The Opportunity

Bremelanotide (BMT) is in phase 3 development as a treatment for female sexual dysfunction (FSD) in premenopausal women. Bremelanotide, a first-in-class melanocortin receptor 4 agonist, is the only on-demand pharmaceutical agent for FSD to successfully complete and meet the objectives of a robust and well-designed phase 2B randomized and controlled clinical trial. Pivotal phase 3 clinical trials in the U.S. were initiated in December 2014 / January 2015 and enrollment completed in December 2015. Top-line data is expected to be available in 3Q2016. This would provide for an NDA filing in 1H2017 and NDA approval in 1H2018.

Based on the Phase 2B clinical results, bremelanotide is anticipated to have several distinct advantages over Addyi® (flibanserin), the only FDA approved treatment for FSD.

Bremelanotide is the most advanced on-demand treatment for FSD; for phase 3 and commercialization, bremelanotide is administered with a simple to use single dose, disposable autoinjector.

Phase 3 Status Overview

Bremelanotide development overview for the treatment of FSD:

- BMT protocols 301 and 302 of its Phase 3 reconnect study will randomize approximately 1,100 women (~550 per trial) to evaluate the efficacy and safety of bremelanotide in premenopausal women with hypoactive sexual desire disorder (HSDD) in the United States and Canada. Further information on the trial protocols can be found at clinicaltrials.gov and reconnectstudy.com.

- The two Phase 3 studies completed patient enrollment on time in December 2015 and top-line data is expected in 3Q2016.

Clinical Development

The phase 2B clinical trial was a 327 patient double-blind, placebo-controlled, 20-week, at-home study and evaluated three doses of BMT versus placebo in premenopausal women with various types of FSD. Drug was administered on demand (as-needed) by subcutaneous injection. The study yielded clear-cut and unambiguous results. Sixty-seven clinical trial sites in the US and Canada enrolled patients.

The study met its primary endpoint, improvement in the number of Satisfying Sexual Events (SSEs) in patients taking BMT versus placebo, with a mean change for BMT from 1.6 at baseline increasing to 2.4, compared with placebo which increased from 1.7 at baseline to 1.9 ($p=0.018$).
This represented a 50% increase in SSEs with BMT versus 12% with placebo. The study also met its two key secondary endpoints, improvement in overall sexual function and personal distress associated with sexual dysfunction. Secondary endpoints were evaluated using psychometrically validated Patient Reported Outcome (PRO) instruments.

These endpoints were improvement in sexual function measured using the Female Sexual Function Index (FSFI), with an increase in total score for the 1.75 mg/1.25 mg dose groups of 3.6 for the BMT group versus 1.88 for placebo ($p=0.0017$), and improvement in personal distress associated with sexual dysfunction as measured using the Female Sexual Distress Scale (FSDS), with a mean change of -11.1 for the BMT group versus -6.8 for placebo ($p=0.036$).

Statistical significance was reached with both the 1.75 mg dose of BMT and pooled results for the 1.25 and 1.75 mg doses of BMT, with the 1.25 mg dose reaching significance on some endpoints with a strong trend on other endpoints.

Pivotal phase 3 trial protocols were prepared based on FDA written guidance and employ a design similar to our phase 2B trial. Two U.S. pivotal phase 3 studies each target ~550 evaluable subjects (~275 per arm, 1.75 mg and placebo); with an ex-U.S. (EU) study potentially also targeting ~275 evaluable subjects per arm, including a possible low dose of 1.25 mg.

**Regulatory**

Bremelanotide is currently being developed for premenopausal women with a primary diagnosis of acquired hypoactive sexual desire disorder (HSDD) with or without decreased arousal. Required non-clinical studies and chemistry, manufacturing and controls (CMC) protocols have been submitted to the FDA. Key dates for the U.S. development and FDA regulatory submissions are:

- **End-of-Phase 2 / Pre-Phase 3 Meetings with FDA**: Completed (1H2014)
- **Commence Phase 3 Trials in the U.S.**: Initiated (4Q2014/1Q2015)
- **NDA Submission to FDA**: 1H2017
- **FDA Action/Approval**: 1H2018

**Chemistry, Manufacturing and Controls (CMC)**

A manufacturing process for the drug substance has been developed and validated with a major pharmaceutical manufacturer, and drug substance profiles established. Sufficient drug substance is available for phase 3 trials. The drug product is defined, with the formulated product packaged in prefilled syringes and secondarily fitted into the autoinjector. Full manufacturing process and process controls have been established. Drug product stability...
testing has established that the commercial dosage form will be stable for at least 2 years of controlled room temperature.

**Non-Clinical Development**

Bremelanotide is a high-affinity ligand and agonist for melanocortin receptors, including MC1r, MC3r, and MC4r. The pharmacological effect for treatment of FSD is believed to primarily result from agonist of MC4r. Bremelanotide has completed all FDA required preclinical safety pharmacology and toxicology testing and is ready for NDA submission.

**Marketing Opportunity**

Based on several prevalence studies applied to 2011 U.S. Census Bureau numbers, it is estimated that at least 33 million women in the U.S. age 20-49 have some form of sexual dysfunction, with 8.2 million of those women having HSDD, including associated distress, and 1/3 (~2.7 million) seeking formal treatment. Forecasted U.S. annual sales of bremelanotide at peak are projected to be ~$850 million. Assuming multiple treatment options, several market analysts estimate the female sexual dysfunction global market to be worth over $2 billion annually.

**Advantages / Differentiating Factors to Addyi (flibanserin)**

In August 2015, Addyi was approved by the FDA for the treatment of premenopausal women with acquired, generalized HSDD. Shortly after the FDA approval, Valeant Pharmaceuticals International, Inc. acquired Sprout Pharmaceuticals, Inc., the developer of Addyi (flibanserin), on a debt-free basis for approximately $1 billion in cash ($500 million upfront and $500 million due early 2016), plus a share of future profits based upon the achievement of certain milestones.

Based on the Phase 2B clinical results, bremelanotide is anticipated to have several distinct advantages over Addyi (flibanserin). The most significant of these are:

- **Administration**
  - Addyi must be taken once daily and requires 4-6 weeks before initial onset of efficacy
  - BMT is an on-demand treatment taken as-needed with onset of efficacy in ~30 minutes and a treatment effect for 8-10 hours

- **Label**
  - Addyi has a boxed warning for hypotension and syncope in certain settings. Use of Addyi and alcohol increases the risk of severe hypotension and syncope. Patients using Addyi are advised to abstain from the use of alcohol. Severe hypotension and syncope can also occur when Addyi is used with moderate or strong CYP3A4 inhibitors or in patients with hepatic impairment. Addyi contraindications include alcohol, moderate or strong CYP3A4 inhibitors, hepatic impairment. Due to significant safety concerns by the FDA, Addyi is only available through a restricted REMS program.
o BMT is not anticipated to have a boxed warning. BMT does not interact with alcohol and is not anticipated to have any contraindications. BMT is not anticipated to have a restrictive REMS program.

**Intellectual Property**

Palatin has all global rights to bremelanotide for FSD.

Palatin has issued patents on BMT in the U.S., major countries in Europe, Japan, Australia, Canada and Mexico. Compositions of matter patents expire late 2020, with extensions of up to five years under Hatch-Waxman and counterpart provisions in other countries possible. Based on analysis by an outside law firm, Palatin expects to receive the maximum five year extension. An additional application has been filed, which if granted will extend patent protection until 2033. An international search report has been received related to this additional application indicating patentable subject matter. Second-generation melanocortin agonists, with improved specificity and safety profiles, have been developed and patent applications filed throughout the world.

Addyi® is a registered trademark of Sprout Pharmaceuticals, Inc.