EJACULATION DISORDER

The Asia-Pacific Flexible Dose Study of Dapoxetine and Patient Satisfaction in Premature Ejaculation Therapy: The PASSION Study

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ABSTRACT

Introduction: Dapoxetine is a short-acting selective serotonin reuptake inhibitor for treatment of premature ejaculation (PE).

Aim: To evaluate the efficacy and safety of dapoxetine 30 and 60 mg as needed in Asia-Pacific men with PE.

Methods: The study was a prospective, 12-week, open-label study to evaluate the efficacy and safety of flexible-dose dapoxetine in men with PE diagnosed by a Premature Ejaculation Diagnostic Tool score of at least 11, a self-estimated intravaginal ejaculation latency time (IELT) no longer than 2 minutes, and an International Index of Erectile Function erectile function domain score of at least 21.

Main Outcome Measures: Percentage of subjects reporting their PE as at least "slightly better" using the Clinical Global Impression of Change (CGIC) question.

Results: Two hundred eighteen of 285 randomized subjects completed the study. The mean subject age was 45.9 years and 57.7% were Korean. Dosages 1 (30 mg), 2 (30 → 60 mg), and 3 (30 → 60 → 30 mg) were used in 141, 124, and 13 subjects, respectively. At study end, a PE CGIC rating of at least "slightly better" was reported by 77.3%, 92.8%, and 100% of subjects for dosages 1, 2, and 3, respectively ($P = .49$). At study end, a CGIC rating of "slightly better" was reported by 85.2% and 85.3% of subjects with lifelong PE and acquired PE, respectively ($P = .50$). At study end, a CGIC rating of "slightly better" was reported by 84.1% and 86.4% of subjects with an estimated baseline IELT no longer than and at least $\leq$1 minute, respectively ($P = .16$). The incidence of a CGIC rating of at least "slightly better" was lower in subjects reporting an adverse event of moderate or severe severity and in subjects who increased to and maintained a dapoxetine dose of 60 mg and higher in subjects older than 50 years and in subjects with a baseline estimated IELT of at least 1 minute.

Conclusion: In this study, flexible dosing of dapoxetine (30 and 60 mg) appeared effective in the treatment of PE.

Key Words: Dapoxetine; Premature Ejaculation; PASSION Study

INTRODUCTION

Premature ejaculation (PE) is a common male sexual disorder associated with a substantial personal and interpersonal negative psychological burden.[1–4] During the past 20 to 30 years, the PE treatment paradigm, previously limited to behavioral psychotherapy, has expanded to include drug treatment.[5–7] Animal and human sexual psychopharmacologic studies have found that serotonin (5-hydroxy-tryptamine) and its receptors are involved in ejaculation and have confirmed a role for selective serotonin reuptake inhibitors (SSRIs) in the treatment of PE.[8–10] Multiple well-controlled evidence-based studies have reported on the efficacy and safety of SSRIs in delaying ejaculation, confirming their role as first-line agents for the treatment of lifelong and acquired PE.[11] More recently, there has been increased attention to the

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psychosocial consequences of PE, its epidemiology, its etiology, and its pathophysiology by clinicians and the pharmaceutical industry.[1,2,12–15]

Dapoxetine (Priligy, Menarini Industrie Farmaceutiche Riunite Srl, Florence, Italy) is the first compound specifically developed for the treatment of PE. Dapoxetine is a potent SSRI that undergoes rapid absorption and elimination, resulting in minimal accumulation, and has dose-proportional pharmacokinetics that are unaffected by multiple dosing and do not vary among ethnic groups.[16–18]

The results of two phase 2 and seven phase 3 trials have been published.[19–26] All were conducted before the development of the International Society for Sexual Medicine definitions of PE[27,28] and instead used *Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition* criteria and a baseline intravaginal ejaculation latency time (IELT) no longer than 2 minutes on 75% of at least four sexual intercourse events as inclusion criteria. An analysis of pooled phase 3 data confirmed that dapoxetine 30 and 60 mg increased IELTs and improved patient-reported outcomes (PROs) of control, ejaculation-related distress, interpersonal distress, and sexual satisfaction compared with placebo.[29] Efficacy results were similar across the individual trials, indicating that dapoxetine is consistently more efficacious than placebo regardless of a subject's demographic characteristics. Across trials, dapoxetine 30 and 60 mg were well tolerated with a low incidence of severe adverse effects. The most frequently reported adverse events (AEs) were nausea, diarrhea, headache, dizziness, insomnia, somnolence, fatigue, and nasopharyngitis.

There are several PE intervention outcome measurements. The Clinical Global Impression of Change (CGIC) is a simple, brief, validated, patient-reported single-question scale used to assess the response of PE to treatment as much worse," "worse," "slightly worse," "no change," "slightly better," "better," or "much better." Althof et al[30] reported that the CGIC is a valid measurement in men with PE and provides clinicians with a valid and brief outcome assessment of their patient's condition.

The primary objective of this study was to measure the percentage of subjects with PE who reported their PE as at least slightly better using the CGIC question after 12 weeks of treatment with flexible dosing of dapoxetine (30 and 60 mg).

METHODS

The study was a prospective, observational study to evaluate the efficacy and safety of flexible-dose on-demand dapoxetine administered 1 to 3 hours before planned sexual intercourse at a starting dose of 30 mg that could be increased to 60 mg if the response was insufficient and the side effects were acceptable. The total study duration was 16 weeks, comprising a 2-week pretreatment phase and a 12-week open-label treatment phase, followed by a telephone contact 2 weeks after week 12 to follow up on AEs. The study was conducted at 23 sites in three countries. There were 13 sites in South Korea, 5 sites in Australia, and 5 sites in Thailand.

Inclusion and Exclusion Criteria

The study population was comprised of subjects with PE who were heterosexual men, at least 18 years old, were in a stable monogamous sexual relationship with a woman for at least 6 months, scored at least 11 on the Premature Ejaculation Diagnostic Tool (PEDT), reported a self-estimated IELT no longer than 2 minutes, had an International Index of Erectile Function (IIEF) erectile function domain score of at least 21, had PE that was not due exclusively to the direct effects of a substance, were in good general health, had systolic and diastolic blood pressures of 180 and 100 mmHg, respectively, at screening and at the baseline visit, and whose partner was not pregnant at screening. Subjects who had specified conditions related to the urogenital, sexual, endocrine, cardiovascular, metabolic and psychiatric systems or abnormal laboratory findings or received specified medications were excluded from participating in the study. A washout period of 30 days was required for subjects previously treated with an off-label antidepressant drug.

Study Efficacy End Points

Primary Efficacy End Point

The primary end point was the dapoxetine response rate with 95% CI expressed as the percentage of subjects who reported their PE as at least slightly better using the CGIC question after 12 weeks of treatment with flexible dosing of dapoxetine (30 and 60 mg).

Secondary Efficacy End Points

The following secondary end points were evaluated using the Premature Ejaculation Profile (PEP) for subjects and their partners who opted to participate in the study, at baseline, and at weeks 4, 8, and 12: control over ejaculation, satisfaction with sexual intercourse, personal distress, interpersonal difficulty, and CGIC rating. The PEP is a validated, self-reported outcome instrument comprised of four single-item measurements, a response profile, and an index score for evaluating the domains of PE and response to treatment.[31]

Study Overview

At visit 1 (screening), eligibility for enrollment in the study was contingent upon the diagnosis of PE with a PEDT score of at least 11, a self-estimated average IELT no longer than 2 minutes during the previous 4 weeks, and the absence of moderate to severe erectile dysfunction with a combined score of at least 21 for the erectile function domain of the IIEF. The PEDT is a five-item, multidimensional, psychometrically, and linguistically validated instrument for diagnosing PE, which captures the elements of control, frequency, minimal stimulation, distress, and interpersonal difficulty.[32–34] The IIEF is a 15-item, self-administered questionnaire that can assess the presence and severity of erectile dysfunction.[35]

In addition, subjects with but not limited to the following conditions were ineligible for the study: hypoactive sexual desire, known or suspected hypogonadism, hyperprolactinemia or untreated or

insufficiently treated hypothyroidism, significant cardiovascular disease with a cerebrovascular accident or myocardial infarction within the previous 6 months, a history of or current major psychiatric disorder or depression, current use or failure to complete the required washout period for SSRI or serotonin and norepinephrine reuptake inhibitor compounds, previous exposure to dapoxetine or a partner who was pregnant, planning to become pregnant, breastfeeding, or had significant female sexual dysfunction.

During the subsequent 2-week pretreatment period, subjects and their partners were required to attempt sexual intercourse at least two times and to complete a baseline event log to reconfirm eligibility for enrollment at visit 2 (baseline). At visit 2 (baseline), subjects and consented partners completed the PEP.

At visit 2 (baseline), eligible subjects were given study medication (dapoxetine 30 mg) and a treatment log to complete at each dosing. The subject was instructed to take one tablet of dapoxetine 30 mg, as needed, 1 to 3 hours before sexual activity.

At visits 3 (week 4) and 4 (week 8), subject treatment logs, occurrence of AEs, and new concomitant therapy use were monitored and dose titration (30 to 60 mg) was conducted for subjects who had used and tolerated dapoxetine 30 mg at least four times and wanted a better treatment outcome. In addition, at visit 4 (week), subjects previously up-titrated to 60 mg who had used and not tolerated dapoxetine 60 mg for at least one time were down-titrated to 30 mg. At visits 3 (week 4) and 4 (week 8), subjects and their partners were asked to complete the CGIC question and the PEP.

At visit 5 (week 12, final visit or early termination), subjects and their partners were asked to complete the CGIC question and the PEP. A telephone contact 2 weeks after the final visit or early termination was conducted to follow up on reported AEs.

Safety Assessments

Safety and tolerability were evaluated throughout the study by examining the incidence, severity, and type of AEs and serious AEs, clinical laboratory results, 12-lead electrocardiogram, vital sign measurements, and physical examination results. If, during the study, a subject developed signs or symptoms consistent with syncope, then additional details were collected and reported. Each subject who reported an AE was followed until the AE resolved.

Statistical Analysis

Sample Size

Sample size was calculated as 285 subjects based on the response rate of subjects reporting a CGIC rating of at least slightly better in previous dapoxetine studies and an expected dropout rate of 15% to achieve a precision of 5% of half-width of 95% CI for the true response rate.

Efficacy Analysis

Descriptive statistics with 95% CIs were used to summarize the efficacy of dapoxetine primary and secondary end points.

Subgroup analysis was conducted and defined by the following factors.

1. Dapoxetine dose
   a. Subjects who remained on dapoxetine 30 mg until the end of the study (dosage 1)
   b. Subjects who up-titrated to dapoxetine 60 mg because of an insufficient response and remained on 60 mg until the end of the study (dosage 2)
   c. Subjects who up-titrated to dapoxetine 60 mg because of an insufficient response and subsequently down-titrated to 30 mg owing to intolerable adverse effects (dosage 3)
2. Type of PE
   a. Subjects with lifelong PE
   b. Subjects with acquired PE

The dapoxetine response rate with 95% CI for these subgroups was calculated using the Cochran-Mantel-Haenszel χ^2 test for intergroup comparison. Frequencies and proportions for each response category for control over ejaculation, satisfaction with sexual intercourse, personal distress, interpersonal difficulty, and CGIC items for subjects and their partners were calculated using rank-sum testing to determine the difference in each secondary end point between subgroups if appropriate.

This study was conducted in accordance with the ethical principles originating in the Declaration of Helsinki, good clinical practices, and all applicable laws and regulations. The institutional review board or ethics committee at each site approved the study, and all men provided written informed consent before undergoing any study procedure or receiving any study therapy. An independent data monitoring committee monitored the safety and efficacy of subjects during the study, and an independent external statistics reporting group conducted one interim analysis during the course of the study.

RESULTS

In total, 285 subjects were enrolled in the study. Two hundred eighteen of 285 subjects (76.5%) completed the study and 67 of 285 subjects (23.5%) discontinued the study including four subjects who did not take the study drug. The most frequent reasons for discontinuation were withdrawn consent (23, 8.1%) and loss to follow-up (21, 7.4%). The mean age of all subjects was 45.9 years, and most subjects were Korean (n = 162, 57.65%), Thai (n = 60, 22.42%), and Caucasian (n = 49, 17.44%; Table 1). One hundred forty-one subjects were treated with dosage 1 (30 mg), 124 with dosage 2 (30 → 60 mg), and 13 with dosage 3 (30 → 60 → 30; Table 2). Of the 137 subjects whose dosage was increased from 30 to 60 mg, 11 subsequently decreased to 30 mg, generally because of decreased tolerability (n = 9 of 11) and 2 decreased because greater efficacy with the 60-mg dose was not appreciated.

Table 1. Patients' Demographic Characteristics (Subgroups by Dosage)

	Dosage 1 = 30 mg (n = 141)	Dosage 2 = 30 → 60 mg (n = 124)	Dosage 3 = 30 → 60 → 30 mg (n = 13)	*P* value	Total (n = 281)
Age (y)					
Mean ± SD	45.5 ± 10.43	46.9 ± 10.47	41.1 ± 7.77	NS	45.9 ± 10.39
Median	46	48	41		47
Range	23–68	21–69	28–53		21–69
Age group, n (%)	144	124	13		281
18–29	7 (4.86)	5 (4.03)	1 (7.69)		13 (4.63)
30–39	35 (24.31)	27 (21.77)	3 (23.08)		65 (23.13)
40–49	44 (30.56)	32 (25.81)	7 (53.85)		83 (29.54)
50–64	56 (38.89)	57 (45.97)	2 (15.38)		115 (40.93)
>65	2 (1.39)	3 (2.42)	0 (0.00)		5 (1.78)
Weight (kg), mean ± SD	72.29 ± 10.80	75.46 ± 12.79	71.9 ± 12.80	NS	73.67 ± 11.87
BMI					
Mean ± SD	24.69 ± 2.79	25.33 ± 3.20	23.90 ± 2.78		24.94 ± 3.0
Median	24	24.76	24.52		24.49
Ethnicity, n (%)	144	124	13		281
Chinese	1 (0.69)	0 (0.00)	0 (0.00)		1 (0.36)
Indian	0 (0.00)	4 (3.23)	0 (0.00)		4 (1.42)
Thai	44 (30.56)	12 (9.68)	7 (53.85)		63 (22.42)
White	12 (8.33)	33 (26.61)	4 (30.77)		49 (17.44)
Korean	85 (59.03)	75 (60.48)	2 (15.38)		162 (57.65)
Other	2 (1.39)	0 (0.00)	0 (0.00)		2 (0.71)

BMI = body mass index; NS = not significant.

Efficacy

Primary End Point

At study end, the proportion of subjects who CGIC rated their PE as at least slightly better was 77.3% for dosage 1, 92.8% for dosage 2, and 100% for dosage 3 ($P = .49$; Table 3).

Secondary End Points

Response to CGIC. At study end, the proportion of subjects who rated their PE as at least better using CGIC was 54.6% for dosage 1, 56.5% for dosage 2, and 46.2% for dosage 3 ($P = .17$; Table 3).

Table 2. Dosing Titration Patterns for Enrolled Subjects

Dosage group	Dosing titration pattern (n = 278)	n (%)
Dosage 1 (n = 141)	30 → x mg*	30 (10.8)
	30 → 30 → x mg	15 (5.4)
	30 → 30 → 30 mg*	96 (24.5)
Dosage 2 (n = 124)	30 → 30 → 60 mg	19 (6.9)
	30 → 60 → x mg	9 (3.2)
	30 → 60 → 60 mg†	96 (34.5)
Dosage 3 (n = 13)	30 → 60 → 30 mg	13 (4.7)

x = unknown dose of dapoxetine because of early withdrawal of subject.
*Includes subjects who withdrew early but took only 30 mg.
†Includes subjects who withdrew early and whose dose escalated to 60 mg.

At study end, a PE CGIC rating of slightly better, better, and much better was reported by 94 (36.6%), 101 (39.3%), and 33 (12.8%) subjects, respectively. Fewer than 12% of subjects described their PE as unchanged or worse (ie, slightly worse, worse, or much worse).

Of the subjects treated with dosage 1, 2, or 3, approximately 75% to 90% CGIC rated their PE as at least slightly better at visits 3, 4, and 5 (Table 3), whereas approximately 32% to 52% rated their PE as at least better at visits 3, 4, and 5 (Table 3).

Of subjects with lifelong PE, 85.2% CGIC rated their PE as slightly better, whereas 85.3% of subjects with acquired PE rated their PE as slightly better at the final visit ($P = .50$). Of subjects with an estimated baseline IELT no longer than 1 minute, 84.1% CGIC rated their PE as slightly better, whereas 86.4% of subjects with an estimated baseline IELT longer than 1 minute described their PE as slightly better at the final visit ($P = .16$).

Control over ejaculation. Overall, 49.6%, 53.2%, and 53.9% of subjects treated with dosages 1, 2, and 3, respectively, were observed to achieve a composite end point comprising an at least two-category improvement in control over ejaculation and an at least one-category decrease in distress related to ejaculation at the final visit ($P = .93$; Table 4).

Of subjects with lifelong and acquired PE, 56.5% and 47.9% of subjects, respectively, achieved the composite end point at study end ($P = .80$). Of those subjects with a baseline estimated IELT no longer than 1 minute, 57.3% achieved the composite

Table 3. "At Least Slightly Better" and "At Least Better Response" Status in Clinical Global Impression of Change in Premature Ejaculation by Study Visit (Subgroups by Dosage)

	Dosage 1 = 30 mg (n = 141)	Dosage 2 = 30 → 60 mg (n = 124)	Dosage 3 = 30 → 60 → 30 mg (n = 13)	Total (n = 281)	*P* value
Visit 3 (week 4)					
At least "slightly better," n (%)	97 (87.39)	80 (65.04)	11 (84.62)	188 (76.11)	.0003
95% CI	79.74–92.93	55.92–73.42	54.55–98.08	70.30–81.29	
At least "better," n (%)	51 (45.95)	24 (19.51)	4 (30.77)	79 (31.98)	<.0001
95% CI	36.45–55.67	12.92–27.63	9.09–61.43	26.21–38.19	
No change or worse, n (%)	14 (12.61)	43 (34.96)	2 (15.38)	59 (23.89)	
Visit 4 (week 8)					
At least slightly "better," n (%)	102 (91.89)	111 (89.52)	12 (92.31)	225 (90.73)	.8058
95% CI	85.17–96.23	82.74–94.30	63.97–99.81	86.41–94.03	
At least "better," n (%)	56 (50.45)	43 (34.68)	5 (38.46)	104 (41.94)	.0491
95% CI	40.80–60.08	26.36–43.75	13.86–68.42	35.72–48.34	
No change or worse, n (%)	9 (8.11)	13 (10.48)	1 (7.69)	23 (9.27)	
Visit 5 (week 12)					
At least "slightly better," n (%)	109 (90.83)	107 (86.29)	12 (92.31)	228 (88.72)	.4896
95% CI	84.19,95.33	78.96–91.81	63.97–99.81	84.20–92.31	
At least "better," n (%)	68 (56.67)	62 (50.00)	4 (30.77)	134 (52.14)	.1671
95% CI	47.31–65.68	40.89–59.11	9.09–61.43	45.84–58.39	
No change or worse, n (%)	11 (9.17)	17 (13.71)	1 (7.69)	29 (11.28)	

end point, whereas 45.7% of subjects with a baseline estimated IELT of at least 1 minute achieved the composite end point at study end ($P = .34$; Table 4).

Satisfaction with intercourse. Overall, 73.8%, 86.3%, and 84.6% of subjects treated with dosages 1, 2, and 3, respectively, were observed to achieve at least a one-category improvement in satisfaction with intercourse at the final visit ($P = .22$; Table 4).

Of those subjects with lifelong PE, 80.0% were observed to achieve at least a one-category improvement in satisfaction with intercourse, whereas 79.8% of subjects with acquired PE achieved this response ($P = .46$). Of those subjects with a baseline estimated IELT no longer than 1 minute, 77.5% were observed to achieve at least a one-category improvement in satisfaction with intercourse, whereas 82.1% of subjects with a baseline estimated IELT longer than 1 minute achieved this response ($P = .99$).

Table 4. Summary of Efficacy Results at Study End by Subgroup

			Study end point		
Subgroup	CGIC at least "slightly better," n (%)	CGIC at least "better," n (%)	Control ≥ 2 and distress ≥ 1, n (%)	Distress ≥ 1, n (%)	Satisfaction ≥ 1, n (%)
All subjects (n = 278)	237 (85.25)	153 (55.04)	143 (51.44)	203 (73.02)	222 (79.86)
Dosage group 1 (n = 141)	109 (77.30)	77 (54.61)	70 (49.65)	93 (65.96)	104 (73.76)
Dosage group 2 (n = 124)	115 (92.74)	70 (56.45)	66 (53.23)	100 (80.65)	107 (86.29)
Dosage group 3 (n = 13)	13 (100.00)	6 (46.15)	7 (53.85)	10 (76.92)	11 (84.62)
Lifelong PE (n = 115)	98 (85.22)	68 (59.13)	65 (56.52)	86 (74.78)	92 (80.00)
Acquired PE (n = 163)	139 (85.28)	85 (52.15)	78 (47.85)	117 (71.78)	130 (79.75)
IELT < 1 min (n = 138)	116 (84.06)	74 (53.62)	79 (57.25)	103 (74.64)	107 (77.54)
IELT > 1 min (n = 140)	121 (86.43)	79 (56.43)	64 (45.71)	100 (71.43)	115 (82.14)
Total	237 (85.25)	153 (55.04)	143 (51.44)	203 (73.02)	222 (79.86)
Last dose 60 mg	109 (77.30)	77 (54.61)	70 (49.65)	93 (65.96)	104 (73.76)

CGIC = Clinical Global Impression of Change; IELT = intravaginal ejaculation latency time; PE = premature ejaculation.

Personal distress. Overall, 66.0%, 80.1%, and 77.0% of subjects treated with dosages 1, 2, and 3, respectively, were observed to achieve at least a one-category decrease in distress related to ejaculation at the final visit ($P = .03$; Table 4).

Of those subjects with lifelong PE, 74.8% were observed to achieve at least a one-category decrease in distress related to ejaculation, whereas 71.8% of subjects with acquired PE achieved this response ($P = .62$). Of those subjects with a baseline estimated IELT no longer than 1 minute, 74.6% were observed to achieve at least a one-category decrease in distress related to ejaculation, whereas 71,4% of subjects with a baseline estimated IELT longer than 1 minute achieved this response ($P = .81$).

Interpersonal difficulty. There was no significant difference in interpersonal difficulty for each visit (from visit 2 to 5) among subgroups of dosage (ie, 1, 2, or 3), PE type (ie, lifelong or acquired), and baseline estimated IELT (ie, ≤1 or >1 minute), except for a significant difference ($P = .0012$) between the subgroup with a baseline estimated IELT no longer that 1 minute compared with those with a baseline estimated IELT longer than 1 minute at visit 2.

Logistic regression failed to show any relation between any change in the dosing of dapoxetine and potential factors including demographics (age and race), IELT subgroup (estimated baseline IELT ≤ 1 vs >1 minute), PEDT score, tolerability (report of mild AE vs any moderate or severe AE), and response to study drug (ie, CGIC rating of as least slightly better vs no change or worse).

Logistic regression used to explore possible factors affecting CGIC response demonstrated that the oldest group was significantly associated with CGIC response (odds ratio [OR] = 11.531, 95% CI = 1.364–97.476) compared with the youngest group. Compared with the Indian population, Thai, white, and Korean subjects showed a significant positive association with the CGIC response (Table 5). The proportion of subjects describing their PE as at least slightly better using the CGIC was statistically significantly lower for subjects who reported an AE of moderate or severe severity compared with those who reported an AE of mild severity.

The proportion of subjects CGIC rating their PE as at least slightly better was statistically significantly lower for subjects who required an increase in the dose of dapoxetine to 60 mg and maintained this dose compared with subjects who received only 30 mg throughout the duration of the study. Similar results were shown for association with race. A larger proportion of subjects with a baseline estimated IELT longer than 1 minute CGIC rated their PE as at least slightly better compared with those with a baseline estimated IELT shorter than 1 minute (OR = 3.934, 95% CI = 1.024–15.113).

Safety. AEs were reported by 134 subjects (47.69%), of whom 101 (37.59%) reported an AE related to study medication (Table 6). Thirteen subjects (4.63%) permanently discontinued the study drug because of AEs, of which 10 (3.56%) reported an AE considered related to the study drug. This group was comprised of nine subjects (6.25%) treated with dosage 1 and one subject (6.25%) treated with dosage 2. The most common AE responsible for discontinuation was nausea (3, 1.07%), which was limited to subjects treated with dosage 1. No subjects reported syncope and two subjects reported serious AEs.

Table 5. Analysis of Factors Related to Clinical Global Impression of Change Response with Logistic Regression

Variable	Levels	OR (95% CI)	*P* value
Age	Q1–median	0.329 (0.088–1.236)	.0997
	median–Q3	0.593 (0.141–2.501)	.4770
	Q3–maximum	4.840 (0.496. 47.237)	.1749
Race	Thai	699.320 (20.238–24,164.24)	.0003
	White	35.633 (2.428–522.860)	.0091
	Korean	17.198 (1.201–246.334)	.0362
	Other	—	—
PEDT		0.782 (0.244–2.512)	.680
IELT		3.934 (1.024–15.113)	.461
AE		0.312 (0.080–1.213)	.0927
Dosage group	30 → 60 → 60 mg	1.483 (0.407–5.405)	.5500
	30 → 60 → 30 mg	0.318 (0.057–1.767)	.1906

AE = adverse event; IELT = intravaginal ejaculation latency time; OR = odds ratio; PEDT = Premature Ejaculation Diagnostic Tool; Q = quartile.

In total, 132 subjects (46.98%) reported treatment-emergency AEs (TEAEs). The most commonly reported TEAEs were nausea (n = 38, 13.52%) and dizziness (n = 32, 11.39%). These TEAEs (nausea and dizziness) were more common in subjects treated with dosage 3 than with dosage 1 or 2 (Table 6). Overall, erectile dysfunction was reported by only 0.71% of subjects. In general, most TEAEs were mild (Table 7). Three TEAEs related to study medication were reported as severe (headache, n = 2; dizziness, n = 1).

Two subjects had serious AEs. One subject treated with dosage 1 developed severe dizziness, which was regarded as very likely related to the study drug, and resolved the next day. The other subject reported two events, including a road traffic accident and facial bone fracture, which were severe and considered not related to the study drug because no study drug was taken before these events.

DISCUSSION

PE PROs are psychometrically validated single-item diary questions or multi-item multidomain questionnaires used as diagnostic tools and intervention outcome measurements to assess clinical improvement, intercourse-related subject and partner sexual satisfaction, relationship satisfaction, personal and interpersonal distress, and subject and partner quality of

Table 6. Treatment-Emergency Adverse Events in at Least 1% of Subjects by Preferred Term (Subgroups by Dosage)

Total patients, n (%)	Dosage 1 = DPX 30 mg (n = 144)	Dosage 2 = DPX 30 → 60 mg (n = 124)	Dosage 3 = DPX 30 → 60 → 30 mg (n = 13)	Total (n = 281)
AE	47 (32.64)	47 (37.90)	10 (76.92)	104 (37.01)
Nausea	14 (9.72)	18 (14.52)	6 (46.15)	38 (13.52)
Dizziness	14 (9.72)	12 (9.68)	6 (46.15)	32 (11.39)
Headache	13 (9.03)	12 (9.68)	1 (7.69)	26 (9.25)
Somnolence	5 (3.47)	4 (3.23)	0 (0.00)	9 (3.20)
Dry mouth	3 (2.08)	4 (3.23)	0 (0.00)	7 (2.49)
Palpitations	4 (2.78)	3 (2.42)	0 (0.00)	7 (2.49)
Diarrhea	0 (0.00)	4 (3.23)	1 (7.69)	5 (1.78)
Fatigue	2 (1.39)	3 (2.42)	0 (0.00)	5 (1.78)
Hot flush	3 (2.08)	1 (0.81)	0 (0.00)	4 (1.42)
Abdominal discomfort	0 (0.00)	3 (2.42)	0 (0.00)	3 (1.07)
Increased AST	3 (2.08)	0 (0.00)	0 (0.00)	3 (1.07)
Upper respiratory tract infection	0 (0.00)	3 (2.42)	0 (0.00)	3 (1.07)

AE = adverse effect; AST = aspartate aminotransferase; DPX = dapoxetine.

life.[30–32] PROs used in clinical trials of investigational drugs should conform to the guidelines of the relevant regulatory agency.[36]

Although PE PROs have been operationalized, they might not be equally weighted, might vary in importance between subjects, and might have different meanings in different cultures where the attitude of the partner and culturally determined extent of emancipation can have an impact on the subject's subjective diagnosis of PE. In the assessment of PE intervention outcomes that capture changes to the multiple dimensions of PE such as control, patient and partner bother, and other negative psychological effects and sexual satisfaction, the CGIC measurement is often used to provide a clinically meaningful integrated summary of an individual's response to treatment.

Published clinical trial results have found that CGIC ratings are sensitive to change in men with PE treated with dapoxetine.[21,24,29,37] In a post hoc analysis of 1,162 patients from 22 countries who participated in a randomized, double-blinded, parallel-group, placebo-controlled phase 3 trial of dapoxetine, Althof et al[30] assessed the validity and determinants of the patient-reported CGIC rating of treatment response. Althof et al reported that the IELT progressively increased for each category of improvement on the CGIC: 1.63, 4.03, and 7.15 minutes for slightly better, better, and much better, respectively. Similarly, higher CGIC ratings were correlated with greater improvement in control ($r = 0.73$), satisfaction ($r = 0.62$), greater decrease in distress ($r = -0.52$), and interpersonal difficulty ($r = -0.39$). Total variance accounted for 57.4%: control (48.7%), satisfaction (4.5%), IELT (2.8%), and distress (1.15%). Althof et al concluded that the CGIC provides clinicians in practice with a valid and brief outcome assessment of their patient's response to intervention.

In this study, the use of a flexible dosing regimen of dapoxetine (30 and 60 mg) appeared effective in the treatment of Asia-Pacific men with PE. Using the CGIC, 85.3% of subjects described their PE as at least slightly better at study end. This included 77.3% of subjects who described their PE as at least slightly better using the CGIC at visit 5 for subjects treated with dosage 1, 92.4% treated with dosage 2, and 100% treated with dosage 3.

Clinical efficacy was comparable between subgroups for disease type (lifelong vs acquired PE) and IELT categories (≤ 1 vs ≥ 1 minute). The proportion of subjects who CGIC rated their PE as at least slightly better was 85.3% among subjects with lifelong PE and 85.2% among those with acquired PE. The proportion of subjects who CGIC rated their PE as at least slightly better was 84.1% among subjects with a baseline estimated IELT no longer than 1 minute and 86.4% of those with a

Table 7. Treatment-Emergency Adverse Events by Severity (Subgroups by Dosage)

Adverse event	Dosage 1 = 30 mg (n = 144)	Dosage 2 = 30 → 60 mg (n = 124)	Dosage 3 = 30 → 60 → 30 mg (n = 13)	Total (n = 281)
Mild	53 (36.81)	53 (42.74)	11 (84.62)	117 (41.64)
Moderate	14 (9.72)	10 (8.06)	2 (15.38)	26 (9.25)
Severe	3 (2.08)	1 (0.81)	0 (0.00)	4 (1.42)
Total	63 (43.75)	57 (45.97)	12 (92.31)	132 (46.98)

baseline estimated IELT of at least 1 minute. The difference among the three dosages was not significant. In addition, 55.0% of subjects described their PE as at least better using CGIC at visit 5 (final visit).

These results were comparable to, if not slightly better than, previous global and regional Asia-Pacific phase 3 trials and an integrated analysis of pooled data from five phase 3 trials.[21,24,25] In the integrated analysis of pooled data from five phase 3 trials, a CGIC rating of at least slightly better was reported at study end by 62.1% and 71.7% of subjects using dapoxetine 30 and 60 mg, respectively. Furthermore, a CGIC rating of at least better was reported at study end by 30.7% and 38.3% of subjects using dapoxetine 30 and 60 mg, respectively.[29] In the Asia-Pacific Study, McMahon et al[24] reported a CGIC rating of at least slightly better in 71.4% and 79.2% of subjects treated with dapoxetine 30 and 60 mg, respectively. Furthermore, a CGIC rating of at least better was reported at study end by 37.4% and 41.5% of subjects with dapoxetine 30 and 60 mg, respectively. Similarly, Pryor et al[21] reported a CGIC rating of at least slightly better in 58% and 67% of subjects treated with dapoxetine 30 and 60 mg, respectively.

Logistic regression showed that the incidence of a PE CGIC rating of at least slightly better was lower in subjects who reported an AE of moderate or severe severity compared with those who reported an AE of mild severity and in subjects who required an increase in the dose of dapoxetine to 60 mg and maintained this dose compared with subjects who received only 30 mg throughout the duration of the study. Furthermore, logistic regression showed a significant and positive relation between a PE CGIC rating of at least slightly better in Thai, Korean, and Caucasian subjects older than 50 years (OR = 11.531) and a baseline estimated IELT longer than 1 minute (OR = 3.934).

The improvement in the composite end point of control over ejaculation and distress, the satisfaction with sexual intercourse end point, and the personal distress end point were similar among those subjects treated with the three dosages, those with lifelong vs acquired PE, and those with a baseline estimated IELT no longer than vs longer than 1 minute. The differences among all subgroups were not significant.

The achievement of the composite end point of a two-category improvement in control over ejaculation and a one-category decrease in distress by 51.4% of subjects in this study exceeds that reported in previous studies of similar subject populations. In the Asia-Pacific study, McMahon et al[24] reported that treatment with dapoxetine 30 and 60 mg achieved the composite end point in 34.7% and 37.2% of subjects, respectively.

Similarly, 79.9% of all subjects achieved a greater than one-category increase in satisfaction with sexual intercourse, and 73.0% of all subjects reported a greater than one-category decrease in distress. This is comparable to or slightly exceeds that reported by McMahon et al[24] (satisfaction at 30 mg = 69.3%; satisfaction at 60 mg = 75.9%; personal distress at 30 mg = 66.6%; personal distress at 60 mg = 72.7%).

Previous studies have associated improvement in the composite end point of control (greater than one-category improvement in control and/or satisfaction) and distress (greater than one-category decrease in distress) with a clinically significant fold increase in IELT.[24] Although this study did not use patient-estimated or stopwatch IELT as end points, the improvement noted in the composite and single PROs suggests that subjects achieved improvement in IELT.

This study showed that 84.1% and 86.4% of subjects with a baseline IELT shorter than and longer than 1 minute, respectively, CGIC rated their PE as at least slightly better after treatment with dapoxetine. Contrary to these findings, McMahon et al[24] in the Asia-Pacific study reported that subjects with a baseline IELT shorter than and longer than 1 minute had a lower CGIC rating of at least slightly better after treatment (<1 minute with 30 mg = 69.9%; <1 minute with 60 mg = 75.2%; >1 minute with 30 mg = 72.7%; >1 minute with 60 mg = 82.6%).

Dapoxetine was generally well tolerated in this study, which used a flexible-dosing regimen (30 and 60 mg). Reported AEs were generally mild or moderate and there were no unexpected or important new findings regarding the AE profile of dapoxetine or new safety concerns identified. The overall and individual incidences of AEs were similar for dosages 1 and 2 and failed to replicate the dose-related incidence seen in earlier phase 3 studies. The reason for this is unclear but probably reflects the observation that AEs often attenuate and resolve with continued drug usage. The incidence of AEs was higher with dosage 3, which could reflect the option of the subject to decrease the dapoxetine dose from 60 to 30 mg owing to intolerable AEs.

This study is limited by the lack of a blinded placebo or active comparator arm. Some degree of subject and/or investigator bias could have influenced the results. The lack of validation of the PEDT, PEP, and CGIC in non-English Asia-Pacific languages before the commencement of study is regarded by the authors as a potential but minor limitation of this study. In addition, the lack of IELT data after dapoxetine treatment might be considered another potential limitation when comparing data from this study to those of the dapoxetine phase 3 registration program. The sample size could limit the detection of infrequent AEs.

CONCLUSIONS

Consistent with results from previous phase 3 studies, dapoxetine 30 and 60 mg as needed significantly improved the CGIC rating of PE, the composite responder end point of at least a two-category improvement in control over ejaculation, and at least a one-category decrease in distress related to ejaculation and the individual PRO end points of ejaculatory control, satisfaction with sexual intercourse, personal distress, and interpersonal distress. Clinical efficacy was comparable between subgroups for disease type (lifelong vs acquired PE) and IELT categories (≤1 vs ≥1 minute). Dapoxetine was well tolerated and TEAEs were mild.

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Conflict of Interest: Dr McMahon is a consultant and investigator for Johnson & Johnson, Janssen Cilag Asia Pacific, and Menarini. Dr Lee is a consultant and investigator for Johnson & Johnson, Janssen Cilag Asia Pacific, and Menarini. Dr Kim is a consultant and investigator for Johnson & Johnson, Janssen Cilag Asia Pacific, and Menarini. Dr Du Geon Moon is a consultant and investigator for Johnson & Johnson, Janssen Cilag Asia Pacific, and Menarini. Dr Kongkanand is a consultant and investigator for Johnson & Johnson, Janssen Cilag Asia Pacific, and Menarini. Dr Tantiwongse is a consultant and investigator for Johnson & Johnson, Janssen Cilag Asia Pacific, and Menarini.

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