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PEP

Premature Ejaculation Profile

User's Manual and Scoring Guide

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PURPOSE OF THIS MANUAL

The purpose of this manual is to describe the development, measurement and psychometric properties, and potential applications of the Premature Ejaculation Profile (PEP) and to facilitate administration, scoring, and interpretation of PEP results. This manual addresses the original development and validation of the United States (US) English PEP version, the original cross-sectional validation and psychometric performance of the instrument in four European languages (French, German, Spanish, and Swedish), the subsequent longitudinal validation of the PEP (from two different clinical trial periods), and the cross-cultural translation methodologies for all non-US English versions of the PEP.

ACKNOWLEDGEMENTS

We would like to acknowledge the important contributions of Dennis Gagnon, MA; Kai Fai Ho, PhD; Pauline McNulty, PhD; Scott Bull, PharmD from Johnson and Johnson, and François Giuliano, MD, Ph.D.

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- Giuliano F, Patrick DL, Porst H, et al. Premature ejaculation: results from a five-country European observational study. *Eur Urol* 2008; 53:1048-57.
- Rowland DL, Patrick DL, Rothman M, Gagnon DD. The psychological burden of premature ejaculation. *J Urol* 2007; 177: 1065–70.
- Patrick DL, Althof SE, Pryor JL, Rosen R, Rowland DL, Ho KF, McNulty P, Rothman M, Jamieson C. Premature Ejaculation: An Observational Study of Men and Their Partners. The Journal of Sexual Medicine. May 2005; 2(3): 358-367.
- Shabsigh R, Patrick DL, Rowland DL, Bull SA, Tesfaye F, Rothman M. Perceived control over ejaculation is central to treatment benefit in men with premature ejaculation: results from phase III trials with dapoxetine. BJU Int. 2008 Sep;102(7):824-8. Epub 2008 Jul 21.

- Patrick DL, Giuliano F, Ho KF, Gagnon DD, McNulty P, Rothman M. The Premature Ejaculation Profile: validation of self-reported outcome measures for research and practice. BJU Int. 2009 Feb;103(3):358-64. Epub 2008 Sep 12.

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This Agreement shall be governed by and construed in accordance with the laws of the State of Washington. Any disputes will be adjudicated first through the UNIVERSITY OF WASHINGTON and subsequently through courts in the State of Washington.

IN WITNESS WHEREOF, the parties hereto have caused this agreement to be executed by their duly authorised representatives as of the date first above written.

User/University/Company:	**UNIVERSITY OF WASHINGTON**
Name:	Name:
Title:	Title:
Signature:	Signature:
Date:	Date:

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EXISTING LANGUAGE VERSIONS

The PEP4 is a one page measure, containing four items, using a total of 3 response scales. The PEP4 items were originally a part of a larger set of items previously developed for use in early phase clinical trials. Therefore, the preparation of the different language versions available was completed at different points in time. In some cases, as the study designs changed, slight differences (for example, recall period) were incorporated into the translations.

While the translation methods followed for these early versions generally adhered to currently accepted criteria included in the ISPOR Principles of Good Practice, (forward translation, evaluated backwards translation, cognitive interviews, international harmonization, and finalization of new language version) it also yielded a group of language versions that were slightly at difference with each other.

Therefore, an additional quality control and harmonization process was undertaken to extract the PEP4 items from the larger clinical trial documents, and conduct the following steps:

Step 1 (Development of initial language version)

- Review of existing translation of the larger documents, and identification of the correct PEP4 items
- Preparation of review grids of the PEP-4 items

Step 2 (Review)

- One independent review of existing translation (using local translators who are bi-lingual in English and the target language)
- Evaluation of the review suggestions to bring the PEP4 content into consistency
- Evaluation by in-country translation consultant if suggestions involved change in item content

Step 3 (Finalization of language version)

- Resolution of suggested changes
- Final formatting and proofreading
- Development of evaluation report to track any needed changes in the originally translated items.

Of the 37 new language versions, 21 needed no further revision to be consistent with the final text of the PEP4. Several needed minor changes in punctuation or changes in the recall period. Only a few needed changes in the translation content in order to properly match the final version of the PEP4. Table 1 shows the existing language versions at the time of the writing of this User's Manual.

Table 1: Existing Language Versions of the PEP *(as of November 2009)*

	Cross-cultural Adaptation	Cross-sectional Validity	Longitudinal Validity
ORIGINAL VERSION			
United States			
ENGLISH VERSIONS			
English (Australia)			
English (UK)			
English (Malaysia)			
English (Singapore)			
NON-ENGLISH VERSIONS			
Afrikaans (South Africa)			
Bulgarian (Bulgaria)			
Czech (Czech Republic)			
Dutch (Belgium)			
Dutch (Netherlands)			
English (Australia)			
English (UK)			
English (Malaysia)			
English (Singapore)			
Finnish (Finland)			
French (Belgium)			
French (Canada)			
French (France)			
German (Germany)			
Hebrew (Israel)			
Hungarian (Hungary)			
Italian (Italy)			
Korean (South Korea)			
Malay (Malaysia)			
Malay (Singapore)			
Norwegian (Norway)			
Polish (Poland)			
Portuguese (Brazil)			
Portuguese (Portugal)			
Simplified Chinese (China)			
Simplified Chinese (Malaysia)			
Simplified Chinese (Singapore)			

NON-ENGLISH VERSIONS			
Spanish (Argentina)			
Spanish (Mexico)			
Spanish (Spain)			
Spanish (US)			
Swedish (Sweden)			
Tagalog (Philippines)			
Thai (Thailand)			
Traditional Chinese (Hong Kong)			
Traditional Chinese (Taiwan)			
Universal Spanish			

INTRODUCTION

The Premature Ejaculation Profile (PEP)

The PEP is a new instrument for the assessment of PE that deals with all domains of the condition as defined by the DSM-IV-TR: perceived control over ejaculation, personal distress related to ejaculation, and interpersonal difficulty related to ejaculation, as well as satisfaction with sexual intercourse, which is also felt to be important by experts in the field of sexual medicine [Shabsigh 2007]. Each of these is assessed using a single item; responses are rated on a five-point scale; and higher scores indicate better functioning (Table 1) [Rosen 2007, Rowland 2007]. The measures of the PEP have been used in various studies of men with PE, including observational studies and clinical trials of treatments for PE [Patrick 2005, Pryor 2006, Giuliano 2008], and have also been used to characterize the differences between men with and without PE [Rosen 2007, Rowland 2007, Patrick 2007].

Table 2: The Premature Ejaculation Profile (PEP)

Concept	Question	Scores and response option
Perceived control over ejaculation	Over the past month, was your control over ejaculation during sexual intercourse*:	0: Very poor 1: Poor 2: Fair 3: Good 4: Very good
Satisfaction with sexual intercourse	Over the past month, was your satisfaction with sexual intercourse:	0: Very poor 1: Poor 2: Fair 3: Good 4: Very good
Personal distress related to ejaculation†	How distressed are you by how fast you ejaculate (come) during sexual (vaginal) intercourse? *	0: Extremely 1: Quite a bit 2: Moderately 3: A little bit 4: Not at all
Interpersonal difficulty related to ejaculation†	To what extent does how fast you ejaculate (come) during sexual (vaginal) intercourse cause difficulty in your relationship with your partner? *	0: Extremely 1: Quite a bit 2: Moderately 3: A little bit 4: Not at all

* In the USA observational study, the recall period was 2 weeks.

† So that higher scores would indicate better functioning on all measures, the response scale indicated here has been reverse coded from that presented to patients. The original response scale was from 0, 'not at all' to 4, 'extremely'.

Guidance on Use of Patient-reported Health Outcomes

A patient-reported outcome is any report coming directly from patients, without interpretation by physicians or others, about how they function or feel in relation to a health condition and its therapy (FDA, 2006). PRO instruments (e.g., questionnaire items, instructions, and guidelines for scoring and interpretation) are used to measure these patient reports. The term 'PRO' addresses the source of the report, and not the concept or content of the report.

In January 2006, the EMEA Committee for Medicinal Products for Human Use (CHMP) issued the Reflection Paper on the Regulatory Guidance for the Use of Health-Related Quality of Life (HRQL) Measures in the Evaluation of Medicinal Products (EMEA, 2006). In the EMEA reflection Paper, HRQL is defined as the patient's subjective perception of the impact of his disease and its treatment(s) on his daily life, physical, psychological and social functioning and well-being.

The US Food and Drug Administration developed a draft Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims, which was distributed for public comment in February 2006 (FDA, 2006). The draft guidance describes HRQL as a multidomain concept that represents the patient's overall perception of the impact of an illness and its treatment. It is stated that HRQL should not be equated with quality of life, which is described as a general concept that implies an evaluation of the impact of all aspects of life on general well-being. An HRQL measure captures, at a minimum, physical, psychological (including emotional and cognitive), and social functioning.

Both documents describe expectations for adequate measurement of patient (self)-reported endpoints to be used to support medical product claims. The 2 guidance documents differ primarily in their focus. The CHMP document addresses only endpoints related to HRQL, and evaluates the proposed claim based on the strength of the evidence and the relevance (pertinence and importance) of the finding. The FDA draft guidance includes all patient-reported outcome endpoints in its guidance and evaluates submissions based on consistency between the concepts, instruments, clinical trial data, and claims sought for inclusion in the patient label.

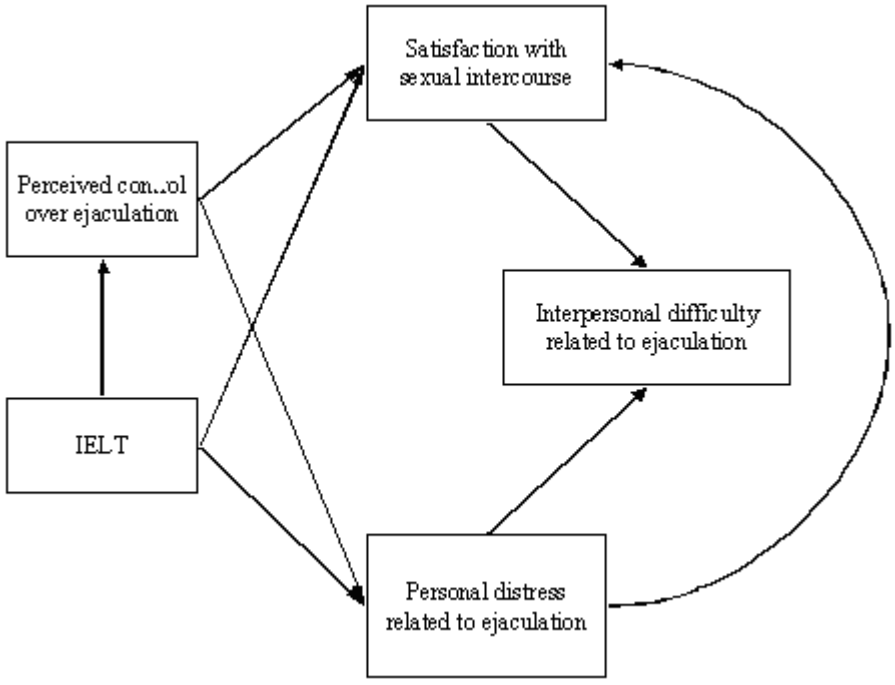
Both guidances are anticipated to influence the evaluation of all clinical trial endpoints, including objective (e.g., laboratory measures) and subjective (e.g., caregiver reported and patient-reported outcomes) assessments. Specifically, all outcome measures should have a record of measurement performance, including reliability and validity, as well as experience on how to interpret changes over time.

EARLY DEVELOPMENT

Introduction

There is accumulating evidence that PE can have a negative effect on men, their partners and the relationship (see Figure 1). In a large, internet-based survey (Premature Ejaculation Prevalence and Attitudes [PEPA] survey), conducted among men ages 18-70 in the US, Germany and Italy (n=12,133), men with self-reported PE were more likely to report psychological disturbances (e.g., depression, anxiety, excessive stress) than men without PE (P<0.05) (Porst et al, 2006). Another study found that men with PE had lower levels of satisfaction in all areas of life compared with men without PE (McCabe, 1997). Other investigators have found that men with PE express decreased self-confidence and increased distress and interpersonal difficulty relative to men without PE (Hartmann et al, 2005; Patrick et al, 2005). In a series of qualitative interviews with 28 men ages 25 to 70 years who self-reported PE (≥2-year history), the 2 major themes that emerged were the effect of PE on self-esteem (68% mentioned that their confidence was affected by their PE) and the effect of PE on relationships (50% reported relationship issues, especially a reluctance to establish new relationships) (Symonds et al, 2003).

Figure 1: Model of Domains Relevant to Premature Ejaculation



Female partners of men with PE were evaluated in a US observational study (Patrick et al, 2005). In this study, 61.8% of partners of men with PE (n=207) versus 10.1% of partners of men without PE (n=1380) reported fair to very poor satisfaction with sexual intercourse (P<0.001). Further, a higher proportion of partners of men with PE reported interpersonal difficulty related to PE compared with partners of men without PE (44% vs. 5%, respectively; P<0.001).

Interpersonal difficulty is found to be a common consequence of PE in several studies (Symonds et al, 2003; Hartmann et al, 2005; Sotomayor, 2005). In a qualitative study, approximately half of men with PE reported distress about their relationships (Symonds et al,

2003). Rust et al found that PE was significantly correlated with marital discord (r=0.35; $P<0.05$) (1988).

The full impact of PE on men is unknown due in part to the reluctance of men with this condition to discuss the problem with their partner or physician. In one study, men with PE were more likely to report that they avoided discussing sexual problems with their partner compared to men without PE (62.4% vs. 43.3%, respectively; $P<0.001$) (Rowland et al, 2004). In the PEPA survey, only 9% of men with PE reported having consulted a physician for the condition (Porst et al, 2006). In another survey, less than 3% of men with self-reported PE had received treatment for the condition (Carson et al, 2003). Symonds et al (2003) found that 47% of those who did not consult a physician about their PE believed that there was no treatment, and therefore did not consider discussing the problem with a physician.

Evaluating Content Validity

Content validity is an assessment of the extent to which the content of the measure is relevant and important to the target population and the extent to which the items in the measure provide comprehensive coverage of the concept.

Content validity of the PEP is supported by qualitative research from US focus groups and European one-to-one interviews and cognitive debriefing studies conducted in the US, Europe, and Pan-Asia (Table 3).

Table 3: Data Sources for Content Validity of Patient-reported Outcomes Related to Premature Ejaculation

Data Source	Concepts Supported
US qualitative research: focus groups	• Content validity
US cognitive debriefing study	• Content validity, including subject comprehension of item and response wording, and subject interpretation of outcome measures
European qualitative study: one-to-one exploratory interviews, cognitive debriefing	• Cultural and linguistic validation • Content validity, including subject comprehension of item and response wording, and subject interpretation of outcome measures
Pan-Asia cognitive debriefing	• Cultural and linguistic validation • Content validity, including subject comprehension of item and response wording

US Qualitative Research (Focus Groups)

The US focus groups were used to examine subject perceptions of important outcomes for PE. Fourteen (14) focus groups (11 groups of heterosexual men with PE and 3 groups of female partners of men with PE) were conducted. A qualitative evaluation of the focus group data was performed based on a structured review of transcripts following the grounded theory approach, which requires that the themes identified be grounded or rooted based on the observation of the data (Strauss, 1987).

In total, 51 men with PE and 17 female partners of men with PE participated in the US focus group discussions. Qualitative research identified 34 different codes capturing various components of PE. These 34 codes were grouped within 6 major themes: satisfaction with intercourse, distress (e.g., feelings of inadequacy, disappointment, frustration, anxiety, anger), the male/partner relationship, ejaculatory control, communication, and coping.

Satisfaction with intercourse was influenced by being able to satisfy the partner. Components of the ejaculatory control theme included time (expressed as an ability to last longer) and control (expressed as controlling the timing of ejaculation). The male/partner relationship theme occurred throughout the focus groups embedded in various other themes, including partner satisfaction. Partner disappointment and frustration were common components within the relationship theme. In some cases, partner frustration ultimately led to concerns about continuing the relationship. Having a supportive partner was helpful to some men in alleviating anxiety over PE. Several participants indicated that if they had control over ejaculation or were satisfied with intercourse, the actual time of ejaculation would not be an issue for them.

Common distress emotions expressed by men with PE included inadequacy, disappointment, frustration, anxiety, and anger. Difficulty talking was the most frequent subcategory coded to the communication theme. The ability to communicate their feelings about PE appeared to affect how men perceived their condition. For example, if men found it difficult to talk with a clinician or were unable to discuss their problem with their partner, they expressed a greater sense of lack of control. If discussions about PE were positive, men expressed greater satisfaction with sexual intercourse. Coping mechanisms included both physical strategies (e.g., stop-start and squeeze techniques) and emotional strategies (e.g., thinking of other things, humor, minimizing magnitude of problem). Failure of coping mechanisms was associated with reduced control over ejaculation and decreased satisfaction with sexual intercourse.

Participants in the female partner focus groups were consistent with statements made by the men with PE.

US Cognitive Debriefing Study

The US cognitive debriefing study assessed PE-related PRO measures, including control over ejaculation, satisfaction with sexual intercourse, personal distress, interpersonal difficulty due to PE, severity of the PE, firmness of erections, occurrence and frequency of PE, and 2 items for estimating IELT. Twenty (20) men were recruited from 2 sites in the US to participate in one-to-one interviews. Eligible subjects were at least 18 years of age, had a diagnosis of PE based on DSM-IV-TR criteria, and were currently in a monogamous, heterosexual relationship of at least 6 months. During the cognitive debriefing interview, participants were asked to describe their overall impression and interpretation of each item and their interpretation of the associated response options. Participants were asked if they thought 1 month was an acceptable recall time. The equivalence of response choices for the selected items was examined using a visual analog scale (VAS).

In total, 19 men, aged 26 to 67 years, completed cognitive debriefing interviews.

Control over ejaculation was interpreted to mean the ability/inability to ejaculate at will and also included an element of speed or time to ejaculation. When asked to define control over ejaculation, 74% (14/19) said bodily control over ejaculation while 26% (5/19) said time to ejaculation. All men responded that better control was related to longer latency time. Five men mentioned the time needed to satisfy their partner.

When asked about satisfaction with sexual intercourse, responses were chosen based not only on the man's satisfaction but also included perceived or actual partner satisfaction. The meaning of satisfaction with sexual intercourse included partner satisfaction for 68% (13/19) of the respondents. Response options were chosen based on the length of time between penetration and ejaculation by 47% (9/19) of respondents, the degree of partner satisfaction and ability to bring her to climax during vaginal intercourse by 42% (8/19), the degree of control over ejaculation by 16% (3/19), and the whole experience and sexual relationship by 16% (3/19).

Respondents defined distress as feelings of inadequacy, disappointment, annoyance, failure, frustration, irritation, anxiety, bother, preoccupation, worry, feeling distraught, an impact on ego, and the concern about partner's perceptions due to the PE. Three men said that the word distress was inappropriate or too strong a word or that it may be confused with the word stress. Four men thought further explanation was needed; particularly clarification of the extent of feelings, e.g. "upset all the time" versus "desire to last longer." Level or degree of distress for selecting each response was gauged on several factors, including perceived partner's satisfaction, personal mental and emotional state due to PE, the level of tension and dissatisfaction that PE is causing between the man and his partner, avoidance of sex, time to and control over ejaculation, and seeking treatment for PE.

For interpersonal difficulty, most men (84% [16/19]) indicated they considered how the issue affected their partner and their relationship. Level of difficulty in the relationship was determined by the man's perception of their partner's sexual satisfaction, sexual interest, anger, disappointment, tension between the couple and if PE is causing problems between the couple.

Overall, the study demonstrated that the instructions, item content, and response options were understood and appropriately interpreted by men with PE in the United States.

European Qualitative Study

The European qualitative study included one-to-one cognitive debriefing interviews and exploratory interviews discussing the effect of PE on male participants and their partners. Because focus groups have not been a useful strategy for eliciting personal experience from participants outside the US, the sponsor was advised to use one-to-one interviews for assessing the content validity of PE-related PRO measures in Europe (Steve Wolf, Synovate Inc; personal communication, 2004).

The European qualitative study was designed to complement information obtained in the US population. Five European countries participated in the study: France, Germany, Italy, Poland, and United Kingdom. Self-report and partner-report (male and female) versions of the outcome measures were evaluated, including control over ejaculation, satisfaction with sexual intercourse, personal distress, interpersonal difficulty with partner due to PE, satisfaction with this sexual experience (per event), severity of PE problem, ejaculation before desired, ejaculation before penetration, medication effect in improving condition, and global evaluation of change in condition. Male respondents were also asked to estimate average time between vaginal entry and ejaculation, and firmness of erections. The study materials were translated using full translation methods based on FACIT Multilingual Translation Methodology (Eremenco et al, 2005) (and all translations were certified).

Twenty (20) men with PE and 10 female partners of men from each country were recruited. Participants were 25 to 70 years of age and currently in a monogamous, heterosexual relationship of at least 6 months. Subjects had a self-reported diagnosis of PE assessed by:

(1) problems or partner problems with control over ejaculation and short duration of erection before ejaculation during sexual intercourse; (2) estimated IELT of 2 minutes or less; (3) experienced PE in >50% of sexual intercourse events, and (4) reported distress or difficulties associated with PE for greater than 6 months.

Participants underwent a face-to-face cognitive debriefing interview in their native language to discuss their understanding of the outcome items and the response choices. The cognitive debriefing interview was followed by an exploratory interview discussing 10 open-ended questions about the impact of PE on participants and their partners.

Qualitative research in Europe was conducted as part of the European qualitative study. A total of 141 participants completed the exploratory one-to-one interviews (95 male; 46 female). The results showed consistent experiences expressed by men with PE and partners of men with PE across the 5 European countries.

The translations for the PRO items and response choices were understood in all 5 European countries. No changes to language or word choice were deemed necessary to improve the translations/adaptations for France, Germany, Italy and the UK. To improve comprehension, one word change was made to the translated interpersonal difficulty item for Poland. The final versions of the translated PE-related items and response options were culturally and linguistically acceptable for the countries examined.

Sexual satisfaction for men was strongly influenced by their perception of their partner's level of satisfaction with the sexual experience. Male respondents often expressed frustration by an inability to provide sexual satisfaction and orgasm for their partners through vaginal intercourse. Men were also frustrated by their lack of control and inability to influence the condition. Men reported anxiety and reluctance for fear of disappointing their partner during sexual intercourse.

The effect of PE on the relationship varied depending on the nature of the relationship and the ability to cope with the condition. Factors that influenced the effect of PE on the relationship included the duration and stability of the relationship, presence of children in the home, and age of the couple. Older men in longer, more stable relationships experienced less distress and worry about the relationship than younger men. In general, couples in longer and more stable relationships found ways to communicate about and cope with PE; therefore, PE was perceived as less of a problem for the relationship. For younger men and those in shorter-term relationships, the extent and nature of communication between couples was an important driver in perceptions of personal and interpersonal distress. The degree of personal distress was attenuated in situations where there was good communication in the relationship.

Female partners of men with PE often expressed disappointment and dissatisfaction with their sexual relationship and attributed these problems to PE. Partners tended to view PE as having a greater negative effect on the overall relationship than men with PE. In some cases females were concerned about damaging their partner's ego and self-esteem, so communication regarding the condition was avoided.

The concerns and problems raised by men and their partners in these European exploratory interviews are consistent with the findings from the US focus groups.

Cognitive debriefing interviews in Europe were conducted as part of the European qualitative study. In total, 101 men aged 26 to 67 years (mean 40 years) and 49 female partners aged 23 to 61 years (mean 40 years) completed cognitive debriefing.

Men interpreted control over ejaculation as the ability to stop or hold back their ejaculation until they brought their partner to climax or until they wanted to ejaculate. For Italian men, it was also associated with the mental ability to control ejaculation. Response options were chosen based on length of time of vaginal intercourse (after insertion of the erect penis) before ejaculating and the ability to please their partner through prolonged vaginal intercourse.

Although interpretation of satisfaction with sexual intercourse varied slightly across the 5 countries, it was strongly associated with the partner's satisfaction. The satisfaction with sexual intercourse item was primarily interpreted as self and partner reaching climax, ultimately at the same time, or the attainment of pleasure for both individuals during the majority of sexual activities. Response options were selected based on a combination of length of time between penetration and ejaculation, the perceived degree of partner satisfaction, ability to bring their partner to climax (orgasm) during vaginal intercourse, and their sexual relationship.

Personal distress was associated with the perception of the impact on their partner and the intimate relationship with their partner. Respondents defined personal distress as feelings of embarrassment, annoyance, anxiety about possibly losing their partner due to her dissatisfaction with sexual intercourse, frustration, and worry about not being able to satisfy their partner sexually, and concern about their partner's feelings. In each language, there were small nuances associated with defining the word distress. French respondents used the term 'disappointment' or 'feeling upset' to discuss this concept. German respondents considered distress as dichotomous (have it or don't). Despite some minor variations in interpretation, there were no difficulties in understanding the concept of personal distress related to ejaculation. Responses were based on perceived partner satisfaction, the ability to discuss the issue with their partner, the level of tension and dissatisfaction associated with PE, and the sexual relationship with their partner.

For interpersonal difficulty, male respondents most often considered the current relationship with their partner, but there was some variation depending on the duration of the relationship. In general, older men and those in long-term relationships perceived PE as having less impact on their overall relationship. Older couples tended to use coping mechanisms, such as sexual acts other than vaginal intercourse to achieve mutual pleasure and sexual satisfaction. Younger men or those in shorter relationships expressed concern that PE would likely, and in some cases already had, ruined the relationship due to partner sexual dissatisfaction or the effects that the sexual relationship had on their overall relationship. Interpersonal difficulties were described as arguments, bad feelings, and fear of losing their partner. While all respondents understood this issue as the effect on their relationship, French respondents questioned the extent to which the item applied mainly to the effects on their sexual relationship or on their overall relationship. Several German subjects suggested that concrete examples of types of interpersonal difficulty be included to improve the outcome item (eg, burden on relationship, frequent arguments, etc.).

Overall, the results of the cognitive debriefing showed that the instructions, item content, and response options of the outcome measures were understood by men with PE and their partners across the 5 European countries. The measures were interpreted as intended and captured concepts important to men with PE and female partners.

Pan-Asia Cognitive Debriefing

Male and female versions of PE-related PRO measures used in the European qualitative study were translated into the following languages: mainland Chinese (China), traditional Chinese

(Hong Kong), Korean, Malay (Malaysia) Tagalog (Philippines), and Thai (Thailand). Full translation methodology based on FACIT Multilingual Translation Methodology was performed (Eremenco et al, 2005) (and all translations were certified). The traditional Chinese items were reviewed for use in Taiwan. English adaptations of the outcome measures were developed for use in the Philippines and Singapore.

Five men with PE in each country participated in the testing. After the translation process, cognitive debriefing of the translated items was performed to confirm the linguistic validity and acceptability of the items and provide information on the optimal language for self administration. Qualitative data concerning the participants' perceptions of the translation were also obtained.

The translations of PRO items and response choices were understood in Pan-Asian countries tested. No changes to language or word choice were deemed necessary to improve the translation in any country. Three Tagalog speakers in the Philippines expressed confusion with the translated word for distress. The language coordinator noted that there are numerous translations for distress in Tagalog. Since the meaning of the term used in the outcome item was not incorrect and in order to maintain consistency throughout the questionnaire no translation changes were made.

The final versions of the translated/adapted PE-related items and response options were found to be culturally and linguistically acceptable for the countries examined. An English adaptation of PRO items for use in Singapore was created but due to testing site difficulties was not tested. Female versions of the PRO measures were not tested.

In all countries, participants indicated they were comfortable with the outcome items and felt that they addressed issues that are important to their condition.

MEASUREMENT PROPERTIES OF THE PEP

Introduction

An evaluation of measurement properties of the PRO instruments used in clinical trials demonstrates the extent to which scores generated from the instrument are reliable, valid, and able to detect change. The measurement properties of a given instrument are influenced by several factors, including item design and mode of administration, study population, and scoring system.

Reliability is an assessment of the extent to which a PRO instrument yields consistent, reproducible estimates. Test-retest reliability measures the degree to which an instrument yields stable scores over time, assuming that the underlying condition of subjects has not changed. Internal consistency reliability can be measured to determine agreement among responses to different items if multiple highly correlated items are used to generate a single score for a given instrument. If a single-item score is used to measure a domain or subconcept, internal consistency is not an appropriate measure of reliability.

Validity is the extent to which the PRO measures what it is intended to measure. To evaluate validity, the instrument must be tested in the population of interest (disease severity, language/culture, and demographic characteristics) and in a context roughly similar to that in which the clinical trials are to be performed. At a minimum, the content validity of a PRO instrument should be demonstrated based on studies showing that the PRO instrument captures the issues that patients in the target population indicate are relevant and important Construct validity refers to the degree to which scores obtained from self-reported measures behave as expected given hypothesized relationships among concepts/constructs and the pattern of results. Construct validity is evaluated using prospectively defined hypotheses that predict relationships between known groups and among measured variables of both highly related (higher correlations or convergent) and less highly related (lower correlations or discriminant) constructs.

Ability to detect change is a measure of validity. If a concept is expected to change with treatment, the scores for a PRO instrument measuring that concept should change with effective treatment. If an ability to detect change cannot be demonstrated, the validity of the PRO instrument is doubtful. Ability to detect change is usually examined by effect size statistics where larger scores indicate higher effect sizes.

Data Sources

Data used to support the validity and reliability of the PEP were obtained from (1) US and European cognitive debriefing, (2) non-interventional, observational studies conducted in the US and Europe, and (3) three dapoxetine phase 3 clinical studies (Table 4).

Table 4: Data Sources for Measuring Performance of PEP

Data Source	Concepts Supported
Cognitive debriefing US cognitive debriefing study European qualitative study	• Recall period • Response scale
Observational studies US C-2004-004 European R096769-PRE-3004	• Response variability • Test-retest reliability • Construct validity
Dapoxetine phase 3 double-blind, randomized, placebo-controlled studies US C-2002-012 US C-2002-013 Withdrawal R096769-PRE-3002	• Recall period • Response variability • Construct validity • Ability to detect change

US Observational Study (C-2004-004)

This was a multicenter observational study of 4 weeks' duration. No treatment was administered to subjects during the study.

Participants were healthy heterosexual men, ≥18 years of age, in a stable, monogamous sexual relationship with a female partner ≥18 years for at least the previous 6 months. Subjects included men with and without PE who had not previously participated in a dapoxetine clinical trial. Premature ejaculation status was determined by the investigator using DSM-IV-TR diagnostic criteria. Subjects and their partners agreed to attempt sexual intercourse at least 2 times per week during the 4-week study period.

Subjects and their partners completed health outcome measures and recorded their IELT in event logs throughout the study. There were 3 study visits (screening, baseline, and follow-up) at approximately 2-week intervals.

European Observational Study (R096769-PRE-3004)

This was a multicenter, multinational (France, Germany, Italy, Poland, UK) observational study of 8 weeks' duration. No treatment was administered to subjects during the study.

Participants were men in general good health, ≥18 years of age, in a stable monogamous sexual relationship with the same woman for at least the previous 6 months, and with plans to maintain this relationship for the duration of the study. Premature ejaculation status was determined by the investigator using DSM-IV-TR diagnostic criteria. Subjects were blinded throughout the study with respect to the investigator's diagnosis of their PE or non-PE condition. The subject and his partner agreed to attempt sexual intercourse at least 2 times a week over the 8-week study period.

Subjects and their partners completed health outcome measures and recorded their IELT in event logs throughout the study. There were 3 study visits: visit 1 (screening/enrollment), visit 2 (week 4), and visit 3 (week 8).

Phase 3 Clinical Trials of Dapoxetine

The three phase 3 clinical trials used to evaluate the measurement properties of PROs were the 2 US studies (C-2002-012 and C-2002-013) and the withdrawal study, (R096769-PRE-3002).

Mode of Administration

Standardization of the mode of administration of patient-reported heath outcomes is important to optimize study quality and minimize inconsistencies in trial conduct (FDA, 2006). Standardization of the timing and order of administration of the PROs used to assess dapoxetine in phase 3 clinical studies was examined.

The mode of administration was standardized for all PROs in all phase 3 clinical studies, except for the order of administration of study assessments.

The PRO questionnaires were self-administered using paper and pencil after participants were given instructions. At the baseline visit, when the men and their partners were in the clinic, they completed the questionnaires independently in separate areas. After the baseline visit, men filled out questionnaires during their clinic visits and partners completed questionnaires at home and mailed them back.

The order of administration of the study assessments was not specified by protocol in the US studies (C-2002-012, C-2002-013). In the withdrawal (R096769-PRE-3002) and European (R096769-PRE-3001) studies, the protocol specified that self-administered assessments were to be performed before staff-administered assessments. In the Pan-Asia study (R096769-PRE-3003), the protocol specified that self-administered assessments were to be performed before other procedures or assessments.

Intravaginal ejaculatory latency time was always recorded using a stopwatch held by the partner reporting male duration.

Recall Period

Findings from survey research indicate that there is no single recall period that is most appropriate for capturing PROs (Leidy, 2005). Factors affecting recall include complexity of the task, saliency of the event, duration of the recall period, intervening events, response shift, and patient demographics. The magnitude of bias varies across PRO measures, with divergency particularly apparent in global assessments, health-related quality of life, symptoms (particularly pain), and satisfaction. Based on a review of the current literature, Leidy concluded that patients respond on the basis of their interpretations of the questions regardless of the recall period; however, the recall period can set the context for interpretation (Leidy, 2005). The recall period for PRO measures was examined in the US and European cognitive debriefing studies.

In the US studies (C-2002-012 and C2002-013), there was no recall at baseline (subjects were asked for real-time assessment, i.e., “at this time”) for PRO measures with a baseline assessment. At follow-up, recall was over the past month. The PGI was administered at 1 month, 2 months, and 3 months with reference to the start of the study.

In the US observational study (C-2004-004), baseline recall was over the past month and follow up recall was 2 weeks (applied to test-retest reliability only). In the European observational study (R096769-PRE-3004) and the withdrawal study (R096769-PRE-3002),

2 recall periods were used (1-month and immediate [per event]). Immediate recall was only applied to satisfaction with sexual intercourse.

In the US cognitive debriefing study, the majority of participants (89%) thought 1 month was an appropriate time frame for assessing control over ejaculation and satisfaction with sexual intercourse. In the European cognitive debriefing study, all of the participants thought that the past month or past 4 weeks was a relevant recall time period for assessing PROs.

Data from the European observational study (R096769-PRE-3004) and the withdrawal study (R096769-PRE-3002) suggest that for satisfaction with sexual intercourse a 1-month recall is strongly correlated with immediate recall (Table 5). In these studies, 2 different recall periods were used for subjects' assessment of satisfaction with sexual intercourse. For one measure (1-month recall), subjects responded to the question, "Over the past month was your satisfaction with sexual intercourse: very poor, poor, fair, good, very good." For the second measure (immediate recall), subjects evaluated their satisfaction after each occurrence of sexual intercourse by answering "yes" or "no" to the question, "Were you satisfied overall with this sexual experience." This information was recorded in an event log.

As shown in Table #, subjects who responded "very poor" or "poor" to the satisfaction with sexual intercourse question with a 1-month recall period generally reported fewer satisfactory sexual experiences based on the event log, while subjects who reported "good" or "very good" satisfaction with sexual intercourse reported a higher number of satisfactory experiences based on their event log data. The data indicate a strong association between subject responses to satisfaction with sexual experiences measured after each occurrence of intercourse (immediate recall) and measured using a single-item instrument with a 1-month recall.

Taken together, the available evidence suggests that a 1-month recall period should be adequate for reasonably reliable subject assessment of the PE condition.

Table 5: Number of Satisfactory Sexual Experiences Recorded on an Event Log (Immediate Recall) by Subject Response on Satisfaction with Sexual Intercourse (1-Month Recall): European Observational Study (R096769-PRE-3004) and Withdrawal Study (R096769-PRE-3002)

Satisfactory sexual experiences on event log (immediate recall)†	Responses to Patient-reported Satisfaction With Sexual Intercourse (1-Month Recall)*				
	Very poor	Poor	Fair	Good	Very good
European Observational Study R096769-PRE-3004					
Subjects with PE					
Mean (SD)	1.2 (2.71)	2.7 (2.64)	6.8 (3.89)	9.8 (3.48)	9.7 (5.39)
Median	0.0	2.0	6.0	9.0	8.5
Range	0 – 8	0 – 13	0 – 26	2 – 20	3 – 27
N‡	11	49	66	52	18
Subject without PE					
Mean (SD)	NA	3.8 (3.37)	8.4 (3.55)	10.7 (4.02)	13.0 (6.33)
Median		4.0	8.0	10.0	11.0
Range		0 – 8	0 – 18	5 – 40	4 – 48
N‡	0	6	69	503	320
Withdrawal Study R096769-PRE-3002§					
Subjects with PE					
Mean (SD)	0.6 (1.57)	1 (1.76)	3.8 (3.89)	7.4 (4.32)	10.5 (5.87)
Median	0.0	0.0	3.0	7.0	9.0
Range	0 – 9	0 – 11	0 – 33	0 – 31	1 – 35
N‡	47	207	272	359	165

*Subjects responded to the following question: "Over the past month was your satisfaction with sexual intercourse: very poor, poor, fair, good, very good."

†For each subject, the number of satisfactory sexual experiences recorded on the event log was calculated using the events with a 'yes' response to the question, "Were you satisfied overall with this sexual experience." Summary statistics were computed using these individual event numbers.

‡The number of subjects with non-missing responses for both the satisfaction question in the event log and the satisfaction with sexual intercourse single-item patient-reported outcome measure.

§Only subjects with PE were included in this study; hence, there are no data for subjects without PE.

NA= not applicable; PE = premature ejaculation; SD = standard deviation

Response Scale

The number of points in a response scale can influence the magnitude of change observed in an outcome measure. Intravaginal ejaculatory latency time is a continuous measure; therefore response scale is not a factor. All other outcome measures used in dapoxetine clinical studies are categorical scales. Control over ejaculation, satisfaction with sexual intercourse, and partner satisfaction with sexual intercourse were assessed using the following 5-point response scale: "very poor", "poor", "fair", "good", "very good." Personal distress and interpersonal difficulty were assessed on a 5-point response scale as follows: "not at all", "a little bit", "moderately", "quite a bit", "extremely."

The interval properties of PRO response scales were examined in the US and European cognitive debriefing studies. The equivalence of response choice relative to a VAS anchor was also examined in these studies.

The findings from the US cognitive debriefing study showed that the implied interval properties of the response scale for PE-related PRO items were understood by men with PE in the US. Respondents ordered the responses appropriately and reported generally equidistant intervals for the response options.

The information obtained from European cognitive debriefing was consistent with that from US cognitive debriefing. Male and female subjects in all European countries investigated reported that the response scales of PRO items were understood. Respondents rank ordered the responses consistently and generally reported equidistant intervals for the response options.

Response Variability

Response variability captures the extent to which the full range of item responses are represented in the population of interest (Patrick and Erickson, 1993; Streiner and Norman, 2003:67-68). If a PRO measure lacks variability or has floor and/or ceiling effects at baseline, interpretation can be problematic. A floor effect is a high response rate at the bottom of the scale so respondents cannot report worsening. A ceiling effect is a high response rate at the top of the scale so respondents cannot report improvement. Skewed distributions sometimes make PROs difficult to interpret. No standard has been established for indicating a floor effect or ceiling effect; however, 2/3 responses in the top or bottom category can be used as a general guide. In a study expected to measure improvement, a high floor effect at baseline would be expected and would not be as problematic as a floor effect in an observational study designed to measure change over time in either direction.

Response variability was addressed in 2 ways: (1) the range of item responses in the PE population in the US and European observational studies (C-2004-004 and R096769-PRE-3004) and (2) baseline distributions using pooled data from the US studies (C-2002-012 and C-2002-013).

The range of PRO item responses reported by men with PE in the US and European observational studies (C-2004-004 and R096769-PRE-3004) is summarized in Table 6. Response variability in each scale was demonstrated in that all response categories were utilized in both studies, with the exception of the “extremely” option for interpersonal difficulty in the European observational study.

Table 6: Range of Item Responses in the Premature Ejaculation (PE) Population for Patient-reported Outcome Measures: US and European Observational Studies (C-2004-004 and R096769-PRE-3004)

	Distribution of Response Categories	
	US C-2004-004	Europe R096769-PRE-3004
Subject Outcome Measure		
Control Over Ejaculation, n(%)	198 (100%)	196 (100%)
0 = very poor	44 (22.2%)	29 (14.8%)
1 = poor	98 (49.5%)	78 (39.8%)
2 = fair	43 (21.7%)	63 (32.1%)
3 = good	11 (5.6%)	22 (11.2%)
4 = very good	2 (1.0%)	4 (2.0%)
Satisfaction With Sexual Intercourse, n(%)	198 (100%)	196 (100%)
0 = very poor	16 (8.1%)	11 (5.6%)
1 = poor	46 (23.2%)	49 (25.0%)
2 = fair	75 (37.9%)	66 (33.7%)
3 = good	47 (23.7%)	52 (26.5%)
4 = very good	14 (7.1%)	18 (9.2%)
Personal Distress, n(%)	198 (100%)	196 (100%)
0 = not at all	2 (1.0%)	14 (7.1%)
1 = a little bit	21 (10.6%)	52 (26.5%)
2 = moderately	48 (24.2%)	44 (22.4%)
3 = quite a bit	92 (46.5%)	70 (35.7%)
4 = extremely	35 (17.7%)	16 (8.2%)
Interpersonal Difficulty, n(%)	198 (100%)	196 (100%)
0 = not at all	24 (12.1%)	73 (37.2%)
1 = a little bit	63 (31.8%)	62 (31.6%)
2 = moderately	50 (25.3%)	39 (19.9%)
3 = quite a bit	44 (22.2%)	22 (11.2%)
4 = extremely	17 (8.6%)	0 (0%)
Partner Outcome Measures		
Control Over Ejaculation, n(%)	196 (100%)	195 (100%)
0 = very poor	36 (18.4%)	28 (14.4%)
1 = poor	68 (34.7%)	67 (34.4%)
2 = fair	67 (34.2%)	67 (34.4%)
3 = good	17 (8.7%)	31 (15.9%)
4 = very good	8 (4.1%)	9 (4.6%)
Partner Outcome Measures (Continued)		
Satisfaction With Sexual Intercourse, n(%)	196 (100%)	195 (100%)
0 = very poor	16 (8.2%)	11 (5.6%)
1 = poor	39 (19.9%)	39 (20.0%)
2 = fair	66 (33.7%)	75 (38.5%)
3 = good	59 (30.1%)	55 (28.2%)
4 = very good	16 (8.2%)	15 (7.7%)

	Distribution of Response Categories	
	US C-2004-004	Europe R096769-PRE-3004
Personal Distress, n(%)	198 (100%)	195 (100%)
0 = not at all	19 (9.6%)	39 (20.0%)
1 = a little bit	34 (17.2%)	53 (27.2%)
2 = moderately	58 (29.3%)	44 (22.6%)
3 = quite a bit	64 (32.3%)	48 (24.6%)
4 = extremely	23 (11.6%)	11 (5.6%)
Interpersonal Difficulty, n(%)	198 (100%)	195 (100%)
0 = not at all	52 (26.3%)	86 (44.1%)
1 = a little bit	52 (26.3%)	47 (24.1%)
2 = moderately	44 (22.2%)	33 (16.9%)
3 = quite a bit	39 (19.7%)	24 (12.3%)
4 = extremely	11 (5.6%)	5 (2.6%)

In pooled data from US studies (C-2002-012 and C-2002-013), baseline mean (SD) IELT was 0.91 (0.48) (median = 0.85). No ceiling effects were observed for any of the PRO measures. There was a trend toward a floor effect for control over ejaculation (58.5% of subjects reported very poor control at baseline). A floor effect was not observed for any of the other PRO measures.

Because item distributions for some categorical PRO measures were skewed, all major analyses were run using parametric and non-parametric techniques. The non-parametric analyses using the Wilcoxon Rank-Sum test produced results comparable with those using parametric analyses. Since no substantive differences were found and no conclusions were changed using non-parametric analyses, parametric analyses are generally presented in this manual.

Test-Retest Reliability

The daily or weekly fluctuation in measures of PE has not been investigated. Although this is a potential limitation, test-retest reliability was examined in the US observational study (C-2004-004) with a retest period of 2 weeks and in the European observational study (R096769-PRE-3004) with a retest period of 4 weeks. Analyses were performed on 2 different populations: (1) subjects identified using external criteria as being stable over the observation period and (2) all eligible subjects for whom outcome data were collected at both time points.

To define stable subjects, global impression of change items for control over ejaculation and satisfaction with sexual intercourse were used. For IELT, stable subjects were defined as those whose response was “no change” on the item measuring global impression of change for control over ejaculation. For subject control over ejaculation and satisfaction with sexual intercourse, stable subjects were defined as those whose response was “no change” on the items measuring global impression of change for control over ejaculation and satisfaction with sexual intercourse, respectively. For subject-assessed personal distress and interpersonal difficulty and all partner outcomes, stable subjects were defined as those with an absolute

change in IELT <30 seconds since there was no item measuring global impression of change. An IELT change of <30 seconds was chosen using a PGI anchor, i.e., the mean change in IELT associated with subjects who reported "no change" on PGI was less than 30 seconds in pooled data from US studies.

The reproducibility of responses over time was analyzed using intraclass correlation coefficients (ICCs) (Deyo et al, 1991; Streiner and Norman, 2003:133-137). The ICC was estimated from an analysis of variance (ANOVA) model including subjects and visits as main effects.

The value of an ICC considered sufficient for group comparisons depends on the sample studied and the methods of analysis used. Intraclass correlation coefficients that exceed 0.70 are generally assumed to be sufficient for group comparisons (Nunally and Bernstein, 1994). Test-retest reliability of the PRO measures was examined against these benchmarks.

In the US observational study, the ICC across all outcome measures ranged from 0.66 to 0.88 for men with stable PE (Table 7). Using all eligible subjects, the ICC across all outcome measures ranged from 0.63 to 0.87 for men with PE (Table 8). As expected, ICCs for stable subjects were higher than those for all subjects. ICCs for the IELT were 0.88 and 0.87, respectively.

In the European observational study, the ICC for IELT in the stable population was high for men with PE (0.84) (Table 7), indicating good test-retest reliability over a 4-week period. Across all PRO measures, ICCs ranged from 0.66 to 0.84 for men with stable PE. Using all eligible subjects (Table 8), the ICC was high for IELT in men with PE (0.86). Across all outcome measures, ICCs ranged from 0.61 to 0.86 for men with PE.

The ICCs for all PRO measures in men with stable PE exceeded or were close to the recommended benchmark of 0.70 for group comparisons.

Table 7: Intraclass Correlation Coefficients Measuring Test-Retest Reliability of Patient-reported Outcome Measures – Stable Subjects: US and European Observational Studies (C-2004-004 and R096769-PRE-3004)

Baseline and Follow-up	US C-2004-004						Europe R096769-PRE-3004					
	PE		Non-PE		Total		PE		Non-PE		Total	
	n	ICC	n	ICC	n	ICC	n	ICC	n	ICC	n	ICC
Subject Outcome Measures												
Control Over Ejaculation	128	0.70	887	0.69	1015	0.82	125	0.66	725	0.61	850	0.76
Satisfaction with Sexual Intercourse	117	0.66	824	0.54	941	0.69	123	0.83	684	0.57	807	0.77
Personal Distress	89	0.74	294	0.73	383	0.85	95	0.70	211	0.46	306	0.79
Interpersonal Difficulty	89	0.73	294	0.74	383	0.84	95	0.67	211	0.66	306	0.80
Partner Outcome Measures												
Control Over Ejaculation	88	0.74	293	0.74	381	0.86	94	0.72	211	0.74	305	0.84
Satisfaction with Sexual Intercourse	88	0.77	292	0.61	380	0.78	94	0.67	211	0.50	305	0.70
Personal Distress	89	0.77	291	0.69	380	0.84	94	0.71	210	0.67	304	0.82
Interpersonal Difficulty	89	0.68	291	0.55	380	0.76	94	0.67	210	0.47	304	0.75
IELT	119	0.88	786	0.90	905	0.91	112	0.84	666	0.84	778	0.86

*Retest period = 2 weeks

†Retest period = 4 weeks

Stable subjects were defined as follows: IELT and subject control over ejaculation = "no change" on global impression of change for control over ejaculation question; subject satisfaction with intercourse = "no change" on global impression of change for satisfaction with sexual intercourse question; subject personal distress and interpersonal difficulty = change in IELT <30 seconds; partner control over ejaculation, satisfaction with intercourse, personal distress, and interpersonal difficulty = change in IELT <30 seconds.

ICC = Intraclass Correlation Coefficient; IELT = intravaginal ejaculatory latency time; PE = premature ejaculation.

Table 8: Intraclass Correlation Coefficients Measuring Test-Retest Reliability of Patient-reported Outcome Measures – All Eligible Subjects: US and European Observational Studies (C-2004-004 and R096769-PRE-3004)

Baseline and Follow-up	US C-2004-004*						Europe R096769-PRE-3004†					
	PE		Non-PE		Total		PE		Non-PE		Total	
	n	ICC	n	ICC	n	ICC	n	ICC	n	ICC	n	ICC
Subject Outcome Measures												
Control Over Ejaculation	194	0.63	1340	0.64	1534	0.77	193	0.61	890	0.60	1083	0.74
Satisfaction with Sexual Intercourse	194	0.64	1340	0.51	1534	0.66	193	0.75	888	0.57	1081	0.74
Personal Distress	194	0.64	1338	0.69	1532	0.81	193	0.65	889	0.50	1082	0.74
Interpersonal Difficulty	194	0.67	1337	0.66	1531	0.78	193	0.65	889	0.62	1082	0.75
Partner Outcome Measures												
Control Over Ejaculation	191	0.74	1339	0.65	1530	0.78	192	0.71	885	0.56	1077	0.72
Satisfaction with Sexual Intercourse	191	0.70	1338	0.57	1529	0.69	192	0.73	886	0.53	1078	0.69
Personal Distress	193	0.73	1338	0.65	1531	0.78	192	0.73	885	0.59	1077	0.77
Interpersonal Difficulty	193	0.74	1338	0.57	1531	0.73	192	0.68	884	0.51	1076	0.72
IELT	183	0.87	1176	0.87	1359	0.88	175	0.86	822	0.85	997	0.87

*Retest period = 2 weeks

†Retest period = 4 weeks

All eligible subjects = subjects for whom outcome data were collected at both time points.

ICC = Intraclass Correlation Coefficient; IELT = intravaginal ejaculatory latency time; PE = premature ejaculation.

Construct Validity

Construct validity of PRO measures was assessed in the US and European observational studies (C-2004-004 and R096769-PRE-3004) by:

1. Known-groups analyses examined the ability of the PRO measures to discriminate between populations known to be different. Mean responses for PE and non-PE groups were compared using a t-test for each outcome measure.

2. Convergent and discriminant validity analyses examined the degree of correlation between PRO measures and specific items/domains of established instruments addressing similar constructs or different constructs. The instruments used to assess convergent validity were the Golombok Rust Inventory of Sexual Satisfaction (GRISS) (Rust et al, 1988) and the Self-Esteem and Relationship Questionnaire (SEAR) (Althof et al, 2003). Neither instrument is specific for PE, but each has items and/or domains that are related to the PE condition. The Medical Outcome Study Short Form 36-Item Health Survey (MOS SF-36) was used to examine discriminant validity. Spearman-Rank correlation coefficients between and among endpoints were calculated.

Certain hypothesized relationships were prespecified in the protocol, while others were detailed in the statistical analysis plan. The following hypotheses were prespecified by the protocol:

1. Men with PE will exhibit lower scores on control over ejaculation and satisfaction with sexual intercourse than men without PE (known-groups analysis).

   This hypothesis was assessed by comparing the responses to items rating subject perceptions of control over ejaculation and satisfaction with sexual intercourse in the PE and non-PE groups via a distribution of responses for each outcome measure and a t-test comparing mean responses (interpreted as numeric scores) for the PE and non-PE groups.

2. Scores for subject perception of control over ejaculation will be more highly correlated with scores on measures related to perceptions of control over ejaculation than with scores on measures of different constructs.

   This hypothesis was assessed by examining the correlation of scores on the subject control over ejaculation item and related items in the GRISS. Specifically, it was hypothesized that moderate to high correlations would be observed between responses to the subject control item and items 4, 13, and 24 in the GRISS. Lower correlations were expected between the subject control item and the Physical Function domain score of the MOS SF-36.

3. Scores for subject perception of satisfaction with sexual intercourse will be more highly correlated with scores for measures related to satisfaction with sexual functioning than with scores on measures of different constructs.

   This hypothesis was assessed by examining the correlation of scores on the subject satisfaction with sexual intercourse item and related items in the GRISS and SEAR. Specifically it was hypothesized that moderate to high correlations would be observed between responses to the subject satisfaction with sexual intercourse item and item 8 in the GRISS and items 3, 7, and 8 in the SEAR. Lower correlations were also expected between the subject satisfaction with sexual intercourse item and the Physical Function domain score of the MOS SF-36.

The following additional hypotheses were prospectively defined in the statistical analysis plan.

Known-groups Analyses: In the known-groups analyses, for each single-item measure, the PRO response levels were interpreted as numeric scores and the difference between mean values for subjects with and without PE was tested using independent sample t-tests.

It was expected that as IELT increased there would be a corresponding increase in control over ejaculation, satisfaction with sexual intercourse, and partner satisfaction with sexual intercourse. To test this relationship, the IELT data from the US and European observational studies were stratified into lower, middle and upper tertiles.

Convergent and Discriminant Validity Hypotheses: Construct validity hypotheses were evaluated for the following PRO measures administered in the US and European observational studies at baseline: subject perception of control over ejaculation, satisfaction with sexual intercourse, personal distress, and interpersonal difficulty.

Construct Validity: Known-groups Validity

As shown in Table 9, statistically significant differences in baseline outcome measures between the PE and non-PE groups were observed for subject and partner control over ejaculation, satisfaction with sexual intercourse, personal distress, and interpersonal difficulty. These data indicate that the PROs are able to reliably differentiate between DSM-IV-TR defined PE and non-PE populations.

Table 9: Known-groups Validity of Patient-reported Outcome Measures: US and European Observational Studies (C-2004-004 and R096769-PRE-3004)

Baseline	PE			Non-PE			*P* value
Outcome Measures	N	Mean	SD	N	Mean	SD	
US Observational Study C-2004-004							
Subject Outcome Measures							
Control Over Ejaculation	198	1.14	0.86	1355	2.97	0.81	<0.0001
Satisfaction with Sexual Intercourse	198	1.98	1.04	1355	3.32	0.69	<0.0001
Personal Distress	198	2.69	0.92	1352	0.69	0.85	<0.0001
Interpersonal Difficulty	198	1.83	1.16	1351	0.28	0.62	<0.0001
Partner Outcome Measures							
Partner Control Over Ejaculation	196	1.45	1.02	1353	3.28	0.81	<0.0001
Partner Satisfaction with Sexual Intercourse	196	2.10	1.07	1352	3.36	0.72	<0.0001
Partner Personal Distress	198	2.19	1.15	1352	0.41	0.77	<0.0001
Partner Interpersonal Difficulty	198	1.52	1.23	1352	0.22	0.60	<0.0001
IELT (minutes)	190	3.00	4.32	1215	9.15	7.17	<0.0001
European Observational Study R096769-PRE-3004							
Subject Outcome Measures							
Control Over Ejaculation	196	1.45	0.95	899	3.03	0.77	<0.0001
Satisfaction with Sexual Intercourse	196	2.09	1.05	898	3.27	0.62	<0.0001
Personal Distress	196	2.11	1.11	899	0.41	0.69	<0.0001
Interpersonal Difficulty	196	1.05	1.01	899	0.11	0.38	<0.0001
Partner Outcome Measures							
Partner Control Over Ejaculation	195	1.67	1.07	900	3.14	0.81	<0.0001
Partner Satisfaction with Sexual Intercourse	195	2.12	1.00	901	3.20	0.67	<0.0001
Partner Personal Distress	195	1.69	1.21	900	0.29	0.60	<0.0001
Partner Interpersonal Difficulty	195	1.05	1.16	899	0.09	0.36	<0.0001
IELT (minutes)	182	3.27	3.53	844	9.99	6.88	<0.0001

IELT = intravaginal ejaculatory latency time; PE = premature ejaculation.

Known-groups validity was also observed when PRO scores were stratified by IELT tertiles representing 3 different severity levels, i.e., upper (mild), middle (moderate), and lower (severe). As shown in Table 10, shorter latency time resulted in poorer perceived control over ejaculation and less satisfaction with sexual intercourse for both men and their partners. In the US observational study, all subject and partner PRO items, except partner perception of interpersonal difficulty, showed statistically significant differences between tertile scores. In the European observational study, all subject and partner PRO items, except subject perception of interpersonal difficulty, showed statistically significant differences between tertile scores.

Table 10: Known-groups Analyses by IELT Tertile – All Eligible Subjects (PE + Non-PE): US and European Observational Studies (C-2004-004 and R096769-PRE-3004)

Baseline	IELT (minutes)										
US Observational Study C-2004-004											
	Lower (0 – <4.5)			Middle (4.5 – <9)			Upper (≥9)			*P* value	
	N	Mean	SD	N	Mean	SD	N	Mean	SD	Middle vs. Lower	Upper vs. Middle
Subject Outcome Measures											
Control Over Ejaculation	472	2.06	1.12	467	2.88	0.82	462	3.27	0.67	<0.0001	<0.0001
Satisfaction with sexual Intercourse	472	2.75	1.04	467	3.25	0.72	462	3.51	0.60	<0.0001	<0.0001
Personal Distress	472	1.61	1.21	465	0.74	0.90	461	0.50	0.81	<0.0001	<0.0001
Interpersonal Difficulty	472	0.90	1.12	464	0.34	0.68	461	0.21	0.61	<0.0001	0.0027
Partner Outcome Measures											
Control Over Ejaculation	471	2.34	1.22	467	3.25	0.81	461	3.53	0.62	<0.0001	<0.0001
Satisfaction with sexual Intercourse	470	2.77	1.05	467	3.28	0.76	461	3.51	0.66	<0.0001	<0.0001
Personal Distress	473	1.17	1.23	467	0.51	0.87	460	0.28	0.71	<0.0001	<0.0001
Interpersonal Difficulty	473	0.68	1.06	467	0.28	0.69	460	0.22	0.62	<0.0001	0.1438
European Observational Study R096769-PRE-3004											
	Lower (0 – <4.6)			Middle (4.6 – <10.3)			Upper (≥10.3)			*P* value	
	N	Mean	SD	N	Mean	SD	N	Mean	SD	Middle vs. Lower	Upper vs. Middle
Subject Outcome Measures											
Control Over Ejaculation	338	2.10	1.14	343	2.88	0.78	342	3.24	0.69	<0.0001	<0.0001
Satisfaction with sexual Intercourse	338	2.61	1.03	342	3.16	0.69	342	3.36	0.60	<0.0001	<0.0001
Personal Distress	338	1.33	1.24	343	0.54	0.81	342	0.33	0.64	<0.0001	0.0001
Interpersonal Difficulty	338	0.62	0.91	343	0.13	0.41	342	0.08	0.33	<0.0001	0.1281
Partner Outcome Measures											
Control Over Ejaculation	337	2.31	1.20	342	3.00	0.82	343	3.31	0.74	<0.0001	<0.0001
Satisfaction with sexual Intercourse	337	2.58	0.98	343	3.08	0.70	343	3.34	0.65	<0.0001	<0.0001
Personal Distress	336	1.03	1.21	343	0.41	0.72	343	0.18	0.47	<0.0001	<0.0001
Interpersonal Difficulty	336	0.56	0.98	342	0.13	0.47	343	0.06	0.29	<0.0001	0.0075

IELT = intravaginal ejaculatory latency time; PE = premature ejaculation.

Construct Validity: Convergent Validity

Prospectively defined correlation criteria were analyzed by Spearman-Rank correlations for PRO measures in the US and European observational studies (C-2004-004 and R096769-PRE-3004). Results for the PE and non-PE groups combined in the US observational study are shown in Table 11.

Spearman-Rank correlation coefficients for control over ejaculation and male GRISS Questions 4, 13, and 24 were ≥0.4, indicating moderate to stronger associations. The correlation of the control over ejaculation item with the MOS SF-36 Physical Functioning subscale was weak (0.10), supporting the pre-specified hypothesis.

Spearman-Rank correlation coefficients for satisfaction with sexual intercourse and SEAR Questions 3, 7, and 8 were also ≥0.4, indicating moderate or stronger associations. The

correlation coefficient for satisfaction with sexual intercourse and male GRISS Question 8 (0.29) did not meet the criteria for moderate or stronger association.

Correlation between personal distress and the SEAR Self-Esteem scale and between interpersonal difficulty and the SEAR Sexual Relationship and Overall Relationship scales were all ≥0.4, indicating moderate to stronger associations. The correlation of personal distress with the MOS SF-36 Physical Functioning subscale was weak in all cases, supporting prespecified hypotheses.

Table 11: Spearman-Rank Correlation Coefficients for Correlation Analyses Between Test Patient-reported Outcome Measures and Other Patient-reported Outcome Measures of the Same or Different Constructs – All Eligible Subjects (PE + Non-PE): US Observational Study C-2004-004

	Control	Satisfaction	Distress	Difficulty
GRISS: 5 response options: never, hardly ever, occasionally, usually, always				
Q4: Are you able to delay ejaculation during intercourse if you think you may be "coming" too quickly?	-0.61*			
Q8: Do you enjoy having sexual intercourse with your partner?		-0.29		
Q13: Can you avoid ejaculating too quickly during intercourse?	-0.65*			
Q24: Do you ejaculate without wanting to almost as soon as your penis enters your partner's vagina?	-0.53*			
SEAR: 5 response options: almost always/always, most times, sometimes, a few times, almost never/never				
Sexual Relationship Scale (Items 1 through 8)				-0.56*
Self-Esteem Scale (Items 9 through 12)			-0.52*	
Overall Relationship Scale (Items 13 and 14)				-0.42*
Q3: I was satisfied with my sexual performance		0.57*		
Q7: I was satisfied with our sex life		0.59*		
Q8: My partner was unhappy with the quality of our sexual relations		0.48*		
MOS SF-36				
Physical Functioning Scale (10 items comprising Q3)	0.10	0.07	-0.12	-0.16

*Correlation coefficients ≥0.4 indicating moderate to stronger associations.

Test patient-reported outcome measures = control over ejaculation (Control), satisfaction with sexual intercourse (Satisfaction), personal distress (Distress), and interpersonal difficulty (Difficulty).

All correlation coefficients were statistically significantly different from 0 at $P<0.01$ except the correlation coefficient between severity and SF-36 Physical Functioning Scale.

GRISS=Golombok Rust Inventory of Sexual Satisfaction, Q=Question, SEAR=Self-Esteem and Relationship Questionnaire, MOS SF-36= Medical Outcome Study Short-Form 36.

Table 12 presents the results for the PE and non-PE groups combined in the European observational study. The correlation coefficients between the PRO measures and related items of other questionnaires, i.e., GRISS (Male), SEAR, and International Index of Erectile Function (IIEF) (convergent validity), were ≥0.4, showing moderate or strong associations; whereas, the correlations between the PRO measures and the unrelated MOS SF-36 Physical Functioning Subscale (discriminant validity) were less (≤0.1), showing a weak association. The results confirm prospectively defined hypotheses supporting the validity of these PRO measures.

Taken together, Spearman-Rank correlations based on prospectively defined hypotheses in both the US and European observational studies provided strong evidence supporting the validity of these PRO measures.

Table 12: Spearman-Rank Correlation Coefficients for Correlation Analyses Between Test Patient-reported Outcome Measures and Other Patient-reported Outcome Measures of the Same or Different Constructs – All Eligible Subjects (PE + Non-PE): European Observational Study R096769-PRE-3004

	Subject				Partner
	Control	Satisfaction	Distress	Difficulty	Satisfaction
GRISS: 5 response options: never, hardly ever, occasionally, usually, always					
Male GRISS					
Q4: Are you able to delay ejaculation during intercourse if you think you may be "coming" too quickly?	-0.58*				
Q8: Do you enjoy having sexual intercourse with your partner?		-0.42*			
Q13: Can you avoid ejaculating too quickly during intercourse?	-0.57*				
Q24: Do you ejaculate without wanting to almost as soon as your penis enters your partner's vagina?	-0.51*				
Q27: Do you ejaculate by accident just before your penis is about to enter your partner's vagina?	-0.41*				
Female GRISS					
Q22: Do you feel dissatisfied with the amount of time your partner spends on intercourse itself					-0.48*
Premature Ejaculation Scale	-0.62*				
SEAR: 5 response options: almost always/always, most times, sometimes, a few times, almost never/never					
Q3: I was satisfied with my sexual performance		0.52*			
Q7: I was satisfied with our sex life		0.58*			
Q8: My partner was unhappy with the quality of our sexual relations		0.41*			
Self-Esteem Scale (Items 9 through 12)			-0.52*		
Overall Relationship Scale (Items 13 and 14)				-0.45*	
IIEF:					
Q7: When you attempted sexual intercourse how often was it satisfactory for you (response options range: almost always/always to almost never/never)		0.54*			
Q8: How much have you enjoyed sexual intercourse (response options range: very highly enjoyable to not enjoyable)		0.62*			
Overall Satisfaction Scale (Items 13, 14)		0.65*			
MOS SF-36					
Physical Functioning Scale (10 items comprising Q3)	0.07	0.10	-0.08	-0.09	

*Correlation coefficients ≥0.4 indicating moderate to stronger associations.

Test patient-reported outcome measures = control over ejaculation (Control), satisfaction with sexual intercourse (Satisfaction), personal distress (Distress), and interpersonal difficulty (Difficulty).

GRISS=Golombok Rust Inventory of Sexual Satisfaction, IIEF=International Index of Erectile Function; Q=Question, SEAR=Self-Esteem and Relationship Questionnaire, MOS SF-36= Medical Outcome Study Short Form 36-Item Health Survey.

Ability to Detect Change

Ability to detect change was evaluated by calculating an effect size using data from the withdrawal study (R096769-PRE-3002) which included the 4 PRO measures: control over ejaculation, satisfaction with sexual intercourse, personal distress, and interpersonal difficulty.

Effect size for each PRO was calculated according to the following formula:

$$\text{Effect size} = \frac{\text{mean change value in patients whose condition changed} - \text{mean change value in stable patients}}{\text{standard deviation of mean change value in stable patients}}$$

Stable patients were defined as those who rated "No Change" on the PGI. For patients whose condition changed, a separate calculation was performed for each level of improvement on the PGI, i.e., "Slightly Better," "Better," and "Much Better." Data from all treatment groups were combined.

Table 13 shows the effect sizes of PRO measures anchored to the PGI in the withdrawal study (R096769-PRE-3002).

Across all PRO measures, effect sizes ranged from 0.51 (anchored to PGI ratings of 'slightly better') to 3.51 (anchored to PGI ratings of 'much better'). These effect sizes reach or are greater than effect sizes considered medium or large by Cohen (1988).

Table 13 also shows that the effect sizes for all PRO measures increased with increasing improvement in the PGI, providing evidence not only of ability to detect change but also ability to distinguish between different magnitudes of improvement (e.g., slightly better, better, much better).

Table 13: Ability to Detect Change – Effect Size: Withdrawl Study (R096769-PRE-3002)

PRO Measure Level of Improvement in PGI	Mean Change from Baseline* A	SD B	Effect Size |A – A (no change)| / B (no change)
Control over ejaculation			
No change (n=327)	0.39	0.69	
Slightly better (n=335)	1.26	0.77	1.26
Better (n=226)	1.99	0.84	2.32
Much better (n=172)	2.81	0.96	3.51
Personal distress			
No change (n=327)	-0.40	0.91	
Slightly better (n=335)	-1.07	0.91	0.74
Better (n=226)	-1.77	0.98	1.51
Much better (n=173)	-2.46	1.00	2.26
Satisfaction with sexual intercourse			
No change (n=327)	0.14	0.83	
Slightly better (n=335)	0.84	0.88	0.84
Better (n=226)	1.57	0.96	1.72
Much better (n=172)	2.23	1.04	2.52
Interpersonal difficulty			
No change (n=327)	-0.28	0.98	
Slightly better (n=335)	-0.78	1.00	0.51
Better (n=226)	-1.33	1.00	1.07
Much better (n=173)	-1.68	1.09	1.43

*At week 9 or the last available postbaseline evaluation.
PGI = patient global impression of change; SD = standard deviation.

Responder Definition

One approach to defining a treatment responder based on PROs is to anchor change in the outcome scores to subjects' rating of global impression of change in their condition. This approach was applied using the PGI to anchor change in control over ejaculation. Responses were combined across treatment groups using pooled data from the 2 US studies (C-2002-012 and C-2002-013). Based on these results, a ≥2 category improvement in control over ejaculation was selected for further evaluation.

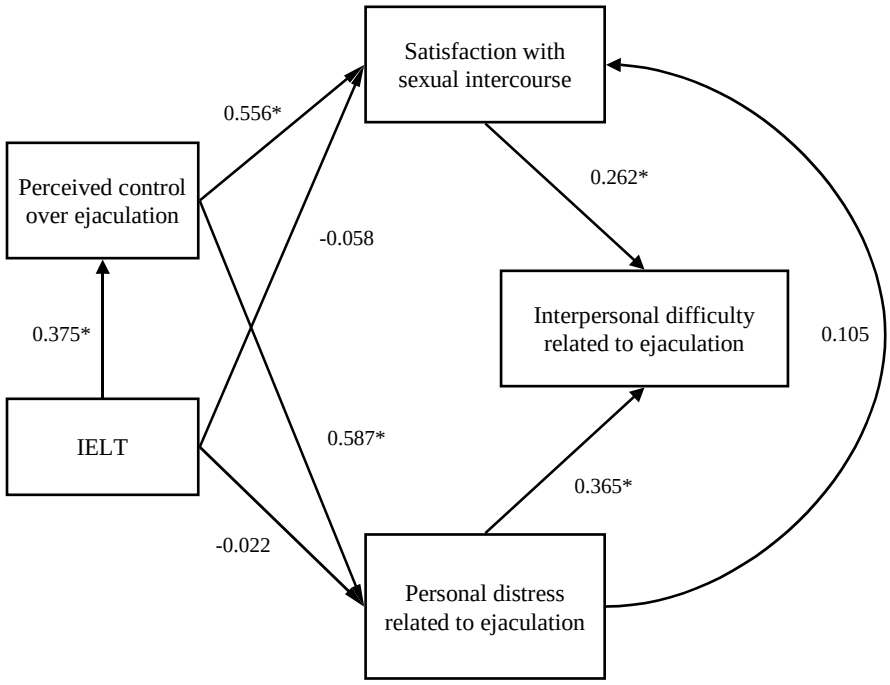
The strength of the ≥2 category improvement in control over ejaculation based on the PGI findings was further evaluated by (1) comparing change in outcome variables between subjects who did and did not meet this criterion in clinical trials and (2) comparing response profiles of men who met this criterion and men without PE in observational studies.

The ability of the defined treatment responder (*≥2 category increase in control over ejaculation plus a ≥ 1 category decrease in personal distress*) and its control over ejaculation component to distinguish between placebo and active treatment was assessed *retrospectively* based on response rates derived from the 2 US studies (pooled data) and the withdrawal study (R096769-PRE-3002).

As shown by path analysis (Figure 2), a man's perception of control over ejaculation plays a central role in relation to other effects of PE, having significant direct effects on satisfaction

with sexual intercourse and personal distress. Based on these findings, control over ejaculation was selected as the outcome of interest in defining a treatment responder.

Figure 2: Model of Domains Relevant to Premature Ejaculation Using Path Analysis: US Observational Study (C-2004-004)



Arrows indicate regression coefficients for the paths between domains. Low scores indicate worse outcomes. A positive coefficient indicates that a favorable score on one measure is associated with a favorable score on another measure.

*Critical ratio >1.96 indicates significant direct effect at $P \leq 0.05$.

IELT = intravaginal ejaculatory latency time; categorized in to 15-second intervals.

A summary of the anchor-based approach used to assess the association between PGI and various category changes in control over ejaculation using pooled data from the 2 US studies (C-2002-012 and C-2002-013) is presented in Table 1. As shown in the table, 95.7% of subjects with a ≥2 category increase in control over ejaculation reported some degree of improvement in their condition. Based on this finding, a ≥2 category increase in control over ejaculation was selected for further evaluation.

Table 14: Association Between Patient Global Impression (PGI) of Change and Category Change in Control Over Ejaculation From Baseline to Study Endpoint: US Phase 3 Studies Pooled Data (C-2002-012 and C-2002-013)

	Number (%) of Subjects Meeting Control Over Ejaculation Definition			
PGI Response at study endpoint	No Change	≥1 Change	≥2 Change	≥3 Change
N	748	1502	748	276
Much worse	2 (0.3%)	1 (0.1%)	0	0
Worse	15 (2.0%)	4 (0.3%)	0	0
Slightly worse	24 (3.2%)	7 (0.5%)	2 (0.3%)	0
No change	619 (82.8%)	400 (26.6%)	30 (4.0%)	2 (0.7%)
Slightly better	80 (10.7%)	509 (33.9%)	214 (28.6%)	19 (6.9%)
Better	5 (0.7%)	371 (24.7%)	296 (39.6%)	112 (40.6%)
Much better	3 (0.4%)	210 (14.0%)	206 (27.5%)	143 (51.8%)

Study endpoint = week 12 or the last available postbaseline evaluation.

N = number of subjects who had at least 1 postbaseline evaluation for the PGI within the subpopulation who had the corresponding category change in control over ejaculation (columns). Percentages based on N.

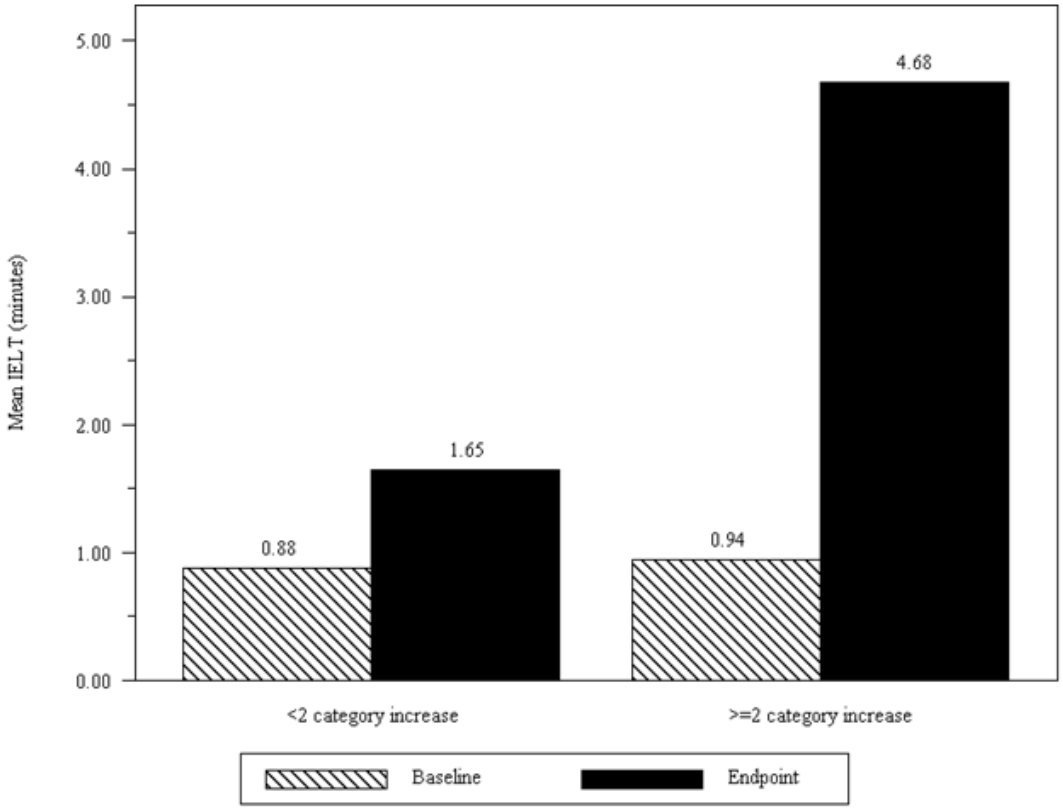
Shaded area indicates subjects reporting improvement in PGI and a ≥2 category increase in control over ejaculation.

The strength of the ≥2 category increase in control over ejaculation as a measure of a meaningful treatment effect was further evaluated by (1) comparing change in outcome variables between subjects who did and did not meet this criterion in clinical trials and (2) comparing response profiles of men who met this criterion and men without PE in observational studies. This evaluation is described below using the following outcome variables: IELT, satisfaction with sexual intercourse, and personal distress.

Taken together, the data provide adequate evidence that a ≥2 category increase in control over ejaculation represents a meaningful treatment effect.

In pooled data from the US studies (C-2002-012 and C-2002-013), the men who achieved a ≥2 category increase in control over ejaculation had a mean average IELT of 4.68 minutes at endpoint compared with 0.94 minutes at baseline. For those who had less than a 2 category increase in control over ejaculation, mean average IELT was 1.65 minutes at study endpoint versus 0.88 minutes at baseline (Figure 3).

Figure 3: Intravaginal Ejaculatory Latency Time (IELT) at Baseline and Study Endpoint for Subjects Who Did and Did Not Achieve a ≥2 Category Increase in Control Over Ejaculation: US Phase 3 Studies Pooled Data (C-2002-012 and C-2002-013)



≥2 category = ≥2 category increase in control over ejaculation at study endpoint
<2 category = <2 category increase in control over ejaculation at study endpoint.
Study endpoint = week 12 or the last available postbaseline evaluation.

Number Needed to Treat (NNT)

While percent response is one way to express the benefit of a medication as observed in a randomized clinical trial, it doesn't directly account for the percentage of patients who respond to a placebo. NNT estimates do adjust for the placebo response rate. The NNT represents the number of patients who need to be treated for 1 patient to achieve a specified change in an outcome that would not have occurred had the patient received placebo (net of placebo). Ideally, the NNT for a medication would be 1, where every single patient who receives the medication benefits from the treatment.

The NNT estimates were derived using the following formula, which requires grouping subjects by whether they improved by a specified outcome level or did not improve (remained the same or deteriorated):

$$NNT = 1/(p_T - p_C)$$

Where,

p_T is the proportion of patients who improved in the treatment group, and
p_C is the proportion of patients who improved in the control group

Numbers needed to treat were derived based on the improvement thresholds for IELT (≥1 minute, ≥2 minutes, ≥3 minutes) and percentage of responders (a ≥2 category increase in control plus a ≥1 category decrease in distress).

There is no established interpretation for an acceptable NNT. To help understand the findings for dapoxetine, NNTs were calculated based on published phase 3 studies for currently available therapies for related indications (erectile dysfunction and other urological conditions).

NNTs for dapoxetine based on IELT thresholds derived from the European (R096769-PRE-3001) and Pan-Asia (R096769-PRE-3003) studies is presented in Table 15. Using this table, a clinician would need to treat 4 to 5 patients with dapoxetine 30 mg or 3 to 4 patients with dapoxetine 60 mg for 1 patient to achieve change in IELT ≥1 min. Across all IELT thresholds in the 2 studies, NNTs ranged from 4 to 12 for dapoxetine 30 mg and from 3 to 5 for dapoxetine 60 mg.

NNTs for dapoxetine based on the responder definition is presented in Table 16. Using this table, a clinician would expect to treat 8 patients with dapoxetine 30 mg or 4 to 7 patients with dapoxetine 60 mg for 1 patient to achieve at least a 2-category increase in control over ejaculation and at least a 1-category decrease in personal distress.

The NNTs derived for dapoxetine in PE can be compared to NNTs derived for approved treatments for other types of male sexual dysfunction. For example, the NNTs for Levitra® ranged from 4.6 to 2.6, for the 5 mg and 20 mg doses, respectively, based on the number of subjects with erectile dysfunction who had an IIEF score of ≥26 (ie, "Return to normal functioning") at study endpoint (Padma-Nathan et al, 2007). For Viagra®, NNTs range from 3.0 to 5.5 for the 100 mg and 25 mg doses, respectively, based on the response criteria of 60% of intercourse attempts being successful. (Moore et al, 2002). The NNTs for dapoxetine in PE can also be compared with those for treatment of other urologic conditions, such as benign prostatic hyperplasia (BPH). For example, the NNT for avoiding acute urinary retention over 24 months was 49 (Edwards et al, 2002). The NNTs for prevention of overall clinical progression of BPH were 13.7 for doxazosin, 15.0 for finasteride, and 8.4 for combination therapy (McConnell et al, 2003).

Taken together, NNT estimates for dapoxetine treatment of PE based on the responder definition (NNTs of 4 to 8) were similar to those derived for approved treatments of erectile dysfunction (NNTs of 3 to 6) and were lower than those for treatments of benign prostatic hyperplasia (NNTs of 8 to 49).

Table 15: Number Needed to Treat Based on IELT Threshold: European (R096769-PRE-3001) and Pan-Asia (R096769-PRE-3003) Phase 3 Studies

Study Change in IELT (min)	Placebo	Dapoxetine 30 mg		Dapoxetine 60 mg	
	n (%)*	n (%)*	NNT	n (%)*	NNT
R096769-PRE-3001					
≥ 1	81 (24.0%)	175 (48.2%)	4.1	206 (58.2%)	2.9
≥ 2	50 (14.8%)	108 (29.8%)	6.7	140 (39.6%)	4.0
≥ 3	35 (10.4%)	69 (19.0%)	11.6	105 (29.7%)	5.2
R096769-PRE-3003					
≥ 1	143 (41.8%)	212 (63.7%)	4.6	214 (64.7%)	4.4
≥ 2	81 (23.7%)	146 (43.8%)	5.0	175 (52.9%)	3.4
≥ 3	47 (13.7%)	103 (30.9%)	5.8	121 (36.6%)	4.4

*Number and percentage of subjects achieving a specific level of change or greater in IELT at study endpoint (R096769-PRE-3001, week 24; R096769-PRE-3003, week 12).
NNT = number needed to treat.

Table 16: Number Needed to Treat Based on Responder Definition: European (R096769-PRE-3001) and Pan-Asia (R096769-PRE-3003) Phase 3 Studies

Study	Placebo	Dapoxetine 30 mg		Dapoxetine 60 mg	
	n (%)*	n (%)*	NNT	n (%)*	NNT
R096769-PRE-3001	45 (13.0%)	91 (25.3%)	8.1	131 (37.1%)	4.1
R096769-PRE-3003	74 (21.7%)	114 (34.7%)	7.7	125 (37.2%)	6.5

*Number and percentage of responders at study endpoint (R096769-PRE-3001, week 24; R096769-PRE-3003, week 12).
Responder = subjects with ≥2 category increase in control over ejaculation and ≥1 category decrease in personal distress at study endpoint
CI = confidence interval;
NNT = number needed to treat.

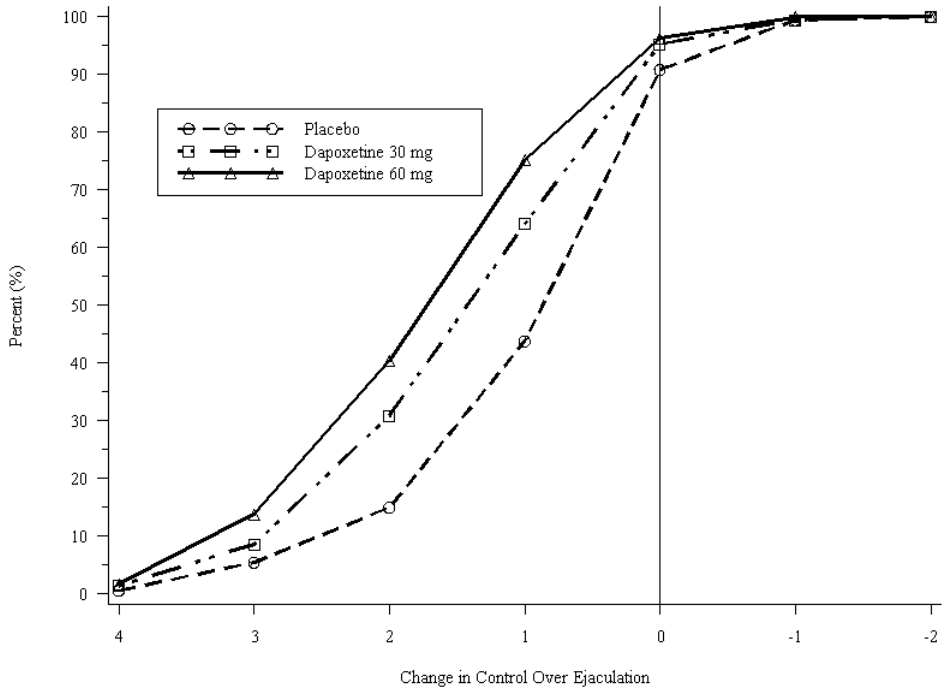
Cumulative Distribution

Treatment benefit of dapoxetine was examined *prospectively* based on the responder definition, which was included in the European (R096769-PRE 3001) and Pan-Asia (R096769-PRE 3003) studies. Three key secondary endpoints, including the responder definition, were finalized prior to database lock of these studies.

Analysis of the cumulative distribution of subjects' response in each active treatment group compared with response in the control group can help in evaluating the consistency of effect across the entire distribution and the extent to which overall results are driven by outliers who improve or worsen more than others. A cumulative distribution curve provides information on the type of responses that contributed to the mean group response and may be more informative than a simple point estimate of the difference between group mean changes.

Cumulative distribution curves are presented for the control over ejaculation outcome using data from the European (R096769-PRE-3001) and Pan-Asia (R096769-PRE-3003) clinical trials. This item was shown to play a central role in a man's interpretation of his PE condition. The spectrum of change in control over ejaculation at study endpoint in the dapoxetine and placebo treatment groups in the European (R096769-PRE-3001) and Pan-Asia (R096769-PRE-3003) studies is illustrated in Figure 4 and Figure 5, respectively. In both studies, for all possible change values, the percentage of subjects achieving a specific level of change in control over ejaculation was greater in dapoxetine-treated subjects than placebo patients.

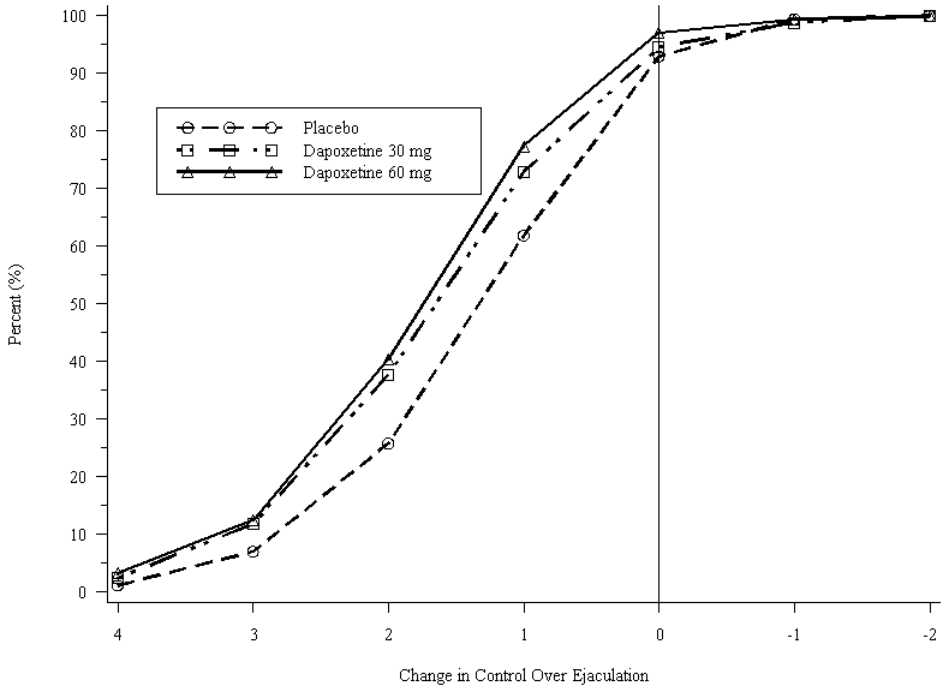
Figure 4: Cumulative Distribution of Change in Control Over Ejaculation at Study Endpoint: European Phase 3 Study (R096769-PRE-3001)



Study endpoint = week 24 or the last available postbaseline evaluation.

The value on the y-axis represents the percentage of subjects achieving a given level of change or better in control over ejaculation.

Figure 5: Cumulative Distribution of Change in Control Over Ejaculation at Study Endpoint: Pan-Asia Phase 3 Study (R096769-PRE-3003)



Study endpoint = week 12 or the last available postbaseline evaluation.

The value on the y-axis represents the percentage of subjects achieving a given level of change or better in control over ejaculation.

SCORING THE PEP

Each item (domain) of the PEP is assessed on its own; responses are rated on a five-point scale; and higher scores indicate better functioning.

Depending on the specific clinical research objective, one can focus on the individual measures, use the PEP as a profile, or use an overall index score.

The PEP index score is derived as the average score of the four individual PEP items. The reliability and validity of the PEP index score was evaluated based on ICCs, known-groups validity, and the ability to detect change in PE, as described previously. Several principal components analyses were conducted on data from both observational studies to determine the adequacy of representing the information from the four PEP items as a single-index value. The Kaiser criterion of retaining components with an eigenvalue of > 1.0 was applied to reduce the dimensionality of the index (Kaiser 1960).

RECOMMENDATIONS FOR USE

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SUMMARY

From consensus-based definitions (e.g., ICD-10, DSM-IV), the following domains emerge as key elements for diagnosing premature ejaculation (PE):

- Short ejaculatory latency
- Lack of perceived control over ejaculation
- Negative impact of the condition including personal distress or interpersonal difficulty related to ejaculation

Premature ejaculation is a self-reported condition. Assessment of PE in clinical trials is most often based on intravaginal ejaculatory latency time (IELT) as measured by a stopwatch. An IELT measure alone, however, does not provide a comprehensive characterization of the PE condition and its consequences. Thus, it is necessary to include patient-reported outcomes (PROs) in assessment of treatment benefit. A PRO is any report coming directly from patients, without interpretation by physicians or others, about how they function or feel in relation to a health condition and its therapy.

The purpose of this User's Manual is to: (1) to examine the development / content validity of the PEP; (2) to evaluate the measurement properties of the PEP; and (3) to examine the process used to develop a responder definition of the PEP.

The development of the PEP was based on concepts that are important to men with PE. A conceptual framework was developed followed by the development of the measure and refinement based on qualitative research and cognitive debriefing. The measurement properties of the PEP were examined in observational studies and clinical trials. The measure was adapted for use cross-culturally.

The primary concepts associated with PE that emerged during focus groups in the United States were satisfaction with intercourse, distress (e.g., feelings of inadequacy, disappointment, frustration, anxiety, anger), the male/partner relationship, and ejaculatory control. Cognitive debriefing of the PEP developed to measure these concepts showed that the instructions, item content, and response options were understood and appropriately interpreted by men with PE in the US.

European qualitative research, based on one-to-one interviews, found that the concerns and problems raised by men with PE and their partners across 5 countries (France, Germany, Italy, Poland, and United Kingdom) were consistent with the findings from the US focus groups. European research focused on 4 PE-related PRO measures: control over ejaculation, satisfaction with sexual intercourse, personal distress, and interpersonal difficulty. The final versions of the translated PRO items and response options were shown to be culturally and linguistically acceptable in the countries examined. Cognitive debriefing showed that the instructions, item content, and response options of the outcome measures were understood and appropriately interpreted by men with PE and their partners across the 5 European countries.

The PEP was translated/adapted for the following Pan-Asian countries: mainland China, Hong Kong, Malaysia, Philippines, and Thailand. The final versions of the PEP items and response choices were understood and culturally and linguistically acceptable in the countries examined. Qualitative research found that participants with PE were comfortable with the items and felt that they addressed issues that are important to their condition.

Measurement Properties Patient-reported Outcomes Related to Premature Ejaculation

Discussion of measurement properties focuses on the following 4 PRO measures: control over ejaculation, satisfaction with sexual intercourse, personal distress, and interpersonal difficulty.

The mode of administration was standardized for all PRO measures in all phase 3 clinical studies. In US and European cognitive debriefing, a 1-month recall of the outcome measures was perceived by participants as a satisfactory time period for assessing PE. Cognitive debriefing in the US and Europe showed that the response scales of PE-related PRO items were understood. Subjects were able to rank order responses appropriately and reported equidistant intervals for response options.

Test-retest reliability was examined in US and European observational studies, where the retest period was 2 weeks and 4 weeks, respectively. Intraclass correlation coefficients (ICCs) for IELT in both observational studies showed high test-retest reliability for men with PE in subjects whose condition was stable over the observation period (0.88 and 0.84 in the US and European observational studies, respectively). Across all outcome measures in both studies, ICCs ranged from 0.66 to 0.88 for men with stable PE.

Construct validity was evaluated in US and European observational studies using prospectively defined hypotheses predicting relationships between groups and among measured constructs. The known-group analyses for all PRO measures showed statistically significant differences between PE and non-PE groups, indicating that the PRO measures used in the clinical program for dapoxetine could differentiate between subjects with and without PE. Prospectively defined hypotheses of the relationship between PRO measures and specific items/domains of established instruments addressing similar constructs (GRISS and SEAR) and a different construct (MOS SF-36) were confirmed by Spearman-Rank correlation coefficients and prespecified criteria for moderate or stronger association. These analyses provide evidence that the PRO measures were assessing what was intended.

Ability to detect change was evaluated by calculating effect sizes anchored to the PGI using data from the withdrawal study. Across all PRO measures, effect sizes ranged from 0.51 (anchored to PGI ratings of ‘slightly better’) to 3.51 (anchored to PGI ratings of ‘much better’). Effect sizes for all PRO measures increased with increasing improvement in the PGI, providing good evidence not only of ability to detect change but also ability to distinguish between different magnitudes of improvement (eg, slightly better, better, much better).

Development of a Responder Definition

Because different men perceive the magnitude and meaningfulness of a given change in IELT differently, it is necessary to interpret IELT through PROs. To understand the interrelationships among PE-related outcomes and to assist in the development of a responder definition, a path analysis was conducted using data from men with PE in US and European observational studies. The results indicated that a man’s perception of control over ejaculation plays a central role in how he interprets his PE condition.

To identify a magnitude of change in control over ejaculation that would represent a meaningful treatment effect to men with PE, control over ejaculation was examined in relation to men’s perception of overall improvement in PE as assessed by the PGI. Using pooled data from 2 US trials, 95.7% of subjects with a ≥2 category increase in control over ejaculation reported some degree of improvement in their condition. Based on this finding, a

≥2 category increase from baseline in control over ejaculation was selected for further evaluation. Support for this component of the responder definition was shown by (1) the substantial differences in other PE-related outcomes between men who did and did not meet this criterion in clinical trials and (2) by the similar response profiles of men who met this criterion and men without PE in observational studies.

A personal distress component was added to the control over ejaculation outcome based on: (1) consensus definitions of PE; (2) aim to assess patient functioning as well as patient feelings, which are included in the concept of treatment benefit in the FDA draft guidance on use of PROs; and (3) CHMP scientific advice and sexual medicine expert opinion. The definition of a responder to treatment was therefore set as a *≥2 category increase in control over ejaculation plus a ≥1 category decrease in personal distress*. This responder definition sets a high threshold for achieving treatment benefit, requiring criteria be met for a combination of outcomes central to the PE definition including a substantial movement in the subject's perceived control over ejaculation.

The responder definition was assessed *retrospectively* using data from the withdrawal study. In this study, the percentage of responders in the dapoxetine 60 mg prn group (47.6%) was more than 2-fold higher than that in the placebo group (21.7%) ($P<0.0001$).

Conclusions

Concepts important for evaluating the treatment benefit of dapoxetine were identified based on published literature, consultation with sexual medicine experts, and qualitative research involving men with PE and female partners of men with PE in the US and Europe.

Cognitive debriefing demonstrated that the instructions, item content, and response options of the PRO measures examined were understood and appropriately interpreted by men with PE in the US and Europe. The final versions of the translated PRO items and response options were understood and culturally and linguistically acceptable in the European and Pan-Asia countries examined.

The measurement properties of the PROs examined were shown to be sufficiently reliable and valid using data from cognitive debriefing, US and European observational studies, and 3 phase 3 clinical trials (2 US studies and the withdrawal study). The measurement properties of the PROs assessed in US and European observational studies were similar, suggesting that the PRO measures performed consistently across cultures.

A definition of a responder to treatment was established as a *≥2 category increase in control over ejaculation plus a ≥1 category decrease in personal distress*, based on path analysis of observational study data and *retrospective* analysis of data from the US clinical trials. This responder definition sets a high threshold for achieving treatment benefit, requiring criteria be met for a combination of outcomes central to the PE definition including a substantial movement in the subject's perceived control over ejaculation. The robustness of the responder definition is confirmed by the magnitude of mean average IELT achieved by responders at study endpoint (>5 minutes) relative to baseline (≤1 minute).

Abbreviations

APA	American Psychiatric Association
AUA	American Urological Association
BPH	benign prostatic hyperplasia
CI	confidence interval
CHMP	Committee for Medicinal Products for Human Use
CORE	Center on Outcomes Research and Education
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Version IV, Text Revision
EMEA	European Medicines Agency
GRISS	Golombok Rust Inventory of Sexual Satisfaction
HRQL	health-related quality of life
ICC	intraclass correlation coefficients
ICD-10	Classification of Diseases, 10th Revision
IELT	intravaginal ejaculatory latency time
IIEF	International Index of Erectile Function
LPOCF	last postbaseline observation carried forward
LS	least squares (mean)
MOS SF-36	Medical Outcome Study Short Form 36-Item Health Survey
NNT	number needed to treat
PE	premature ejaculation
PEPA	Premature Ejaculation Prevalence and Attitudes (survey)
PGI	patient global impression of change [Note: same as Clinical global impression of change (GGI)]
prn	as needed
PRO	patient-reported outcome
qd	once daily
SEAR	Self-Esteem and Relationship (questionnaire)
VAS	visual analog scale
WHO	World Health Organization

PEP: Patient-reported Outcome Measures

US Observational Study (C-2004-004)

Measure	Question Text	Scores and Response Options
Control Over Ejaculation	Subject: Over the past month, was your control over ejaculation during sexual intercourse: Partner: Over the past month, was your partner's control over ejaculation during sexual intercourse:	0: Very poor 1: Poor 2: Fair 3: Good 4: Very good
Satisfaction With Sexual Intercourse	Subject and Partner: Over the past month, was your satisfaction with sexual intercourse:	0: Very poor 1: Poor 2: Fair 3: Good 4: Very good
Severity of PE	Subject: Over the past month, the severity of my premature ejaculation problem was: Partner: Over the past month, the severity of my partner's premature ejaculation problem was:	0: None 1: Mild 2: Moderate 3: Severe
Personal Distress	Subject: How distressed are you by how fast you ejaculate (come) during sexual (vaginal) intercourse? Partner: How distressed are you by how fast your partner ejaculates (comes) during sexual (vaginal) intercourse?	0: Not at all 1: A little bit 2: Moderately 3: Quite a bit 4: Extremely
Interpersonal Difficulty	Subject: To what extent does how fast you ejaculate (come) during sexual (vaginal) intercourse cause difficulty in your relationship with your partner? Partner: To what extent does how fast your partner ejaculates (comes) during sexual (vaginal) intercourse cause difficulty in your relationship with your partner?	0: Not at all 1: A little bit 2: Moderately 3: Quite a bit 4: Extremely

European Observational Study (R096769-PRE-3004)

Measure	Question Text	Scores and Response Options
Control Over Ejaculation	Subject: Over the past month, was your control over ejaculation during sexual intercourse: Partner: Over the past month, was your partner's control over ejaculation during sexual intercourse:	0: Very poor 1: Poor 2: Fair 3: Good 4: Very good
Satisfaction With Sexual Intercourse	Subject and Partner: Over the past month, was your satisfaction with sexual intercourse:	0: Very poor 1: Poor 2: Fair 3: Good 4: Very good
Personal Distress	Subject: Over the past month, how distressed were you by how fast you ejaculated during sexual intercourse? Partner: Over the past month, how distressed were you by how fast your partner ejaculated during sexual intercourse?	0: Not at all 1: A little bit 2: Moderately 3: Quite a bit 4: Extremely
Interpersonal Difficulty	Subject: Over the past month, to what extent did how fast you ejaculated during sexual intercourse cause difficulty in your relationship with your partner? Partner: Over the past month, to what extent did how fast your partner ejaculated during sexual intercourse cause difficulty in your relationship with your partner?	0: Not at all 1: A little bit 2: Moderately 3: Quite a bit 4: Extremely
Clinical Global Impression of change	Subject: Compared to your last visit, would you describe your control over ejaculation during sexual intercourse as: Partner: Compared to your last visit, would you describe your satisfaction with sexual intercourse as:	-3: Much worse -2: Worse -1: Slightly worse 0: No change 1: Slightly better 2: Better 3: Much better

US Phase 3 Studies (C-2002-012 and C-2002-013)

Measure	Question Text	Scores and Response Options
Control Over Ejaculation	Subject: Over the past month, was your control over ejaculation during sexual intercourse: Partner: Over the past month, was your partner's control over ejaculation during sexual intercourse:	0: Very poor 1: Poor 2: Fair 3: Good 4: Very good
Satisfaction With Sexual Intercourse	Subject and Partner: Over the past month, was your satisfaction with sexual intercourse:	0: Very poor 1: Poor 2: Fair 3: Good 4: Very good
Patient Global Impression (PGI) of change	Subject: Compared to the start of the study, would you describe your rapid ejaculation problem as: Partner: Compared to the start of the study, would you describe your partner's rapid ejaculation problem as:	0: Much worse 1: Worse 2: Slightly worse 3: No change 4: Slightly better 5: Better 6: Much better
Severity of PE	Subject: Over the past month, the severity of my premature ejaculation problem was: Partner: Over the past month, the severity of my partner's premature ejaculation problem was:	0: None 1: Mild 2: Moderate 3: Severe
Medication Helpfulness	Subject: Over the past month, how would you rate the study medication in improving your condition? Partner: Over the past month, how would you rate the study medication in improving your partner's condition?	0: Poor 1: Fair 2: Good 3: Very good 4: Excellent

European Phase 3 Study (R096796-PRE-3001)

Measure	Question Text	Scores and Response Options
Control Over Ejaculation	Subject: Over the past month, was your control over ejaculation during sexual intercourse: Partner: Over the past month, was your partner's control over ejaculation during sexual intercourse:	0: Very poor 1: Poor 2: Fair 3: Good 4: Very good
Satisfaction With Sexual Intercourse	Subject and Partner: Over the past month, was your satisfaction with sexual intercourse:	0: Very poor 1: Poor 2: Fair 3: Good 4: Very good
Personal Distress	Subject: Over the past month, how distressed were you by how fast you ejaculated during sexual intercourse? Partner: Over the past month, how distressed were you by how fast your partner ejaculated during sexual intercourse?	0: Not at all 1: A little bit 2: Moderately 3: Quite a bit 4: Extremely
Interpersonal Difficulty (defined as relationship distress in the protocol)	Subject: Over the past month, to what extent did how fast you ejaculated during sexual intercourse cause difficulty in your relationship with your partner? Partner: Over the past month, to what extent did how fast your partner ejaculated during sexual intercourse cause difficulty in your relationship with your partner?	0: Not at all 1: A little bit 2: Moderately 3: Quite a bit 4: Extremely
Symptom severity Impression	Subject: Over the past month, the severity of your premature ejaculation problem was: Partner: Over the past month, the severity of your partner's premature ejaculation problem was:	0: None 1: Mild 2: Moderate 3: Severe
Clinical Global Impression of change	Subject: Compared to the start of the study, would you describe your premature ejaculation problem as: Partner: Compared to the start of the study, would you describe your partner's premature ejaculation problem as:	-3: Much worse -2: Worse -1: Slightly worse 0: No change 1: Slightly better 2: Better 3: Much better
Medication Helpfulness	Subject: Over the past month, how would you rate the study medication in improving your condition? Partner: Over the past month, how would you rate the study medication in improving your partner's condition?	0: Poor 1: Fair 2: Good 3: Very good 4: Excellent
Satisfaction with Sexual Intercourse (per event)	Subject: Were you satisfied overall with this sexual experience?	Yes No

Pan-Asia Phase 3 Study (R096796-PRE-3003)

Measure	Question Text	Scores and Response Options
Control Over Ejaculation	Over the past month, was your control over ejaculation during sexual intercourse:	0: Very poor 1: Poor 2: Fair 3: Good 4: Very good
Satisfaction With Sexual Intercourse	Over the past month, was your satisfaction with sexual intercourse:	0: Very poor 1: Poor 2: Fair 3: Good 4: Very good
Personal Distress	Over the past month, how distressed were you by how fast you ejaculated during sexual intercourse?	0: Not at all 1: A little bit 2: Moderately 3: Quite a bit 4: Extremely
Interpersonal Difficulty (defined as relationship distress in the protocol)	Over the past month, to what extent did how fast you ejaculated during sexual intercourse cause difficulty in your relationship with your partner?	0: Not at all 1: A little bit 2: Moderately 3: Quite a bit 4: Extremely
Symptom severity Impression	Over the past month, the severity of your premature ejaculation problem was:	0: None 1: Mild 2: Moderate 3: Severe
Clinical Global Impression of change	Compared to the start of the study, would you describe your premature ejaculation problem as:	-3: Much worse -2: Worse -1: Slightly worse 0: No change 1: Slightly better 2: Better 3: Much better
Medication Helpfulness	Over the past month, how would you rate the study medication in improving your condition?	0: Poor 1: Fair 2: Good 3: Very good 4: Excellent
Satisfaction with Sexual Intercourse (per event)	Were you satisfied overall with this sexual experience?	Yes No

Withdrawal Study (R096796-PRE-3002)

Measure	Question Text	Scores and Response Options
Control Over Ejaculation	Over the past month, was your control over ejaculation during sexual intercourse:	0: Very poor 1: Poor 2: Fair 3: Good 4: Very good
Satisfaction With Sexual Intercourse	Over the past month, was your satisfaction with sexual intercourse:	0: Very poor 1: Poor 2: Fair 3: Good 4: Very good
Personal Distress	Over the past month, how distressed were you by how fast you ejaculated during sexual intercourse?	0: Not at all 1: A little bit 2: Moderately 3: Quite a bit 4: Extremely
Interpersonal Difficulty (defined as relationship distress in the protocol)	Over the past month, to what extent did how fast you ejaculated during sexual intercourse cause difficulty in your relationship with your partner?	0: Not at all 1: A little bit 2: Moderately 3: Quite a bit 4: Extremely
Symptom severity Impression	Over the past month, the severity of your premature ejaculation problem was:	0: None 1: Mild 2: Moderate 3: Severe
Clinical Global Impression of change	Compared to the start of the study, would you describe your premature ejaculation problem as:	-3: Much worse -2: Worse -1: Slightly worse 0: No change 1: Slightly better 2: Better 3: Much better
Medication Helpfulness	Over the past month, how would you rate the study medication in improving your condition?	0: Poor 1: Fair 2: Good 3: Very good 4: Excellent
Satisfaction with Sexual Intercourse (per event)	Were you satisfied overall with this sexual experience?	Yes No