The Opportunity

Palatin Technologies is initiating its Phase II development plan of PL-3994, the Company’s lead product candidate for the treatment of heart failure.

PL-3994 is a subcutaneously injected guanylate-cyclase type A (GC-A) receptor agonist. It is in development for patients with heart failure (NYHA Class II-IV) to reduce the risk of cardiovascular death and hospitalization. PL-3994 is also being developed for heart failure patients with a loss-of-function corin mutation or other clinically meaningful natriuretic peptide deficiencies, a patient population that is particularly resistant to the current standard of care. Corin is an enzyme that converts the inactive prohormone form into active natriuretic peptides.

Clinical studies have shown that PL-3994 is a potent GC-A agonist, with a half-life suitable for chronic subcutaneous self-administration, with pharmacokinetic and pharmacodynamic properties superior to other natriuretic peptides, including products approved in the U.S. and elsewhere.

PL-3994 has successfully completed two Phase I safety trials. Palatin targets initiating a multiple ascending dose study in heart failure patients in 1H16. Data is anticipated in 2H16. We would then be ready to advance PL-3994 into Phase IIb proof-of-principle studies. Palatin owns the global rights to PL-3994 for all uses.

Scientific Rationale

The natriuretic peptide system (NPS) provides critical compensatory actions that oppose the pathophysiological changes caused by heart failure. The NPS is one of the body’s primary mechanisms for addressing the disease processes which underlie heart failure. The NPS is a well validated but under exploited target for the development of novel heart failure treatments.

The first generation of direct-acting agonists of natriuretic peptide receptors were all short acting IV-infused peptides that relied on acute hemodynamic changes for potential efficacy. These products have limited clinical utility and can cause symptomatic hypotension.

Research conducted in academic laboratories and by Palatin demonstrate that the second generation of agonists directed at GC-A receptors (such as PL-3994) can have profound effects on reducing cardiac hypertrophy and fibrosis, downregulating the renin-angiotensin-aldosterone system (RAAS) and restoring cardiac function without causing hypotension. The ability to address disease processes at non-hypotensive doses is key to the commercial potential of this approach.

Clinical Overview

Palatin has conducted two placebo controlled single ascending dose Phase I studies. In the first study, PL-3994 was administered as a single subcutaneous dose to healthy subjects. The second study administered a single subcutaneous dose of PL-3994 to subjects with controlled hypertension. In both studies endpoints included: safety, blood pressure, heart rate, diuresis,
natriuresis and cyclic guanosine monophosphate (cGMP) plasma levels. Treatment was well tolerated, with no acute safety concerns and a dose response for prolonged pharmacological effects. The duration of action (8-12 hours) and pharmacology support chronic use.

**Study Timeline**

Palatin will conduct a multiple ascending dose escalation study in heart failure subjects in 1H 2016. The study population will include patients with stable NYHA II-III heart failure and a subset of patients with a loss-of-function corin gene mutation. Data is anticipated in 2H16.

Palatin is developing a protocol for a subsequent Phase IIb proof-of-principle clinical trial in patients with heart failure, with treatment for a three to six month period, and evaluation of cardiac function, effects on remodeling, symptom improvement and hospitalization admission rates.

**Administration and Mechanism of Action**

PL-3994 is administered by a minimally invasive autoinjector device once or twice daily. Effects of the compound begin within 45 minutes of administration and last 8-12 hours. PL-3994 can be stored at room temperature. We are actively exploring use of subcutaneous continuous infusion devices as an alternative to subcutaneous injection.

PL-3994 acts by activating the GC-A receptor which plays a key role in cardiovascular homeostasis. In preclinical studies PL-3994 has been shown to promote natriuresis and diuresis, suppress the renin-angiotensin-aldosterone axis and reduce cardiac hypertrophy and fibrosis. The pharmacologic effects of PL-3994 are consistent with those seen for the endogenous natriuretic peptide system, which plays a key role in opposing the detrimental effects of heart failure.

**Marketing Opportunity - Targeted Market**

There is a specific market opportunity for corin-deficient patients who are resistant to standard of care, with an addressable patient population of 35,000. Corin-deficient patients have difficult-to-treat hypertension and higher event rates relative to the general heart failure population. The defined population should allow for premium pricing. A recent Navigant study estimates peak revenue of over $350 million, with 4 years to peak sales.

**Marketing Opportunity - Broader Heart Failure Market**

PL-3994 is well positioned to take advantage of the growing interest in NPS-based therapeutics in the treatment of heart failure, with a significant potential to treat patients with high unmet medical need not addressed by current treatments.

There is significant potential for PL-3994 in the broader NYHA III/IV heart failure patient population. The addressable population of NYHA III/IV heart failure patients currently on three or more heart failure medications is over 600,000 in the United States alone. Patients have a high unmet need due to the limited number of treatment options and the progressive nature of the disease. Given this need, premium pricing would be likely driven in part by pharma-economic savings from the reduction in rehospitalization rates. Initial estimates for the commercial opportunity by a recent Navigant study indicate a potential peak revenue of approximately $600 million, with eight years to peak sales.
**Intellectual Property**

Palatin’s composition of matter patents for PL-3994 expire in the United States on March 30, 2027. The patents are subject to up to a five-year term “Hatch-Waxman” extension (until 2032), which Palatin expects to receive. There are issued patents worldwide, claiming priority to WO 2007/114175 and WO 2007/115164, which also expire March 30, 2027.

We have a pending international application, WO 2015/175502, on the use of PL-3994 and related compounds as replacement therapy in patients with natriuretic peptide deficiencies, including corin deficiencies. The international search report indicated patentable subject matter. If granted, patents under this application will expire May 12, 2035.