



Platinum Priority – Sexual Medicine

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A Randomized Double-Blind, Placebo-Controlled Multicenter Study to Evaluate the Efficacy and Safety of Two Doses of the Tramadol Orally Disintegrating Tablet for the Treatment of Premature Ejaculation Within Less Than 2 Minutes

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Abstract

Background: Premature ejaculation (PE) is a widely observed male sexual dysfunction with a major impact on quality of life for many men and their sexual partners.

Objective: To assess the safety of tramadol orally disintegrating tablet (ODT) (Zertane) and its efficacy in prolonging intravaginal ejaculation latency time (IELT) and improving Premature Ejaculation Profile (PEP) scores.

Design, setting, and participants: We conducted an integrated analysis of two identical 12-wk randomized double-blind, placebo-controlled phase 3 trials across 62 sites in Europe. Healthy men 18–65 yr of age with a history of lifelong PE according to the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision*, and an IELT ≤ 120 s were included. There were 604 intent-to-treat subjects included in the analysis.

Intervention: Subjects were randomized to receive 1:1:1 placebo ($n = 200$), 62 mg tramadol ODT ($n = 206$), or 89 mg tramadol ODT ($n = 198$).

Measurements: We measured overall change and fold increase in median IELT and the mean change in all four measures of the PEP. Differences across treatment groups were analyzed using Wilcoxon rank-sum tests, analysis of variance, and chi-square analyses.

Results and limitations: Tramadol ODT resulted in significant increases in median IELT compared with placebo; increases were 0.6 min (1.6 fold), 1.2 min (2.4 fold), and 1.5 min (2.5 fold) for placebo, 62 mg tramadol ODT, and 89 mg tramadol ODT, respectively ($p < 0.001$ for all comparisons). Men saw significantly greater improvement in all four measures of the PEP in both doses compared with placebo ($p < 0.05$ for all comparisons). Tramadol ODT was well tolerated; study discontinuation occurred in 0%, 1.0%, and 1.6% of subjects in placebo, 62 mg, and 89 mg tramadol ODT groups, respectively. Limitations include study inclusion for men with IELT up to 120 s.

Conclusions: On-demand 62 mg tramadol ODT is an effective treatment for PE in a low and safe therapeutic dose and provides a new option for managing mild to severe PE.
Trial registration: ClinicalTrials.gov identifiers NCT00983151 and NCT00983736; <http://clinicaltrials.gov/>.

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1. Introduction

Premature ejaculation (PE) is a widely observed male sexual dysfunction with an estimated prevalence between 2% [1] and 23% [2]. Studies have shown that PE is associated with poor satisfaction with sexual intercourse and high levels of ejaculation-related personal distress and interpersonal difficulty [3–5].

The several proposed pharmacotherapies for the treatment of PE include topical agents, creams, sprays, and systemic therapies [6]. Dapoxetine (Priligy, Janssen-Cilag) is currently the only approved oral drug to treat PE. On-demand tramadol hydrochloride (HCl) has shown promise in the treatment of PE; a small placebo-controlled study reported that tramadol HCl significantly increased intravaginal ejaculation latency time (IELT) compared with placebo [7]. Tramadol HCl was initially developed in the 1970s and approved by the US Food and Drug Administration as an analgesic for the US market in 1995 and has an excellent safety record established over >30 yr of human use. Recently a new orally disintegrating tablet (ODT) formulation of tramadol HCl, tramadol ODT (Zertane), has shown safety and efficacy for the treatment of PE in unpublished randomized phase 2 clinical trials.

Although the mechanism by which tramadol ODT delays ejaculation has not been identified, numerous laboratory studies have shown that tramadol acts as a mild μ -opioid agonist [8,9], N-methyl-D-aspartate receptor antagonist [10], 5-hydroxytryptamine type 2C receptor antagonist [11], 5 nicotinic acetylcholine receptor antagonist [12], M1 and M3 muscarinic acetylcholine receptor antagonist [13,14], and a serotonin and norepinephrine modulator [8]. It is possible that one or a combination of these effects leads to a delay in ejaculation.

The objectives of the study were to evaluate the efficacy of two dosages of tramadol ODT in delaying the IELT, improving satisfaction with sexual intercourse and control over ejaculation, and decreasing ejaculation-related personal distress and interpersonal difficulty. The secondary objective was to evaluate the safety and tolerability of tramadol ODT when given to delay ejaculation.

2. Patients and methods

2.1. Subjects

Healthy men aged 18–65 yr with a history of lifelong PE who met the criteria in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision (DSM-IV-TR [15]) and had a stable, monogamous, heterosexual relationship with a duration >6 mo were eligible for the study. At the time of study enrollment, the DSM-IV-TR definition was the only available and accepted definition for PE. A new proposed definition of PE was published by the International Society for Sexual Medicine (ISSM) in 2009 [16] and more recently in 2010 [17] that defines lifelong PE as “ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration.” Eligibility for continuation in the study was based on the diary-documented IELT stopwatch results of at least three events of sexual intercourse during the screening period showing a baseline median IELT of ≤ 120 s. The population baseline median IELT was <60 s in each treatment arm.

Exclusion criteria included PE attributable to situational issues, evidence/history of other psychiatric disorders requiring therapy/medication, suicide risk, physical illnesses (14 listed illnesses), other sexual dysfunction including erectile dysfunction as defined by the DSM-IV-TR criteria, sexual intercourse usually less than once per week, partner sexual dysfunction, current use of dapoxetine or tramadol, sensitivity to phenylketone, history of abuse of prescription or illegal addictive drugs, or use of medication within 30 d of screening with potential to cause sexual dysfunction.

2.2. Study design

This randomized double-blind, placebo-controlled multicenter study consisted of an initial 3-wk screening period (baseline), a 3-wk single-blind placebo lead-in-period, and a 12-wk double-blind treatment period (double blind). Patients were enrolled between August 2009 and October 2010 across 62 clinical sites from the following 11 countries: Austria, Belgium, Bulgaria, Czech Republic, France, Germany, Hungary, Poland, Romania, Spain, and Sweden. The trials are registered at ClinicalTrials.gov with identifiers NCT00983151 and NCT00983736.

During the treatment phase, subjects were randomized in a 1:1:1 ratio to receive placebo, 62 mg tramadol ODT, or 89 mg tramadol ODT. We previously performed a bioequivalence study that showed tramadol ODT is equivalent to tramadol HCl, as well as a phase 2 dose-ranging study that examined dose-related efficacy and tolerability/adverse events (AEs); all three dosages studied had some effect on PE; however, the highest dose (120 mg) was the least tolerated. The doses 62 mg and 89 mg were chosen to maximize the ability to demonstrate a treatment effect while minimizing the incidence of AEs.

2.3. Subject instructions

Subjects were instructed to take study medication 2–8 h before engaging in vaginal intercourse, with an interval between sexual intercourse events of at least 20 h to ensure washout of the drug and its effect. Female partners were instructed to time the IELT for each event by using the provided stopwatch and recording the time in a study diary. Subjects returned to the study site every 3 wk between visit 1 (screening) and visit 7 (week 18, end of double-blind period), at which time IELT, Premature Ejaculation Profile (PEP) scores, vital signs, and AEs were recorded.

2.4. Efficacy end points

Data from both studies are reported here as an integrated analysis, defined a priori. Efficacy analyses were performed in the intent-to-treat (ITT) population, which consisted of study participants who were randomized and received at least one dose of the study medication and had IELT and PEP data for at least one visit during the double-blind treatment period (Fig. 1). We defined a priori two coprimary end points: IELT and PEP measures. The coprimary end points of IELT and PEP were chosen to demonstrate a prolonged time to ejaculation (IELT) and that this prolongation is clinically meaningful (significant improvements in PEP subscores).

The sample size estimate was based on coprimary end points of IELT and PEP. A total of 825 subjects per study provided 90% power at a two-sided 0.025 type error to detect a 0.70 (standard deviation: 2.43) min difference in IELT and a 15% improvement in PEP score. The licensee sponsor was acquired by another company whose focus was not on sexual dysfunction; due to this refocused business strategy, the trial was closed early after enrollment and randomization of 677 subjects. This decision was not based on safety or efficacy because the sponsor did not have knowledge of the study's results.

IELT is defined as the time from vaginal penetration to ejaculation in the vagina. All previously published phase 3 studies of on-demand oral

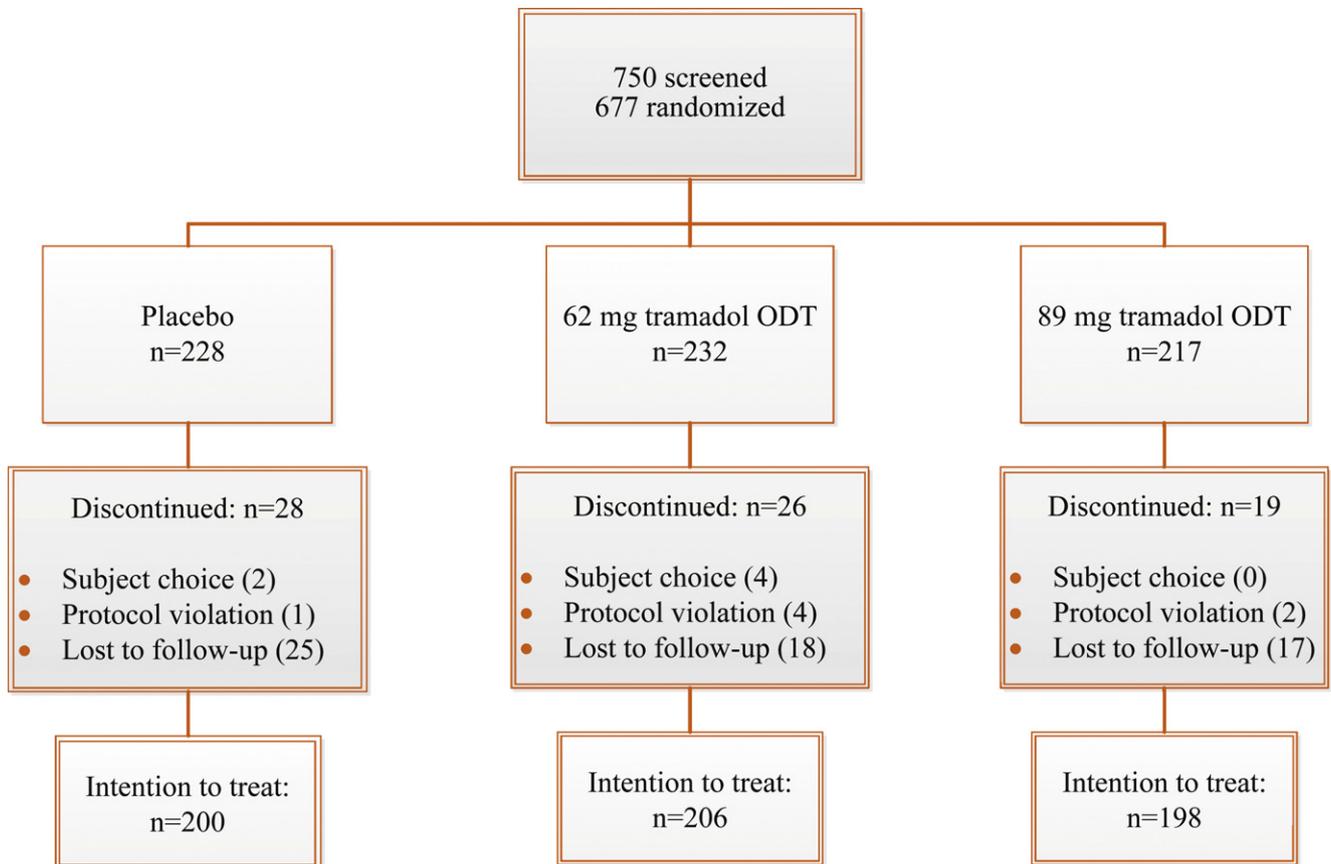


Fig. 1 – Subject distribution by treatment group.

treatment for PE calculated the arithmetic mean IELT per subject visit and reported differences in either arithmetic mean or geometric mean per treatment group [7,18–21]. Waldinger and colleagues cautioned researchers against calculating arithmetic mean IELT to summarize data of individuals or group results because it could overestimate the treatment effect [22]. We examined median IELT per subject and per treatment group because IELT is highly positively skewed and the median is a nonparametric summary statistic that makes no assumption about the underlying distribution.

The PEP is a validated self-report questionnaire used to assess the four measures of PE defined by the DSM-IV-TR [23]: satisfaction with sexual intercourse, control over ejaculation, ejaculation-related distress, and interpersonal difficulty. Each measure regarding ejaculation is scored on a 5-point scale. Criteria for clinical benefit were defined as achieving a two-category or greater increase in the change in control over ejaculation and a one-category or greater increase in the change in ejaculation-related distress at the study end point compared with baseline values [18–20].

Female partners also completed the PEP at each visit; questions related to the woman's satisfaction with intercourse, ejaculation-related distress, and interpersonal difficulty, as well as her perception of the man's control over ejaculation.

2.5. Safety

AEs, concomitant drug use, and vital sign measurements were recorded at all visits. All treatment-emergent adverse events (TEAEs) were recorded by system organ class, severity, and relation to study medication. All AEs occurring in at least 1% of subjects and AEs leading to withdrawal were tabulated. No safety data were imputed.

2.6. Statistical analysis

Statistical analyses were performed using SAS software, v.9.2 (SAS Institute, Cary, NC, USA). We performed all statistical analyses in the ITT population (using the study protocol definition based on the DSM-IV-TR), as well as in the subset of subjects with baseline IELT ≤ 1 min (based on the newly proposed ISSM definition), defined a priori.

The median change in IELT was calculated as the absolute change (double-blind median IELT minus baseline median IELT) and the fold change (double-blind median IELT divided by baseline median IELT). Median differences in the absolute and fold changes in median IELT between treatment groups were analyzed using Wilcoxon rank-sum tests ($p < 0.05$, with Bonferroni corrected p values of 0.025). Based on the study protocol, we also analyzed mean differences between treatment groups in the absolute and fold change in median IELT using an analysis of variance (ANOVA) model; to control family-wise (type I) error we performed pairwise tests based on a priori hypotheses.

The mean change for individual PEP questions was normally distributed. Differences between treatment groups were analyzed using ANOVA; a multiple test procedure with a priori hypotheses was used to control for family-wise error. Differences between treatment groups in the proportion of patients who achieved a one category or greater improvement and in the proportion of patients who achieved criteria for clinical benefit were analyzed using two separate Pearson chi-square tests (62 mg vs placebo, and 89 mg vs placebo) with $p < 0.05$ (Bonferroni corrected p values of 0.025).

We reported the IELT and PEP differences from baseline using data from all of the double-blind treatment period instead of using the last observation carried forward approach because the treatment effect was

Table 1 – Baseline demographic and clinical characteristics

Characteristic	Placebo (<i>n</i> = 200), % (<i>n</i>)	Tramadol ODT 62 mg (<i>n</i> = 206), % (<i>n</i>)	Tramadol ODT 89 mg (<i>n</i> = 198), % (<i>n</i>)
Age, yr, mean (SE)	35.5 (0.78)	36.8 (0.77)	36.1 (0.75)
White, % (<i>n</i>)	97.0 (194)	98.1 (201)	99.0 (196)
Region, % (<i>n</i>)			
Western Europe [*]	35.5 (66)	33.9 (63)	30.6 (57)
Eastern Europe ^{**}	32.1 (134)	34.2 (143)	33.7 (141)
Body mass index ≥ 30 kg/m ²	13.5 (27)	9.8 (20)	11.1 (22)
Intravaginal ejaculation latency time, % (<i>n</i>)			
<1 min	51.0 (102)	54.4 (112)	50.5 (100)
1–2 min	49.0 (98)	45.6 (94)	49.5 (98)
Premature Ejaculation Profile questions, % (<i>n</i>)			
Satisfaction with sexual intercourse [^]	76.0 (152)	84.5 (174)	78.8 (156)
Control over ejaculation [^]	93.0 (186)	96.6 (199)	91.4 (181)
Ejaculation-related interpersonal difficulty ^{^^}	46.0 (92)	50.5 (104)	53.0 (105)
Ejaculation-related distress ^{^^}	76.5 (153)	82.5 (170)	81.3 (161)

SE = standard error.
 No significant differences were seen in the baseline demographic characteristics for the patients assigned to placebo versus tramadol ODT.
^{*} Austria, Belgium, France, Germany, Spain, Sweden (*n* = 418).
^{**} Bulgaria, Czech Republic, Hungary, Poland, Romania (*n* = 186).
[^]Very poor or poor.
^{^^}Extreme or quite a bit.

apparent at the first visit during the double-blind treatment period (data not shown). Rather than using baseline average IELT as a covariate, we used each subject as his own control because we felt this better represented the per patient and per treatment group increase in efficacy with treatment. No imputation of missing data was made. All ANOVA tests were two sided and had an α value of 0.05.

3. Results

3.1. Subjects

There were 677 patients randomized, with 604 patients making up the ITT population (Fig. 1). The final population by treatment group is as follows: placebo (*n* = 200), 62 mg tramadol ODT (*n* = 206), and 89 mg tramadol ODT (*n* = 198).

Baseline demographic information for the study population by treatment group is shown in Table 1; no significant differences were seen in the demographic characteristics for the patients assigned to placebo versus tramadol ODT at baseline.

3.2. Intravaginal ejaculation latency time

Table 2 shows the IELT across treatment groups. Tramadol ODT resulted in significant increases in median IELT ($p < 0.01$ for both doses vs placebo). The fold increase in median IELT was significantly greater with both doses of tramadol ODT (2.4 and 2.5, respectively) compared with placebo (1.6; $p < 0.001$ for all). We also examined the

Table 2 – Median intravaginal ejaculation latency time at baseline and double-blind treatment period

Outcome measure	≤ 1 min baseline IELT			Overall		
	Placebo <i>n</i> = 105	62 mg tramadol ODT <i>n</i> = 114	89 mg tramadol ODT <i>n</i> = 103	Placebo <i>n</i> = 200	62 mg tramadol ODT <i>n</i> = 206	89 mg tramadol ODT <i>n</i> = 198
IELT, min, median (IQR)						
Baseline	0.66 (0.4–0.8)	0.58 (0.4–0.8)	0.60 (0.4–0.9)	0.98 (0.7–1.4)	0.95 (0.5–1.3)	0.98 (0.6–1.4)
Treatment period	0.92 (0.5–1.9)	1.32 (0.8–3.3)	1.88 (0.9–4.0)	1.66 (0.9–3.4)	2.24 (1.1–4.1)	2.51 (1.3–4.2)
IELT increase, min (IQR)	0.26 (0.04–1.3)	0.69 (0.2–2.5)	1.20 (0.3–3.1)	0.56 (0.1–2.1)	1.18 (0.3–2.9)	1.48 (0.3–3.1)
Wilcoxon <i>p</i> value vs placebo [*]		0.005	<0.001		0.002	<0.001
Fold increase, min (IQR)	1.59 (1.1–3.9)	2.44 (1.4–5.8)	3.33 (1.6–6.8)	1.61 (1.1–3.1)	2.37 (1.4–4.4)	2.49 (1.4–4.6)
Wilcoxon <i>p</i> value vs placebo [*]		0.002	<0.001		<0.001	<0.001
Average IELT, min, median (SE)						
Baseline	0.60 (0.03)	0.59 (0.02)	0.60 (0.03)	1.03 (0.04)	0.98 (0.04)	1.02 (0.04)
Treatment period	1.91 (0.27)	2.78 (0.42)	3.19 (0.40)	2.67 (0.20)	3.28 (0.27)	3.38 (0.24)
IELT increase, min (SE)	1.31 (0.26)	2.19 (0.41)	2.59 (0.39)	1.64 (0.19)	2.30 (0.26)	2.36 (0.23)
ANOVA <i>p</i> value vs placebo [^]		0.09	0.02		0.04	0.03
Fold increase in IELT, min (SE)	3.17 (0.42)	5.20 (0.91)	6.00 (0.84)	2.75 (0.23)	4.07 (0.50)	4.26 (0.45)
ANOVA <i>p</i> value vs placebo [^]		0.06	0.01		0.03	0.01

IELT = intravaginal ejaculation latency time; ODT = orally disintegrating tablet; IQR = interquartile range; SE = standard error; ANOVA = analysis of variance.

^{*} Bonferroni corrected, significance set at $p < 0.025$.

[^] Multiple test procedure with a priori hypotheses was used to control for family-wise error rate; two-sided 5% significance level.

average absolute and fold increase in median IELT using ANOVA; both doses of tramadol ODT significantly prolonged IELT compared with placebo (Table 2).

In the subset of patients whose baseline median IELT was ≤ 1 min ($n = 314$), both doses of tramadol ODT significantly prolonged the absolute and fold increases in median IELT compared with placebo (Table 2). The fold increases during treatment period in this patient subset were 1.6, 2.4, and 3.3 for placebo, 62 mg tramadol ODT, and 89 mg tramadol ODT, respectively.

3.3. Premature Ejaculation Profile

3.3.1. Male subjects

The mean change for all four measures of the PEP was significantly higher in both tramadol ODT treatment groups

compared with placebo (Table 3). The largest mean change was observed in control over ejaculation. A significantly higher proportion of men met the criteria for clinical benefit with both doses of tramadol ODT compared with placebo. We observed similar results in the subset of patients whose baseline median IELT was ≤ 1 min (Table 3).

3.3.2. Female partners

Baseline PEP scores show a large percentage of women had poor or very poor satisfaction with sexual intercourse (69%) and the partner's control over ejaculation (86%), and quite a bit or extreme distress related to their partner's speed of ejaculation (52%) and interpersonal difficulty (40%).

Compared with placebo, the 62 mg tramadol ODT group had a significantly higher proportion of women who achieved a one-category or greater improvement in

Table 3 – Change in male Premature Ejaculation Profile (PEP) score and percentage improvement from baseline by PEP question

PEP question	≤ 1 min baseline IELT			Overall		
	Placebo $n = 102$	62 mg tramadol ODT $n = 112$	89 mg tramadol ODT $n = 100$	Placebo $n = 200$	62 mg tramadol ODT $n = 206$	89 mg tramadol ODT $n = 198$
Satisfaction with sexual intercourse						
Mean change (treatment period: baseline) (SE)	0.40 (0.11)	0.92 (0.11)	1.06 (0.11)	0.56 (0.08)	0.93 (0.08)	1.00 (0.08)
ANOVA p value*		<0.001	<0.001		<0.001	<0.001
Achieved one category or greater improvement, n (%)	54 (53)	75 (67)	71 (71)	113 (57)	145 (70)	139 (70)
p value vs placebo [†]		0.04	0.01		0.004	0.005
Control over ejaculation during sexual intercourse						
Mean change (treatment period: baseline) (SE)	0.60 (0.10)	1.17 (0.09)	1.18 (0.10)	0.68 (0.07)	1.15 (0.07)	1.11 (0.07)
ANOVA p value*		<0.001	<0.001		<0.001	<0.001
Achieved one category or greater improvement, n (%)	59 (58)	90 (80)	75 (75)	121 (61)	162 (79)	147 (74)
p value vs placebo [†]		<0.001	0.01		<0.001	0.004
Ejaculation-related distress [°]						
Mean change (treatment period: baseline) (SE)	0.55 (0.12)	0.99 (0.11)	1.05 (0.12)	0.63 (0.08)	1.06 (0.08)	1.02 (0.08)
ANOVA p value*		0.01	0.003		<0.001	<0.001
Achieved one category or greater improvement, n (%)	68 (67)	80 (71)	71 (71)	128 (64)	153 (74)	142 (72)
p value vs placebo [†]		0.45	0.51		0.025	0.10
Ejaculation-related interpersonal difficulty [°]						
Mean change (treatment period: baseline) (SE)	0.36 (0.13)	0.73 (0.12)	0.74 (0.13)	0.53 (0.09)	0.89 (0.09)	0.80 (0.09)
ANOVA p value*		0.03	0.04		0.003	0.03
Achieved one category or greater improvement, n (%)	53 (52)	70 (63)	55 (55)	111 (56)	139 (67)	119 (60)
p value vs placebo [†]		0.12	0.67		0.01	0.35
Achieved criteria for clinical benefit at end point, n (%) [§]	8 (8)	26 (23)	30 (30)	23 (12)	51 (25)	52 (26)
p value vs placebo [†]		0.002	<0.001		0.001	<0.001

IELT = intravaginal ejaculation latency time; ODT = orally disintegrating tablet; SE = standard error; ANOVA = analysis of variance.

* Multiple test procedure with a priori hypotheses was used to control for family-wise error rate. All tests were two sided and conducted with a 5% significance level.

[†] Bonferroni corrected, significance set at $p < 0.025$.

[°] This question was assessed using a reverse-coded scheme so that higher scores are indicative of better outcomes.

[§] Criteria for clinical benefit were defined as achieving a two-category or greater increase in the mean change in control and a one-category or greater increase in the mean change in distress.

satisfaction with sexual intercourse (65% vs 53%; $p = 0.01$), in their partner's control over ejaculation (74% vs 58%; $p < 0.001$), and in distress related to partner's speed of ejaculation (69% vs 58%; $p = 0.02$). Likewise, compared with placebo, the 89 mg tramadol ODT group had a significantly higher proportion of women who achieved a one-category or greater improvement in satisfaction with sexual intercourse (67% vs 53%; $p = 0.004$) and in their partner's control over ejaculation (74% vs 58%; $p = 0.001$).

3.4. Safety

The incidence of TEAEs was 4.84% (1.5%, 5.0%, and 8.2% for placebo, 62 mg tramadol ODT, and 89 mg tramadol ODT, respectively.) The overall AE rate was 11.8% (6.7%, 12.4%, and 16.4% for placebo, 62 mg tramadol ODT, and 89 mg tramadol ODT, respectively.) Erectile dysfunction occurred in 1.0% of men ($n = 6$). All other AEs had an incidence of $< 1.0\%$: vertigo was observed in 0.9% of patients ($n = 5$); dizziness, headache, drowsiness, and common cold were observed in 0.5% of patients ($n = 3$ each). No difference was observed in the incidence of withdrawal by treatment group (0.0% placebo, 1.0% 62 mg tramadol ODT, 1.6% 89 mg tramadol ODT; $p = 0.08$). There were no serious AEs. Further, there were no relevant differences with regard to the mean change from baseline between active treatment groups and placebo for any vital sign or electrocardiogram parameter at any visit during the double-blind treatment period (data not shown).

4. Discussion

The results of this study demonstrate that tramadol ODT is an effective treatment for PE, resulting in a significant prolongation of IELT that showed clinical improvements in satisfaction with sexual intercourse and control over ejaculation, and decreases in ejaculation-related personal distress and interpersonal difficulty. Tramadol ODT was well tolerated; the overall AE rate was 7% for placebo and 12% and 16%, respectively, for subjects taking study medication.

Salem et al. previously examined the safety and efficacy of the same active ingredient present in tramadol ODT (tramadol HCl) for the treatment of PE [7]. Their AE rate in patients taking the study drug (13%) was similar to our study (12–16%). The authors examined the efficacy of the study drug by comparing mean changes in mean IELT by treatment group. It is well known that IELT is highly positively skewed and the mean IELT is an inappropriate estimator of effect size; we repeated their analyses for comparison purposes only. Salem and colleagues reported a mean end point IELT of 7.4 min with 25 mg tramadol HCl; these findings are disparate from ours (3.8 min for 62 mg tramadol ODT and 3.9 min for 89 mg tramadol ODT).

Chronic use of serotonergic and selective serotonin reuptake inhibitor (SSRI) agents is known to be effective in delaying ejaculation, and as a result they are used off-label to treat PE. However, chronic use of SSRIs is associated with serious AEs including psychiatric and neurologic consequences and unwanted sexual side effects [24]; dose reduction or discontinuation is associated with

discontinuation syndrome, a cluster of somatic and psychological symptoms [25]. On-demand use of SSRIs, including paroxetine, has shown some efficacy in treating PE, most recently with a 1.49-fold increase in IELT [26]. Dapoxetine, an on-demand short-acting SSRI, is the only currently approved oral treatment for PE. McMahon et al. [3] performed a meta-analysis of data using the results of five phase 3 clinical trials of dapoxetine [18–21]. The IELT results were reported as mean average and geometric mean average IELT at study end point; end point was defined using the last observation carried forward approach. Using those same analytic methods, tramadol ODT appeared to provide similar improvements in IELT for dose A (62 mg tramadol ODT vs 30 mg dapoxetine) and dose B (89 mg tramadol ODT vs 60 mg dapoxetine). The geometric mean average IELTs (standard error) at end point for tramadol ODT versus dapoxetine were as follows: dose A: 2.3 min (1.07) versus 2.0 min (1.03), and dose B: 2.4 min (1.08) versus 2.3 min (1.03). The increase in geometric mean average IELT at end point was significantly greater with both doses of tramadol ODT compared with placebo ($p = 0.001$ for all). Both doses of tramadol ODT appeared to provide similar therapeutic benefit, as measured by the PEP, as dapoxetine at study end point, compared with baseline. The increase in the percentage of patients reporting good or very good satisfaction with sexual intercourse for tramadol ODT and dapoxetine were as follows: dose A: 26% versus 23%; dose B: 32% versus 27%. Decreases in the percentage of patients reporting quite a bit or extreme ejaculation-related distress for tramadol ODT and dapoxetine were as follows: dose A: –51% versus –43%; dose B: –50% versus –48%. Decreases in the percentage of patients reporting quite a bit or extreme interpersonal difficulty were as follows: dose A: –33% versus –22%; dose B: –29% versus –24%.

This is the first study to examine an on-demand oral treatment for PE in a population that included patients with mild PE. Published phase 3 clinical trials excluded men whose PE was considered mild at baseline, defined as either having “not at all” or “a little bit” of interpersonal difficulty or ejaculation-related distress [18–20] or self-reported mild PE [21]. In our study, 27% of men were considered to have mild PE at baseline; the effect of treatment group on IELT and PEP efficacy outcomes were not different in men with mild versus moderate/severe PE. We believe our study is more generalizable because our results show a significant treatment effect in men with mild to severe PE, whereas the other studies reported outcomes in men with moderate to severe PE.

The opioid effect of tramadol and its metabolites are almost exclusively mediated by action at the μ -opioid receptor, which distinguishes it from other opioid drugs. Thus tramadol has only a very minor abuse potential and is not controlled like other opioid analgesics [27,28]. The long-term abuse potential has not been determined in our dosage formulations; however, based on studies in tramadol HCl, we believe the abuse potential is low or nonexistent [29].

The first limitation of our study is that the a priori power calculation estimated 825 subjects were needed to show

significance, yet we were only able to randomize 677 subjects into the study. If our data were such that we were unable to show significance, then one possible explanation would have been that we were insufficiently powered. However, because our data showed significance with a smaller sample size, it is reasonable to expect that greater enrollment would have shown similar or higher significance. Second, we performed these parallel phase 3 clinical trials in Europe, where most subjects were white. This limits the generalizability of our findings until clinical trials of PE using tramadol ODT are repeated in other populations. Third, men who were not in monogamous stable relationships were excluded. Finally, we limited our population to men 18–65 yr of age. Although erectile dysfunction affects older men more frequently than their younger counterparts, the prevalence of PE is similar for men of all ages [30]. We do not believe age exclusion limits the generalizability of our findings.

5. Conclusions

Randomized controlled clinical trials have demonstrated that on-demand tramadol ODT is an effective treatment for PE, providing a new option for managing mild to severe PE. The 62-mg dose of tramadol ODT has a superior safety profile with equivalent efficacy as the 89-mg dose compared with placebo and should be used as a low and safe therapeutic dose.

Author contributions: David Bar-Or had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Bar-Or, Winkler, Kendle International Inc.

Acquisition of data: Kendle International Inc.

Analysis and interpretation of data: Salottolo, Orlando (efficacy data); Kendle International Inc (safety data).

Drafting of the manuscript: Salottolo, Bar-Or, Winkler.

Critical revision of the manuscript for important intellectual content: Bar-Or, Winkler.

Statistical analysis: Orlando, Salottolo.

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Supervision: Bar-Or.

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