A Placebo-Controlled, Randomized, Double-Blind, Three Period, Three-Way Crossover Study on the Hemodynamic and Pharmacokinetic Interactions of Bremelanotide and Ethanol

Johna Lucas,[1] Leonard R. DeRogatis (presenter),[2] Robert Jordan[1]

[1]Palatin Technologies, Inc., Cranbury, NJ; [2]Maryland Center for Sexual Health, Lutherville, MD

Disclosures

- Dr DeRogatis has received research support or consulting fees from Palatin Technologies, Inc.
- Dr Lucas and Mr Jordan are employees and stockholders of Palatin Technologies, Inc.

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Background

- Female sexual dysfunction is a multifactorial condition with anatomical, physiological, medical, psychological, and social components
- Bremelanotide is a synthetic peptide analog of α-melanocyte stimulating hormone
- Bremelanotide activates endogenous CNS pathways involved in the sexual desire and arousal response
- Bremelanotide is being developed as a potential on-demand (used only as-needed) treatment for hypoactive sexual desire disorder
- Phase 3 pivotal studies are ongoing and have completed enrollment

Study Objectives

- To evaluate, in healthy adult women and men, the safety and tolerability of bremelanotide coadministered with ethanol, and the hemodynamic and pharmacokinetic interactions between bremelanotide and ethanol

Study Subjects

Key inclusion criteria:

- Healthy women or men, 21 to 45 years of age, weighing 50 to 100 kg, and within 20% of ideal weight
- Negative urine drug screen
- For women, a confirmed last menstrual period, and use of a highly effective birth-control method

Key exclusion criteria:

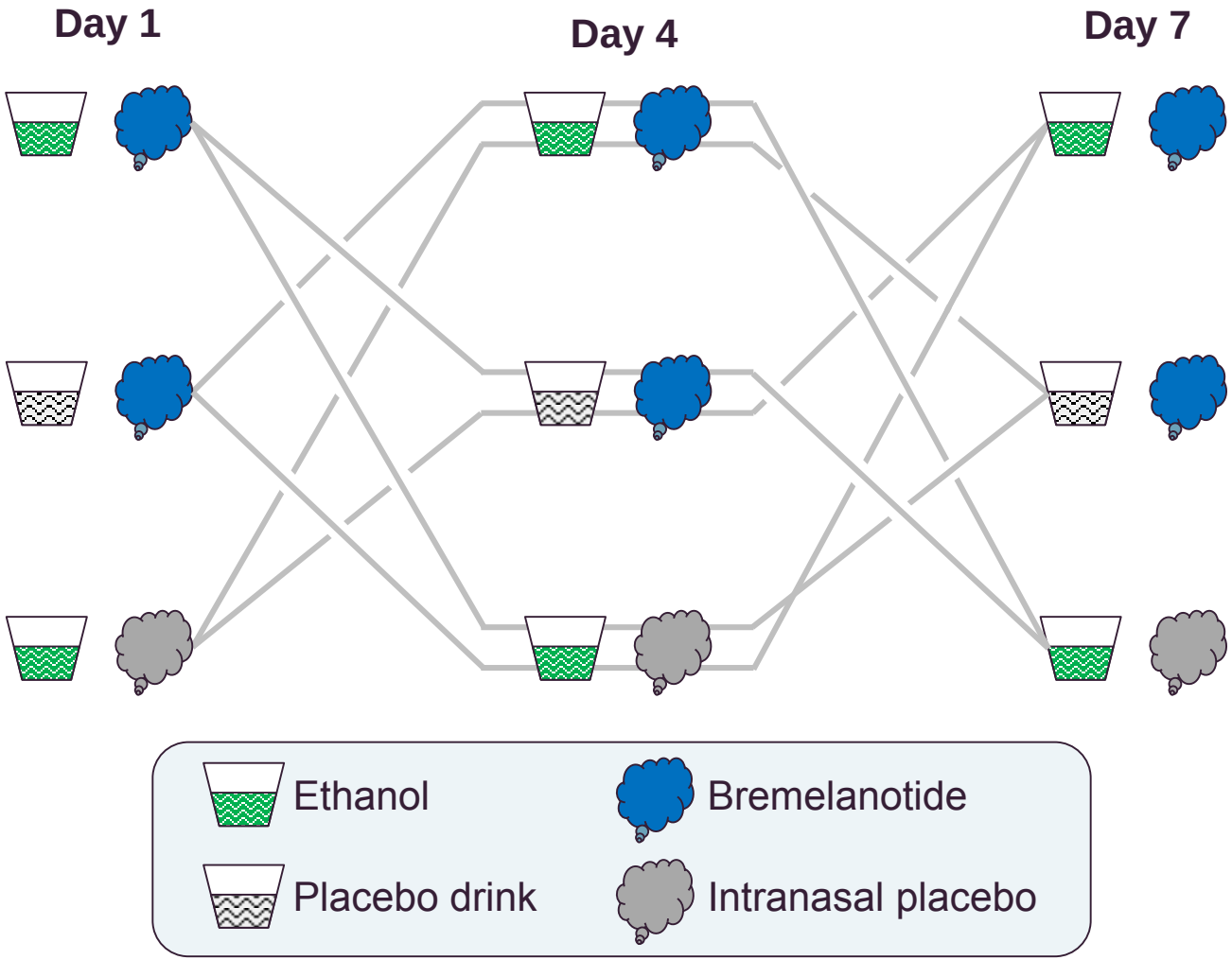
- Any clinically significant medical or psychiatric condition, physical finding, or laboratory/ECG abnormality
- Alcoholism
- Ethanol abstinence

Study Design

- A Phase 1, randomized, double-blind, 3-period, 3-way crossover study
- All subjects remained at the research facility for 7 consecutive days
- On Days 1, 4, and 7, subjects received single intranasal doses of bremelanotide (20 mg) or placebo, administered 10 minutes after oral dosing of ethanol (0.6 g/kg)[a] or a placebo drink[b]
- In the crossover design, each subject received 3 treatments: bremelanotide + ethanol; bremelanotide + non-ethanol; and placebo + ethanol
- The intranasal bremelanotide dose used in the study had an exposure 1 to 2 times that of the subcutaneous dose currently being studied in phase 3 development

[a]The equivalent of 4 oz vodka, or 2 glasses of wine, or 3 beers. Prepared as a 1:3 mixture of 100-proof vodka and orange juice.
[b]Prepared as 2 drops of ethanol floated on orange juice.

Crossover Treatment Paths[a]



[a]Four persons (2 women, 2 men) were randomly assigned to each of six treatment paths. No placebo/placebo path.

Key Outcome Measures

- Treatment-emergent adverse events (TEAEs)
- Bremelanotide and ethanol pharmacokinetics, from blood samples drawn predose, at 15, 30, and 45 minutes postdose, and then at 1, 2, 3, 4, 8, and 12 hours

Subjects' Baseline Characteristics

Variable	All participants	Women	Men
N[a]	24	12	12
Age, years Mean (SD) Range	 31.0 (7.3) 21–43	 31.0 (7.6) 22–42	 31.0 (7.4) 21–43
Race, n (%) Hispanic Black White Other	 10 (42%) 9 (38%) 4 (17%) 1 (4%)	 6 (50%) 3 (25%) 3 (25%) 0	 4 (33%) 6 (50%) 1 (8%) 1 (8%)
Body weight, kg, mean (SD)	72.5 (13.4)	63.5 (10.4)	81.5 (9.4)
Body mass index, kg/m^2, mean (SD)	25.3 (3.5)	24.3 (3.9)	26.2 (3.0)

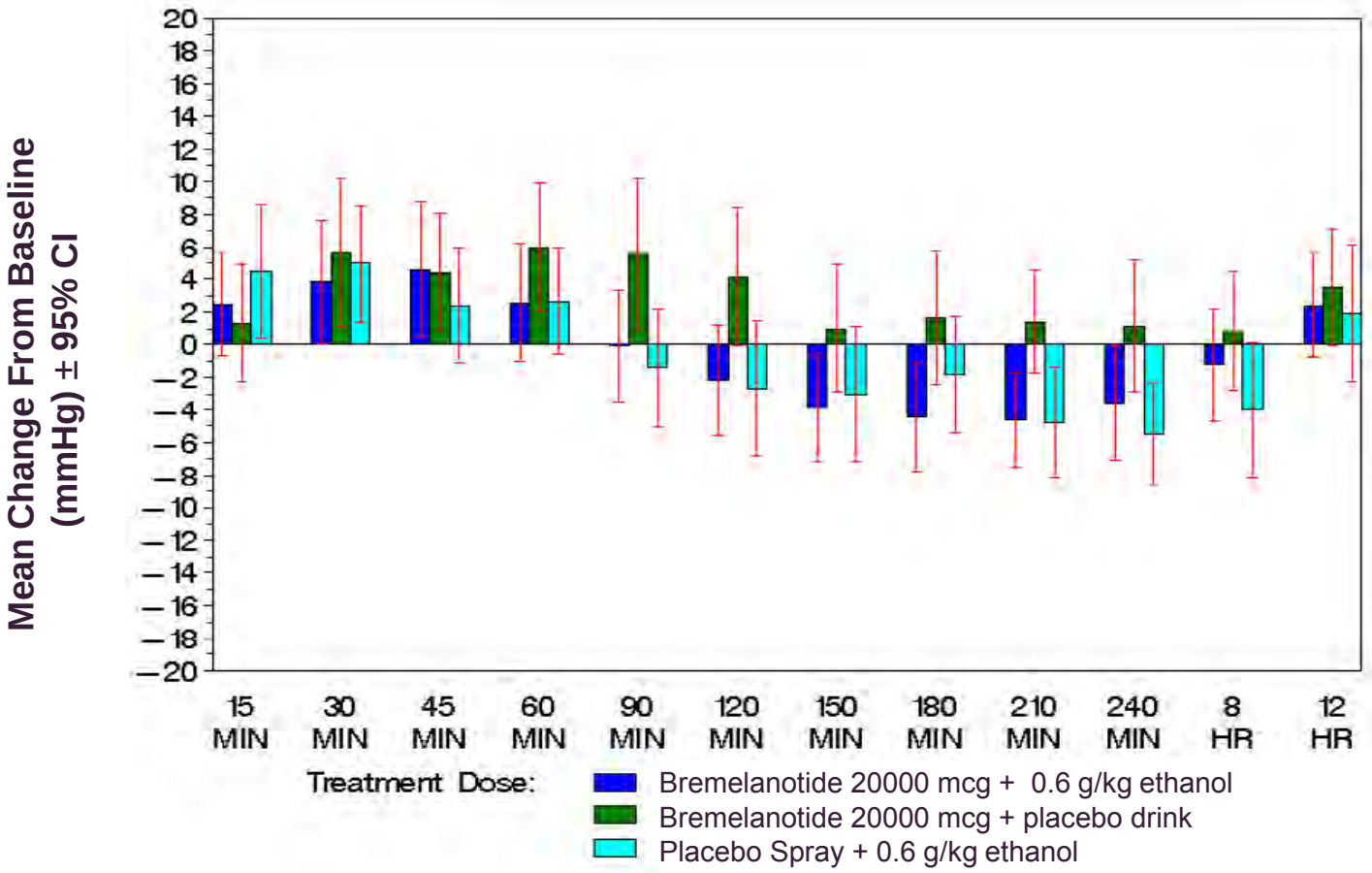
[a]All participants completed the study.
SD, standard deviation.

TEAEs

Incidence, n (%)[a]	Bremelanotide + ethanol		Bremelanotide alone		Ethanol alone	
	Women	Men	Women	Men	Women	Men
Any event	11 (91)	7 (58)	7 (58)	9 (75)	9 (75)	5 (42)
Flushing	6 (50)	4 (33)	5 (42)	5 (42)	2 (17)	1 (8)
Somnolence	3 (25)	4 (33)	0	3 (25)	5 (42)	4 (33)
Headache	5 (42)	0	1 (8)	0	4 (33)	0
Nausea	1 (8)	1 (8)	1 (8)	0	2 (17)	0
Dizziness[b]	2 (17)	0	1 (8)	0	1 (8)	0
Dizziness postural	0	0	1 (8)	0	0	1 (8)
Feeling hot	1 (8)	1 (8)	0	1 (8)	0	0
Nasal congestion	2 (17)	0	1 (8)	0	0	0
Hiccups	2 (17)	0	0	0	0	0
Taste disturbance	0	0	0	2 (17)	0	0

[a]The listing includes all events reported by more than 1 participant. No serious events were reported for any treatment. [b]Excluding vertigo.

Mean Post-treatment Changes in Sitting Systolic BP



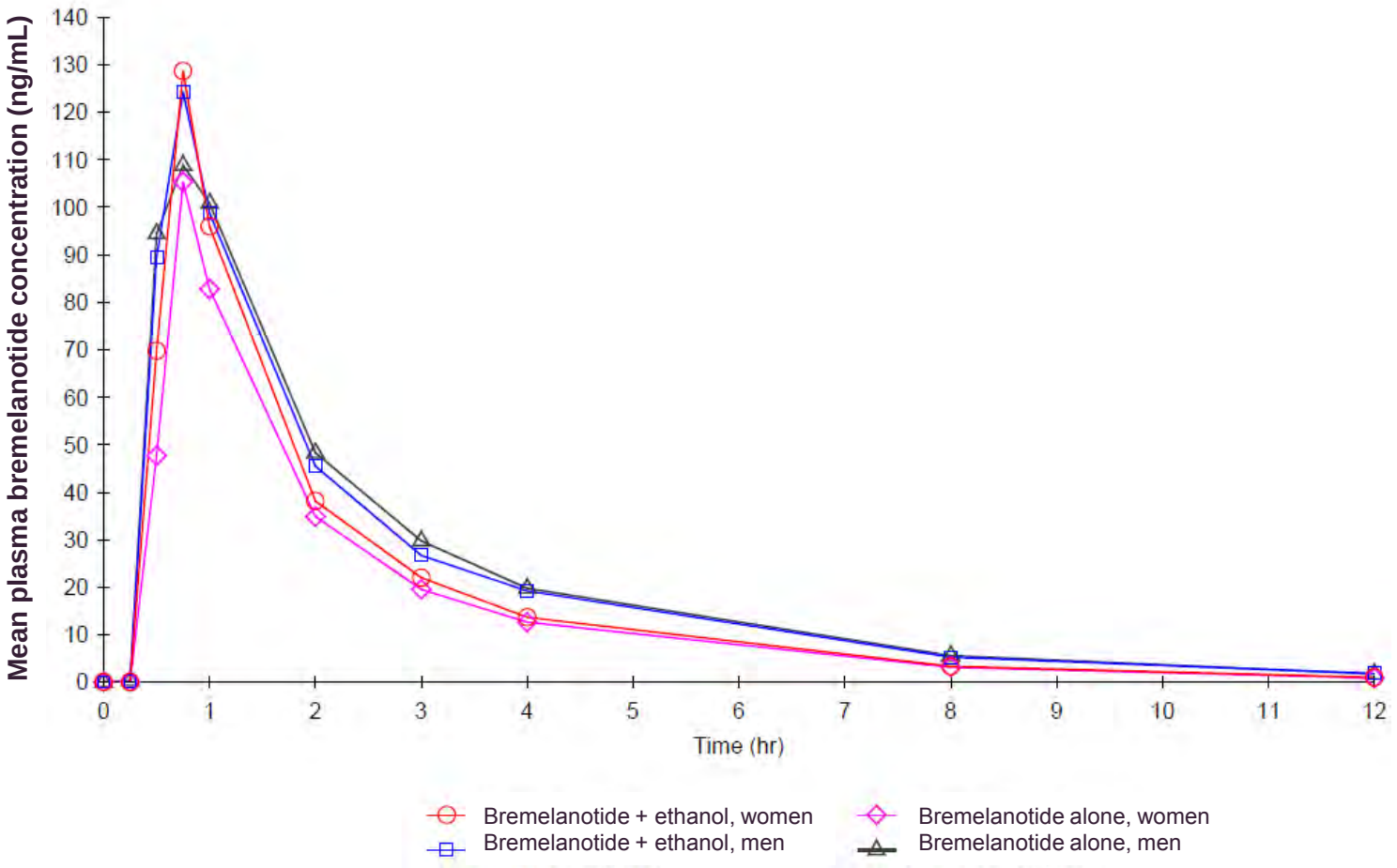
Pharmacokinetic Results

Mean (SD)	Bremelanotide + ethanol		Bremelanotide alone		Ethanol alone	
	Women	Men	Women	Men	Women	Men
Bremelanotide						
T_{max}, hours	0.70 (0.15)[a]	0.71 (0.14)	0.79 (0.14)	0.69 (0.19)	NA	NA
C_{max}, ng/mL	140.9 (104.2)[a]	127.8 (97.2)	106.0 (88.0)	117.3 (9.5)		
AUC(0-t), ng·h/mL	223.3 (163.3)[a]	248.3 (182.8)	177.0 (154.5)	255.5 (194.7)		
$t_{1/2}$, hours	2.18 (0.39)[a]	2.29 (0.42)	2.27 (0.48)	2.29 (0.28)		
Ethanol						
T_{max}, hours[b]	1.56 (0.54)	1.67 (0.75)	NA	NA	1.27 (0.56)	0.83 (0.22)
C_{max}, mg/dL	94.4 (24.0)	72.1 (12.8)			96.1 (15.7)	93.1 (17.7)
AUC(0-t), mg·h/dL	275.7 (64.5)	213.3 (42.1)			277.3 (57.8)	242.4 (31.0)
$t_{1/2}$, hours[c]	4.14 (2.49)	3.61 (1.34)			3.38 (1.30	2.93 (0.90)

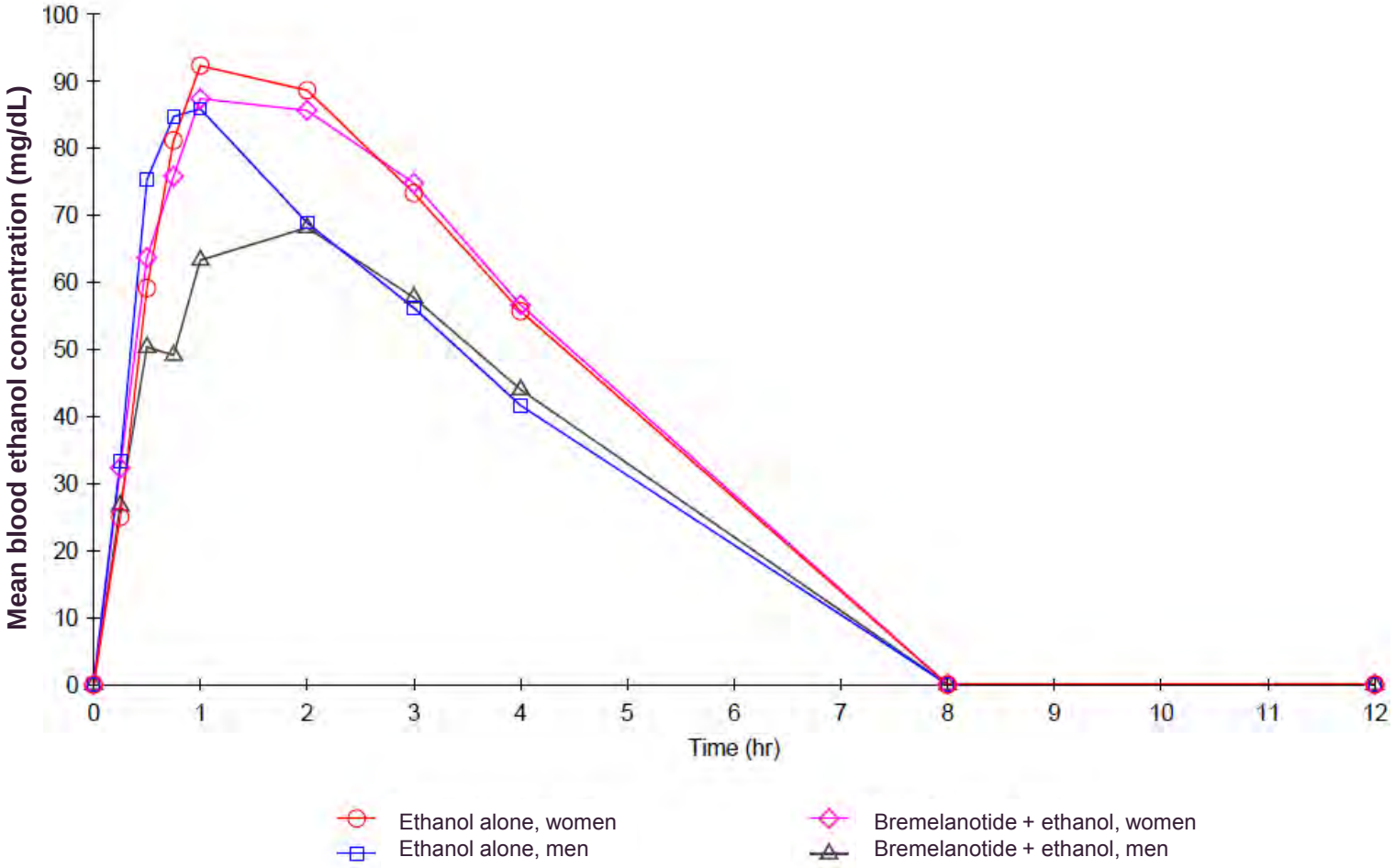
[a]After receiving bremelanotide + ethanol, 1 participant's data lacked sufficient bremelanotide values above the lower limit of quantification.
[b]Across all participants, $P < 0.01$ for ethanol alone vs bremelanotide + ethanol by paired t-test. After 1 hour post-dose, however, the sampling interval increased to 1 hour. Hence, apparent differences in T_{max} may be due to sampling bias.
[c]Across all participants, $P = 0.1543$ for ethanol alone vs bremelanotide + ethanol by paired t-test.

AUC, area under the curve; NA, not applicable; SD, standard deviation.

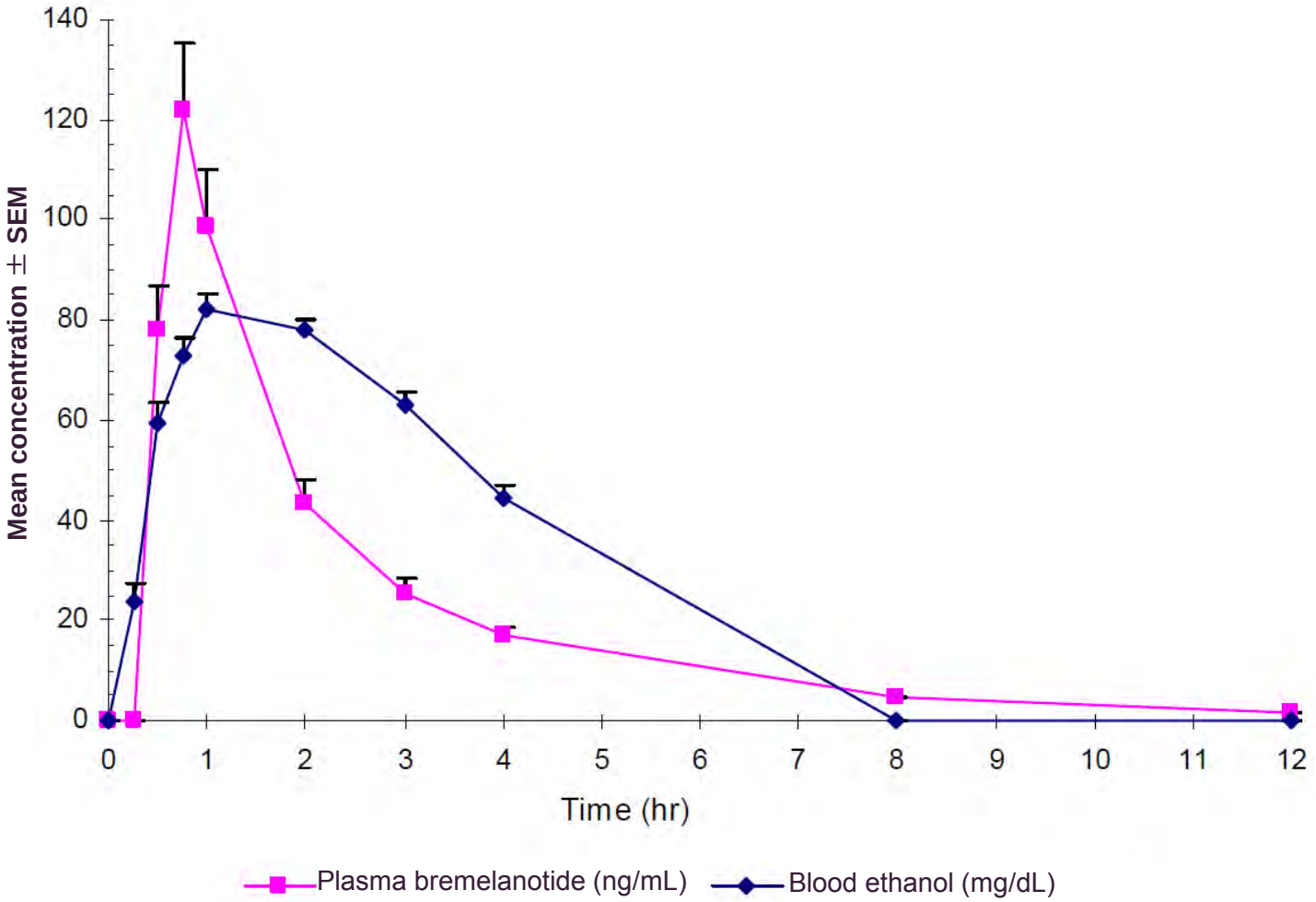
Plasma Bremelanotide Concentration-vs-Time Profiles, by Treatment and Sex



Blood Ethanol Concentration-vs-Time Profiles, by Treatment and Sex



Plasma Bremelanotide and Blood Ethanol Concentration-vs-Time Profiles, All Participants



SEM, standard error of the mean.

Conclusions

- In healthy adult women and men, single intranasal doses of bremelanotide with or without oral ethanol intake were safe and generally well tolerated
- Treatment with bremelanotide did not result in a significantly increased frequency of AEs, either in women or in men. No serious AEs occurred, and no participants discontinued
- Small decreases in sitting, immediate standing and 2-minute standing SBP and DBP were noted following bremelanotide + ethanol administration that appeared to be primarily due to ethanol's vasodilatory effects.
  - Overall, co-administration of bremelanotide + ethanol did not result in a pronounced or exaggerated hypotensive effect nor were significant orthostatic changes noted
- Pharmacokinetic findings suggested no clinically significant effect of ethanol on bremelanotide or of bremelanotide on ethanol, either in women or in men
- Overall, this phase 1 study demonstrates that bremelanotide and ethanol can be safely coadministered