biochemistry of memory that strengthens or weakens the connection between two neurons is dependent on a pathway that can be modulated by our drug. In that pathway, the key signaling molecule is a substance known as cyclic AMP. Phosphodiesterase 4D is an enzyme that destroys cyclic AMP. This enzyme is important for establishing the spatial and temporal patterning of information in our brain. Ultimately, its activity leads to a change in the connections between neurons. That is how we store memories in the long-term, and that is what our drug is designed to facilitate.

CEOCFO: ***What have you learned in the Phase 1 study that supports your hypothesis?***
Mr. Gurney: Phase 1 studies are the very early studies of tolerability, pharmacokinetics, whether or not a drug is absorbed, and how it distributes in the body. Primarily what we are looking for is safety data that will enable us then to expand and run larger clinical trials in patient populations. Today, Tetra has run two Phase 1 studies. The first early study was a single-dose study, and that was followed by a multiple dose study. In aggregate we have now tested the drug in 109 healthy volunteers. In our second study, the multiple ascending dose study, we decided to look for a cognition signal

benefit in terms of some domain in learning or memory. For that purpose, we enrolled 45 elderly subjects. The subjects were greater than 60 years of age and the mean age was 67. We know that as we age, our brains are less able to form and store memories. That is unfortunately just a normal component of ageing. We would all like to be as smart and as capable as we were in our twenties, but hopefully we are wiser in our sixties. With the 45 subjects, we explored three different doses of the drug, and we found that with the lower doses there was an improvement in a measure of memory called working memory. Working memory is a form of short-term memory. For example, in order for you to understand this sentence you need to hold this sentence in your memory and then understand where the verb and subject is and what I actually meant by what I just said. We found a clear efficacy signal for working memory in healthy elderly.

CEOCFO: ***Are there potential side-effects?***
Mr. Gurney: For this class of drugs known as PD4 inhibitors, there is ample precedent for understanding potential side-effects. There are two approved PD4 inhibitors that are currently marketed. Their generic names are Roflumilast and Apremilast, the latter of which is marketed in the United States as OTEZLA®. Both of those drugs are used to treat diseases in the body. The first drug, Roflumilast, is used to treat Chronic Pulmonary Obstructive Disorder and the other drug, Apremilast, is used to treat psoriasis and Psoriatic arthritis. Apremilast is an anti-inflammatory drug and is an alternative to TNF blocking agents. The common side-effect with either Roflumilast or Apremilast is that as you dose them up, patients will experience nausea and emesis. That is because those drugs inhibit all four subtypes of the PDE4 enzymes, and they are inhibitors rather than allosteric modulators. What we have done at Tetra is design a drug that is selective for only one subtype, PD4D, and it is a negative allosteric modulator rather than a complete inhibitor. We find that we see the nausea and emesis at a high dose, but that is 10 times the dose that we need to see benefit in terms of working memory. By designing a negative allosteric modulator, we think that we are now controlling the side-effects of this class of drugs, and our compound has a much better tolerability profile than anyone has seen previously.

CEOCFO: ***Would that be throughout the population or would it depend on factors such as other medications or conditions related to each patient?***
Mr. Gurney: In an early-stage program such as ours, we do in vitro tests for drug-drug interactions. Many drugs are metabolized through a system of enzymes called the Cytochrome P450s. There is one enzyme in that pathway known as 3A4, which is responsible for something like 80% to 90% of the drug metabolism in liver. What we know about our new compound, BPN14770, is that it is not metabolized by the Cytochrome P450s, nor does it inhibit the Cytochrome P450s. We think in terms of drug-drug interaction, this new compound should have a favorable profile.

CEOCFO: ***Is the medical community aware or is it too early?***
Mr. Gurney: Our medical advisors are very intrigued by the profile of this new compound. We plan to share these results both through publication and presentation at conferences. I think as we have the chance to go out and present our data, that there will be considerable excitement. As far as I am aware, this is the first time that a PDE4 drug for improving cognition has shown benefit in healthy elderly subjects. I think the implications are intriguing.

CEOCFO: ***What are the next steps for Tetra?***
Mr. Gurney: Our next step is that we are planning for a Phase II study in Alzheimer's disease. We will be enrolling mild to moderate Alzheimer's patients. We will be looking at whether or not we see cognitive benefit. The mechanism of action of this drug is related to the formation of new connections between neurons. If that happens in the brain of an Alzheimer's patient, there is a possibility that the drug will either modify the course of disease or actually restore function. We have a number of activities underway that should allow us to launch a Phase II Alzheimer's study towards the end of 2017, hopefully in the fall.

CEOCFO: ***Do you have funding for your next steps?***
Mr. Gurney: We just raised $10 million this last year in a Series A and then received additional funding from the National Institute of Health. The National Institute on Ageing has generously funded the clinical Phase I multiple ascending dose study that just completed. Those funds will take the company through three months toxicology studies and the preparation of clinical supplies for the Alzheimer's trial. We have the challenge of raising an additional $10 million or so to fund that Alzheimer's trial in the fall.

CEOCFO: ***Different diseases are in and out of favor with the investment community. What do you understand about garnering attention from the investment community so that you standout in the Alzheimer's arena?***
Mr. Gurney: There is an intense interest in Alzheimer's disease, particularly given the number of Phase III studies that are underway. Key studies of Beta-Secretase inhibitors and the amyloid pathway will be reporting out next year. There are a number of Phase III studies with monoclonal antibodies against different forms of amyloid or a-beta peptide that are also

reporting out next year. So far we have not seen a lot of success in those programs. Hopefully that will change. I think what is interesting about BPN14770, is that it can be positioned on top of a Beta-Secretase inhibitor or anti-amyloid monoclonal antibody, and that it is a drug that will potentially help neurons make new connections. So if one of these other agents is able to stabilize disease or slow disease, BPN14770 should provide additional benefit. It may improve brain resilience, or it may restore function.

CEOCFO: ***What surprised you as you have been working in this arena and on this drug?***
Mr. Gurney: The biochemistry of memory has been studied by many notable academic physician scientists. For example, Professor Eric R. Kandel, MD of Columbia won a Noble Prize for his seminal studies in this area. Our challenge was to develop chemistry against the PD4 enzyme target which would differentiate one subtype from another. What we discovered during the course of our chemistry optimization program is that it was possible to design a compound that inhibited the phosphorylated, activated form of PD4D and not the basal form. We have a 130-fold window between inhibition of those two forms of the enzyme. What happens is that the PD4D enzyme is being modulated by phosphorylation in the same way that information is flowing through this pathway due to cyclic AMP signaling. It was a surprise to us that we could get separation in inhibition of the activated form versus the basal form. That translated into discovery of a potent compound in terms of efficacy but with reduced side-effects.

The second surprise is we have an orphan path for development of the drug with a condition known as Fragile X or Fragile X with Mental Retardation and Autistic Spectrum Disorder. This is a disease in which there is impaired learning and memory. Because it is a genetic disease, there are very nice preclinical models in model organisms such as fruit flies as well as in mice. We have collaborated with the FRAXA Foundation, a foundation that promotes research on Fragile X. Through them we were able to access the Fragile X mouse model. Preclincally, it is known that there is disregulation of cyclic AMP metabolism, both in patients and in the model organisms, and that PD4 inhibitors or a genetic deletion of PD4 showed benefit in the preclinical models. We tested BPN14770 in the Fragile X mice in collaboration with the FRAXA Foundation. We thought we had a good chance of showing some improvement in learning and memory. What surprised me was that we saw improvement in the spectrum of behavioral phenotype in these mice. The mice show some symptoms of autism, they have less social interaction and that normalizes when we give the adult Fragile X mice our drug. We also see benefit in terms of hyper arousal which is a phenotypic change in behavior that is seen both in the mice and in patients. We see improvement of daily activities of the mice. Mice normally build nests and the Fragile X mice do not build nests. If we give them the drug, that improves as well. On top of that, we were able to see structural changes in the connections between neurons in the Fragile X mouse brain. There are differences in the structure of the Fragile X brain both in mice and in patients that are different from normal. That was a real surprise that the drug might have benefit across all of these different aspects of the Fragile X disorder.

CEOCFO: ***Why is Tetra Discovery Partners a company to watch?***
Mr. Gurney: This is the challenge of our lifetime: how can we slow the progression of Alzheimer's? We have a graying population, especially in Europe and Asia. In the end there are not enough young people to take care of all the older people that are at risk for Alzheimer's, so this is our challenge. I think Tetra is on the path towards developing an important new drug to address this medical condition.