Original Research

Phase I Randomized Placebo-controlled, Double-blind Study of the Safety and Tolerability of Bremelanotide Coadministered With Ethanol in Healthy Male and Female Participants

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ABSTRACT

Purpose: This was a Phase I study to evaluate the safety, tolerability, and hemodynamic and pharmacokinetic effects of bremelanotide (BMT) coadministered with ethanol to healthy male and female participants.

Methods: This was a randomized, placebo-controlled, double-blind, 3-period, 3-way crossover study. Individuals meeting the inclusion/exclusion criteria received BMT or placebo with or without ethanol at the research facility for 7 consecutive days. Participants were randomized to receive 1 of 6 treatment paths; each participant received single intranasal doses of BMT (20 mg) or placebo on days 1, 4, and 7, with or without oral ethanol (0.6 g/kg) while in a fasted state. The intranasal 20-mg dose of BMT has an exposure equivalent to ~1 to 2 times the subcutaneous dose currently being evaluated in Phase III studies. Vital signs, self-rated sedation scores, nursing and medical observations, and spontaneous reporting by participants provided the basis for evaluation of adverse events. A physical examination and a resting 12-lead electrocardiogram were performed at baseline and on study day 7. Blood and urine samples were obtained for clinical safety profile laboratory tests.

Findings: A total of 24 participants were enrolled (12 men; 12 women) and completed the study. Single doses of 20 mg intranasal BMT, administered with or without 0.6 g/kg ethanol, were found to be safe and generally well tolerated with mean maximum ethanol concentrations exceeding 80 mg/dL in women. No clinically significant pharmacokinetic interactions were found between ethanol and BMT either overall or by sex. No significant drug-related hypotensive or orthostatic hypotensive effects were noted. Treatment with BMT did not result in an increased frequency of treatment-emergent adverse events, and no participants discontinued the study because of adverse events. Physical examination, electrocardiography, and laboratory tests disclosed no clinically significant changes.

Implications: Female sexual dysfunction is a multifactorial condition with anatomic, physiologic, medical, psychological, and social components. BMT is a synthetic peptide analogue of the naturally occurring hormone α-melanocyte–stimulating hormone and a melanocortin receptor agonist that is being developed for the treatment of hypoactive sexual desire disorder. Its mechanism of action involves activation of endogenous melanocortin hormone pathways involved in the sexual desire and arousal response. The results of this Phase I study found that BMT and ethanol can be safely coadministered and are generally well tolerated with no reports of drug-related serious adverse events. Phase III trials of subcutaneous BMT for the treatment of hypoactive sexual desire disorder in premenopausal women are in progress. ClinicalTrials.gov identifiers NCT02338960 and NCT02333071. (*Clin Ther.* 2017;39:514–526) © 2017 The Authors. Published by Elsevier HS Journals, Inc.

Chemical compound studied in this article: Bremelanotide (PT-141; PubChem CID: 9941379).

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Key words: bremelanotide, female sexual dysfunction, hypoactive sexual desire disorder, melanocortin receptor agonist.

INTRODUCTION

Healthy female sexual function depends on the interplay of psychosocial and neurobiological factors. Disruption of any of these factors can lead to sexual dysfunction.[1,2] The most common sexual concern expressed by women is diminished or lack of desire for sexual activity,[3–6] which may be diagnosed as hypoactive sexual desire disorder (HSDD). As defined in the *Diagnostic and Statistical Manual of Mental Disorders* Fourth Edition, Text Revision, the hallmarks of HSDD include persistently deficient (or absent) sexual fantasies and desire for sexual activity that is not better accounted for by another condition or the effect of medication and which causes marked distress or interpersonal difficulty.[7] With the *Diagnostic and Statistical Manual of Mental Disorders* Fifth Edition, HSDD is included as part of the diagnostic category of sexual interest/arousal disorder.[8] Regardless of the classification, it is generally believed that HSDD is associated with decreased quality of life.[9,10]

Bremelanotide (BMT; formerly PT-141) is a synthetic peptide analogue of the α-melanocyte–stimulating hormone.[11] The developmental dose range-finding studies in female mice and rats found no systemic maternal or developmental adverse effects at doses ≤300 mg/kg/d SC (mice) and 2.5 mg/kg/d IV (rats). In beagle dogs, the maternal lowest observed effect level and the developmental no observed effect level were 2 mg/kg/d and 20 mg/kg/d, respectively. No evidence of genotoxic or carcinogenic potential with BMT was observed (Data on file, Palatin Technologies, Inc.). In preclinical studies, BMT was found to modulate brain pathways involved in sexual response and to significantly and selectively increase appetitive sexual behaviors in female rats.[11–13] BMT is being developed as a potential self-administered, subcutaneous (SC), as-desired treatment for women with HSDD. In premenopausal women with HSDD, BMT was safe and well tolerated. Treatment was associated with significant improvements on 5 clinically relevant measures of female sexual dysfunction.[14–16] Because it is likely that in the "at-home" setting BMT may be taken in the context of alcohol consumption, it is important to assess any potential interaction. This was a single-center, randomized, Phase I, placebo-controlled, double-blind, 3-period, 3-way crossover study to evaluate the hemodynamic effect, potential pharmacokinetic (PK) interaction, and safety profile and tolerability of a single intranasal (IN) dose of BMT coadministered with ethanol in healthy male and female participants.

PARTICIPANTS AND METHODS

Study Population

Eligible individuals included healthy men and women aged 21 to 45 years, weighing 50 to 100 kg (110–220 lb) and within 20% of their ideal weight (based on height and body frame). All participants were required to have a negative urine drug screen, normal nasal structure and mucosa, a sitting systolic blood pressure (SBP) <140 mm Hg, and a sitting diastolic blood pressure (DBP) <90 mm Hg. Women had to have had a menstrual period documented to be recent and be either surgically sterile or using a medically accepted and highly effective method of birth control for ≥30 days before study entry and during participation in the study. Participants with any clinically significant medical condition, physical examination finding, or laboratory or electrocardiographic (ECG) abnormality were excluded from participation. Any use of over-the-counter drugs or dietary, herbal, or megavitamin supplements within 48 hours or consumption of caffeine-containing foods or beverages within 24 hours before receiving study medication was also cause for exclusion. Persons also were excluded if they had any condition, which in the opinion of the investigator, would interfere with their ability to provide informed consent or to comply with study instructions, or which might confound interpretation of study results or endanger the participant if he or she took part in the trial. Use of any investigational drug or product or participation in a drug research study within 30 days before receiving study medication was prohibited. With respect to alcohol, a recent history of alcoholism (<2 years) or of moderate ethanol use (an average of ≥3 drinks/d or a total of 21 drinks/wk), use of ethanol within 24 hours before receiving the dose of study medication, or abstinence from ethanol over the previous 12 months were all cause for exclusion.

A properly constituted institutional review board, the Essex Institutional Review Board, Inc (Lebanon, New Jersey), approved the protocol and informed consent, in accordance with Title 21, *Code of Federal Regulations*, Parts 56.107 through 56.115. The study was performed in accordance with applicable *Code of Federal Regulations* sections, Good Clinical Practice