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).

Accepted for publication January 10, 2017.
http://dx.doi.org/10.1016/j.clinthera.2017.01.018
0149-2918/$ - see front matter

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

standards, and International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines. This study was conducted in accordance with Food and Drug Administration regulations, as well as International Council on Harmonisation Good Clinical Practice guidelines and the World Medical Association Declaration of Helsinki.

Study Medication

BMT and matching placebo were supplied by Palatin Technologies, Inc (Cranbury, New Jersey). The IN BMT dose (20 mg) was selected for use in this study to produce a high drug exposure of BMT. Prior clinical experience found the 20-mg dose to be safe and well tolerated. Results of a PK analysis from a Phase I study indicated that the C_{max} and $AUC_{(0-t)}$ of BMT increased in an approximate dose proportional fashion. Mean C_{max} ranged from 14.9 ng/mL for the 4-mg dose group to 140.5 ng/mL for the 20-mg dose group. Mean $AUC_{(0-t)}$ ranged from 30.5 to 273.3 ng/h/mL.[17] Exposure of BMT IN 20 mg is ~1 to 2 times that of the SC BMT dose currently being evaluated in Phase III studies. The IN placebo was an aqueous spray indistinguishable from the study drug. The IN formulation was used in this study because that was the formulation in development at the time. The sponsor has since switched to the development of a SC formulation.

The oral ethanol dose (0.6 g/kg) was the equivalent of ~4 oz of vodka, 2 glasses of wine, or 3 beers. This dose was selected as representing a significant and relevant amount of ethanol that might be ingested in close proximity to administration of BMT by patients in the "at-home" setting. The drink was prepared as a 1:3 mixture of 100-proof vodka and orange juice to maintain the integrity of the blind. The mixture was administered to the participants at a dose of 6 mL/kg. The placebo drink was prepared as 2 drops of ethanol floated on orange juice and was administered on an empty stomach (or with no morning food intake). Participants remained at the research facility for 7 consecutive days. Participants were randomly assigned to 1 of 6 treatment regimens (Table I; Figure 1). The ethanol or placebo drink was consumed over a 10-minute period. All meals during study days 1, 4, and 7 were standardized and were provided at ~4 and 10 hours after dosing.

Table I. Treatment paths.

Treatment Path	Day 1	Day 4	Day 7
1	20 mg BMT + placebo drink	20 mg BMT + 0.6 g/kg ethanol	Placebo spray + 0.6 g/kg ethanol
2	20 mg BMT + placebo drink	Placebo spray + 0.6 g/kg ethanol	20 mg BMT + 0.6 g/kg ethanol
3	20 mg BMT + 0.6 g/kg ethanol	Placebo spray + 0.6 g/kg ethanol	20 mg BMT + placebo drink
4	20 mg BMT + 0.6 g/kg ethanol	20 mg BMT + placebo drink	Placebo spray + 0.6 g/kg ethanol
5	Placebo spray + 0.6 g/kg ethanol	20 mg BMT + placebo drink	20 mg BMT + 0.6 g/kg ethanol
6	Placebo spray + 0.6 g/kg ethanol	20 mg BMT + 0.6 g/kg ethanol	20 mg BMT + placebo drink

BMT = bremelanotide.

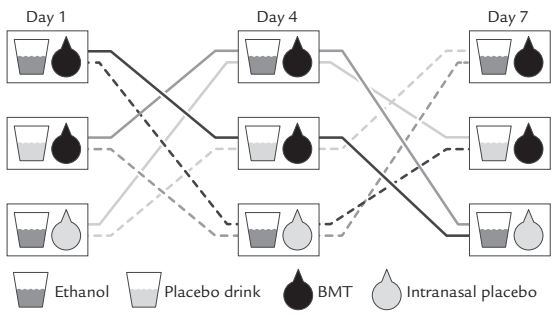

Figure 1. Treatment regimens. BMT = bremelanotide.

Safety Assessments

AE Reporting

The incidence of adverse events (AEs) was compared across treatments, based on spontaneous AE reporting and nursing and medical observations. Blood and urine samples were obtained for clinical laboratory tests (chemistry, endocrinology, hematology, and urinalysis) at baseline (before dose on day 1) and 12 hours after dosing on day 7.

Hemodynamic Effects

The hemodynamic effect of coadministration of BMT and ethanol was compared with BMT or ethanol alone using orthostatic vital sign checks (sitting, immediate standing, and 2-minute standing SBP, DBP, and pulse rate [PR]), which were obtained ~15 minutes before dosing, then every 15 minutes for the first hour after dosing, then every 30 minutes until 4 hours after dosing, and again at 8 and 12 hours after dosing.

Orthostatic vital sign changes of potential clinical concern were defined as an absolute SBP <85 mm Hg in any position or a decrease of >30 mm Hg in SBP from sitting to immediate or 2-minute standing positions with or without accompanying symptoms of hypotension; an absolute DBP <45 mm Hg in any position or a decrease of >20 mm Hg in DBP from sitting to immediate or 2-minute standing positions with or without accompanying symptoms of hypotension; or an absolute PR >120 beats/min in any position or an increase of >30 beats/min in PR from sitting to immediate or 2-minute standing positions with or without accompanying symptoms of hypotension.

Sedation

Self-rated sedation scores (SRSSs) were obtained 15 to 30 minutes before dosing and at 30 minutes and 1, 2, 3, and 4 hours after dosing. The scale consisted of the following 5 items: 0, feeling wide awake and alert; 1, feeling awake, but lethargic; 2, feeling tired, not at full alertness; 3, sleepy, prefer to be lying down; and 4, very sleepy, losing struggle to remain awake.

Clinical Laboratory Tests

All participants were tested for drugs of abuse and for the presence of ethanol in the urine at the screening visit and on admission to the facility before day 1 dosing. Women also received a urine pregnancy (β-human chorionic gonadotropin) test at these times.

Blood and urine samples were obtained at the screening visit, baseline, and before discharge on day 7. Blood chemistry tests at the screening visit, baseline, and day 7 visits included sodium, potassium, chloride, calcium, glucose, carbon dioxide, blood urea nitrogen, blood urea nitrogen/creatinine ratio, creatinine, serum glutamic-pyruvic transaminase (alanine aminotransferase [ALT]), serum glutamic-oxaloacetic transaminase (aspartate aminotransferase), alkaline phosphatase, and total cholesterol. Hematologic tests included hemoglobin, hematocrit, red blood cell count (with indices), white blood cell count (including differential), and platelet count. Urinalysis included appearance, color, specific gravity, pH, creatinine, glucose, ketones, leukocyte esterase, nitrites, protein, blood, bilirubin, urobilinogen, and microscopic examination. On days 1, 4, and 7, serial glucose measurements were obtained before and after dosing at the PK time points using backup plasma PK samples. A 12-lead resting ECG was obtained at screening; 45 minutes after dosing on days 1, 4, and 7; and before discharge (12 hours after the dose on study day 7).

All clinical laboratory assessments were performed by Bio-Reference Laboratories, Inc. (Elmwood Park, New Jersey) except for the urine drug screen, urine ethanol test, and the urine pregnancy (β-human chorionic gonadotropin) test, which were performed at the Clinical Research Center at Advanced Biomedical Research, Inc.

PK Parameters

PK analysis was performed using nonparametric methods with WinNonlin, version 3.2 (Pharsight Corporation, Mountain View, California). Blood samples for PK evaluations of BMT and ethanol were

drawn before the dose and at 15, 30, and 45 minutes and 1, 2, 3, 4, 8, and 12 hours after dosing. Plasma samples to determine BMT concentration were obtained and analyzed according to a validated method (ABC Study 46442-MI; ABC Laboratories [now EAG Laboratories, San Diego, California]).

The calibration standards were prepared fresh for each run in human plasma, containing sodium EDTA as the anticoagulant and ~36 KIU aprotinin/mL as protease inhibitor. Quality control samples were stored at approximately –70°C to simulate the storage conditions of study samples. The accuracy and precision of the measured concentrations of BMT in fortified human plasma during the 3 primary runs of method validation were used to establish the validity of the assay.

An aliquot of 1.00 mL of plasma sample was placed into a 5-mL polypropylene round-bottom tube; 100 μL of working internal standard solution was added to each sample and rotated for about 1 minute, then centrifuged (Centricon® YM-10, EMD Millipore, Darmstadt, Germany) for 90 minutes at ~5000 rpm before being transferred to auto-injector vials for LC-MS/MS analysis. The HPLC system consisted of a Shimadzu LC-10Avp controller and pump, a Perkin Elmer Series 200 injector, and a Phenomenex, Luna, C-18 3μ (100 × 4.6 mm) column. Solvent delivery was as follows: Mobile Phase A was 10 mM ammonium acetate in water, 1% acetic acid; Phase B was 10 mM ammonium acetate in 90:10 methanol/water, 1% acetic acid at a flow rate of 1.0 mL/min. Detection was by mass spectrometry (PE Sciex API 3000) using Multiple Reaction Monitoring (dwell time, 250 ms; pause time, 5.0 ms). To establish the lower limit of quantitation for BMT, 6 replicates at 0.5016 ng/mL were prepared and analyzed as samples (independent from the calibration curve) on each of the 3 primary days of validation. The mean accuracy and precision obtained at 0.5016 ng/mL met the acceptance criteria of within ±20% error relative to nominal (RE) and ≤20% coefficient of variance (CV), respectively.

On extraction and analysis of clinical samples using the validated method, only ~10% recovery of the internal standard was observed (the recovery of BMT was not affected). Therefore, the method validation results for sensitivity, accuracy, and precision from the 3 primary days were calculated based on the peak area of BMT instead of the peak area ratio. From the accuracy and precision data for the 3 primary runs of validation calculated without the internal standard ratio, the acceptance criteria were extended to within ±30% RE and ≤30% CV. In addition, the lower limit of quantitation was raised to ~1.00 ng/mL for calculations without internal standard. Although the validation procedure for the determination of BMT in human plasma samples with analysis by HPLC-MS/MS without internal standard (splenopentin) quantitation (ABC Method 46581-MI) were out of the normal specifications, the results were found to be reliable within ±30% RE and ~30% CV for calibration standards and quality control samples within the investigated concentration range of ~1 to 500 ng/mL. Blood samples to determine ethanol were analyzed by Bio-Reference Laboratories, Inc, using an enzyme immunoassay method.

Statistical Methods

Baseline demographic and medical history data were summarized. The hemodynamic effect of coadministration of BMT and ethanol was examined and compared with BMT or ethanol alone. The time course, severity, and frequency of clinically significant orthostatic vital signs and orthostatic vital signs of potential clinical concern were compared using a *t* test for pairwise comparison of each vital sign indicator between the different treatments. SRSSs were summarized descriptively by treatment. Safety profile was assessed by recording the nature, severity, frequency, timing, and duration of any AEs and their relationship to treatment. The participants were also evaluated using clinical laboratory tests, physical examinations, and 12-lead ECGs. Summary statistical tables and data listings were generated using SAS version 8.2 (SAS Institute Inc, Cary, North Carolina) on a PC-compatible workstation running on a Microsoft Windows 2000 operating system (Microsoft, Redmond, Washington).

PK parameters, including AUC_{0-t} and $AUC_{(0-\infty)}$, C_{max}, T_{max}, and $t_{1/2}$ of plasma BMT and blood ethanol alone and in combination, were calculated using noncompartmental methods. A formal sample size calculation was not performed. The sample size was based on clinical and PK considerations such that a meaningful number of participants would have safety profile, PK, and pharmacodynamic data in each group (ie, BMT + ethanol, BMT, and ethanol).

RESULTS

Participants

Sixty-seven participants were screened; 24 were enrolled, randomized to receive treatment, and

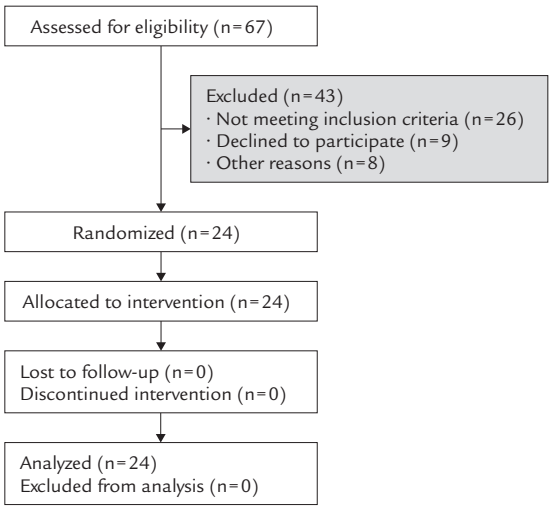

Figure 2. Disposition of participants.

completed the study (Figure 2). Four participants (2 women, 2 men) were randomized to receive each of the 6 treatment regimens. The baseline characteristics of the study population are outlined in Table II.

Safety and Tolerability

AEs

When administered to healthy men and women, single doses of IN BMT + ethanol, BMT, or ethanol were safe and generally well tolerated. Coadministration of BMT and ethanol did not lead to increased AE frequencies, either overall or in women versus men. No AEs were rated as serious, and no participants discontinued the study because of AEs. Overall, no significant difference ($P > 0.05$) was found in the number of participants with AEs: 18 participants (75%) experienced a total of 42 AEs after receiving BMT + ethanol; 16 (67%) experienced a total of 24 AEs after receiving BMT alone; and 14 (58%) experienced a total of 23 AEs after receiving ethanol. The most common AEs reported in ≥5% of all participants receiving BMT + ethanol, BMT, or ethanol were flushing, somnolence, headache, hiccups, nausea, feeling hot, dizziness (excluding vertigo), taste disturbance, and nasal congestion. Some AEs, such as nausea, headache, and flushing, were reported more often in women, whereas somnolence was reported more often in men. The incidence of AEs by treatment and sex is summarized in Table III.

Hemodynamic Effects

Coadministration of BMT + ethanol did not result in a pronounced or exaggerated hypotensive effect, nor were significant orthostatic changes noted. Small decreases (~2–6 mm Hg) in mean SBP and DBP and increases in PR (~2–6 beats/min) were evident from ~1.5 to 8 hours after dosing in the BMT + ethanol and ethanol groups compared with the BMT group. These differences in vital signs were likely caused by

Table II. Baseline characteristics of study participants.

Variable	All Participants (n = 24)	Women (n = 12)	Men (n = 12)
Age, years			
Mean (SD)	31.0 (7.3)	31.0 (7.6)	31.0 (7.4)
Range	21–43	22–42	21–43
Race, n (%)			
Hispanic	10 (42)	6 (50)	4 (33)
Black	9 (38)	3 (25)	6 (50)
White	4 (17)	3 (25)	1 (8)
Other	1 (4)		1 (8)
Body weight, mean (SD), kg	72.5 (13.4)	53.5 (10.4)	81.5 (9.4)
BMI, mean (SD), kg/m^2	25.3 (3.5)	24.3 (3.9)	26.2 (3.0)

BMI = body mass index.

Table III. Adverse events reported by ≥1 study participant.

	BMT + Ethanol			BMT Alone			Ethanol Alone		
Adverse Events	All Participants (n = 24)	Women (n = 12)	Men (n = 12)	All Participants (n = 24)	Women (n = 12)	Men (n = 12)	All Participants (n = 24)	Women (n = 12)	Men (n = 12)
Any event	18 (75)	11 (91)	7 (58)	16 (67)	7 (58)	9 (75)	14 (58)	9 (75)	5 (42)
Flushing	10 (42)	6 (50)	4 (33)	10 (42)	5 (42)	5 (42)	3 (13)	2 (17)	1 (8)
Somnolence	7 (29)	3 (25)	4 (33)	3 (13)	0	3 (25)	9 (38)	5 (42)	4 (33)
Headache	5 (21)	5 (42)	0	1 (4)	1 (8)	0	4 (17)	4 (33)	0
Nausea	2 (8)	1 (8)	1 (8)	1 (4)	1 (8)	0	2 (8)	2 (17)	0
Dizziness*	2 (8)	2 (17)	0	1 (4)	1 (8)	0	1 (4)	1 (8)	0
Dizziness postural	0	0	0	1 (4)	1 (8)	0	0	0	1 (8)
Feeling hot	2 (8)	1 (8)	1 (8)	1 (4)	0	1 (8)	0	0	0
Nasal congestion	2 (8)	2 (17)	0	1 (4)	1 (8)	0	0	0	0
Hiccups	2 (8)	2 (17)	0	0	0	0	0	0	0
Taste disturbance	0	0	0	2 (8)	0	2 (17)	0	0	0

Values are n (%).
BMT = bremelanotide.
*Excluding vertigo.

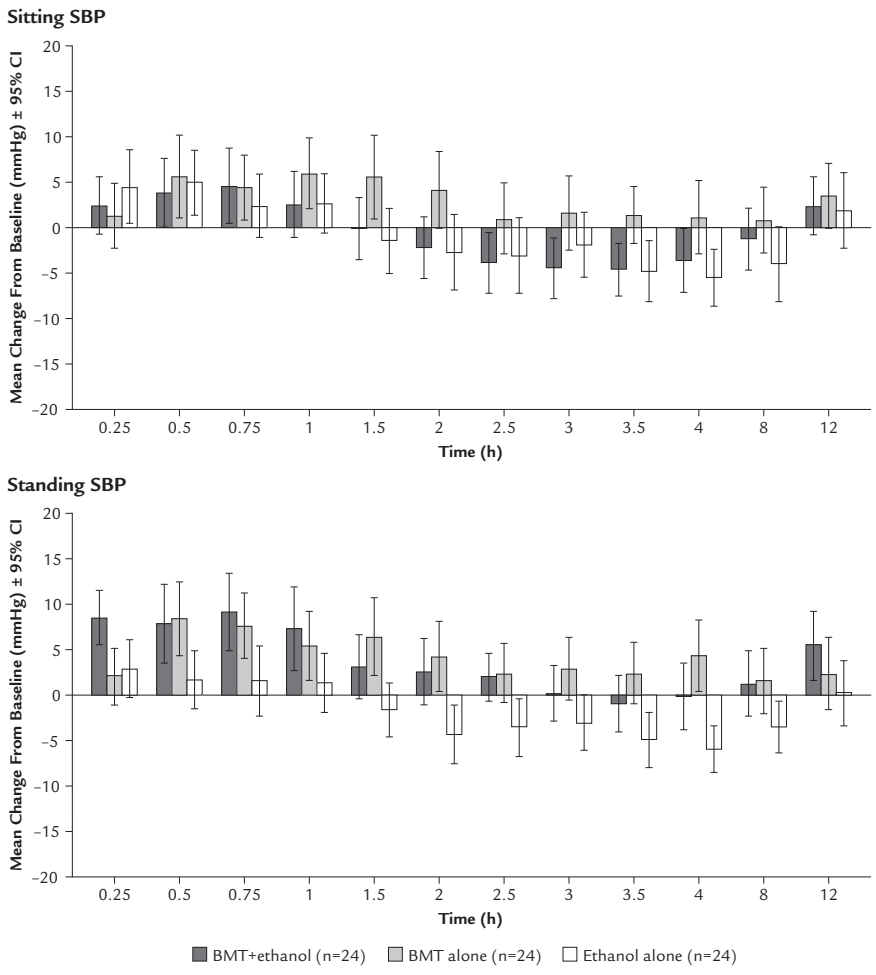

Figure 3. Mean posttreatment changes in SBP sitting (top) and standing (bottom) for 2 minutes. BMT = bremelanotide; SBP = systolic blood pressure.

the vasodilating effects of ethanol and did not appear to be exacerbated by coadministration of BMT. Figure 3 shows the mean posttreatment changes in SBP while sitting (top) and after standing for 2 minutes (bottom).

Sedation

Some degree of sedation was noted on the SRSSs from ~1 to 4 hours after dosing, particularly in treatments that included ethanol; however, the sedative effect was not greater with BMT + ethanol than with ethanol alone. Most participants reported SRSSs of 0 or 1 (no or minimal sedation) after 1 hour (67% and 63%, BMT + ethanol and ethanol alone, respectively). By 4 hours 54% of participants taking BMT + ethanol and 46% of participants taking ethanol alone had a score of 0 or 1.

Physical Examinations and Laboratory Outcomes

No clinically significant abnormal findings were found on either the physical examination or ECGs. Occasional premature ventricular contractions were noted on the predischarge ECG for 1 male participant who had received BMT + ethanol on day 7. These were not noted on prior ECGs and had resolved on a repeat ECG 4 days later. The participant had normal intervals on all ECGs during the treatment phase, with no evidence of QT interval prolongation or other conduction abnormalities; no evidence of arrhythmias was noted. This participant also experienced a brief

15-second syncopal episode ~2 hours 30 minutes after the start of the ethanol/orange juice drink. Plasma glucose levels were measured at 51 mg/dL at 2 hours 39 minutes after the dose compared with 118 mg/dL at 1 hour after the dose, 117 mg/dL at 2 hours after the dose, and 110 mg/dL at 3 hours after the dose. The investigator attributed this response to the glucose load in the 532 mL of orange juice that was ingested after an overnight fast. Further analysis of serial plasma glucose levels in this participant found a substantial decrease below normal levels (65–139 mg/dL) during all 3 treatments after the temporary glucose-induced increase. An analysis of serial glucose levels in all participants found no evidence during any treatment of an effect of BMT and/or ethanol on serial glucose levels, other than a modest and transient increase in serum glucose after orange juice ingestion.

Coadministration of BMT + ethanol did not result in an increased incidence of laboratory abnormalities. Mild elevations in liver enzymes (~1.5- to 3-fold increases from baseline) were noted in 8 participants and were considered most likely due to ethanol, with the exception of 1 participant who had a reversible elevation in ALT (serum glutamic-pyruvic transaminase) of 124 U/L after administration of BMT + ethanol on day 7. This was reported as a moderate-intensity AE, possibly related to study medication.

PK Results

Mean (SD) C_{max} and $AUC_{(0-t)}$ values for BMT were slightly higher in the ethanol group (94.6 [16.4] mg/dL and 259.8 [48.7] mg/h/dL) than in the BMT + ethanol group (83.3 [22.0] mg/dL and 244.5 [62.1] mg/dL), whereas the mean T_{max} and $t_{1/2}$ values were higher in the BMT + ethanol group (1.61 [0.64] hours and 3.88 [1.97] hours vs 1.05 [0.47] hours and 3.15 [1.12] hours) than for ethanol alone. For the T_{max} values the difference was significant ($P < 0.01$, paired *t* test). No statistically significant differences in ethanol PK parameters were observed between men and women. Mean C_{max}, T_{max}, $t_{1/2}$, and $AUC_{(0-t)}$ were generally similar in the BMT + ethanol and BMT groups, both overall and between men and women.

The mean (SD) C_{max}, T_{max}, $AUC_{(0-t)}$, and $t_{1/2}$ values for BMT + ethanol, BMT alone, and ethanol alone for all participants and by sex are shown in Table IV. BMT plasma and ethanol blood concentration time profiles are shown in Figure 4.

DISCUSSION

In the future, BMT, which is being evaluated for the self-administered, as-desired treatment of female sexual dysfunction, may be administered in the "at-home" setting in conjunction with alcohol. We conducted the present study to determine the hemodynamic effects of BMT when administered with alcohol to characterize any PK interactions between BMT and alcohol and to examine the safety profile and tolerability of a single dose of BMT when administered with alcohol. In addition, in previous Phase II studies BMT reported good efficacy and safety in men with erectile dysfunction, and this is a population that could be studied further in the near future. No difference was found in exposure between men and women, and this study serves as an ethanol drug–drug interaction study for male and female treatment populations.

The mean concentration of 1.75 mg SC is ~73 ng/mL, whereas the mean concentration of 20 mg IN is ~111 ng/mL. The dose of 20 mg IN was selected for this study to provide high exposure of BMT, and because it was found to have a pharmacodynamic effect (erectile response) in previous studies involving healthy men and in men with erectile dysfunction responsive to sildenafil.[18] The 20-mg IN dose also provides greater exposure than the 1.75-mg SC dose, thus allowing for an even greater safety margin for coadministration with alcohol for the 1.75-mg SC dose currently in Phase III development for HSDD. The alcohol dose of 0.6 g/kg was selected to provide a rigorous assessment of a possible interaction of BMT and ethanol. The doses used in this study are in line with the US Food and Drug Administration's recommendation for drug interaction studies, which states that the doses of both drugs should maximize the possibility of finding an interaction.[19] Our study is also similar in design and dose to the alcohol interaction study conducted for flibanserin, a recently approved treatment for HSDD.[20] Because this is a Phase I study, no formal statistical determination of sample size was performed.

Coadministration of BMT + ethanol did not result in an increased frequency of treatment-emergent AEs. No overall significant differences were found in the number of participants with AEs based on the Kruskal-Wallis exact test ($P > 0.05$). Thorough orthostatic vital sign monitoring was used in the present study. Small decreases of ~2 to 6 mm Hg, on average, and in sitting, immediate standing, and

Table IV. Pharmacokinetic results.

Results	BMT + Ethanol			BMT Alone			Ethanol Alone		
	All Participants (n = 24)	Women (n = 12)	Men (n = 12)	All Participants (n = 24)	Women (n = 12)	Men (n = 12)	All Participants (n = 24)	Women (n = 12)	Men (n = 12)
BMT									
T_{max}, h	0.71 (0.14)*	0.70 (0.15)*	0.71 (0.14)	0.74 (0.17)	0.79 (0.14)	0.69 (0.19)	NA	NA	NA
C_{max}, ng/mL	134.1 (98.5)*	140.9 (104.2)*	127.8 (97.2)	111.6 (88.0)	106.0 (88.0)	117.3 (9.5)	NA	NA	NA
$AUC_{(0-t)}$, ng/h/mL	236.3 (170.2)*	223.3 (163.3)*	248.3 (182.8)	216.3 (176.5)	177.0 (154.5)	255.5 (194.7)	NA	NA	NA
$t_{1/2}$, h	2.24 (0.40)*	2.18 (0.39)*	2.29 (0.42)	2.28 (0.38)	2.27 (0.48)	2.29 (0.28)	NA	NA	NA
Ethanol									
T_{max}, h	1.61 (0.64)†	1.56 (0.54)	1.67 (0.75)	NA	NA	NA	1.05 (0.47)	1.27 (0.56)	0.83 (0.22)
C_{max}, mg/dL	83.3 (22.0)	94.4 (24.0)	72.1 (12.8)	NA	NA	NA	94.6 (16.4)	96.1 (15.7)	93.1 (17.7)
$AUC_{(0-t)}$, mg/h/dL	244.5 (62.1)	275.7 (64.5)	213.3 (42.1)	NA	NA	NA	259.8 (48.7)	277.3 (57.8)	242.4 (31.0)
$t_{1/2}$, h	3.88 (1.97)‡	4.14 (2.49)	3.61 (1.34)	NA	NA	NA	3.15 (1.12)	3.38 (1.30)	2.93 (0.90)

Values are mean (SD).
BMT = bremelanotide; NA = not applicable.
*After receiving BMT + ethanol, 1 participant's data lacked sufficient BMT values above the lower limit of quantitation.
†Across all participants, $P < 0.01$ for ethanol alone versus BMT + ethanol by paired *t* test. One hour after dosing, however, the sampling interval increased to 1 hour. Hence, apparent differences in T_{max} may be due to sampling bias.
‡Across all participants, $P = 0.1543$ for ethanol alone versus BMT + ethanol by paired *t* test.

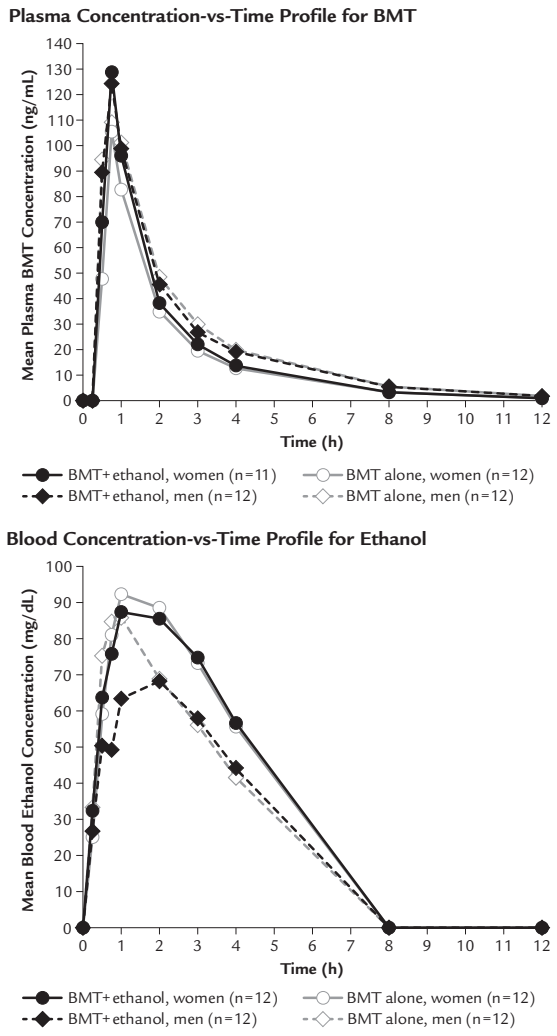

Figure 4. Plasma concentration versus time profile for BMT (top) and blood concentration versus time profile for ethanol (bottom) by treatment and sex. BMT = bremelanotide.

2-minute standing SBP and DBP were noted after BMT + ethanol administration, as well as administration of ethanol alone, and appeared to be primarily caused by ethanol's vasodilatory effects. Small increases of ~2 to 6 beats/min, on average, in sitting, immediate standing, and 2-minute standing PR were observed after all treatments. Overall, coadministration of BMT + ethanol did not result in a pronounced or exaggerated hypotensive effect nor were significant orthostatic changes observed. BMT C_{max}, T_{max}, $AUC_{(0-t)}$, and $t_{1/2}$ values after single-dose administration of IN BMT 20 mg (with or without ethanol) were similar to those seen in a previous study.[18] With the exception of 1 participant with evidence of occasional unifocal premature ventricular contractions at discharge that had resolved on re-evaluation 4 days later, no clinically significant abnormalities were noted for discharge ECGs. Increased SRSSs were noted beginning ~1 to 4 hours after dosing, particularly after BMT + ethanol or ethanol administration. This was not unexpected and is most likely attributable to ethanol. A small number of participants had mild increases in ALT or aspartate aminotransferase values at discharge (~1.5- to 3-fold increases from baseline) that were most likely due to ethanol. No other clinically significant abnormal laboratory tests attributable to treatment were noted, with the exception of a reversible elevation in ALT of 124 U/L after BMT + ethanol administration in 1 participant, which was reported as a moderate AE possibly related to treatment.

A comparison of the PK profiles of BMT and alcohol for all participants in all treatment groups found extensive overlap between the BMT plasma concentration–time profile and the blood alcohol concentration–time profile. Phase I studies have reported that BMT is rapidly absorbed in humans, reaching peak plasma concentrations at ~60 and 30 minutes after SC and IN administration, respectively. The elimination half-life for both routes of administration is ~2 hours (Palatin Technologies, Inc. Data on file). Thus, the significant differences in T_{max} between the ethanol group and the BMT + ethanol group may reflect blood sampling time biases (because samples were drawn at 1-hour intervals after the 1-hour postdose time point) rather than an effect of BMT on ethanol PK, because 1 hour after the dose, the sampling interval increased to 1 hour. In addition, BMT was not expected to have a drug–drug interaction with ethanol.

CONCLUSIONS

In healthy adult women and men, single IN doses of BMT administered with or without ethanol were safe and generally well tolerated, with no clinically relevant hemodynamic effects, PK interactions, or serious AEs. This Phase I study reports that BMT and ethanol can be safely coadministered. The IN 20-mg dose of BMT has an exposure equivalent to ~1 to 2 times the SC dose currently being evaluated in ongoing Phase III

studies. As explained earlier the IN dose was selected for this study to provide the most conservative test of a possible ethanol interaction; there is no reason to expect that the results would be different if the SC route of administration had been used. The SC route of administration was chosen for further development because it provides tighter control of exposure. The objective of the Phase III studies is to evaluate self-administered, "at-home", as-desired SC BMT for the treatment of HSDD in premenopausal women. No special instructions or restrictions on the use of alcohol are included in the Phase III studies (ClinicalTrials.gov identifiers NCT02338960 and NCT02333071).

ACKNOWLEDGMENTS

This study was funded by Palatin Technologies, Inc. With the authors, Palatin Technologies participated in the study design, collection, analysis, and interpretation of data and in the decision to submit the manuscript for publication. They also reviewed the final manuscript. Under the direction of the authors, editorial assistance was provided by Maria Vinall of The Curry Rockefeller Group, LLC, which was funded by Palatin Technologies, Inc. Each author participated in the development of the study design, collection, analysis, interpretation of data, and the decision to submit the manuscript for publication. All authors have reviewed the final manuscript and approved it for submission to *Clinical Therapeutics*.

CONFLICTS OF INTEREST

A.H. Clayton has received royalties from the Changes in Sexual Functioning Questionnaire, Guilford Publications; has received research support or consulting fees from Auspex, Forest Research Institute, Inc (now Allergan), Genomind, Lundbeck, Palatin Technologies, Inc., Pfizer Inc, S1 Biopharma, and Sprout Pharmaceuticals, a division of Valeant; and has stocks, stock options, or ownership interest, excluding diversified mutual funds, from Euthymics and S1 Biopharma. L.R. DeRogatis has received research support or consulting fees from Palatin Technologies, Inc. J. Lucas and R. Jordan are employees and stockholders of Palatin Technologies, Inc. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

SUPPLEMENTARY MATERIAL

Supplemental material accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.01.018.

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SUPPLEMENTARY MATERIAL

Summary Statistics of Routine Chemistry Test Results at Screening Visit, Baseline and Discharge

Parameter		Screening	Baseline	Discharge
Sodium (mEq/L)	N	24	24	24
	MEAN	139.50	140.13	139.58
	SD	1.69	2.07	2.06
	MEDIAN	140.00	140.50	139.50
	MIN	136.00	135.00	136.00
	MAX	142.00	144.00	143.00
Potassium (mEq/L)	N	24	24	24
	MEAN	4.35	4.10	4.53
	SD	0.42	0.26	0.53
	MEDIAN	4.30	4.10	4.40
	MIN	3.70	3.50	3.70
	MAX	5.40	4.70	5.70
Chloride (mEq/L)	N	24	24	24
	MEAN	101.00	101.75	100.42
	SD	2.13	2.44	1.82
	MEDIAN	101.00	101.50	101.00
	MIN	96.00	98.00	95.00
	MAX	106.00	110.00	102.00
Calcium (mg/dL)	N	24	24	24
	MEAN	9.57	9.28	9.04
	SD	0.39	0.33	0.35
	MEDIAN	9.50	9.20	9.05
	MIN	9.00	8.70	8.30
	MAX	10.30	10.00	9
Glucose (mg/dL)	N	24	24	24
	MEAN	81.04	88.71	98.13
	SD	10.45	16.52	11.54
	MEDIAN	82.00	87.50	98.00
	MIN	49.00	57.00	77.00
	MAX	100.00	139.00	126.00
Carbon Dioxide (CO2) (mmol/L)	N	24	24	24
	MEAN	24.92	24.08	25.13
	SD	2.39	2.02	1.98
	MEDIAN	25.00	24.00	25.00
	MIN	19.00	20.00	20.00
	MAX	30.00	28.00	29.00
Blood Urea Nitrogen (BUN) (mg/dL)	N	24	24	24
	MEAN	13.25	12.46	11.08
	SD	5.39	3.41	2.24
	MEDIAN	13.00	12.00	10.50
	MIN	7.00	6.00	7.00
	MAX	34.00	23.00	16.00

(continued)

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Parameter		Screening	Baseline	Discharge
BUN/Creatinine Ratio	N	24	24	24
	MEAN	14.06	13.48	11.68
	SD	4.81	3.40	2.22
	MEDIAN	12.60	13.15	11.45
	MIN	6.40	7.50	8.30
	MAX	26.20	20.00	17.10
Creatinine (mg/dL)	N	24	24	24
	MEAN	0.97	0.95	0.98
	SD	0.25	0.22	0.24
	MEDIAN	0.95	0.90	0.95
	MIN	0.60	0.60	0.60
	MAX	1.40	1.30	1.40
SGPT (ALT) (U/L)	N	24	24	24
	MEAN	22.29	21.42	37.08
	SD	10.71	10.56	28.37
	MEDIAN	21.50	17.00	27.50
	MIN	7.00	8.00	8.00
	MAX	42.00	47.00	124.00
SGOT (AST) (U/L)	N	24	24	24
	MEAN	23.58	22.29	29.63
	SD	6.60	5.40	13.36
	MEDIAN	23.00	21.00	27.50
	MIN	13.00	14.00	14.00
	MAX	37.00	33.00	71.00
Alkaline Phosphatase (U/L)	N	24	24	24
	MEAN	75.25	83.29	76.54
	SD	18.22	35.51	16.76
	MEDIAN	67.50	76.00	73.50
	MIN	50.00	52.00	50.00
	MAX	114.00	225.00	110.00
Total Cholesterol (mg/dL)	N	24	24	24
	MEAN	178.13	172.58	180.71
	SD	38.42	32.30	33.87
	MEDIAN	172.50	167.00	175.00
	MIN	117.00	110.00	133.00
	MAX	263.00	237.00	244.00

Distribution of Shifts from Baseline to Discharge for Routine Chemistry Laboratory Test Results

		Discharge							
		Low		Normal		High		Total	
Baseline		N	%	N	%	N	%	N	%
Sodium (mEq/L)	Low	0	0	0	0	0	0	0	0
	Normal	0	0	24	100.00	0	0	24	100.00
	High	0	0	0	0	0	0	0	0
	Total	0	0	24	100.00	0	0	24	100.00
Potassium (mEq/L)	Low	0	0	0	0	0	0	0	0
	Normal	0	0	20	83.33	4	16.67	24	100.00
	High	0	0	0	0	0	0	0	0
	Total	0	0	20	83.33	4	16.67	24	100.00
Chloride (mEq/L)	Low	0	0	0	0	0	0	0	0
	Normal	1	4.17	22	91.67	0	0	23	95.83
	High	0	0	1	4.17	0	0	1	4.17
	Total	1	4.17	23	95.83	0	0	24	100.00
Calcium (mg/dL)	Low	0	0	0	0	0	0	0	0
	Normal	1	4.17	23	95.83	0	0	24	100.00
	High	0	0	0	0	0	0	0	0
	Total	1	4.17	23	95.83	0	0	24	100.00
Glucose (mg/dL)	Low	0	0	2	8.33	0	0	2	8.33
	Normal	0	0	17	70.83	3	12.50	20	83.33
	High	0	0	2	8.33	0	0	2	8.33
	Total	0	0	21	87.50	3	12.50	24	100.00
Carbon Dioxide (CO2) (mmol/L)	Low	0	0	2	8.33	0	0	2	8.33
	Normal	1	4.17	21	87.50	0	0	22	91.67
	High	0	0	0	0	0	0	0	0
	Total	1	4.17	23	95.83	0	0	24	100.00
Blood Urea Nitrogen (BUN) (mg/dL)	Low	0	0	1	4.17	0	0	1	4.17
	Normal	0	0	23	95.83	0	0	23	95.83
	High	0	0	0	0	0	0	0	0
	Total	0	0	24	100.00	0	0	24	100.00
BUN/Creatinine Ratio	Low	1	4.17	2	8.33	0	0	3	12.50
	Normal	3	12.50	18	75.00	0	0	21	87.50
	High	0	0	0	0	0	0	0	0
	Total	4	16.67	20	83.33	0	0	24	100.00
Creatinine (mg/dL)	Low	0	0	0	0	0	0	0	0
	Normal	0	0	21	87.50	1	4.17	22	91.67
	High	0	0	1	4.17	1	4.17	2	8.33
	Total	0	0	22	91.67	2	8.33	24	100.00
SGPT (ALT) (U/L)	Low	0	0	0	0	0	0	0	0
	Normal	0	0	18	75.00	5	20.83	23	95.83
	High	0	0	0	0	1	4.17	1	4.17
	Total	0	0	18	75.00	6	25.00	24	100.00

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Baseline		Discharge							
		Low		Normal		High		Total	
		N	%	N	%	N	%	N	%
SGOT (AST) (U/L)	Low	0	0	0	0	0	0	0	0
	Normal	0	0	16	66.67	8	33.33	24	100.00
	High	0	0	0	0	0	0	0	0
	Total	0	0	16	66.67	8	33.33	24	100.00
Alkaline Phosphatase (U/L)	Low	0	0	0	0	0	0	0	0
	Normal	0	0	23	95.83	0	0	23	95.83
	High	0	0	1	4.17	0	0	1	4.17
	Total	0	0	24	10.00	0	0	24	100.00
Total Cholesterol (mg/dL)	Low	0	0	0	0	0	0	0	0
	Normal	0	0	16	66.67	4	16.67	20	83.33
	High	0	0	0	0	4	16.67	4	16.67
	Total	0	0	16	66.67	8	33.33	24	100.00

Summary Statistics of Routine Hematology Test Results at Screening Visit, Baseline and Discharge

Parameter		Screening	Baseline	Discharge
RBC (miL/mm^3)	N	24	24	24
	MEAN	4.68	4.51	4.32
	SD	0.46	0.45	0.53
	MEDIAN	4.65	4.45	4.40
	MIN	3.80	3.70	3.10
	MAX	5.40	5.30	5.30
Hemoglobin (g/dL)	N	24	24	24
	MEAN	14.02	13.63	12.68
	SD	1.63	1.50	1.59
	MEDIAN	13.85	13.75	12.85
	MIN	10.10	10.90	9.40
	MAX	16.90	16.10	14.80
Hematocrit (%)	N	24	24	24
	MEAN	42.50	40.37	38.62
	SD	3.89	3.75	4.46
	MEDIAN	41.80	40.10	38.20
	MIN	33.40	34.10	29.40
	MAX	50.70	47.00	47.40
MCV (fL)	N	24	24	24
	MEAN	91.20	89.93	89.68
	SD	4.73	4.70	4.84
	MEDIAN	91.35	90.65	89.60
	MIN	78.60	77.40	77.20
	MAX	100.00	98.60	98.60
MCH (pg)	N	24	24	24
	MEAN	30.03	30.33	29.47
	SD	1.92	2.15	2.44
	MEDIAN	30.55	30.95	29.35
	MIN	25.40	25.10	23.40
	MAX	33.50	33.60	33.00
MCHC (g/dL)	N	24	24	24
	MEAN	32.93	33.70	32.84
	SD	1.19	1.13	1.61
	MEDIAN	32.95	33.55	32.55
	MIN	30.20	30.90	29.80
	MAX	35.30	36.50	35.80
RDW (%)	N	24	24	24
	MEAN	13.30	13.10	13.13
	SD	0.89	0.91	0.85
	MEDIAN	13.30	12.80	12.90

(continued)

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Parameter		Screening	Baseline	Discharge
	MIN	11.90	11.80	12.00
	MAX	15.50	15.30	15.20
Platelets (x 10^3/mm^3)	N	24	24	24
	MEAN	275.71	269.25	288.92
	SD	80.33	58.17	66.18
	MEDIAN	266.50	261.50	284.50
	MIN	166.00	150.00	166.00
	MAX	563.00	381.00	467.00
WBC (x 10^3/mm^3)	N	24	24	24
	MEAN	5.76	6.28	7.62
	SD	1.17	1.78	1.95
	MEDIAN	5.70	6.25	7.75
	MIN	3.80	3.60	4.40
	MAX	8.20	12.50	10.80
Neutrophils (%)	N	24	24	24
	MEAN	53.79	51.75	54.63
	SD	8.42	8.83	18.82
	MEDIAN	54.50	51.00	50.50
	MIN	36.00	36.00	4.00
	MAX	70.00	80.00	86.00
Lymphocytes (%)	N	24	24	24
	MEAN	33.83	35.38	29.25
	SD	7.75	7.87	12.33
	MEDIAN	33.50	35.00	32.00
	MIN	20.00	12.00	3.00
	MAX	56.00	46.00	51.00
Basophils (%)	N	24	24	24
	MEAN	0.54	0.50	0.58
	SD	0.72	0.51	0.65
	MEDIAN	0.00	0.50	0.50
	MIN	0.00	0.00	0.00
	MAX	3.00	1.00	2.00
Eosinophils (%)	N	24	24	24
	MEAN	2.96	2.92	2.79
	SD	2.29	1.64	2.83
	MEDIAN	2.00	2.00	2.00
	MIN	1.00	1.00	0.00
	MAX	9.00	7.00	12.00
Monocytes (%)	N	24	24	24
	MEAN	8.88	9.46	9.46
	SD	1.96	2.48	3.50
	MEDIAN	8.50	9.00	9.00

(continued)

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Parameter		Screening	Baseline	Discharge
	MIN	5.00	6.00	4.00
	MAX	13.00	15.00	18.00
Bands (%)	N	24	24	24
	MEAN	0.00	0.00	0.21
	SD	0.00	0.00	0.83
	MEDIAN	0.00	0.00	0.00
	MIN	0.00	0.00	0.00
	MAX	0.00	0.00	4.00

Distribution of Shifts from Baseline to Discharge for Routine Hematology Laboratory Test Results

		Discharge							
		Low		Normal		High		Total	
Baseline		N	%	N	%	N	%	N	%
RBC (miL/mm^3)	Low	0	0	0	0	0	0	0	0
	Normal	3	12.50	21	87.50	0	0	24	100.00
	High	0	0	0	0	0	0	0	0
	Total	3	12.50	21	87.50	0	0	24	100.00
Hemoglobin (g/dL)	Low	2	8.33	0	0	0	0	2	8.33
	Normal	4	16.67	18	75.00	0	0	22	91.67
	High	0	0	0	0	0	0	0	0
	Total	6	25.00	18	75.00	0	0	24	100.00
Hematocrit (%)	Low	5	20.83	1	4.17	0	0	6	25.00
	Normal	4	16.67	14	58.33	0	0	18	75.00
	High	0	0	0	0	0	0	0	0
	Total	9	37.50	15	62.50	0	0	24	100.00
MCV (fL)	Low	1	4.17	0	0	0	0	1	4.17
	Normal	0	0	23	95.83	0	0	23	95.83
	High	0	0	0	0	0	0	0	0
	Total	1	4.17	23	95.83	0	0	24	100.00
MCH (pg)	Low	0	0	0	0	0	0	0	0
	Normal	2	8.33	22	91.67	0	0	24	100.00
	High	0	0	0	0	0	0	0	0
	Total	2	8.33	22	91.67	0	0	24	100.00
MCHC (g/dL)	Low	0	0	0	0	0	0	0	0
	Normal	1	4.17	18	75.00	0	0	19	79.17
	High	0	0	1	4.17	4	16.67	5	20.83
	Total	1	4.17	19	79.17	4	16.67	24	100.00
RDW (%)	Low	0	0	0	0	0	0	0	0
	Normal	0	0	24	100.00	0	0	24	100.00
	High	0	0	0	0	0	0	0	0
	Total	0	0	24	100.00	0	0	24	100.00
Platelets (x 10^3/mm^3)	Low	0	0	0	0	0	0	0	0
	Normal	0	0	23	95.83	1	4.17	24	100.00
	High	0	0	0	0	0	0	0	0
	Total	0	0	23	95.83	1	4.17	24	100.00
WBC (x 10^3/mm^3)	Low	0	0	0	0	0	0	0	0
	Normal	0	0	23	95.83	0	0	23	95.83
	High	0	0	1	4.17	0	0	1	4.17
	Total	0	0	24	100.00	0	0	24	100.00
Neutrophils (%)	Low	0	0	0	0	0	0	0	0
	Normal	3	12.50	18	75.00	2	8.33	23	95.83
	High	0	0	1	4.17	0	0	1	4.17
	Total	3	12.50	19	79.17	2	8.33	24	100.00

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Baseline		Discharge							
		Low		Normal		High		Total	
		N	%	N	%	N	%	N	%
Lymphocytes (%)	Low	0	0	0	0	0	0	0	0
	Normal	2	8.33	21	87.50	1	4.17	24	100.00
	High	0	0	0	0	0	0	0	0
	Total	2	8.33	21	87.50	1	4.17	24	100.00
Basophils (%)	Low	0	0	0	0	0	0	0	0
	Normal	0	0	24	100.00	0	0	24	100.00
	High	0	0	0	0	0	0	0	0
	Total	0	0	24	100.00	0	0	24	100.00
Eosinophils (%)	Low	0	0	0	0	0	0	0	0
	Normal	1	4.17	21	87.50	2	8.33	24	100.00
	High	0	0	0	0	0	0	0	0
	Total	1	4.17	21	87.50	2	8.33	24	100.00
Monocytes (%)	Low	0	0	0	0	0	0	0	0
	Normal	1	4.17	17	70.83	3	12.50	21	87.50
	High	0	0	2	8.33	1	4.17	3	12.50
	Total	1	4.17	19	79.17	4	16.67	24	100.00
Bands (%)	Low	0	0	0	0	0	0	0	0
	Normal	0	0	24	100.00	0	0	24	100.00
	High	0	0	0	0	0	0	0	0
	Total	0	0	24	100.00	0	0	24	100.00

Summary Statistics of Routine Urinalysis Test Results at Screening Visit, Baseline and Discharge

Parameter		Screening	Baseline	Discharge
pH (num)	N	23	24	24
	MEAN	6.391	6.063	6.813
	SD	0.543	0.517	0.622
	MEDIAN	6.500	6.000	7.000
	MIN	5.500	5.500	5.500
	MAX	7.500	7.500	8.000
Specific Gravity (num)	N	23	24	24
	MEAN	1.015	1.018	1.017
	SD	0.008	0.008	0.007
	MEDIAN	1.015	1.020	1.018
	MIN	1.005	1.005	1.005
	MAX	1.030	1.030	1.030
Urobilinogen (U/dL)	N	23	24	24
	MEAN	0.235	0.300	0.267
	SD	0.167	0.270	0.226
	MEDIAN	0.200	0.200	0.200
	MIN	0.200	0.200	0.200
	MAX	1.000	1.000	1.000

Distribution of Shifts from Baseline to Discharge for Routine Urinalysis Laboratory Test Results

		Discharge									
		Missing		Low		Normal		High		Total	
Baseline		N	%	N	%	N	%	N	%	N	%
pH (num)	Missing	0	0	0	0	0	0	0	0	0	0
	Low	0	0	0	0	0	0	0	0	0	0
	Normal	0	0	0	0	24	100.00	0	0	24	100.00
	High	0	0	0	0	0	0	0	0	0	0
	Total	0	0	0	0	24	100.00	0	0	24	100.00
Specific Gravity (num)	Missing	0	0	0	0	0	0	0	0	0	0
	Low	0	0	0	0	0	0	0	0	0	0
	Normal	0	0	0	0	24	100.00	0	0	24	100.00
	High	0	0	0	0	0	0	0	0	0	0
	Total	0	0	0	0	24	100.00	0	0	24	100.00
Urobilinogen (U/dL)	Missing	0	0	0	0	0	0	0	0	0	0
	Low	0	0	0	0	0	0	0	0	0	0
	Normal	0	0	0	0	24	100.00	0	0	24	100.00
	High	0	0	0	0	0	0	0	0	0	0
	Total	0	0	0	0	24	100.00	0	0	24	100.00

Summary Statistics of Glucose Test Results by Treatment and Time Point

Blood Glucose Concentration (mg/dL)		PT-141 20000 mcg + 0.6 g/kg Ethanol			PT-141 20000 mcg + Placebo Drink			Placebo Spray + 0.6 g/kg Ethanol		
		FEMALE	MALE	All	FEMALE	MALE	All	FEMALE	MALE	All
Pre-Dose	N	12	12	24	12	12	24	12	12	24
	MEAN	80.00	91.17	85.58	86.33	88.50	87.42	86.08	91.08	88.58
	SD	18.01	15.36	17.33	5.71	11.67	9.05	3.80	16.42	11.93
	MEDIAN	88.00	94.50	88.00	86.50	87.50	86.50	87.00	93.50	87.00
	MIN	38.00	55.00	38.00	77.00	70.00	70.00	77.00	47.00	47.00
	MAX	101.00	106.00	106.00	93.00	107.00	107.00	92.00	112.00	112.00
15 MIN	N	12	12	24	12	12	24	12	12	24
	MEAN	98.33	120.08	109.21	100.08	106.08	103.08	102.67	114.83	108.75
	SD	24.31	13.03	22.08	15.49	24.17	20.09	18.58	16.17	18.14
	MEDIAN	103.00	116.50	112.00	100.50	107.00	101.50	100.00	114.00	108.00
	MIN	47.00	102.00	47.00	74.00	52.00	52.00	71.00	85.00	71.00
	MAX	135.00	143.00	143.00	139.00	140.00	140.00	134.00	136.00	136.00
30 MIN	N	12	12	24	12	12	24	12	12	24
	MEAN	107.83	120.17	114.00	106.50	111.75	109.13	111.42	121.17	116.29
	SD	25.59	34.04	30.12	21.61	34.38	28.21	27.75	27.12	27.29
	MEDIAN	110.50	127.00	116.50	106.50	118.50	108.50	107.50	124.00	118.50
	MIN	66.00	50.00	50.00	56.00	62.00	56.00	74.00	81.00	74.00
	MAX	142.00	171.00	171.00	152.00	165.00	165.00	180.00	165.00	180.0
45 MIN	N	11	12	23	12	12	24	12	12	24
	MEAN	96.09	109.58	103.13	95.33	98.92	97.13	100.83	112.33	106.58
	SD	20.04	38.34	31.07	19.33	31.15	25.42	40.27	34.53	37.15
	MEDIAN	105.00	122.00	105.00	94.50	106.00	96.50	96.00	120.50	111.50
	MIN	61.00	30.00	30.00	49.00	54.00	49.00	41.00	63.00	41.00
	MAX	127.00	168.00	168.00	125.00	159.00	159.00	179.00	166.00	179.00
1 HR	N	12	12	24	12	12	24	12	12	24
	MEAN	99.75	103.83	101.79	97.58	100.42	99.00	94.58	104.58	99.58
	SD	17.45	29.32	23.69	23.37	29.63	26.14	36.83	21.63	29.98
	MEDIAN	104.00	105.00	104.00	93.00	90.00	91.00	91.50	114.50	100.50
	MIN	70.00	46.00	46.00	55.00	68.00	55.00	42.00	69.00	42.00
	MAX	125.00	154.00	154.00	150.00	159.00	159.00	153.00	130.00	153.00
2 HR	N	12	12	24	12	12	24	12	11	23
	MEAN	86.83	95.75	91.29	84.67	91.67	88.17	83.75	89.45	86.48
	SD	15.06	16.34	16.03	16.88	13.34	15.30	12.43	9.64	11.31
	MEDIAN	86.50	91.50	87.00	88.50	90.50	88.50	85.50	88.00	86.00
	MIN	61.00	79.00	61.00	37.00	75.00	37.00	52.00	73.00	52.00
	MAX	109.00	120.00	120.00	99.00	122.00	122.00	103.00	104.00	104.00
3 HR	N	12	12	24	12	12	24	12	11	23
	MEAN	83.17	92.75	87.96	81.75	86.42	84.08	83.25	89.82	86.39
	SD	11.18	14.95	13.81	13.61	15.38	14.40	6.55	6.69	7.28
	MEDIAN	86.00	88.50	88.00	83.50	87.50	84.50	83.50	89.00	87.00

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Blood Glucose Concentration (mg/dL)		PT-141 20000 mcg + 0.6 g/kg Ethanol			PT-141 20000 mcg + Placebo Drink			Placebo Spray + 0.6 g/kg Ethanol		
		FEMALE	MALE	All	FEMALE	MALE	All	FEMALE	MALE	All
	MIN	51.00	66.00	51.00	40.00	64.00	40.00	71.00	81.00	71.00
	MAX	94.00	116.00	116.00	91.00	117.00	117.00	93.00	103.00	103.00
4 HR	N	12	12	24	12	12	24	12	11	23
	MEAN	83.08	94.50	88.79	83.67	85.17	84.42	78.75	88.82	83.57
	SD	14.79	10.52	13.84	4.42	11.57	8.60	12.83	6.49	11.31
	MEDIAN	83.00	94.00	89.00	82.50	86.00	84.00	82.50	89.00	86.00
	MIN	53.00	75.00	53.00	77.00	59.00	59.00	49.00	79.00	49.00
	MAX	110.00	115.00	115.00	92.00	100.00	100.00	90.00	100.00	100.00
8 HR	N	12	12	24	12	12	24	12	11	23
	MEAN	94.75	102.33	98.54	91.67	92.17	91.92	95.08	99.09	97.00
	SD	14.26	11.49	13.24	18.62	13.35	15.84	20.96	13.19	17.40
	MEDIAN	97.00	102.50	101.00	96.00	94.00	95.00	93.00	96.00	94.00
	MIN	63.00	78.00	63.00	36.00	62.00	36.00	44.00	76.00	44.00
	MAX	120.00	125.00	125.00	107.00	108.00	108.00	125.00	127.00	127.00
12 HR	N	12	12	24	12	12	24	11	11	22
	MEAN	94.00	105.17	99.58	88.33	90.25	89.29	93.18	98.91	96.05
	SD	18.96	13.80	17.19	20.92	22.58	21.31	15.00	18.80	16.85
	MEDIAN	98.00	103.00	102.00	95.50	94.00	94.50	97.00	101.00	97.50
	MIN	50.00	87.00	50.00	35.00	42.00	35.00	65.00	74.00	65.00
	MAX	120.00	139.00	139.00	107.00	118.00	118.00	113.00	139.00	139.00

Summary Statistics of Changes from Baseline to Discharge for Glucose Test Results by Treatment and Time Point

Blood Glucose Concentration (mg/dL)		PT-141 20000 mcg + 0.6 g/kg Ethanol			PT-141 20000 mcg + Placebo Drink			Placebo Spray + 0.6 g/kg Ethanol		
		FEMALE	MALE	All	FEMALE	MALE	All	FEMALE	MALE	All
15 MIN	N	12	12	24	12	12	24	12	12	24
	MEAN	18.33	28.92	23.63	13.75	17.58	15.67	16.58	23.75	20.17
	SD	18.79	16.96	18.32	13.59	26.55	20.72	18.60	19.62	19.05
	MEDIAN	19.00	31.00	25.00	12.00	22.00	16.50	13.00	25.50	21.50
	MIN	−29.00	1.00	−29.00	−6.00	−55.00	−55.00	−19.00	−17.00	−19.00
	MAX	47.00	61.00	61.00	47.00	50.00	50.00	50.00	60.00	60.00
30 MIN	N	12	12	24	12	12	24	12	12	24
	MEAN	27.83	29.00	28.42	20.17	23.25	21.71	25.33	30.08	27.71
	SD	22.52	25.24	23.40	21.56	36.25	29.21	26.93	23.32	24.76
	MEDIAN	31.00	28.00	30.50	21.00	28.50	24.00	22.50	31.50	28.50
	MIN	−15.00	−9.00	−15.00	−31.00	−45.00	−45.00	−16.00	−18.00	−18.00
	MAX	53.00	69.00	69.00	60.00	88.00	88.00	92.00	61.00	92.00
45 MIN	N	11	12	23	12	12	24	12	12	24
	MEAN	13.36	18.42	16.00	9.00	10.42	9.71	14.75	21.25	18.00
	SD	26.17	27.06	26.15	18.59	27.40	22.91	39.87	31.72	35.39
	MEDIAN	17.00	18.00	17.00	11.00	6.00	10.00	15.00	24.00	23.00
	MIN	−19.00	−25.00	−25.00	−38.00	−32.00	−38.00	−49.00	−36.00	−49.00
	MAX	66.00	66.00	66.00	35.00	55.00	55.00	91.00	75.00	91.00
1 HR	N	12	12	24	12	12	24	12	12	24
	MEAN	19.75	12.67	16.21	11.25	11.92	11.58	8.50	13.50	11.00
	SD	28.00	17.49	23.12	22.00	31.66	26.67	36.41	18.24	28.28
	MEDIAN	12.50	10.50	11.00	8.50	−1.00	6.50	7.00	19.00	14.50
	MIN	−11.00	−9.00	−11.00	−32.00	−17.00	−32.00	−48.00	−24.00	−48.00
	MAX	77.00	52.00	77.00	60.00	89.00	89.00	65.00	34.00	65.00
2 HR	N	12	12	24	12	12	24	12	11	23
	MEAN	6.83	4.58	5.71	−1.67	3.17	0.75	−2.33	−0.36	−1.39
	SD	23.21	15.44	19.31	14.85	13.47	14.08	12.94	11.94	12.23
	MEDIAN	0.00	8.00	0.50	−3.00	1.50	0.00	−2.00	0.00	−1.00
	MIN	−18.00	−22.00	−22.00	−40.00	−14.00	−40.00	−35.00	−17.00	−35.00
	MAX	70.00	27.00	70.00	15.00	39.00	39.00	20.00	29.00	29.00
3 HR	N	12	12	24	12	12	24	12	11	23
	MEAN	3.17	1.58	2.38	−4.58	−2.08	−3.33	−2.83	0.00	−1.48
	SD	14.95	12.52	13.51	11.89	17.94	14.94	6.64	14.57	10.99
	MEDIAN	−1.50	1.00	0.00	−3.50	−5.50	−3.50	−3.00	1.00	0.00
	MIN	−7.00	−23.00	−23.00	−37.00	−36.00	−37.00	−15.00	−22.00	−22.00
	MAX	48.00	30.00	48.00	12.00	28.00	28.00	5.00	34.00	34.00
4 HR	N	12	12	24	12	12	24	12	11	23
	MEAN	3.08	3.33	3.21	−2.67	−3.33	−3.00	−7.33	−1.00	−4.30

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Blood Glucose Concentration (mg/dL)		PT-141 20000 mcg + 0.6 g/kg Ethanol			PT-141 20000 mcg + Placebo Drink			Placebo Spray + 0.6 g/kg Ethanol		
		FEMALE	MALE	All	FEMALE	MALE	All	FEMALE	MALE	All
	SD	22.76	13.91	18.45	5.53	13.94	10.38	12.00	13.46	12.84
	MEDIAN	−2.50	−2.50	−2.50	−4.00	−2.00	−3.50	−4.00	−1.00	−4.00
	MIN	−16.00	−12.00	−16.00	−12.00	−29.00	−29.00	−34.00	−23.00	−34.00
	MAX	72.00	29.00	72.00	9.00	14.00	14.00	2.00	33.00	33.00
8 HR	N	12	12	24	12	12	24	12	11	23
	MEAN	14.75	11.17	12.96	5.33	3.67	4.50	9.00	9.27	9.13
	SD	12.86	10.36	11.57	16.83	18.77	17.46	20.28	19.65	19.53
	MEDIAN	13.50	10.00	10.00	6.00	2.50	4.50	6.00	7.00	7.00
	MIN	−4.00	−2.00	−4.00	−41.00	−27.00	−41.00	−39.00	−18.00	−39.00
	MAX	50.00	37.00	50.00	22.00	38.00	38.00	42.00	45.00	45.00
12 HR	N	12	12	24	12	12	24	11	11	22
	MEAN	14.00	14.00	14.00	2.00	1.75	1.88	7.64	9.09	8.36
	SD	19.68	15.02	17.12	19.95	23.17	21.14	15.16	12.67	13.65
	MEDIAN	14.00	17.50	15.50	9.00	0.00	3.00	10.00	11.00	10.50
	MIN	−17.00	−6.00	−17.00	−42.00	−43.00	−43.00	−21.00	−10.00	−21.00
	MAX	57.00	34.00	57.00	25.00	35.00	35.00	26.00	27.00	27.00