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Evaluation of the safety, pharmacokinetics and pharmacodynamic effects of subcutaneously administered PT-141, a melanocortin receptor agonist, in healthy male subjects and in patients with an inadequate response to Viagra®

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PT-141, a cyclic heptapeptide melanocortin analog, was evaluated following subcutaneous administration to healthy male subjects and to patients with erectile dysfunction (ED) who report an inadequate response to Viagra®. An inadequate response was defined for this study by patient report indicating that achievement of an erection suitable for vaginal penetration occurred ≤50% of the time while taking 100 mg Viagra®. Erectile responses were assessed by RigiScan™ in healthy subjects in the absence of visual sexual stimulation (VSS) and in ED patients in the presence of VSS. Doses ranging from 0.3 to 10 mg were administered to healthy male subjects, resulting in a statistically significant erectile response at doses greater than 1.0 mg. ED patients were treated with placebo, 4 or 6 mg PT-141 in a crossover design in the presence of VSS. The erectile response induced by PT-141 was statistically significant at both doses. PT-141 was safe and well tolerated in both studies. The erectogenic potential of PT-141, its tolerability profile and its ability to cause significant erections in patients who do not have an adequate response to a PDE5 inhibitor suggest that PT-141 may provide an alternative treatment for ED with a potentially broad patient base.
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Introduction

Erectile dysfunction (ED) is associated with a variety of etiologies and/or risk factors, including age, depression, hypertension, diabetes, cardiac disease and benign prostatic hypertrophy. A limited range of medical and surgical treatments are currently available to treat ED.[1] Oral pharmacotherapies, in particular phosphodiesterase type 5 (PDE5) inhibitors,[2–4] are currently recognized as first-line treatments for ED. Sildenafil (Viagra®), the first approved PDE5 inhibitor, has been shown to be effective in 40–80% of patients, depending upon the specific etiology and duration of ED.[5] Patients with a history of pelvic surgery or diabetes mellitus, for example, show a reduced level of response to sildenafil (eg 40–60%).[6–8] Approximately 50% of men who receive a prescription for sildenafil discontinue use of the drug over time.[9] Among other factors, side effects such as headache, flushing and changes in color vision are often cited as reasons for discontinuation of use. Because of the potentiation of hypotension following co-administration of PDE5 inhibitors and organic nitrates, sildenafil is contraindicated in patients taking organic nitrates.

Centrally acting agents have potential as first-line treatments for ED, and might provide additive or synergistic effects given in combination with PDE5 inhibitors.[10] PT-141, a cyclic, heptapeptide melanocortin analog, is an active metabolite of melanotan-II.[11] Results from pharmacological studies demonstrate PT-141 to be an agonist at the melanocortin receptors, including MC3-R and MC4-R,[12] which are primarily expressed in the central nervous system.[13,14]

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An intranasal formulation of the drug has been developed, and the results of Phase 1 and 2A studies in normal volunteers and patients with mild or moderate ED have been reported.[15] The current studies were designed to evaluate the erectogenic potential of subcutaneously (s.c.) administered PT-141 in normal healthy volunteers and in patients with moderate or severe ED who report an inadequate response to Viagra®.

Methods

Study population

Subjects in both studies underwent a complete medical history, physical examination, clinical laboratory tests (including chemistry, hematology, urinalysis and urine drug screen), and a resting 12–lead ECG within 21 days prior to administration of study medication. In the Phase 1 study, eligible subjects were healthy males between 18 and 45 y of age and within 20% of ideal weight, without any history of ED, penile abnormalities or other clinically significant conditions. In the Phase 2A study, eligible patients were adult males between 21 and 55 y of age and within 40% of ideal weight, with a diagnosis of moderate or severe ED as defined by a score of $\leq$16 for the erectile function (EF) domain of the International Index of Erectile Function (IIEF) questionnaire.[16,17] Patients had to report a history of an inadequate response to 100 mg Viagra® within the last 12 months, defined for this study by achievement of an erection suitable for vaginal penetration $\leq$50% of the time while taking Viagra®. Patients could not be current users of Viagra® upon enrollment into the study, and must have discontinued use of Viagra® at least 4 weeks prior to enrollment. Exclusion criteria included ED caused by untreated endocrine disease, anatomic deformations of the penis, prostate cancer or radical prostatectomy, or evidence of clinically significant hepatic, renal, cardiovascular, psychiatric or CNS disease, including stroke or spinal cord injury.

A human ethics committee approved the study protocol and informed consent document for each study prior to the enrollment of research subjects and all subjects gave written informed consent prior to their participation in the study. Both studies were conducted in compliance with a written protocol and applicable FDA regulations and ICH guidelines to insure adherence to Good Clinical Practice standards and regulatory requirements.

Study design and procedures

Study medication. In the Phase 1 study, PT-141 or matching placebo was administered s.c., in the lower right quadrant of the abdomen, in a final volume of 0.3 ml at doses of 0.3, 1.0, 3.0, 5.0, 7.5 and 10.0 mg. Subjects were dosed in the morning following an overnight fast and were kept under observation until 12 h postdose. In the Phase 2A study, PT-141 at doses of 4 or 6 mg, or matching placebo, was administered s.c. in the lower right quadrant of the abdomen, in a volume of 0.3 ml, and patients were kept under observation until 24 h postdose. This was a randomized, double-blind, placebo-controlled crossover design with the constraint that administration of the 4 mg dose preceded administration of the 6 mg dose of PT-141 for each patient.

Pharmacokinetic procedures. Plasma levels of PT-141 were quantified according to a validated HPLC-MS/MS analytical method. Serial blood samples were obtained predose and at 0.25, 0.5, 1, 2, 4, 8 and 12 h postdose in the Phase 1 study, and at 30 min postdose in the Phase 2A study.

Pharmacodynamic procedures. In both studies, penile rigidity and tumescence (erectile response) were measured using the RigiScan™ Plus Rigidity Assessment System (Endocare, Eden Prairie, Minnesota, USA), which continuously measures penile response through displacement of sensor loops at the tip and base of the penis. In the Phase 1 study, erectile response was measured from 30 min predose until 6 h postdose in the absence of VSS. In the Phase 2A study, during each of three visits, scheduled 3–14 days apart, the RigiScan™ device was attached 20 min predose and continuously monitored erectile response until approximately 145 min postdose. VSS was employed during two separate sessions at each visit in the Phase 2A study: from 45 to 75 min postdose and from 95 to 125 minutes post-dose. The primary efficacy end point for both studies was duration of base rigidity $\geq$60%. Secondary end points were duration $\geq$80% base rigidity, $\geq$60 and $\geq$80% tip rigidity, and base and tip rigidity activity units (RAU) and tumescence activity units (TAU). The timing of study procedures in the Phase 2A study is illustrated in Figure 1.

Safety assessments. In the Phase 1 study, vital signs (supine, immediate standing and 2-min standing blood pressure and pulse rate) were evaluated predose, and at 0.25, 0.50, 1, 2, 3, 4, 8 and 12 h postdose. A resting 12-lead ECG was performed predose, 1 h postdose and prior to discharge. In the Phase 2A study, vital signs (sitting, immediate standing and 2-min standing blood pressure and

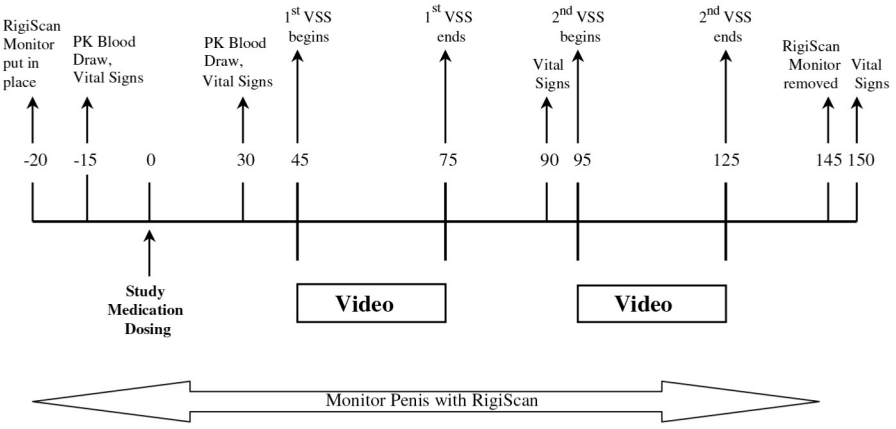

Figure 1 Phase 2A study scheme. ED patients repeated this scheme three times with placebo, 4 or 6 mg PT-141 in a randomly assigned order with the restriction that the 4 mg dose of PT-141 was always administered prior to the 6 mg dose. Preselected videos were viewed during two 30-min sessions. RigiScan™ monitoring occurred from 20 min predose until 145 min postdose.

pulse rate) were measured predose, 90 and 150 min postdose, and prior to discharge (approximately 24 h postdose). A resting 12-lead ECG was performed at the Screening Visit and prior to discharge from the study. For both studies, blood and urine were obtained for clinical safety laboratory tests (chemistry, endocrinology, hematology and urinalysis), and a physical exam was performed predose and prior to discharge from the study. Clinically significant vital sign changes were defined by an absolute value of <85 or >180 mmHg sitting systolic blood pressure, or a change, compared to predose values, of >30 mm Hg; an absolute value of <45 or >110 mmHg sitting diastolic blood pressure, or a change, compared to predose values, of >20 mm Hg; an absolute pulse rate of <50 or >120 bpm, or a change, compared to predose values, of >30 bpm.

Pharmacokinetic and statistical analyses. Pharmacokinetic measurements were analyzed using noncompartmental models. The area under the drug concentration curve from zero to the last postdose quantifiable plasma concentration level ($AUC_{(0\text{-}t)}$), maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}) and apparent half–life ($t_{1/2}$) were calculated for plasma PT-141 concentration data using nonparametric methods with WinNonlin, Version 3.2 (Pharsight Corporation, Mountain View, California, USA).

The total duration of erections with ≥ 60 and $\geq 80\%$ rigidity at the base and tip of the penis was calculated, and sustained erectile activity (RAU and TAU) were determined using the RigiScan™ software. The pharmacodynamic effect of PT-141 was analyzed using a one-way analysis of variance. Comparisons between PT-141 doses and placebo were made using least square means and a one-tailed t-test when applying either analysis of variance (ANOVA) or mixed effect models.

For the Phase 2A study, total duration of erections with ≥ 60 and $\geq 80\%$ rigidity at the base and tip of the penis, as well as RAU and TAU were analyzed using ANOVA. The mixed effect model was employed to evaluate the effect of treatment, sequence (treatment path) and period (visit).

Safety was assessed through monitoring of vital signs, physical exams, laboratory data, ECG evaluations and reported adverse events (AEs). These data were summarized for all subjects receiving each dose of PT-141 or placebo. Statistical analyses were carried out using SAS, Version 6.12 or 8.0 (SAS Institute, Cary, North Carolina, USA).

Results

Subjects

Subject demographic characteristics for both studies are summarized in Table 1. In the Phase 1 study, 48 eligible male subjects received a single dose of PT-141 (six subjects per dose level) or matching placebo (two subjects per dose level). Dose groups were comparable for both mean and range with respect to age, weight, height and race (data not shown).

In the Phase 2A study, eligible male patients with ED received 4 and 6 mg of PT-141 and matching placebo in a three-way crossover design. All patients received the 4 mg dose of PT-141 prior to the 6 mg dose. All patients had a documented diagnosis of ED of at least 6 months duration, with no assessment of causality, and reported a history of an inadequate response to 100 mg Viagra®. The mean of the individual responses to Viagra® was 25%, such that, on average, Viagra® allowed patients in this

Table 1 Demographic and baseline parameters for subjects enrolled in the Phase 1 and Phase 2A studies

	Phase 1 study (healthy males)		*Phase 2A study (ED patients)*
Parameter	*PT-141* N = *36*	*Placebo* N = *12*	N = *25*
Age (y)			
Mean (s.d.)	33.6 (7.9)	31.7 (5.8)	48 (5)
Range	19–44	23–42	37–54
Race, *n* (%)			
White	11 (30.5%)	4 (33.3%)	19 (76%)
Black	18 (50.0%)	7 (58.3%)	5 (20%)
Hispanic	6 (16.7%)	1 (8.3%)	1 (4%)
Other	1 (2.8%)	0 (0%)	0 (0%)
Weight (kg)			
Mean (s.d.)	79.2 (11.7)	82.8 (8.9)	97.4 (17.9)
Range	56.8–100	68.2–96.4	63.6–129.4
Height (cm)			
Mean (s.d.)	175.8 (7.1)	178.3 (8.1)	180 (9.1)
Range	161.3–191.8	165.1–190.5	162.6–208.3
ED duration (yrs)			
Mean (s.d.)	N/A	N/A	8 (4.8)
Range			2–22
IIEF EF score	N/A	N/A	
Mean (s.d.)			11.16 (3.82)
Range			5–16
Comorbidities			
Smoking	0 (0%)	0 (0%)	11 (42%)
Diabetes mellitus	0 (0%)	0 (0%)	2 (8%)
Hypertension	0 (0%)	0 (0%)	7 (29%)
Hyperlipidemia	0 (0%)	0 (0%)	3 (12%)

study to achieve an erection sufficient for intercourse approximately once for every four times the medication was taken and sexual intercourse attempted. Comorbidities included smoking, diabetes mellitus, hypertension and hyperlipidemia. The mean IIEF EF score for enrolled patients was 11.3 (range 5–16), consistent with a diagnosis of moderate (EF score 11–16) or severe (EF score 6–10) ED.[17]

Pharmacokinetics

In the Phase 1 study, administration of PT-141 resulted in a dose-dependent increase in PT-141 plasma concentration levels (Figure 2). Median T_{max} ranged from 0.50 to 1.0 h, and mean $AUC_{(0-t)}$ increased in a dose-dependent manner from 42 to 878 ng · h/mL. Mean half-life ($t_{1/2}$ values for PT-141 ranged from 1.9 to 2.7 h. C_{max} but not $AUC_{(0-t)}$ values appeared to reach a plateau at the 7.5 mg dose level.

A previous RigiScan™ study that evaluated the pharmacodynamic effect of intranasal (IN) PT-141 demonstrated that 20 mg IN PT-141 induced significant erectile activity in Viagra®-responsive ED patients.[15] The 20 mg dose of IN PT-141 resulted in a mean C_{max} of 141 ng/ml, which is slightly lower than the mean C_{max} measured after administration of 5 mg s.c. PT-141 (161 mg/ml). The selection of the 4 and 6 mg doses for this study was predicated on the expectation that 4 mg s.c. PT-141 would approximate the mean C_{max} achieved with 20 mg IN PT-141, and that higher levels might be required in patients who report an inadequate response to PDE5 inhibitors. Mean PT-141 plasma levels in ED patients dosed with 4 or 6 mg s.c. PT-141 were 81 and 114 ng/ml, respectively, at approximately 30 min postdose.

Pharmacodynamic effect

In the Phase 1 study, the administration of PT-141 at doses of 1 mg and above resulted in a significantly

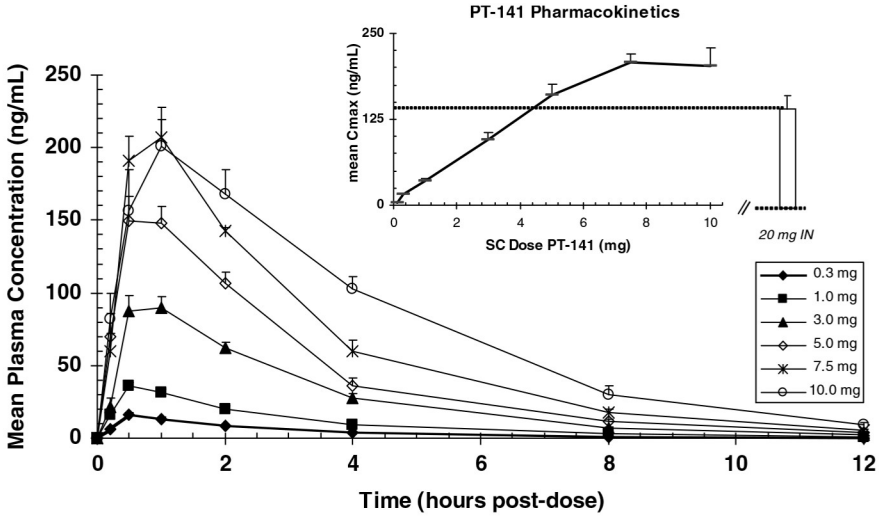

Figure 2 PT-141 pharmacokinetics. Time course of the mean (standard error) PT-141 plasma concentrations after single s.c. doses of 0.3–10 mg of PT-141. Inset: Mean (standard error) C_{max} of PT-141 plasma concentrations at doses of 0.3–10 mg of PT-141, and mean (standard error) C_{max} after intranasal administration of 20 mg of PT-141 (bar).[15]

greater duration of base rigidity ≥60% compared to placebo (Figure 3, Table 2). The effect of the 0.3 mg dose was indistinguishable from placebo and can be considered a no effect dose. Mean duration of base rigidity ≥60% increased from 49 to 234 min for subjects receiving the 1.0–10.0 mg PT–141 doses, respectively, compared to 14 min for subjects receiving placebo. It is noteworthy that this dose-dependent pharmacodynamic effect was observed in healthy males in the absence of VSS.

The time to onset of the first erection, defined by at least 3 consecutive minutes of ≥60% base rigidity, decreased with the 1.0–10 mg doses of PT-141, and first erections occurred approximately 37 min after administration of 10.0 mg PT-141 (Figure 3, inset).

In the Phase 2A study, a clinically and statistically significant erectile response was observed in ED patients, in the presence of VSS, following single doses of PT-141 relative to placebo (Figure 4, Table 2). Mean durations of ≥60% base rigidity were 28 and 41 min for patients receiving the 4 and 6 mg PT–141 doses, respectively, compared to 6 min for patients receiving placebo. Mean durations of base rigidity at ≥80% were 14 and 17 min for patients receiving the 4 and 6 mg PT–141 doses, respectively, compared to 2 min for patients receiving placebo. A greater than two-fold increase in the duration of base rigidity ≥60%, compared to the response of individual patients to placebo, was observed in 82 and 84% of ED patients who received 4 or 6 mg of PT-141, respectively (data not shown).

Analysis of severe ED patients. A total of 10 patients in this study were characterized as having severe ED, based upon an IIEF EF score of 6–10.[17] Analysis of this subgroup revealed that administration of 6 mg PT-141 resulted in a mean duration of ≥60 and ≥80% base rigidity of 36 and 15 min ($P<0.01$), respectively, compared to 8 and 2 min after administration of placebo (Figure 5).

Safety and tolerability

Single doses up to 10 mg (healthy male subjects) and 6 mg (ED patients) of PT-141 were safely administered and well tolerated. In the Phase 1 study, the most common AEs reported in >5% of healthy males receiving 5, 7.5 or 10 mg of PT-141 were flushing, somnolence, nausea, vomiting and headache (Table 3). With the exception of flushing, no AEs were observed in subjects in the 0.3–3 mg dose groups. Vomiting, identified as the dose-limiting

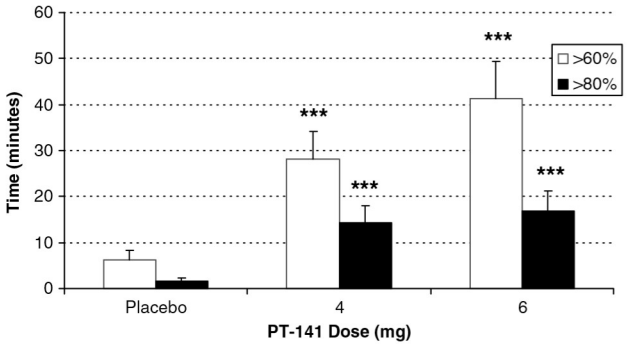

Figure 4 Base rigidity ≥60% or ≥80% in ED patients after s.c. administration of PT-141. Duration of base rigidity ≥60% or ≥80% in patients with moderate or severe ED treated with 4 ($n=24$) or 6 mg ($n=21$) PT-141 during a 2.5 h RigiScan™ monitoring session. *$P<0.05$; **$P<0.01$; ***$P<0.001$, compared to placebo.

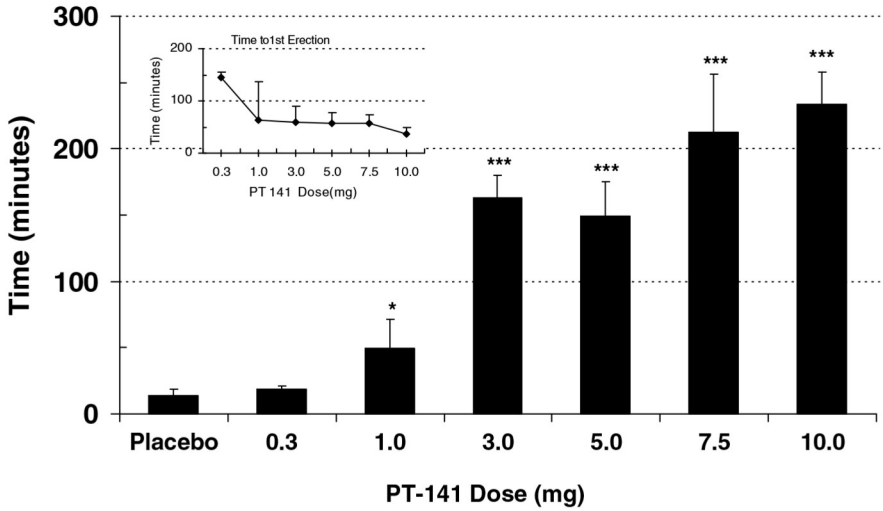

Figure 3 Base rigidity ≥60% in normal volunteers after s.c. administration of PT-141. Duration of base rigidity ≥60% in normal healthy males treated with 0.3–10 mg PT-141 during a 6.5 h RigiScan™ monitoring session. Inset: Time to detection of the first erectile event that was measured at ≥60% base rigidity and persisted for at least 3 consecutive minutes. *$P<0.05$; **$P<0.01$; ***$P<0.001$, compared to placebo.

Table 2 Base and tip RigiScan™ pharmacodynamic parameters following single dose s.c. PT-141 administration

	Phase 1 study (healthy males)							*Phase 2A study (ED patients)*			
	PT-141 (mg)							*PT-141 (mg)*			
	Placebo N = 12	*0.3* N = 6	*1.0* N = 6	*3.0* N = 6	*5.0* N = 6	*7.5* N = 6	*10.0* N = 6	*Placebo* N = 23	*4.0* N = 24	*6.0* N = 21
Base										
Duration of rigidity ≥60% (min)	13.8 (4.8)	18.3 (2.2)	49.1 (22.6)*	163.3 (16.1)***	149.4 (25.6)***	212.7 (44.7)***	233.6 (22.4)***	6.2 (2.0)	28.2 (6.0)***	41.2 (8.2)***
Duration of rigidity ≥80% (min)	5.8 (3.1)	4.3 (1.4)	18.4 (12.5)	26.8 (12.7)*	50.5 (29.2)*	106.2 (29.2)***	73.4 (42.7)**	1.6 (0.6)	14.3 (3.7)***	16.8 (4.5)***
RAU (units)	22.3 (5.5)	24.5 (5.7)	56.0 (16.3)**	118.7 (22.4)***	140.2 (19.5)***	184.8 (29.9)***	202.2 (18.0)***	8.8 (2.1)	29.1 (4.6)***	41.4 (5.9)***
TAU (units)	17.9 (4.1)	17.5 (3.4)	36.8 (8.9)**	79.3 (13.9)***	95.2 (9.9)***	99.0 (15.0)***	113.4 (9.0)***	6.5 (1.8)	17.8 (2.8)***	27.2 (3.9)***
Tip										
Duration of rigidity ≥60% (min)	9.8 (3.3)	7.42 (2.8)	25.9 (10.6)*	139.9 (34.0)***	123.9 (25.6)***	190.2 (48.8)***	184.4 (26.3)***	4.2 (1.5)	18.5 (5.1)**	24.1 (5.8)***
Duration of Rigidity ≥ 80% (min)	1.8 (0.8)	0.3 (0.3)	13.1 (9.2)*	47.5 (25.4)***	27.4 (11.1)***	65.4 (38.1)**	59.9 (2.2)***	0.4 (0.2)	4.6 (1.8)*	8.2 (3.2)**
RAU (units)	14.4 (4.2)	16.2 (3.1)	40.0 (9.7)**	115.2 (29.0)***	127.7 (18.6) ***	168.3 (32.1)***	171.3 (16.8)***	6.8 (1.8)	22.9 (3.7)***	33.4 (5.0)***
TAU (units)	11.3 (3.2)	14.7 (3.9)	26.0 (5.2)**	90.7 (22.5)***	98.3 (13.3)***	111.3 (15.1)***	97.5 (20.5)***	5.1 (1.4)	16.6 (2.6)***	28.0 (3.5)***

Arithmetic mean (standard error) of rigidity and tumescence data at the base and tip of the penis following single-dose administration of placebo or PT-141 to healthy male subjects (Phase 1 Study) and to ED patients (Phase 2A Study). *$P<0.05$; **$P<0.01$; ***$P<0.001$, compared to placebo.

Figure 5 Base rigidity ≥60% or ≥80% in patients with severe ED after s.c. administration of PT-141. Duration of base rigidity ≥60 or ≥80% in patients with severe ED (IIEF EF score 6–10) treated with 4 ($n=11$) or 6 mg ($n=9$) PT-141 during a 2.5 h RigiScan™ monitoring session. *$P<0.05$; **$P<0.01$; ***$P<0.001$, compared to placebo.

toxicity of s.c. PT-141, occurred 6–10 h postdose in one subject each receiving 5.0 and 7.5 mg PT-141, and 6–15 h after administration of 10 mg of PT-141 in three subjects. Vomiting either subsided without intervention (three subjects) or responded to ondansetron, a $5HT_3$ antagonist (two subjects). Compared to pre-dose values, no clinically significant changes in blood pressure, heart rate or ECG evaluations were observed.

In the Phase 2A study, the most common AEs (>5%) following the PT-141 4 and 6 mg dose were nausea, headache, flushing, diaphoresis, lower back pain and vomiting (Table 3). One patient at the 4 mg and one patient at the 6 mg dose experienced vomiting, and one patient experienced vomiting at both doses. Vomiting was delayed 7–9 h postdose, similar to what was observed in the Phase 1 study. Two patients previously diagnosed with hypertension experienced transient and asymptomatic exacerbation of hypertension, evidenced by an increase in sitting systolic blood pressure, after administration of 4 mg PT-141, with no sequelae. One patient's blood pressure reached 193/102 and the other patient had a blood pressure of 186/103 at the 150 and 90 min post-dose evaluations, respectively. The former patient was noncompliant, as he was not taking antihypertensive medication, and this patient also experienced an increase in systolic blood pressure after placebo administration. ECG evaluations and heart rate remained normal for both patients. Among all patients, changes in mean sitting systolic/diastolic blood pressures during the 30–150 min postdose period were −6.0/−0.5, +4.7/+4.5 and +4.3/+5.5 mmHg for placebo, 4 and 6 mg doses of PT-141, respectively. No evidence of hypotension was observed in any patient, and no other clinically significant changes in blood pressure, heart rate or ECG evaluations were observed during the study.

No clinically relevant changes were noted in endocrine status, clinical chemistry, hematology,

Table 3 Summary of AEs that occurred in greater than 5% of subjects following single-dose administration of placebo, 5, 7.5 or 10 mg PT-141 to healthy male subjects (Phase 1 study) and placebo, 4 and 6 mg PT-141 to ED patients (Phase 2A study)

	Placebo 1 study				*Placebo 2A study*		
AE (MedDRA term)	*Placebo* n = *14* n *(%)*	*5 mg* n = *6* n *(%)*	*7.5 mg* n = *6* n *(%)*	*10 mg* n = *6* n *(%)*	*Placebo* n = *24* n *(%)*	*4 mg* n = *25* n *(%)*	*6 mg* n = *22* n *(%)*
Nausea	0 (0%)	1 (16.7%)	0 (0%)	2 (33.3%)	0 (0%)	6 (24.0%)	8 (36.4%)
Headache	1 (7.1%)	1 (16.7%)	0 (0%)	1 (16.7%)	0 (0%)	9 (36.0%)	6 (27.3%)
Vomiting	0 (0%)	1 (16.7%)	1 (16.7%)	3 (50.0%)	0 (0%)	2 (8.0%)	2 (9.1%)
Back pain	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4.0%)	2 (9.1%)
Diaphoresis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (8.0%)	2 (9.1%)
Flushing	1 (7.1%)	1 (16.7%)	2 (33.3%)	2 (33.3%)	0 (0%)	1 (4.0%)	2 (9.1%)
Fatigue	0 (0%)	1 (16.7%)	0 (0%)	0 (0%)	0 (0%)	2 (8.0%)	0 (0%)
Muscle cramps	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4.0%)	2 (9.1%)

urinalysis or physical examination in either study. No subjects experienced a serious AE in either study, and no subjects discontinued participation due to an AE in the Phase 1 study. One patient in the Phase 2A study withdrew consent and was replaced. Due to RigiScan™ equipment failures, five patients required an additional VSS/RigiScan™ visit, and scheduling difficulties resulted in an unacceptable time lapse between visits, the result of which is that the study was terminated prior to three patients completing all visits.

Discussion

PT-141 is a synthetic peptide analog of α-melanocyte-stimulating hormone (α-MSH). In the central nervous system, melanocortins affect multiple physiological responses, including sexual behaviors.[18] Effects of α-MSH on sexual behaviors, such as yawning, grooming, stretching and penile erections, have been observed in laboratory animals, and it is believed to act downstream from dopamine and oxytocin in hypothalamic centers adjacent to the third ventricle.[19–21] The central mechanism of action of PT-141 is inferred by the localization of its target receptors, and by results of animal studies showing enhanced expression of c-*fos* in regions of the brain associated with sexual responses after peripheral administration of PT-141, as well as increased erectile activity when PT-141 is introduced via intracerebroventricular injection at levels that are substantially lower than an effective dose of peripherally administered PT-141.[12]

RigiScan™ analysis of normal healthy male volunteers demonstrated significant erectile activity, in the absence of VSS, with doses greater than 1.0 mg PT-141. Induction of erections in normal healthy males, in the absence of stimulation, while consistent with our previously reported evaluation of intranasally administered PT-141,[15] is a unique finding with respect to most ED therapies and supports the concept that PT-141 initiates, rather than facilitates, erectile activity. Furthermore, administration of either 4 or 6 mg s.c. PT-141, in the presence of VSS, to patients with moderate or severe ED who report an inadequate response to Viagra®, resulted in a significant erectile response as compared to the placebo response.

For study inclusion, patients were required to score ≤ 16 on the EF domain of the IIEF questionnaire, and have a history of an inadequate response to Viagra®, defined by patient report that during the past 12 months, after taking Viagra®, they were able to attain an erection sufficient for vaginal penetration no more than 50% of the time. The average success rate for patients enrolled in this study was 25%. There was not a requirement regarding duration of the period during which Viagra® was tried, nor was the nature of the patient's response, or whether they were appropriately counseled to achieve maximum effectiveness of Viagra®, investigated. No direct comparisons were made in this study between PT-141 and other ED medications.

Most AEs were mild and self-resolving, and, with the exception of vomiting, the frequencies of specific AEs did not increase significantly with increasing doses of s.c. PT-141. Vomiting, identified as the dose-limiting toxicity of s.c. PT-141, was delayed by 6–15 h after s.c. administration of PT-141 and may be correlated with the prolonged systemic exposure of PT-141 after s.c administration as compared to intranasal administration. Flushing, which was transient and cephalic in nature and was not accompanied by blood pressure changes, occurred at a similar frequency at all dose levels. Nausea and headache were the most common AEs reported by ED patients receiving either 4 or 6 mg PT-141. Administration of doses ranging from 5 to 10 mg of PT-141 did not result in a similar incidence of nausea and headache in normal healthy volunteers. The disparity in the AE profiles of the two studies may be a reflection of their slightly different population demographics, particularly with respect to age and comorbidities. Two ED patients who had

been previously diagnosed with hypertension, one of whom was noncompliant, exhibited transient asymptomatic increases in systolic blood pressure, with no sequelae, after administration of 4 mg PT-141. As a similar response was observed in one of these patients after placebo treatment, it is likely that sympathetic nervous system activation, in response to VSS and/or to attainment of erectile activity, may have contributed to this temporary increase in systolic blood pressure.

The incidence of treatment-refractory ED patients (ie, nonresponsive to PDE5 inhibitor therapy) is likely to increase in importance as the number of men beginning ED treatment increases in the coming years.[22] Second-generation PDE5 inhibitors, which may provide greater specificity and potency, and/or longer duration of action, have shown promising results in clinical trials.[3,4] However, the vasodilatory effects of PDE5 inhibitors result in contraindication in patients taking organic nitrates or alpha-blockers.

We have previously reported that 20 mg intranasal PT-141 can induce a significant erectile response in Viagra®-responsive ED patients who are unable to sustain an erection $\geq$60% base rigidity for more than 3 consecutive minutes while viewing VSS after placebo administration.[15] This finding led to investigation of the potential of PT-141 to induce erectile activity in treatment-refractory ED patients. SC administration of PT-141 was chosen for this proof-of-principle study based upon the assumption that treatment-refractory ED patients would require higher exposure levels than achieved by 20 mg IN PT-141, the highest dose evaluated to date. In fact, the systemic exposure offered by s.c. administration may not be necessary, as a highly significant response ($P<0.001$) was achieved with the 4 mg SC dose, which results in a C_{max} approximately equivalent to the C_{max} of the 20 mg intranasal dose of PT-141. The drug was shown to be safe and highly effective in initiating erections, even in patients with severe ED. Future studies will evaluate the efficacy of PT-141 as a combination therapy with PDE5 inhibitors to determine whether the initiator activity of PT-141 will supply an additive or synergistic effect to the facilitating function of PDE5 inhibitors. The first large-scale, at-home evaluation of intranasal PT-141 is currently underway. This study will determine the safety and efficacy of PT-141 in a relevant sexual context.

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