Phase IIb Study of Bremelanotide in the Treatment of ED in Diabetic Males

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ABSTRACT

Introduction and Objective: Bremelanotide is a cyclic heptapeptide, delivered intranasally, being developed for treatment of male erectile dysfunction (ED) and female sexual dysfunction.

Methods: In this Phase IIb study, 294 diabetic ED patients were randomized to receive either placebo or one of 3 bremelanotide doses (10 mg, 12.5 mg, or 15 mg). After a 1-month washout period when other ED drugs were discontinued, patients were followed for 12 weeks of at-home treatment. They were to attempt intercourse at least twice a week for the first month. The primary endpoint of the study was the change in the Erectile Function (EF) domain of the International Index of Erectile Function (IIEF) at 12 weeks or the last observation carried forward. Secondary endpoints included safety, the IIEF domains at 12 weeks and earlier time points, the Sexual Encounter Profile (SEP), the Self-Esteem and Relationship (SEAR) Questionnaire, and the Global Assessment Questionnaire (GAQ).

Results: The patients had a mean age of 58 years with a 6-year history of ED. Almost half had severe disease. Most had previously used PDE5 inhibitors. In the Per Protocol group, the mean change in the EF domain of IIEF was: placebo, 2.3; 10 mg, 3.7; 12.5 mg, 5.9; 15 mg, 7.1. The 12.5- and 15-mg groups were statistically significantly different than placebo. Patients with moderate and severe disease had the greatest improvement. Improvements were seen in questions 2 and 3 of the SEP (penetration and maintenance of erection) but none reached statistical significance. The GAQ was statistically significantly improved relative to placebo at all doses. There were dose-related improvements in the effect size for both major and minor domains of the SEAR. The major adverse events leading to discontinuation were nausea, emesis, and blood pressure increases, the latter two required by protocol. The discontinuations were dose-related and ranged from 4% in placebo to 49% in the 15-mg group. Other adverse events occurring more frequent than in placebo were flushing, headache, spontaneous erection, skin darkening, and nasal symptoms. The serious adverse events (SAEs) were a prolonged erection, which resolved without intervention, and an esophageal tear due to vomiting, which resolved with cautery.

Conclusions: Bremelanotide administration improved ED in diabetic patients as measured by a variety of patient-reported outcome measures.

INTRODUCTION

In recent years, molecular and pharmacologic studies have affirmed the role of the melanocortin system in numerous physiological processes, including both male and female sexual function.[1] Melanocortins affect penile erection via mechanisms in the central nervous system, although the precise roles of the spinal and supraspinal pathways in this regulation are not fully understood. This work has led to the development of bremelanotide, a synthetic peptide melanocortin analog of α-melanocyte stimulating hormone (α-MSH).[2] Bremelanotide is an agonist at melanocortin receptor MC4R, that currently under investigation for the treatment of male erectile dysfunction (ED) and female sexual dysfunction.

Induction of significant erectile activity in normal healthy male volunteers following administration of bremelanotide in the absence of visual or tactile stimulation supports the hypothesis that bremelanotide is a central initiator of erectile activity in men. Clinical trials of bremelanotide in ED patients have demonstrated a significant erectile response in the presence of visual sexual stimulation at subcutaneous doses >1 mg and intranasal (IN) doses >7 mg.[3,4] In addition, findings from a 4-week, randomized, double-blind, placebo-controlled study indicated that at-home administration of 10, 15, and 20 mg of IN bremelanotide produced a clinically and statistically significant improvement in erectile function in ED subjects.

Recognizing that patients with diabetes commonly present with ED that may not respond satisfactorily to conventional therapy, this clinical trial was conducted to evaluate the efficacy and tolerability of several doses of bremelanotide in ED subjects with diabetes.

STUDY OBJECTIVES

To evaluate, under the conditions of home use, the efficacy, safety, tolerability, and dose-response characteristics of IN bremelanotide in subjects with ED and type 1 or type 2 diabetes mellitus (DM).

METHODS

Study Design

- Randomized, double-blind, placebo-controlled, Phase IIb clinical trial.
- Study included a 4-week pre-randomization washout period and 12 weeks of at-home treatment.
- Patients were evaluated at baseline, and at 28, 56, and 84 days.
- First dose given in clinic.
- Vomiting and blood pressure increase to greater than 150 mmHg systolic, 100 mmHg diastolic, or 15% from baseline led to mandatory discontinuation.

Figure 1. Study Design

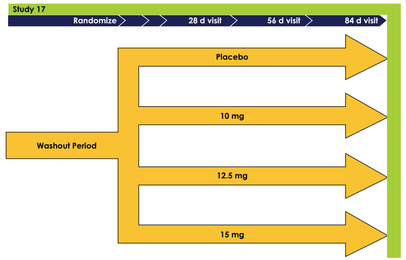


Table 1. Major Entry Criteria

Inclusion	Exclusion
• Age (21 to 70 years)	• Total T less than 2.15 ng/mL
• Stable, monogamous, heterosexual relationship	• Abnormal penile physiology/ pathology
• ED history at least 6 months	• Progressing diabetic retinopathy
• IIEF EF domain score 6–25	• History of:
• Diagnosis of controlled DM (type 1 or type 2)	- Priapism
- HbA1c ≤10%	- Recent MI (less than 90 days)
- <2 episodes of ketoacidosis/year	- CVD, uncontrolled HTN, syncope
- <3 episodes of hypoglycemia/ year	- Ortho hypo- or hypertension
• Discontinue all ED meds, devices, and herbals	- Spinal cord injury
• ≥4 attempts total, ≥1/week during 4-week screening period	- Invasive cancer
• Partner contraception, if needed	- Prostate cancer
	- Psychiatric, liver, or renal disease
	- Obesity (BMI >39)

BMI = body mass index; CVD = cardiovascular disease; ED = erectile dysfunction; EF = Erectile Function; IIEF = International Index of Erectile Function; HTN = hypertension; MI = myocardial infarction

Study Drug

Bremelanotide and matching placebo were supplied as an aqueous formulation that subjects dispensed via an intranasal metered delivery device which delivered 100 µL of liquid.

Figure 2. Intranasal Delivery of Bremelanotide and Matching Placebo

Outcomes

- **Primary Efficacy Outcome:**
  - Mean change from Day 1 (baseline) to Day 84 with last observation carried forward (LOCF) in the Erectile Function (EF) domain score of the International Index of Erectile Function (IIEF) in the per-protocol group
- **Secondary Efficacy Outcomes:**
  - Mean change in the IIEF EF domain score on days 28 and 56.
  - Responses to Sexual Encounter Profile (SEP) question 2 (Were you able to insert your penis into your partner's vagina?) and SEP question 3 (Did your erection last long enough for you to complete intercourse with ejaculation?) at Days 28, 56, and 84.
- **Safety and Tolerability Outcomes:**
  - Treatment-emergent adverse events and clinically significant changes in physical examinations, ECG parameters, vital signs, and clinical laboratory tests.

Statistical Analysis

- Descriptive statistics were calculated for baseline demographics and medical history and all outcome variables. In addition, the change from baseline in the IIEF domain scores were analyzed using the main effects ANCOVA (reduced model with terms for treatment, site, and baseline EF domain score as a covariate) and Dunnett's procedure for pairwise comparisons.
- SEP questions 2 and 3 were analyzed and compared among treatment groups using a logistic regression model, with treatment and site as the main effects, and baseline EF domain score as a covariate.

RESULTS

Table 2. Demographic and Baseline Characteristics of Study Population*

	Placebo (n=82)	Bremelanotide Dose Group 10 mg (n=81)	12.5 mg (n=86)	15 mg (n=45)
Age — yr	58.4±7.5	58.4±7.2	56.9±8.7	58.3±8.5
Weight — lb	216.2±34.8	218.7±37.9	224.8±37.6	212.7±33.7
Height — in	69.8±2.9	70.4±3.4	70.8±3.5	70.3±2.7
Race — no. (%)				
Caucasian	56 (68)	42 (52)	59 (69)	28 (62)
African-American	15 (18)	17 (21)	12 (14)	9 (20)
Hispanic	11 (13)	20 (25)	12 (14)	7 (16)
Asian	0	0	1 (1)	1 (1)
Other	0	2 (2)	2 (2)	0
Age at onset of ED — y	51.0±8.7	52.0±7.2	51.0±9.0	52.3±8.9
Disease severity† — no. (%)				
Mild	17 (21)	17 (21)	19 (22)	9 (20)
Moderate	25 (30)	25 (31)	27 (31)	15 (33)
Severe	40 (49)	39 (48)	40 (47)	21 (47)
IIEF EF domain score	11.9±5.1	12.4±5.6	12.7±5.7	12.2±5.6

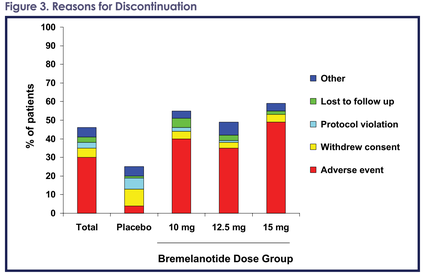
*Plus–minus values are mean ± SD
†Based on IIEF EF domain score: mild = 18–25; moderate = 11–17; severe = 6–10.

Table 3. Patient Disposition

	Total	Placebo	Bremelanotide Dose Group 10 mg	12.5 mg	15 mg
	No. (%)				
Screened	536	--	--	--	--
Randomized	294 (100%)	82 (100%)	81 (100%)	86 (100%)	45 (100%)
Per Protocol*	150 (51%)	56 (70%)	35 (43%)	42 (49%)	17 (38%)
ITT†	250 (85%)	74 (90%)	67 (83%)	73 (85%)	36 (80%)
Safety‡	294 (100%)	82 (100%)	81 (100%)	86 (100%)	45 (100%)
Completed	160 (54%)	62 (76%)	37 (46%)	43 (50%)	18 (40%)

*All randomized subjects who made ≥7 attempts of vaginal intercourse during the 12-week treatment period (including ≥4 attempts during the first 8 weeks of treatment), and who administered study drug for each attempt during the 12-week treatment period, have a baseline and at least 1 post-baseline measurement of the IIEF-EF domain, and completed the study without major protocol violations.
†All randomized subjects who received at least one dose of study drug and who have a baseline and at least one post-baseline measurement of the IIEF-EF domain.
‡All randomized subjects receiving at least one dose of study drug or placebo.

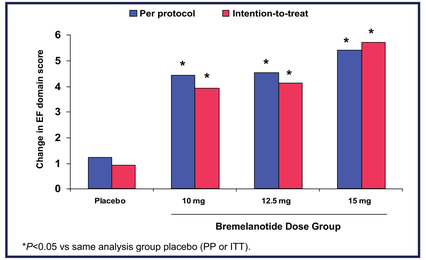
Figure 3. Reasons for Discontinuation



Efficacy of Bremelanotide

All doses of bremelanotide resulted in statistically significant improvements in the EF domain of the IIEF at Day 28.

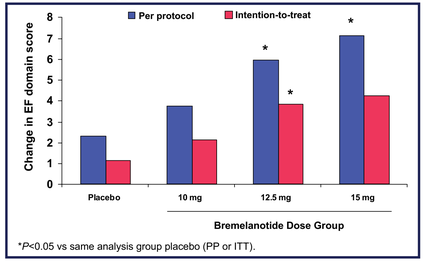
Figure 4. Mean Change from Baseline to Day 28 in EF Domain of IIEF



*P<0.05 vs same analysis group placebo (PP or ITT).

At Day 84 with LOCF, improvements in the EF domain of the IIEF were statistically significant vs placebo in the 12.5-mg dose group (per protocol and ITT analyses) and the 15-mg dose group (per protocol only).

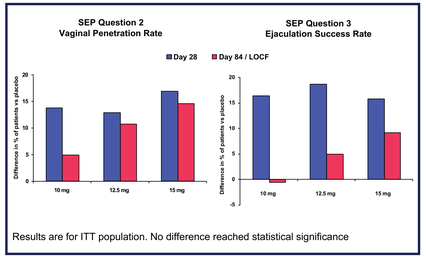
Figure 5. Mean Change from Baseline to Day 84/LOCF in EF Domain of IIEF



*P<0.05 vs same analysis group placebo (PP or ITT).

With the exception of the 10-mg dose group at Day 84, subjects' responses to SEP questions 2 and 3 indicated improvement in vaginal penetration and ejaculation success rates, although the differences vs placebo were not statistically significant.

Figure 6. SEP Questions 2 and 3 Mean Difference vs Placebo



Results are for ITT population. No difference reached statistical significance

Safety and Tolerability Results

In general, bremelanotide was well tolerated at all doses studied.

Table 4. Most Common Adverse Events (Frequency ≥5%)

	Placebo (n=82)	10 mg (n=81)	12.5 mg (n=86)	15 mg (n=45)
At Least 1 AE	37 (45%)	66 (81%)	69 (80%)	39 (87%)
Lacrimation Increase	0	1 (1%)	4 (5%)	0
Nausea	2 (2%)	17 (21%)	26 (30%)	14 (30%)
Vomiting	0	7 (9%)	14 (16%)	9 (20%)
Fatigue	0	4 (5%)	0	0
URI	6 (7%)	9 (11%)	10 (12%)	2 (4%)
Myalgia	0	3 (4%)	0	3 (7%)
Dizziness	2 (2%)	6 (7%)	2 (2%)	5 (11%)
Dysguesia	0	10 (12%)	18 (21%)	7 (16%)
Headache	5 (6%)	13 (16%)	10 (12%)	6 (13%)
Somnolence	0	1 (1%)	2 (2%)	4 (9%)
Spontaneous Erection	0	1 (1%)	6 (7%)	3 (5%)
Nasal Discomfort	1 (1%)	3 (4%)	4 (5%)	9 (20%)
Nasal Congestion	1 (1%)	6 (7%)	8 (9%)	1 (2%)
Rhinorrhea	1 (1%)	4 (5%)	6 (7%)	1 (2%)
Sneezing	0	1 (1%)	4 (5%)	1 (2%)
Skin Hyperpigment.	1 (1%)	4 (5%)	3 (3%)	6 (13%)
Flushing	1 (1%)	17 (21%)	17 (20%)	16 (36%)
Hypertension	3 (4%)	14 (17%)	6 (7%)	6 (13%)

One case of a prolonged penile erection was classified as a serious AE but resolved with conservative therapy. One patient with vomiting had an esophageal tear requiring cautery.

DISCUSSION AND CONCLUSIONS

- Bremelanotide, which acts centrally on melanocortin-4 receptors in the hypothalamus, produced clinically and statistically significant improvements in erectile function in diabetic males for up to 3 months of therapy.
- Adverse events were generally mild to moderate.
- Transient blood pressure increases and nausea / vomiting were dose-related adverse events. The blood pressure increases and vomiting were protocol-mandated reasons for discontinuation.

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