



Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Dapoxetine

Proprietary Product Name: Priligy
Submission No: PM-2007-3614-3
Sponsor: Janssen-Cilag Pty Ltd



November 2010

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I. Introduction to Product Submission

Product Details

<i>Type of Submission</i>	New Chemical Entity
<i>Decision:</i>	30 mg tablet: approved 60 mg tablet: withdrawn
<i>Date of Decision:</i>	27 August 2010
<i>Active ingredient(s):</i>	Dapoxetine hydrochloride
<i>Product Name(s):</i>	Priligy
<i>Sponsor's Name and Address:</i>	Janssen-Cilag Pty Ltd 1-5 Khartoum Road North Ryde NSW 2113
<i>Dose form(s):</i>	Film-coated tablets
<i>Strength(s):</i>	30 mg and 60 mg
<i>Container(s):</i>	PVC/PE/PVDC//Al blister packs
<i>Pack size(s):</i>	3, 6, 18
<i>Approved Therapeutic use:</i>	Priligy is indicated for the treatment of premature ejaculation (PE) in men 18 to 64 years of age, who have all of the following: <ul style="list-style-type: none">• an intravaginal ejaculatory latency time (IELT) of less than two minutes; and• persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the patient wishes; and• marked personal distress or interpersonal difficulty as a consequence of PE; and• poor control over ejaculation.
<i>Route(s) of administration:</i>	Oral
<i>Dosage:</i>	One tablet, as needed, approximately 1 to 3 hours prior to sexual activity. The maximum recommended dosing frequency is once every 24 hours.
<i>ARTG number(s):</i>	147946

Product Background

Dapoxetine is a short-acting potent serotonin reuptake inhibitor (SSRI). Serotonin is thought to play a role in ejaculatory reflex mediation and is believed to act centrally and peripherally to inhibit ejaculation, perhaps via the serotonin (5HT)_{1a} receptor. In the original application to the TGA, the proposed therapeutic indication for dapoxetine was for the treatment of premature ejaculation in male subjects aged 18-64 years who have the following:

- i) persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the patient wishes,
- ii) marked personal distress or interpersonal difficulty as a consequence of premature ejaculation, and
- iii) poor control over ejaculation.

Dapoxetine had not been considered by the Australian Drug Evaluation Committee (ADEC) previously and there are no TGA approved treatments of premature ejaculation.

Regulatory Status

An application for approval of dapoxetine 30 mg and 60 mg for the above proposed indication has been approved in New Zealand, Sweden, Austria, Germany, Finland, Spain, Portugal and Italy. It has also been approved in Korea, Malaysia, Philippines, Argentina, Uruguay and Mexico.

The dapoxetine submission is currently under evaluation in over 23 countries.

The approved indication in Sweden (Reference Member State in the European Union [EU]; February 2009) is as follows:

Priligy is indicated for the treatment of premature ejaculation (PE) in men 18 to 64 years of age.

The following conditions were fulfilled for inclusion in the clinical studies of PE:

- An intravaginal ejaculatory latency time (IELT) of less than two minutes; and
- Persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the patient wishes; and
- Marked personal distress or interpersonal difficulty as a consequence of PE; and
- Poor control over ejaculation.

A New Drug Application (NDA), filed with the US FDA, for dapoxetine received a Prescription Drug User Fee Act (PDUFA) Action Letter stating that dapoxetine was not-approvable for the PE indication in October 2005.¹ Since the time of the US FDA PDUFA Action Letter in October 2005, the sponsor has conducted two Phase I studies, an observational study and three Phase III studies.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

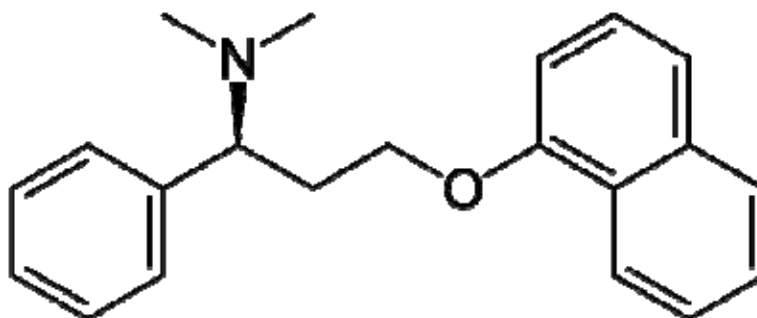
Structure

Dapoxetine hydrochloride is a new chemical entity which is presented as the *S* enantiomer. See structures below.

¹ US FDA Code of Federal Regulations (2004) 21 CFR 314.120 – FDA will send the applicant a not approvable letter if the agency believes that the application may not be approved for one reason under 21 CFR 214.125.

dapoxetine hydrochloride

(+)(*S*)-N,N-dimethyl- α -[2-(1-naphthalenyloxy)ethyl]-benzenemethanamine hydrochloride



Formula = $C_{21}H_{23}NO \cdot HCl$ MW = 341.9 (salt), 305.4 (free base)

CAS No. = [129938-20-1] (salt), [119356-77-3] (free base)

specific rotation = +119.1°	partition coefficient = 5.1 (octanol/water)	melting point 183°C
solubility = aqueous	0.01M HCl	citrate pH 2
100 mg/mL, 10%	71 mg/mL 7.1%	0.9 mg/mL 0.09%
		phosphate pH 7
		0.02 mg/mL 0.002%

The mechanism of action of dapoxetine is presumed to be linked to the inhibition of neuronal reuptake of serotonin and the subsequent potentiation of the neurotransmitter's action at pre- and post-synaptic receptors.

Physical and Chemical Properties

The drug substance is a white to slightly yellow crystalline powder. It exhibits polymorphism, but the desired polymorph is ensured by the conditions used in the final recrystallisation. There is a hydrate, but this is not formed due to the manufacturing conditions. The solubility is dependent on the pH of the medium: in acid it is soluble, but at neutral pH it is practically insoluble. Consequently, it is milled and the particle size distribution controlled.

Specifications

The specifications of dapoxetine hydrochloride (HCl) include satisfactory limits for assay and related substances. Due to the poor solubility at some physiological pHs, the particle size distribution is tightly controlled with appropriate limits. The *R*-enantiomer has not been observed at levels above 0.03% and it was accepted that a formal limit was not required. The residual solvent limits were below limits allowed by International Conference on Harmonisation (ICH) guidance.

Stability

Stability data were provided to support the proposed shelf life of 3 years when stored in an anti-static PE bag as a primary packaging material and an ALU-PE laminated bag as a secondary packaging material. Data were also included to demonstrate that the amount of the *R*-enantiomer does not increase on storage.

Drug Product

Formulations

Two strengths were proposed (30 and 60 mg). The cores are direct scales. The film-coats are different colours to differentiate the strengths, but the masses of these are in direct scale. The tablets are further differentiated by size and debossing.

Manufacture

Manufacture of the drug product is by a typical direct compression process followed by film-coating. The drug product is well controlled with satisfactory expiry limits for assay, degradants and dissolution. The product is not sterile.

Specifications

The proposed specifications, which control identity, potency, purity, dose delivery and other physical, chemical and microbiological properties are relevant to the clinical use of the product.

The limits for degradants comply with ICH thresholds.

Stability

Stability data have been generated under stressed, accelerated and real time conditions to characterise the stability profile of the product. The proposed shelf life for dapoxetine hydrochloride 30- and 60-mg tablets packaged in PVC-PE-PVDC/Al blisters is 3 years when stored below 25°C.

Bioavailability

The company submitted five bioavailability studies. These all used the same analytical method to determine the amount of dapoxetine in subject plasma samples. That method was validated to quantify amounts at and above 1.0 ng/mL.

It was brought to the attention of the Delegate that a number of subjects vomited after receiving the drug. In the studies evaluated in full, the number of subjects that vomited was 8 out of a total of 90, a frequency of ~9%.

Study C-2002-051: This study investigated the absolute bioavailability of a 60 mg ¹⁴C-dapoxetine (as HCl) capsule compared to a 30 mg IV dose. As this study did not use the tablet formulation proposed for marketing, it was only summarised. The results indicated that the absolute bioavailability from the capsule was 42% (90% confidence intervals [CI] for the area under the plasma concentration time curve [AUC] = 28-53%).

Study C-2002-037: This study investigated the effect of food on the bioavailability of dapoxetine from the 60 mg tablet used in the Phase III clinical trials. This study was evaluated in full.

The results indicated that the extent of absorption was not affected by food (90% CI for AUC = 1.05-1.19), but the peak levels were slightly lower (90% CI for the maximal plasma concentration [C_{max}] = 0.78-1.01) and the time to peak (T_{max}) increased by half an hour from 1.3 to 1.8 hours.

Study F2X-LC-HIAE: This study investigated the effect of food on the bioavailability of dapoxetine from 2 x 20 mg capsules as used in the early clinical trials. As a food effect study has been provided on a more relevant tablet (study C-2002-037), this study was not evaluated. For completeness, the results were similar to those from study C-2002-037 (90% CI for AUC = 0.95-1.18, 90% CI for C_{max} = 0.71-0.97 and T_{max} increased from 1.3 to 1.9 hours).

Study C-2002-020: This study investigated the relative bioavailability of 2 x 30 mg tablets as used in the Phase III clinical trials and 1 x 60 mg tablet as used in the Phase III clinical trials. It also investigated the relative bioavailability of 2 x 30 mg capsules (as used in the early clinical trials). This study was evaluated in full.

Study C-2004-009: This study investigated if the particle size distribution of the drug substance had any effect on the bioavailability of dapoxetine from the 60 mg tablet as used in the Phase III clinical trials. This study was evaluated in full.

The results indicated a batch of tablets manufactured with dapoxetine hydrochloride having a median particle size of 131 µm was bioequivalent to a batch of tablets manufactured with dapoxetine hydrochloride having median particle size of 28 µm. These data were used to set

appropriate limits for the particle size distribution of dapoxetine hydrochloride, which includes a limit for the median particle size.

The results of the bioavailability study C-2002-020 indicated that at a total dose of 60 mg, the 30 mg and 60 mg tablets dose regimens are bioequivalent (90% CI for AUC_{τ} = 0.88-1.05, 90% CI for C_{\max} = 0.92-1.09 and no change in T_{\max} - 1.4 hours). The 30 mg capsule was also bioequivalent, though AUC was slightly lower.

The 30 and 60 mg tablets used in these bioavailability studies and in the Phase III clinical studies were the same formulations as those proposed for marketing. The tablets had different markings, but given satisfactory dissolution profile data it was accepted that this would not affect bioavailability.

The evaluator concluded that:

The proposed tablets are adequately formulated.

- The absolute bioavailability of the proposed 60 mg tablet is approximately 40%.
- Food does not affect AUC, but decreases C_{\max} and increases T_{\max} .
- Bioavailability data was provided to support the limits in the specifications of the drug substance for particle size distribution.
- It is accepted that the proposed tablets are bioequivalent to the tablets used in the pivotal Phase III clinical studies.

Quality Summary and Conclusions

Approval of this submission was recommended with respect to chemistry and quality control.

Approval was also recommended with respect to bioavailability, but it was suggested that the statement in the proposed Product Information (PI) relating to the absolute bioavailability be changed from 42% to ~40% and that the different half-lives for slow and fast metabolisers be included in the PI. These suggestions were brought to the attention of the Delegate.

It was also brought to the attention of the Delegate that a number of subjects in the bioavailability studies vomited after administration of the product.

III. Nonclinical Findings

Introduction

Pivotal studies examining the repeat-dose toxicity, genotoxicity, carcinogenicity and reproductive toxicity of dapoxetine were conducted under Good Laboratory Practice (GLP) conditions. Safety-related studies not performed under GLP were conducted in established laboratories and mostly adequately documented.

Supplementary nonclinical data submitted by the sponsor comprised three genotoxicity studies. The original nonclinical evaluation report noted some minor deficiencies in the genotoxicity program but, overall, testing was found to be adequate and the drug was concluded to be non-genotoxic. All of the previous genotoxicity studies, as well as the newly submitted ones, were GLP compliant.

The nonclinical evaluation was conducted on the basis of a maximum recommended dose of 60 mg. Exposure ratios and other dose-related values were calculated on this basis. This dose was subsequently withdrawn so these values have been re-calculated to reflect the approved maximum recommended dose.

Pharmacology

Primary pharmacology

Rationale and mechanism of action

Dapoxetine is a selective serotonin reuptake inhibitor (SSRI) proposed to be used for the treatment of premature ejaculation. Utility for this indication was envisaged based on delayed ejaculation being a recognised side effect of the SSRI class in the treatment of depression (Seagraves, 1998).²

The ejaculatory reflex is regulated by multiple neurotransmitter systems at both the spinal and supraspinal levels, and a major role for the serotonergic system has been identified (reviewed by Wolters and Hellstrom, 2006).³ Three serotonin (5-HT) receptor subtypes have been postulated to mediate serotonin's modulation of ejaculation (Table 1). These have antagonistic actions, but the overall effect of serotonin on ejaculation is inhibitory.

Table 1: Serotonin Receptor Effects on Ejaculation

Receptor subtype	Location	Effect on ejaculation
5-HT _{1A}	brain; somatodendritic	facilitation
	spinal cord; pre-/postsynaptic	unknown
5-HT _{1B}	brain; presynaptic	inhibition [overall effect]
	spinal cord; pre-/postsynaptic	
5-HT _{2C}	brain; postsynaptic	inhibition [overall effect]
	spinal cord; postsynaptic	

Adapted from Giuliano and Clement (2005)⁴

Dapoxetine is proposed to delay ejaculation through potentiation of the actions of serotonin. By inhibiting the serotonin transporter, concentrations of the neurotransmitter in the synapse and the extracellular space around the neuronal cell bodies are increased.

The drug differs from existing marketed SSRIs in having a short initial (disposition) plasma half-life (see *Pharmacokinetics*), and will be used on-demand in patients instead of chronically, taken orally approximately 1–3 hours prior to sexual activity.

Efficacy

Activity at the human serotonin transporter was demonstrated for dapoxetine *in vitro* in binding and functional assays and *ex vivo* in experiments using platelets obtained from treated male volunteers (oral dosing). The median inhibitory concentration (IC₅₀) for inhibition of serotonin uptake in transfected HEK-293 cells, 1.12 nM, compares favourably with the estimated peak concentration of free dapoxetine in the central nervous system (CNS) in patients after a standard 30 mg dose (= 2.8 nM^[5]). The drug's affinity for the rat serotonin transporter was comparable to that of humans. No *in vitro* studies investigating the relative potency of dapoxetine at the transporter isoforms of the other animal species used in the nonclinical program were performed. Pharmacological activity in these other species is indicated, though, by demonstrations of the drug's ability to inhibit p-chloroamphetamine-induced depletion of brain 5-HT (*in vivo* in mice following intraperitoneal [IP] administration) and to inhibit 5-HT uptake by platelets and 5-HT uptake and binding by a known

² Seagraves RT. Antidepressant-induced sexual dysfunction. J Clin Psychiatry 1998; 59 Suppl 4: 48–54.

³ Wolters JP, Hellstrom WJ. Current concepts in ejaculatory dysfunction. Rev Urol 2006; 8: S18–S25.

⁴ Giuliano F, Clément P. Physiology of ejaculation: emphasis on serotonergic control. Eur Urol 2005; 48: 408–417.

⁵ Based on a plasma C_{max} of 297 ng/mL, plasma protein binding of 99.7% and peak levels in CNS tissues being ~95% of that for plasma.

serotonin transporter ligand in hypothalamus homogenates (*ex vivo* in dogs dosed orally; also shown in rats), and observations of signs consistent with serotonergic potentiation in the repeat-dose toxicity studies (for example, pupillary dilation in dogs and monkeys). Dapoxetine is a chiral molecule (+ or *S*-enantiomer); its *R*-enantiomer and racemate were shown to be several-fold less potent.

Orally administered dapoxetine displayed weak ejaculation-delaying activity in rats. Increases in ejaculation latency in treated groups compared with controls were modest in size (~66% at most), only rarely attained statistical significance at the 5% level, were often not dose-related and were not consistently observed across successive ejaculatory series. There was evidence for a stronger effect in the subset of animals that were faster ejaculators (mean latency, ~7 minutes [min] compared with 10 min for all animals), but the observed increase in ejaculatory latency associated with treatment in these animals remained very modest. The highest dose used in this study (300 mg/kg orally) is predicted to have yielded a plasma concentration of dapoxetine at the time of the assessment (3 hours post-dose) slightly greater than the C_{max} anticipated in patients after a single 30 mg dose (315 ng/mL compared with 297 ng/mL). A supraspinal site of action for dapoxetine was indicated in experiments monitoring reflex discharges of pudendal motoneurons in rats. Systemic administration of dapoxetine increased the latency of the reflex discharges in response to electrical stimulation of penile nerves, indicative of an inhibitory effect of the drug on the ejaculatory reflex. This effect was dependent on (and mimicked by) activation of the lateralis paragigantocellularis nuclei-brainstem structures containing serotonergic neurons (Andrezik *et al.*, 1981).⁶ Reflecting the distinct and opposing actions of components of serotonergic transmission on ejaculation, injection of dapoxetine into the spinal cord had a pro-ejaculatory effect (evident as increased amplitude of pudendal motoneuron reflex discharges).

The limited efficacy of dapoxetine to delay ejaculation observed in the submitted nonclinical studies accords with published data for other SSRIs. For fluoxetine, paroxetine, sertraline, fluvoxamine and citalopram, acute administration has no significant or (less commonly) only a minor effect on ejaculation latency in male rats (Ahlenius and Larsson, 1999; Mos *et al.*, 1999; Waldinger *et al.*, 2002; de Jong *et al.*, 2005).^{7,8,9,10} Substantial inhibition of ejaculation has been found to require repeat daily dosing with these agents. For example, Vega-Matuszcyk *et al.* (1998) observed a progressive increase in ejaculatory latency in rats treated with fluoxetine (10 mg/kg/day subcutaneously [SC]) that took until Day 9 to reach statistical significance; on Day 13, the increase compared with controls was 3.1-fold.¹¹ With paroxetine (10 mg/kg/day orally), latency to the first ejaculatory series was increased by 75% on Day 1, while after 14 days of treatment, the increase was 3.5-fold (Waldinger *et al.*, 2002). Chronic SSRI treatment is recognised to cause desensitisation of presynaptic 5-HT_{1A} autoreceptors (Blier and de Montigny, 1983) so that serotonin release is subject to less negative feedback and, consequently, activation of postsynaptic 5-HT receptors is

⁶ Andrezik JA, Chan-Palay V, Palay SL. The nucleus paragigantocellularis lateralis in the rat. Conformation and cytology. *Anat Embryol (Berl)* 1981; 161:355–371.

⁷ Ahlenius S, Larsson K. Synergistic actions of the 5-HT_{1A} receptor antagonist WAY-100635 and citalopram on male rat ejaculatory behavior. *Eur J Pharmacol* 1999; 379: 1–6.

⁸ Mos J, Mollet I, Tolboom JT, Waldinger MD, Olivier B. A comparison of the effects of different serotonin reuptake blockers on sexual behaviour of the male rat. *Eur Neuropsychopharmacol* 1999; 9: 123–135.

⁹ Waldinger MD, van de Plas A, Pattij T *et al.* The selective serotonin re-uptake inhibitors fluvoxamine and paroxetine differ in sexual inhibitory effects after chronic treatment. *Psychopharmacology (Berl)* 2002; 160: 283–289.

¹⁰ de Jong TR, Pattij T, Veening JG *et al.* Citalopram combined with WAY 100635 inhibits ejaculation and ejaculation-related Fos immunoreactivity. *Eur J Pharmacol* 2005; 509: 49–59.

¹¹ Vega-Matuszcyk J, Larsson K, Eriksson E. The selective serotonin reuptake inhibitor fluoxetine reduces sexual motivation in male rats. *Pharmacol Biochem Behav* 1998; 60: 527–532.

increased.¹² This receptor desensitisation can be mimicked in the acute setting through the use of a 5-HT_{1A} receptor antagonist. Co-administration of such an agent with a single dose of citalopram produces a marked delay in ejaculation in the rat (as opposed to no significant effect with either drug alone; Ahlenius and Larsson, 1999; de Jong *et al.*, 2005). These findings suggest that delayed ejaculation with SSRI therapy is chiefly due to the adaptive changes that are induced by chronic inhibition of serotonin reuptake rather than the drug's direct, acute (and with dapoxetine, transient) action to inhibit the activity of the transporter. As such, the expected clinical utility of a short-lasting, on-demand SSRI for the treatment of premature ejaculation is questionable (see also the review of Waldinger *et al.*, 2005).¹³

Secondary pharmacodynamics and safety pharmacology

Dapoxetine was shown to be highly selective for the serotonin transporter over other members of the monoamine transporter family. In radioligand binding assays, the drug's potency at the recombinant human noradrenaline and dopamine transporters was >780- and >5000-times lower, respectively, than at the serotonin transporter; >180- and >1500-times lower relative potency was observed for dapoxetine's inhibition of substrate uptake by the respective transporters in functional assays. Screening against an extensive array of receptors, ion channels, enzymes and other transporters (>100 targets) revealed no clinically significant secondary activities for the drug. Its most potent secondary activity was at the human 5-HT_{2B} receptor; the K_i for inhibition of radioligand binding to this receptor, 126 nM, is >40-times higher than the plasma C_{max} for free dapoxetine expected in patients treated at the approved maximum recommended human dose of 30 mg/day (=3.0 nM; equivalent to 1.0 ng/mL^[14]). Inhibition of the contractile activity of isolated tissues (rat vas deferens and uterus, rabbit thoracic aorta, and guinea-pig ileum and atrium) was observed with high concentrations of dapoxetine; at 1 µM (~300-times higher than the clinical C_{max} for unbound drug at the approved maximum recommended human dose), such effects were absent or minimal.

Specialised safety studies examined potential effects of dapoxetine on the CNS, cardiovascular, respiratory and renal systems. Observed effects on CNS function comprised behavioural changes (hyperreactivity, aggressiveness and increased vocalisation), decreased electroshock-induced seizure activity, increased hexobarbitone-induced sleeping time and analgesia in mice, and appetite suppression in rats. Such effects have been observed with other members of the SSRI class and are presumed to be pharmacologically mediated except for the prolongation of hexobarbitone-induced sleeping time, which is probably produced through a pharmacokinetic interaction (data to confirm this were not provided, however).

In cardiovascular safety studies, increased mean blood pressure was observed in all species examined (rats, guinea pigs and dogs). For rats given dapoxetine (as the tartrate salt) at 27 mg/kg orally, the increase was small (11%) and transient (recovery evident within 15 min); plasma concentrations of the drug in the animals, though, are likely to have been well below the peak level anticipated in patients (pharmacokinetic data were not obtained in the study; relative exposure based on C_{max} is estimated to be 0.34, using an animal value of 120 ng/mL for the calculation, as observed for administration of the drug as the hydrochloride salt to rats at 25 mg/kg orally). Substantial increases in blood pressure (36–50%) occurred in guinea pigs at cumulative intravenous (IV) doses ≥4.38 mg/kg; plasma dapoxetine concentration at this dose is estimated to be similar to the clinical C_{max} (based on linear extrapolation of animal pharmacokinetic data obtained in the

¹² Blier P, de Montigny C. Electrophysiological investigations on the effect of repeated zimelidine administration on serotonergic neurotransmission in the rat. *J Neurosci* 1983; 3: 1270–1278.

¹³ Waldinger MD, Schweitzer DH, Olivier B. On-demand SSRI treatment of premature ejaculation: pharmacodynamic limitations for relevant ejaculation delay and consequent solutions. *J Sex Med* 2005; 2: 121–131.

¹⁴ The calculation is based on a clinical C_{max} value for repeat daily administration of 30 mg dapoxetine of 349 ng/mL and plasma protein binding of 99.7%.

study). The increase in blood pressure seen in dogs was smaller ($\leq 29\%$ at 2 mg/kg IV) and not dose-related (relative exposure unknown). Significant changes in heart rate, varying in direction, were observed in the studies. Heart rate was reduced by 13–24% in guinea pigs at IV doses of 4.87–39.38 mg/kg (dose-dependent; estimated relative exposure, ≥ 2.0) and by 25% in dogs at 0.4 mg/kg IV (relative exposure unknown). A higher dose in dogs (10 mg/kg IV) caused a 25% increase in heart rate. Heart rate was unaffected in rats at 27 mg/kg orally (estimated relative exposure, 0.34) and in dogs at 2 mg/kg IV and 150 mg/kg orally (estimated relative exposure at the oral dose, 0.85). Increased peripheral vascular resistance was observed in dogs treated with dapoxetine IV, but the change was not dose-related. A marked effect on pulmonary vascular resistance and pulmonary arterial pressure was evident in these animals; at 2 mg/kg IV, the parameters were approximately doubled. Anaesthesia seems to have been a contributory factor for the bronchoconstriction, though, as the finding was not replicated in conscious dogs.

Dapoxetine shortened action potential duration in rabbit Purkinje fibres under normal and bradycardic conditions at concentrations $\geq 1 \mu\text{M}$. At $10 \mu\text{M}$, reductions in action potential amplitude and maximum upstroke velocity were also observed, and this concentration was shown to induce ventricular fibrillation in the isolated rabbit heart. hERG K^+ channel blocking activity was also demonstrated for the drug (IC_{50} , $3.26 \mu\text{M}$). These concentrations are very large multiples of the peak free concentration of dapoxetine expected in patients at the approved maximum recommended human dose (specifically, the IC_{50} for hERG K^+ channel inhibition is >850 -times higher). Severe disturbances in cardiac conduction and contractile function were observed *in vivo* in guinea pigs treated with dapoxetine at 39.38 mg/kg IV, with the drug causing shortening of the QTc interval, lengthening of the PQ and QRS intervals, bundle branch block, atrioventricular (AV) block and absent cardiac contraction. The plasma concentration of dapoxetine in the animals at this dose is ~ 15 -times the clinical C_{max} . These effects were absent in the guinea pig at 9.87 mg/kg IV (relative exposure, 3.3), and not seen in the dog cardiovascular safety study (IV dosing; relative exposure, unknown). No electrocardiogram (ECG) abnormalities were observed in the repeat-dose toxicity studies in dogs and monkeys, but plasma C_{max} in these studies did not reach the clinical level (relative exposure, ≤ 0.9). The occurrence of sinus arrest and asystole in a clinical trial subject receiving 60 mg dapoxetine is noted in the sponsor's *Clinical Overview*.

Faster, shallower respiration was observed in the anaesthetised dog at $\geq 2 \text{ mg/kg IV}$ in conjunction with the bronchoconstriction described earlier. Effects on respiratory function were not examined in conscious dogs or other species. Renal function was unaffected in rats at $\leq 100 \text{ mg/kg orally}$.

Pharmacokinetics

As in humans at therapeutic doses, oral absorption of dapoxetine was generally rapid in mice, rats and dogs, with peak plasma concentrations of the drug typically reached within 1.5 hours. Slower absorption was apparent in cynomolgus monkeys (T_{max} , 3–8 hours). Oral bioavailability was lower in the rat than in humans (10.5% compared with 42%). Plasma AUC after oral administration was demonstrated to be dose-proportional in all laboratory animal species examined, and in humans over the therapeutic range. In mice, rats, dogs and humans, plasma clearance of dapoxetine was generally characterised by a major rapid initial Phase (half-life [$t_{1/2}$], ≤ 3 hours) followed by a less significant, slow terminal Phase. Plasma clearance was somewhat slower in the cynomolgus monkey, with less distinction between initial and terminal Phases apparent. Coupled with slower absorption, plasma levels of dapoxetine consequently varied less widely in the monkey over time than in the other species.

Protein binding by dapoxetine was very high in human plasma (99.7%) and similarly high in the plasma of all the laboratory animal species examined (mouse, rat, dog and cynomolgus monkey; 99.6–99.8%). Volume of distribution was moderate in humans and high in rats and monkeys. Accordingly, widespread tissue distribution of radioactivity was observed in rats after oral administration of ^{14}C -dapoxetine. Outside of the gastrointestinal (GI) tract, radioactivity levels were

highest in the preputial gland, liver, Harderian gland, lung and kidney. The preputial gland showed significant retention of radioactivity; the level remaining 7 days after dosing was 15% of the tissue C_{\max} , and equivalent to almost double the peak level detected in plasma. Penetration of the blood-brain barrier to the target tissues in the CNS was demonstrated in the rat and monkey. In the rat, peak levels in the CNS were comparable to, and coincided with, the plasma C_{\max} . Penetration of the blood-testes barrier was also evident.

Metabolism of dapoxetine involved demethylation, N-oxidation and hydroxylation at various sites on the naphthylene ring and subsequent glucuronidation or sulfation. Combinations of these reactions resulted in a large number of metabolites being observed *in vivo* across species and matrices. Experiments with recombinant human enzymes revealed that multiple cytochrome P450 (CYP) isoforms (chiefly 3A4 and 2D6, but also 2C8, 2C9, 2C19, 2B6 and 1A2) and flavin-containing monooxygenase 1 (FMO1) metabolise dapoxetine. Unchanged dapoxetine accounted for a small to very small proportion (<1%–8%) of the total radiocarbon present in the plasma of the laboratory animal species (mouse, rat, dog and cynomolgus monkey) at any time point studied. Metabolism was considerably less extensive in humans, in comparison, with ~20%–50% of the total circulating radiocarbon present in the form of unchanged dapoxetine. All human circulating metabolites were also observed in monkey plasma, and the major human circulating metabolite—dapoxetine N-oxide—was present in the plasma of the other laboratory animal species too (mouse, rat and dog). Dapoxetine N-oxide was shown to be chiefly formed by FMO1, and to only weakly inhibit serotonin uptake (being ~250-times less potent than its parent). Plasma levels of it and the two other most significant primary metabolites (desmethyl- and didesmethyl dapoxetine) were routinely assayed along with dapoxetine in the pharmacokinetic/toxicokinetic analyses. Systemic exposure to dapoxetine N-oxide relative to unchanged dapoxetine was comparable in rats and humans; lower proportional exposure was observed in monkeys. Quantitative data regarding exposure to dapoxetine N-oxide in dogs are not available, but qualitative data (*in vivo* and *in vitro*) indicate that reasonable exposure to the metabolite in the species is likely. In a clinical pharmacokinetic study, the ratio of the area under the plasma concentration time curve from time zero to infinity ($AUC_{0-\infty}$) for dapoxetine to that of dapoxetine N-oxide was lower with oral dosing compared to IV administration (1.1:1 compared with 2.6:1), indicating that the drug is subject to first-pass metabolism. Demethylation contributed to the metabolism of dapoxetine to a much greater extent in rats and monkeys than it did in humans.

Excretion of radioactivity following oral dosing with ^{14}C -dapoxetine was primarily via the urine in mice, monkeys and humans (urine contained ~55–70% of the total recovered dose), while lower renal excretion was observed in the rat and dog (~25–30% of total excretion was renal). Biliary excretion was demonstrated in rats.

Comparisons of the pharmacokinetic profiles of dapoxetine in the laboratory animal species used in the pivotal repeat-dose toxicity studies (rats and cynomolgus monkeys) and humans indicate a significant difference in the extent of metabolism of the drug in animals compared with humans. The greater metabolism in the animal species lessens their ability to serve as appropriate models for the assessment of dapoxetine toxicity in humans.

Pharmacokinetic drug interactions

No pharmacokinetic interaction studies were conducted in laboratory animals. The sponsor's *Clinical Overview* and the draft Product Information document describe numerous clinical studies. *In vitro*, verapamil did not affect the transport of dapoxetine across Caco-2 cell monolayers, suggesting that dapoxetine's pharmacokinetics will not be affected by co-administered P-glycoprotein inhibitors.

Effects by dapoxetine

Dapoxetine displayed only weak inhibitory activity against human CYP isoforms 1A2, 2A6, 2C9, 2C19, 2D6, 2E1 and 3A4 *in vitro*. IC₅₀ values were ≥ 8.0 μ M, more than 7-times higher than the clinical C_{max} for total drug in plasma at the approved maximum recommended human dose. As such, and considering the drug's short plasma half-life in humans, no pharmacokinetic interactions owing to CYP inhibition by dapoxetine are expected in clinical practice.

Hepatic enzyme induction—principally involving CYP1A and CYP2B in rats, and CYP1A in dogs and cynomolgus monkeys—was observed following repeat daily administration of dapoxetine. Marked increases in the activity of these CYP isoforms (at least doubled) occurred in rats at doses ≥ 75 mg/kg/day (4–13 weeks treatment), dogs at ≥ 50 mg/kg/day (3 months treatment) and monkeys at ≥ 30 mg/kg/day orally (4 weeks treatment). Maximum observed increases were 20- and 13-fold in rats (for CYP1A and 2B, respectively), and ~5–6-fold in dogs and monkeys. Systemic exposure levels at the Lowest Observable Effect Levels (LOELs) for such enzyme induction in animals are similar to (rats) or less than (dogs and monkeys) that anticipated in humans at the approved maximum recommended clinical dose. On a body surface area-basis, though, these doses are significant multiples of the approved maximum recommended human dose (9–25-times; 450, 1000 and 375 mg/m²/day in rats, dogs and monkeys, respectively, compared with 18.75 mg/m²/day for a 50 kg human receiving 30 mg/day). This reflects the need for particularly high doses of dapoxetine to be administered to the animal species in order to achieve meaningful systemic exposure to the unchanged drug because of their much greater metabolism of dapoxetine compared to humans. As such, treatment poses a considerable metabolic burden to the animals, and enzyme induction is not an unexpected finding; still, the clinical significance of the finding cannot be entirely discounted. CYPs 1A2, 2A6, 2C9, 2C19, 2D6, 2E1 and 3A4 were not induced *in vitro* in experiments with cultured human hepatocytes exposed to dapoxetine (≤ 30 μ M) for 2 days. In light of the *in vivo* findings, the set of assays should have included measurement of CYP1A1 and CYP2B6 activities in order to assess the enzyme induction potential of dapoxetine more fully.

Effects on dapoxetine

Given the major roles for CYP3A4, CYP2D6 and FMO1 in the metabolism of dapoxetine, co-administered drugs that are inhibitors of these enzymes have the potential to increase exposure to dapoxetine.

Toxicology

Acute toxicity

The oral toxicity of the drug was adequately characterised in two mammalian species (mouse and rat), with animals of both sexes used, observed for a sufficient period, and subjected to necropsy. Acute oral toxicity studies were also conducted in dogs and rhesus monkeys, but these involved testing of only a single dose level. Studies utilising other routes of administration (IP or IV) did not include necropsies; the observation period in the IP mouse study was also too short (6 days). Treated animals displayed signs of CNS toxicity, including ataxia and hypoactivity. Maximum non-lethal doses for dapoxetine by the oral route were 800 mg/kg in mice¹⁵, 1000 mg/kg in rats, ≥ 400 mg/kg in dogs and ≥ 200 mg/kg in rhesus monkeys, indicating a moderate order of acute toxicity for the drug.

Repeat-dose toxicity

Studies of up to 4 months duration were conducted in mice, 6 months in rats and dogs and 9 months in cynomolgus monkeys. All involved oral administration with the exception of a 4-week topical

¹⁵ Although a 500 mg/kg oral dose caused deaths in 4/10 animals in the mouse micronucleus test dose-selection study.

dermal study in mice (which served as a dose-range finding study for a carcinogenicity study). The duration of the pivotal studies, the species used (rats and cynomolgus monkeys), group sizes and the use of both sexes were consistent with ICH guidelines. Dose selection was appropriate in these studies, with the high-dose level in the rat study producing significant suppression of body weight gain and that in the monkey study limited by ataxia/mortality. Non-neoplastic findings in the rodent carcinogenicity studies are also discussed in this section.

Relative exposure

Exposure ratios have been calculated based on animal:human plasma C_{max} and AUC_{0-24h} values for dapoxetine (Table 2); the human reference values are for the approved maximum recommended clinical dose (30 mg/day). Systemic exposure was frequently below or only marginally above the anticipated clinical level; substantial multiples of the clinical exposure were only obtained in a 3-month rat study. Toxicokinetic sampling in the pivotal rat dietary study was extremely limited (that is, at a single time point per day). Only one of the three rodent carcinogenicity studies (mouse; oral) included toxicokinetic analyses.

Major toxicities

The major targets for dapoxetine toxicity were the CNS, liver and kidney, with some effects also observed in respiratory and lymphoid tissues. Treatment-related deaths were observed in rats at doses ≥ 75 mg/kg/day orally (relative exposure based on AUC_{0-24h} , 1.9) and monkeys from 200 mg/kg/day (relative exposure, 2.29). Oral treatment of mice at ≥ 776 mg/kg/day also caused mortality (relative exposure, unknown). There were no deaths among dogs given repeat daily doses of dapoxetine, but relative exposure levels were not as high as in the other species (≤ 1.20).

Table 2: Relative exposure in repeat-dose toxicity and carcinogenicity studies

Study	Species & strain	Study duration	Route	Dose (mg/kg/day)	C_{max}^* (ng/mL)	AUC_{0-24h}^* (ng·h/mL)	Exposure ratio [†]	
							w.r.t. C_{max}	w.r.t. AUC_{0-24h}
TR-01-5005-001	Mouse (FVB/NTac)	4 weeks	topical dermal	375	397	2526	1.14	1.63
				750	588	3322	1.68	2.14
				1500	762	4030	2.18	2.59
				3000	674	4354	1.93	2.80
TOX8402	Mouse (CByBSF1; surrogate for Tg.rasH2)	6 months	PO	25	92.1	191	0.26	0.12
				50	178	415	0.51	0.27
				100	413	728	1.18	0.47
				200	629	2200	1.80	1.42
TR-01-5005-002	Rat (SD)	3 months	PO	25	149	870	0.43	0.56
				75	345	2972	0.99	1.91
				150	415	5464	1.19	3.52
				225	409	5448	1.17	3.51
TR-01-5005-016	Rat (SD)	3 months	PO	325	681	9465	1.95	6.09
				425	694	10067	1.99	6.48
				525	971	12582	2.78	8.10
				625	1202	18753	3.44	12.07
D00589	Dog (Beagle)	3 months	PO	15	71	185	0.20	0.12
				50	184	790	0.53	0.51
				150	315	1860	0.90	1.20
D07490	Dog (Beagle)	6 months	PO	15	46	114	0.13	0.07
				50	102	721	0.29	0.46
				150	315	1408	0.90	0.91

Study	Species & strain	Study duration	Route	Dose (mg/kg/day)	C _{max} * (ng/mL)	AUC _{0-24h} * (ng·h/mL)	Exposure ratio†	
							w.r.t. C _{max}	w.r.t. AUC _{0-24h}
BIO-01-B003-5005	Monkey (Cynomolgus)	5 days	PO	200	257	2590	0.74	1.67
TR-01-5005-014	Monkey (Cynomolgus)	4 weeks	PO	5	29	115	0.08	0.07
				30	115	650	0.33	0.42
				100	275	1374	0.79	0.88
				200	264	3562	0.76	2.29
TR-03-5005-011	Monkey (Cynomolgus)	9 months	PO	1	5.5	23.6	0.02	0.02
				5	24	133	0.07	0.09
				30	119	955	0.34	0.61
				75	217	1917	0.62	1.23
C-2004-010	Human (healthy male volunteers)	7 days	PO	[30 mg/day]	349	1554	—	—
				[60 mg/day]	596	2949		

* = values are the highest observed in the course of the study and are for the sexes combined; † = calculated as animal:human C_{max} or AUC_{0-24h}, using human values obtained at the approved maximum recommended clinical dose (30 mg/day)

Animals treated with dapoxetine displayed clinical signs indicative of altered autonomic function and CNS toxicity. These were most prominent in dogs and monkeys, and comprised mydriasis, slow or incomplete pupillary light response, emesis (dose-limiting in dogs), stool abnormalities (soft/mucoid/runny), excessive salivation, lacrimation, tremors, hypoactivity, recumbent posture, ataxia and apparent hypothermia. A dose of 15 mg/kg/day had only a small effect in dogs (relative exposure based on C_{max}, 0.13), and the NOEL in monkeys was 75 mg/kg/day (relative exposure based on C_{max}, 0.62). Hypersalivation, hypoactivity, chromodacryorrhea, chromorhinorrhea and myoclonic jerking were seen in rats. Similar effects have been observed with other SSRIs.

Increased bodyweight-relative liver weight, associated with the hepatic enzyme induction described earlier (under *Pharmacokinetic drug interactions*), was routinely observed in the various studies. This effect was evident at the microscopic level as centrilobular hypertrophy in rats treated at 225 mg/kg/day for 2 weeks and at ≥75 mg/kg/day for 4–13 weeks. A number of additional—and more significant—hepatic changes were seen in dapoxetine-treated animals. The most notable was moderate to marked centrilobular fatty change, present in all high-dose males in the pivotal rat study (treated at 117 mg/kg/day for 6 months). Hepatic vacuolation was observed in most of the other rat studies, including in the 2-year carcinogenicity study where an increase in incidence and severity, up to moderate, was observed at doses ≥75 mg/kg/day. Vacuoles were large and specialised staining techniques confirmed that they were filled with lipid. Fatty change/vacuolation was not seen in either dogs or monkeys. Large increases in serum alanine transaminase (ALT) and/or alkaline phosphatase (ALP) (more than doubled) were observed at doses exceeding the maximum tolerated dose (MTD) (at 1784 mg/kg/day in rats, 150 mg/kg/day in dogs and 200 mg/kg/day in monkeys). Other changes in serum chemistry indicative of cholestasis (increased gamma-glutamyl transferase [GGT] and/or bilirubin) often accompanied these. In the pivotal studies, though, such increases were only small (rats) or absent (monkeys). Hepatic inflammation was increased in incidence in rats at the high-dose level in the pivotal study (117/129 mg/kg/day for 6 months) and at doses ≥325 mg/kg/day in a 3-month study, and in dogs at ≥50 mg/kg/day for 6 months. The severity was not increased however, with all cases remaining at most slight, even up to the highest dose tested (625 mg/kg/day in the 3-month rat study). One of the rats treated at this dose, though, did display severe centrilobular necrosis/degeneration. Hepatic porphyria was observed in dogs given dapoxetine at 150 mg/kg/day in the 6-month study; this may have occurred

secondary to enzyme induction (De Matteis and Marks, 1996).¹⁶ The NOELs for hepatotoxicity are 41 mg/kg/day in rats, 15 mg/kg/day in dogs and 75 mg/kg/day in monkeys. Systemic exposure to dapoxetine at these doses is below that of humans at the approved maximum recommended dose. Margins based on body surface area-adjusted doses are larger (13-, 16- and 50-times the human dose in the respective species).

Dapoxetine caused renal toxicity in rodents. The most overt effects were in mice treated with the drug at ≥ 776 mg/kg/day orally (dietary) in a 4-month study, with chronic interstitial nephritis, tubular degeneration and dilatation, fibrosis, cortical cysts, abscesses and hydronephrosis, as well as lithiasis in the renal pelvis and urinary bladder, observed. The bladder stones were found to contain glucuronidated metabolites of dapoxetine. Tubular damage and infarction were observed in the mouse oral (gavage) carcinogenicity study (6 months duration; minimally severe at 100 mg/kg/day and up to moderately severe at 200 mg/kg/day; relative exposure based on AUC, 0.38 and 1.33, respectively). All dermal doses tested (≥ 375 mg/kg/day; relative exposure, ≥ 1.63) also caused nephropathy in mice (4-week and 6-month studies). In F344 rats, up to moderate renal tubular degeneration was observed at ≥ 446 mg/kg/day orally (gavage) in a 2-week study, together with 2–3 fold increases in blood urea nitrogen in some animals at 892 or 1784 mg/kg/day. This finding was not reproduced in Sprague Dawley (SD) rats at doses up to 625 mg/kg/day orally (gavage) in a subsequent 3-month study, though. No renal toxicity was evident in the pivotal rat study, the rat carcinogenicity study (SD; oral gavage), nor in any of the dog or monkey studies. Dark urine was observed at doses ≥ 30 mg/kg/day in the 4-week monkey study, but this was not accompanied by changes in kidney histology or serum chemistry; it may reflect increased haem synthesis/usage due to hepatic enzyme induction. NOELs for renal toxicity are 50 mg/kg/day in mice, 225 mg/kg/day in rats, 150 mg/kg/day in dogs and 75 mg/kg/day in monkeys. Exposure ratios at these doses, based on the plasma AUC_{0–24h} for dapoxetine, are 0.27–3.51; on a mg/m² body surface area basis; they are ~8-, 72-, 160- and 50-times, respectively, the approved maximum approved recommended human dose (30 mg).

Altered respiration was observed in all of the studies in rodents utilising gavage administration. In rats, this was principally audible respiration; irregular and laboured breathing occurred in addition at higher doses. (Oral and nasal discharges, red or clear, were also seen in rats). Respiration in affected mice was rapid and shallow. These clinical signs were associated with inflammation and other changes (oedema, exudation, necrosis, attenuation and/or ulceration) in the nasal turbinates, nasopharynx, trachea and lung. LOELs for toxicity to respiratory tissues are 25 and 75 mg/kg/day in mice and rats, respectively (established in the oral carcinogenicity studies; relative exposure based on AUC_{0–24h}, 0.12 [mouse] and 1.91 [rat]). Dietary administration of dapoxetine did not provoke such changes, even at higher doses than those that were toxic by gavage. Specifically, no respiratory tract toxicity was observed in rats at doses ≤ 129 mg/kg/day in the pivotal study (estimated relative exposure, ≤ 3.0) nor at ≤ 432 mg/kg/day in a 2-week study (estimated relative exposure, 3.5; compared with effects at 225 mg/kg/day by oral gavage in other 2-week studies). Similarly, dermal administration of dapoxetine in mice for 6 months at doses ≤ 1500 mg/kg/day did not produce respiratory toxicity even though systemic exposure was higher (relative exposure, 2.59) than that associated with toxicity by gavage administration. These effects were absent in dogs and monkeys too (oral administration by capsule and gavage in the respective species). Local irritation by dapoxetine was evident in the dermal studies in mice and an IV local tolerance study in rabbits. As such, the respiratory effects observed in rodents are considered to reflect irritancy due to direct contact with, and aspiration of, the gavage dosing solution, and not to be clinically relevant.

Lymphoid depletion was present in the spleen and thymus of rats treated at ≥ 525 mg/kg/day for 3 months. These doses clearly exceeded the MTD, and the finding is considered to reflect

¹⁶ De Matteis F, Marks GS. Cytochrome P450 and its interactions with the heme biosynthetic pathway. *Can J Physiol Pharmacol* 1996; 74: 1–8.

non-specific toxicity. Reticuloendothelial hyperplasia, observed in the lymph nodes of rats treated at ≥ 75 mg/kg/day in the carcinogenicity study, probably occurred secondary to the tissue damage in the lung and airways, and was not observed in other studies in rats nor in other species. Reticuloendothelial hyperplasia was not detected in the spleen, liver or other organs.

Genotoxicity

The potential genotoxicity of dapoxetine was investigated in the standard battery of tests and also in assays for unscheduled DNA synthesis (*in vitro*) and sister chromatid exchange (*in vivo*). The studies were conducted in accordance with ICH guidelines. Concentrations/doses were appropriate and limited by cytotoxicity/solubility/mortality. A suitable set of *S. typhimurium* and *E. coli* strains were used in the bacterial gene mutation assay. Animals of both sexes were used in the bone marrow micronucleus test, conducted in mice. All but one of the assays were appropriately validated; an assay for mutagenicity in the TA102 *S. typhimurium* strain with metabolic activation (to detect point mutations at A-T sites) was not valid due to an insufficient response to the positive control article. An acceptably large increase in the number of TA102 revertants was obtained with the positive control in another study; involving dapoxetine spiked with impurities), and the potential for A-T base-pair modifications has also been adequately addressed from assays using the WP2uvrA *E. coli* strain. The number of cells per concentration scored for unscheduled DNA synthesis and chromosomal aberrations was less than that recommended in the relevant OECD guidelines (473, 482), but this is not considered to have had a critical impact on the studies' validity.¹⁷ Negative results were returned for dapoxetine in all of the studies.

An additional mammalian mutagenicity study with dapoxetine was conducted, this time using a longer drug exposure period in the absence of metabolic activation (24 hours) than had been used in the earlier study (4 hours). The two other newly submitted studies investigated the bacterial mutagenicity and *in vitro* clastogenicity of dapoxetine's major human circulating metabolite, dapoxetine N-oxide. Previously conducted assays for bacterial mutagenicity and *in vitro* clastogenicity used dapoxetine in the presence of a metabolising system (rat S9). As formation of dapoxetine N-oxide in incubations of dapoxetine with rat liver microsomes had been demonstrated, the genotoxicity of this metabolite was assessable from the existing data. The new studies were appropriately conducted and, as before, all returned negative results. They provide further support for the conclusion that the drug does not pose a genotoxic hazard.

Carcinogenicity

The carcinogenic potential of dapoxetine by the oral route was investigated in a 6-month study in transgenic mice (Tg.rasH2) and a 2-year study in rats. These studies were appropriately designed; group sizes were adequate, a positive control group was included in the transgenic mouse study and dual negative control groups were used in the rat study. Suitable dose levels were selected, with the animals treated up to maximally tolerated doses. The highest doses produced systemic exposure to dapoxetine that reached the clinical level in the mouse study (relative exposure, ≤ 1.42 [at 200 mg/kg/day]) and did not greatly exceed it in rats (estimated relative exposure, ≤ 3.51 [at 225 mg/kg/day]). No treatment-related increases in tumour incidence were detected in rats. In the mouse study, one animal treated with dapoxetine (at 50 mg/kg/day orally [relative exposure, 0.27]; 1/25 females in the lower mid-dose group) developed a squamous cell carcinoma in the nasal cavity. Being a single incident, and not showing a strong relationship to dose, there is insufficient evidence to conclude that this tumour is treatment-related. Other proliferative changes were observed in the tissue though, with squamous metaplasia with hyperplasia in the nasal cavity

¹⁷ Organisation for Economic Co-operation and Development (OECD) Guidelines for the Testing of Chemicals: 473 – Genetic Toxicology – *In Vitro* Mammalian Cytogenetic Test, adopted 26 May 1983; 482 - Genetic Toxicology: DNA Damage and Repair, Unscheduled DNA Synthesis in Mammalian Cells *In Vitro*, adopted 23 October 1986.

significantly increased in incidence at 200 mg/kg/day (the high-dose level); also, a nasal polyp was observed in one animal at 100 mg/kg/day. The nasal cavity proliferative changes occurred in the context of inflammation, presumably from irritation by the gavage solution. Therefore, despite their occurrence at subclinical exposure levels, they are considered unlikely to be relevant to humans.

Preceding the oral transgenic mouse study was one involving the dermal route. This earlier study was conducted in Tg.AC mice, a model in which the development of epidermal papillomas in the area of topically applied test compound serves as the reporter phenotype (Tennant *et al.*, 2001).¹⁸ Because of the different route of administration, the dermal Tg.AC assay is not considered appropriate for the assessment of the carcinogenic potential of a drug to be given orally; furthermore, target organs for carcinogenicity are not identified. Dapoxetine was positive in the assay, increasing papilloma incidence and speeding tumour development in a dose-dependent fashion at doses ≥ 750 mg/kg/day. However, tumour multiplicity at the highest dose (1500 mg/kg/day; relative exposure, 2.8) was $<4\%$ of that of the positive control substance. The positive finding in the study may reflect the irritancy of dapoxetine and not actual carcinogenicity *per se*. The drug caused microscopic ulceration at the treatment site, and skin injury is recognised to induce papillomas in the Tg.AC model (Cannon *et al.*, 1997; Spalding *et al.*, 1999).^{19,20}

Reproductive toxicity

Although dapoxetine is not indicated for use in females, a set of reproductive toxicity studies covering all stages (fertility, early embryonic development, embryofetal development and pre- and post-natal development) was submitted by the sponsor. Numbers of animals and the timing and duration of treatment were appropriate. Animals were treated up to and beyond maximally tolerated levels in all of the studies (indicated by mortality and/or significant suppression of body weight gain). Moderate placental transfer of dapoxetine and/or its metabolites was demonstrated in rats. Excretion in milk was not investigated.

Male fertility was unaffected in rats treated with dapoxetine in the diet at ≤ 158 mg/kg/day. The relative exposure achieved in the animals is unknown as no pharmacokinetic/toxicokinetic data for dietary administration were provided. Relative exposure is likely to be low though, based on data for oral gavage administration, which indicate an AUC_{0–24h} less than 3.5-times that of patients and a C_{max} equivalent to the clinical level (119%) for this dose level; the actual C_{max} in the animals in the study may be substantially lower than that of patients given that a lower peak level is expected to have been achieved with dietary administration compared with dosing by oral gavage. There was no effect on sperm count or motility in monkeys at ≤ 75 mg/kg/day (examined in the 9-month general toxicity study; relative exposure based on plasma AUC, 1.23). Dapoxetine did not affect female fertility in rats treated at ≤ 100 mg/kg/day (estimated relative exposure, 1.3). Effects on fetuses were observed in both rats and rabbits at the highest dose levels tested. In rats, treatment at 100 mg/kg/day was associated with an increased incidence of incomplete ossification at multiple sites (cervical vertebral arch, sternebra, ischium and skull; relative exposure, 1.3), and incomplete ossification of the pubis and extra ribs were increased in incidence in fetuses of rabbits given dapoxetine at 75 mg/kg/day (relative exposure, unknown). These findings are consistent with the concomitant maternotoxicity. Teratogenicity was not observed. Relative exposure at the No Observable Effect Level (NOEL for embryofetal toxicity in the rat (25 mg/kg/day) is 0.56. No adverse effects on postnatal survival and body weight gain were seen in the offspring of rats given

¹⁸ Tennant RW, Stasiewicz S, Eastin WC, Mennear JH, Spalding JW. The Tg.AC (v-Ha-ras) transgenic mouse: nature of the model. *Toxicol Pathol* 2001; 29 Suppl: 51–59.

¹⁹ Cannon RE, Spalding JW, Trempus CS *et al.* Kinetics of wound-induced v-Ha-ras transgene expression and papilloma development in transgenic Tg.AC mice. *Mol Carcinog* 1997; 20: 108–114.

²⁰ Spalding JW, French JE, Tice RR, Furedi-Machacek M, Haseman JK, Tennant RW. Development of a transgenic mouse model for carcinogenesis bioassays: evaluation of chemically induced skin tumors in Tg.AC mice. *Toxicol Sci* 1999; 49: 241–254.

dapoxetine at ≤ 100 mg/kg/day; functional assessments of pup development were not performed, however.

Immunotoxicity

There was no evidence of specific immunotoxicity by dapoxetine in the repeat-dose studies. In a specialised study, the primary antibody response was unaffected in mice treated with the drug at ≤ 400 mg/kg/day orally (estimated relative exposure, 2.8).

Paediatric use

Dapoxetine is not proposed for paediatric use and no specific studies in juvenile animals were submitted by the sponsor.

Nonclinical Summary and Conclusions

Dapoxetine is a selective serotonin reuptake inhibitor (SSRI). Serotonin modulates the ejaculatory reflex, having an inhibitory effect overall. By potentiating serotonergic transmission, dapoxetine was envisaged to delay ejaculation, an effect seen with other SSRIs. The drug was shown to inhibit the serotonin transporter with nanomolar potency *in vitro*. Oral administration of dapoxetine to rats delayed ejaculation, but only weakly.

Secondary pharmacodynamic studies revealed no clinically significant activities for the drug. Safety pharmacology studies covered the CNS, cardiovascular, respiratory and renal systems. Major findings were CNS effects typical of the SSRI class - increased blood pressure (at plasma levels of dapoxetine less than the clinical C_{max} at the approved maximum recommended human dose) and—most seriously—disturbed cardiac conduction and contractile function. *In vitro*, dapoxetine shortened action potential duration in rabbit Purkinje fibres at concentrations ≥ 1 μ M (305 ng/mL) and induced ventricular fibrillation in the isolated rabbit heart at 10 μ M (compared with clinical C_{max} of 349 ng/mL at 30 mg). *In vivo* in guinea pigs treated IV, the drug shortened QTc interval, lengthened the PQ and QRS intervals, induced bundle branch block, AV block and abolished cardiac contraction at plasma dapoxetine levels ~ 15 -times the clinical C_{max} ; relative exposure at the NOEL for these cardiac effects is 3.3.

Pharmacokinetic studies indicated rapid absorption and clearance of dapoxetine in mice, rats, dogs and humans. Absorption and clearance were slower in monkeys compared to the other species. Plasma AUC was dose-proportional in all species examined. Oral administration of radiolabelled dapoxetine to rats resulted in rapid and wide tissue distribution. Penetration of the blood-brain barrier was demonstrated in the rat and monkey. Plasma protein binding was very high ($\geq 99.6\%$) in humans and laboratory animal species.

Metabolism of dapoxetine involved demethylation, N-oxidation, hydroxylation, glucuronidation and sulfation, and was chiefly mediated by CYP3A4, CYP2D6 and FMO1. The major human plasma metabolite, dapoxetine N-oxide, possesses only weak inhibitory activity at the serotonin transporter. Metabolism was much more extensive in the laboratory animal species than in humans, with unchanged drug accounting for a far smaller proportion of total circulating radiocarbon in animals compared with humans after oral dosing with 14 C-dapoxetine. Excretion of dapoxetine was predominantly via the urine in mice, monkeys and humans, and via the faeces in rats and dogs.

The drug displayed a moderate order of acute oral toxicity in laboratory animal species

Dapoxetine was poorly tolerated in repeat-dose toxicity studies, with severe toxicity encountered at subclinical exposure levels. Pivotal studies were conducted in rats (6 months) and cynomolgus monkeys (9 months). Major toxic effects were evident in the CNS (clinical signs representing SSRI class effects), liver (enzyme induction, hepatic vacuolation and inflammation, centrilobular hypertrophy, fatty change and necrosis/degeneration, and hepatic porphyria) and kidney (tubular degeneration, nephritis, fibrosis, cysts, abscesses, hydronephrosis and urolithiasis). Some effects were also observed in the respiratory tract and lymphoid organs.

Dapoxetine was examined for potential genotoxicity in assays for bacterial and mammalian mutagenicity, unscheduled DNA synthesis, sister chromatid exchange, and *in vitro* and *in vivo* clastogenicity, with universally negative results returned. Dapoxetine was not seen to be carcinogenic by the oral route in a 6-month study in transgenic mice and a 2-year study in rats. A weak carcinogenic effect was observed, though, in transgenic mice treated with dapoxetine for 6 months by topical dermal application.

No effects on male fertility in rats, or sperm count and motility in monkeys, were observed. However, dapoxetine was administered in the diet in the rat fertility study, and there are no pharmacokinetic data for this route to assess relative exposure. Placental transfer of dapoxetine was demonstrated (in rats). Other reproductive toxicity studies showed no effect on female fertility (rats), no teratogenicity (rats and rabbits) and no adverse effects on postnatal development (rats); functional assessments were not performed in the postnatal study, though, with only body weight gain and survival monitored in the offspring. Delayed ossification and/or an increased incidence of skeletal variations were observed in the fetuses of rats and rabbits at maternotoxic doses.

Only limited efficacy could be demonstrated for dapoxetine in the nonclinical studies. This result is consistent with published data that indicate that the efficacy of SSRIs to delay ejaculation is mostly underlain by adaptive changes induced by chronic inhibition of serotonin reuptake rather than acute inhibition of the transporter. Consequently, a short-lasting, on-demand SSRI like dapoxetine is expected to have limited clinical utility.

These statements were based on findings that the ejaculation-delaying effect of dapoxetine in rats was modest in size (~66% increases in ejaculation latency at most), rarely statistically significant at the 5% level, often not dose-related and not consistently observed across successive ejaculatory series. This was contrasted with published animal data for chronically administered SSRIs in which efficacy was shown much more convincingly (for example, >3-fold increases in ejaculation latency in rats). The sponsor did not dispute these findings, but argued that the results of the nonclinical efficacy studies need to be considered in the context of the clinical studies, which were reported to have shown statistically significant increases in intravaginal ejaculation latency and patient- and partner-reported outcome measures. Of course, efficacy will ultimately be assessed from the clinical data set (and with regard to effects that are clinically relevant compared with just statistically significant). The point remains, though, that a considerably greater ejaculation delaying effect would be obtained with chronic compared with acute inhibition of serotonin reuptake. Indeed, supporting this view, published papers describing clinical studies with marketed SSRIs in which *as needed* dosing failed to consistently delay ejaculation, and another in which the maximal ejaculation-delaying effect appeared after 4 or 5 weeks of daily dosing, are cited in the sponsor's response (McMahon and Touma, 1999; Waldinger *et al.*, 1998, 2007).

Severe disturbances to cardiac conduction and contractile function observed in a cardiovascular safety study in guinea pigs raise significant concerns for patient safety—all the more so in light of the reported case of sinus arrest and asystole in a clinical trial participant. Relative exposure at the NOEL for cardiac disturbances (based on animal:human C_{max}) is low at only 3.3.

Dapoxetine caused shortening of the QTc interval, lengthening of the PQ and QRS intervals, bundle branch block, AV block and absent cardiac contraction in an *in vivo* study in guinea pigs at a dose yielding ~15-times the clinical C_{max} ; these effects were absent at the next highest dose level tested (~3.3-times the clinical C_{max}). *In vitro*, the drug shortened action potential duration and decreased action potential amplitude and maximal upstroke velocity in rabbit Purkinje fibres, induced ventricular fibrillation in the isolated rabbit heart, and blocked the hERG K^+ channel, but only at very large multiples of the clinical exposure level. The sponsor responded saying that the findings in guinea pigs should be viewed in conjunction with the results of other *in vivo* studies in which effects on cardiac function/ECG were absent. These studies—a dog cardiovascular safety study and general repeat-dose toxicity studies in dogs and monkeys—can not be used to support the

cardiovascular safety of dapoxetine, however, as peak plasma levels of the drug obtained in the animals are either unknown or below the clinical C_{max} (relative exposure, ≤ 0.9). The sponsor goes on to indicate, though, that questions over the cardiovascular safety of the drug raised by the nonclinical data are addressed by clinical data.

Despite appropriate dose selection, high multiples of the clinical exposure (both with respect to C_{max} and plasma AUC) were not achieved in the pivotal repeat-dose toxicity studies, rodent carcinogenicity studies and reproductive toxicity studies following oral administration, presumably as a consequence of high first-pass metabolism in the animal species. The predictive value of these studies is therefore limited, and strong weight cannot be placed on any negative findings.

Dapoxetine is metabolised to a much greater extent in laboratory animal species compared with humans and, consequently, systemic exposure to unchanged dapoxetine in animals was frequently below or only marginally above the anticipated clinical level. Substantial multiples of the clinical exposure were only obtained in a 3-month rat study. In the response, the sponsor describes the exposure to dapoxetine in animals as “adequate” without providing any further justification other than that animals were dosed up to maximally tolerated levels and that the doses used represent large multiples of the approved maximum recommended human dose on a mg/kg basis. The nonclinical evaluator did not dispute the appropriateness of the dose selection and recognised that the animal doses were significant multiples of the human dose on a body surface area-basis (a more appropriate comparator than mg/kg body weight). Despite this, it remains that animals in the pivotal studies were not exposed to dapoxetine at high multiples of the clinical exposure level and this has a serious impact on the ability of the nonclinical studies to reveal potential toxicity. The sponsor points out that exposure to desmethyl- and didesmethyl dapoxetine in rats and monkeys significantly exceeded human exposure. This reflects their status as major metabolites in the animal species but minor ones in humans. Dapoxetine N-oxide is the sole major human circulating metabolite. Animal:human exposure ratios for dapoxetine N-oxide are similar to (rat) or lower than (monkey) those for unchanged dapoxetine. Therefore, as for dapoxetine itself, large multiples of the human exposure have not been obtained in animals for the major human metabolite.

The CNS, liver and kidney were identified as the major targets of dapoxetine toxicity in repeat-dose studies. Hepatic and renal effects probably reflect the large doses (on a mg/m² basis) that are required to be administered to the animals in order to achieve any significant systemic exposure to unchanged dapoxetine, but their clinical relevance cannot be entirely discounted. Effects on the CNS were typical of the SSRI class and monitorable in patients. Additional toxic effects were observed in the respiratory tract and lymphoid tissues in rodents; these are consistent with irritancy of the gavage solution and non-specific toxicity, respectively.

The sponsor indicates that issues regarding the CNS, renal and hepatic safety of dapoxetine raised by the animal studies are addressed by clinical data.

The carcinogenic potential of dapoxetine remains in question. The apparent absence of tumourigenicity by the oral route in rodents is not reassuring given that the highest doses tested produced systemic exposure to dapoxetine below (transgenic mice) or only a low multiple of (rats) the clinical level. Dapoxetine is not genotoxic, however.

The sponsor contended that the data indicate that dapoxetine does not pose a relevant carcinogenic risk in patients due to the absence of genotoxicity, and the lack of demonstrated tumourigenicity in studies in which exposure in animals was equivalent to the clinical level and which involved daily administration compared with an anticipated usage frequency in patients of twice per week. Potential carcinogenicity may be mediated by a non-genotoxic mechanism. Exposure ratios to unchanged dapoxetine at the highest dose levels tested were 1.42 for the mouse study and ~3.51 in rats (based on plasma AUC). These are not considered high enough to uncover potential tumourigenicity. Animal:human exposure comparisons are made with reference to a human dose of

30 mg/day rather than 30 mg *as needed* as the proposed Product Information document specifies a maximum recommended dosing frequency of once per day.

Registration of Priligy was initially not supported. This was based on potential hazards, most significantly to male fertility, not being adequately investigated/characterised in the nonclinical studies due to the low (or likely low) relative exposure to dapoxetine (in terms of C_{\max} and AUC) achieved in the laboratory animal species. Furthermore, strong reservations exist with regard to the cardiovascular safety of the drug, although this may be addressed by the clinical data.

The male fertility study, conducted in rats, used dietary administration at up to 0.25%, corresponding to a dose of 158 mg/kg/day²¹. No adverse effects on fertility were observed, but relative exposure at the highest dose level tested was considered likely to be low (exposure ratios of 3.5 with respect to AUC and 1.19 with respect to C_{\max} based on data for oral gavage administration). The reliance on pharmacokinetic data for gavage administration to estimate relative exposure was necessitated by the paucity of data for dietary administration (that is, plasma C_{\max} and AUC values were not determined for the route). The sponsor has identified data on mean plasma dapoxetine levels in male rats fed diet containing dapoxetine at 0.25% which were obtained at a single time point (between 8:00–10:00 am); values were 97–120 ng/mL (dose was equivalent to 217 mg/kg/day) and 58–96 ng/mL (179 mg/kg/day). The sponsor claimed that these data indicate an average steady-state plasma concentration in the high-dose animals in the fertility study of ~100 ng/mL given that dapoxetine was delivered constantly as a dietary admixture. This view is not supported given that rats feed primarily at night, plasma was sampled in the morning only, and that dapoxetine is rapidly cleared from plasma in the rat ($t_{1/2}$, ~3 hours). Even so, an average concentration of 100 ng/mL at steady-state (~one-third of the clinical C_{\max}) equates to a plasma AUC_{0-24h} of 2400 ng/mL, which is ~150% of the clinical AUC_{0-24h} at the approved maximum recommended dose. Thus, both AUC and C_{\max} appear to have failed to reach clinical levels in the male fertility study. The sponsor noted that there were no adverse effects on sperm count and motility or testis histopathology in the 9-month monkey study at up to 75 mg/kg/day orally. However, exposure to dapoxetine again did not reach clinical levels (relative exposure, 0.62 with respect to plasma C_{\max} and 1.23 with respect to AUC_{0-24h}). Because of the low exposure, the animal studies are inadequate to gauge the potential for dapoxetine to adversely affect fertility in men treated with Priligy.

IV. Clinical Findings

Introduction

The application includes the results of the full drug development program of dapoxetine (Priligy) with 29 Phase I studies involving 785 subjects and 8 Phase II and III studies in 6404 subjects (placebo: n=2145, dapoxetine: n=4538), mostly for ≤6 months and 654 subjects for 12 months. In addition, there were two observational studies (with no treatment implemented) to assess the validity of the primary and secondary criteria used.

Of the above mentioned studies, the results of the following studies were submitted in this submission after the application was issued a not-approvable letter by the US Food and Drug Administration (FDA) in October 2005:

1 observational study – R096769-PRE-3004. This study began on 25 March 2005 and was completed on 2 September 2005.

²¹ In the sponsor's response, the dietary doses of 0.025%, 0.08% and 0.25% employed in the study are described as being equivalent to 18, 58 and 174 mg/kg/day. This is based on food consumption data for main and satellite rats of both sexes, the companion study to the male fertility study. Doses in male main study animals are equivalent to 17, 52 and 158 mg/kg/day, however, and these are the values that are given in the TGA's Nonclinical Evaluation Report.

2 Phase I studies – R096769-PRE-1001 (11 November 2004-25 March 2005) and C-2004-017 (4 March 2005-21 May 2006)

3 Phase III studies – R096769-PRE-3001 (6 December 2004-31 October 2006), R096769-PRE-3003 (12 April 2005-22 June 2006) and R096769-PRE-3002 (8 November 2004-30 August 2005)

The sponsor documented that all the studies have been approved by the relevant Ethics Committees.

The sponsor also provided supplementary data to address issues raised in the TGA clinical evaluation report. The supplementary submission consisted of one volume of responses by the sponsor to various issues related to efficacy, safety class effects, pharmacokinetics, syncope, depression, risk management and other concerns raised in the TGA clinical evaluation report. In addition, a revised Australian Product Information has been provided with accompanying rationale for substantial changes. Validation of the patient Clinical Global Impression of Change (CGIC) in men with premature ejaculation was provided in an appendix and other appendices provided more details regarding certain efficacy results and safety endpoints. No new study data were submitted in this application. Discussion of the supplementary clinical information is provided following the evaluator's summary and recommendations.

Pharmacodynamics

The mechanism for the dapoxetine effect on ejaculation was studied *in vivo* in the rat. Dapoxetine inhibited the ejaculatory expulsion reflex by acting at a supraspinal level, with the lateral paragigatocellular nucleus (LPGi) as a necessary brain structure in mediating the effect. In addition, it was shown that acute treatment with dapoxetine modulated the ejaculatory reflex in rats by causing an increase in pudendal motoneuron reflex discharge (PMRD) latency and a reduction in PMRD duration. These results provide a possible explanation for the mode of action by which on-demand dapoxetine delays ejaculation in men with premature ejaculation. While delaying ejaculation, dapoxetine had no effects on sexual behaviour in the rat.

In the human clinical Phase I studies, pharmacodynamic (PD) assessments of dapoxetine evaluated changes in *ex vivo* platelet serotonin uptake inhibition and whole blood serotonin concentration.

Study F2X-LC-HIAA

This open-label, crossover, sequential dose-escalation pilot study investigated the pharmacokinetics (PK) and PD of dapoxetine from 5 to 120 mg in 4 subjects. Serotonin reuptake inhibition was measured at 1.5 hours after the 60 mg dose in an *ex vivo* platelet preparation, and found to be inhibited by 25% compared with an untreated patient.

Study F2X-LC-HIAB

This dose-escalation study investigated the PK and PD of dapoxetine 5-40 mg in 20 subjects. Statistical analyses showed that progressively lower whole blood serotonin concentrations down to ~80% were observed after dapoxetine 30 or 40 mg daily. Doses of 5-20 mg once daily had little effect on whole blood serotonin concentration.

Study F2X-LC-HIAF

This single-blind, parallel-group, placebo-controlled study evaluated the safety and PD effects of single doses of dapoxetine capsules 5, 10 or 20 mg, and multiple doses of 5 mg twice daily (bd), 10mg bd or 20 mg once daily in 20 subjects (mean age 39.0 years; 19/20 were Caucasian). Dapoxetine inhibited uptake of serotonin into human platelets *ex vivo* in a dose-dependent manner. The 5 and 10 mg bd regimens inhibited *ex vivo* platelet serotonin uptake for 12 hours. The 20 mg once daily regimen showed greater inhibition than the 5 or 10 mg doses, but uptake had returned to control levels by 24 hours. The peak inhibition of *ex vivo* platelet serotonin uptake occurred at 2-3 hours after administration at each dose.

Pharmacokinetics

Introduction

The following pharmacokinetic (PK) studies for dapoxetine were submitted and evaluated:

- Single- and multiple-dose PK C-2001-004, C-2004-010, F2X-LC-HIAA, F2X-LC-HIAB and F2X-LC-HIAF
- Absorption, distribution, metabolism and excretion and *in vivo* mass balance studies: C2002-051, F2X-LC-HIAC,
- Effect of food: C-2002-037, F2X-LC-HIAE
- Effect of age: C-2002-038
- Effect of CYP2D6 metaboliser status: C-2002-056
- Effect of hepatic (C-2002-019) and renal impairment (C-2002-018)
- Effect of ethnicity: single and multiple dose studies in Japanese versus Caucasian subjects: R096769-PRE-1001
- PK and safety in hypertensive subjects receiving antihypertensive medication: C-2001-007
- Drug-drug interaction studies: drugs investigated included midazolam (C-2003-022), ketoconazole (C-2003-023), glyburide (C-2003-029), warfarin (C-2003-020), ethanol (C-2003-026), desipramine (C-2003-042), fluoxetine (C-2003-024), omeprazole (C-2003-025), phosphodiesterase-5 (PDE5) inhibitors [sildenafil and tadalafil: C-2003-027] and tamsulosin (C-2004-017);
- 3 QT/QTc studies: C-2002-043, C-2002-056, and C-2003-021; and
- bioequivalence studies of tablets versus capsules and of tablets produced with drug substance of different particle sizes: C-2002-020-00, C-2004-009
- population PK studies: C-2002-012 and C-2002-013

The majority of PK studies were performed in healthy adult male subjects aged 18-45 years. Blood and urine sampling for dapoxetine concentrations were performed over 72-168 hours depending on the study protocol and objectives. Plasma dapoxetine concentrations were analysed using LC/MS/MS method. Data were analysed with analysis of variance (ANOVA), Wilcoxon rank sum test and descriptive statistics.

Absorption, distribution, metabolism, excretion & mass balance studies

Study C-2002-051

This single-centre, open-label, two-treatment, two-period study assessed mass balance by determining total radioactivity in plasma, whole blood, urine and faeces and assessed the metabolite profile in plasma, urine and faeces, and absolute bioavailability of dapoxetine, after a single oral dose of ¹⁴C-dapoxetine 60 mg.

Accumulation, measured as the ratio of the area under the concentration-time curve from zero hours to infinity (AUC_{∞}) to the area under the concentration-time curve from zero to 24 hours (AUC_{0-24}), was 1.24 and 1.26 for the respective oral and IV infusion treatments, indicating minimal accumulation. Using a 2-compartment model, mean estimated initial and terminal $t_{1/2}$ values for dapoxetine were 1.57 hours and 18.1 hours after oral administration. Using a 3-compartment model, mean estimated initial, intermediate and terminal $t_{1/2}$ values for dapoxetine were 0.10 hours, 2.19 hours and 19.3 hours after IV dosing. The percent areas of the initial, intermediate and terminal

phases of the AUC were 11.4%, 45.3% and 43.3%, indicating that the terminal $t_{1/2}$ encompasses a smaller fraction of the total AUC_∞.

Mean C_{max} desmethyl dapoxetine was 17.6 ng/mL at 2.44 hours after oral ¹⁴C-dapoxetine 60 mg, and 12.9 ng/mL at 1.5 hours after IV dapoxetine 30 mg. Mean terminal $t_{1/2}$ of desmethyl dapoxetine was 16.6 hours following oral dosing and 22.6 hours following IV dosing. Mean C_{max} didesmethyl dapoxetine was 0.902 ng/mL at 3.09 hours after oral ¹⁴C-dapoxetine 60 mg and 0.218 ng/mL at 3.35 hours after IV dapoxetine 30 mg. Mean terminal $t_{1/2}$ of didesmethyl dapoxetine was 10.0 hours following oral dosing. Terminal $t_{1/2}$ of didesmethyl dapoxetine could only be calculated for 4 subjects for the oral treatment because half the values were below the limit of quantification (LOQ) following C_{max}. Mean C_{max} dapoxetine-N-oxide was 87.4 ng/mL at 2.81 hours after oral ¹⁴C-dapoxetine 60 mg, and 28.7 ng/mL at 6.94 hours after IV dapoxetine 30 mg. Mean terminal $t_{1/2}$ of dapoxetine-N-oxide was 23.8 hours following oral dosing and 25.5 hours following IV dosing.

Based on the ratio of AUC_∞ for dapoxetine and total plasma radioactivity, unchanged dapoxetine accounted for 24.5% of the total plasma radioactivity, indicating that dapoxetine was extensively metabolized. Desmethyl dapoxetine, didesmethyl dapoxetine and dapoxetine-N-oxide AUCs represented 3.08%, 0.12% and 22.5% of the total ¹⁴C-equivalent exposure, suggesting that dapoxetine forms additional metabolites, or that desmethyl dapoxetine, didesmethyl dapoxetine and dapoxetine-N-oxide undergo further metabolism. Dapoxetine-N-oxide was weakly active at the serotonin uptake transporter *in vitro* transporter studies. Desmethyl dapoxetine showed equivalent activity to dapoxetine in a limited number of assays in serotonin reuptake, and didesmethyl dapoxetine has approximately half the potency of dapoxetine in serotonin reuptake assays. However, due to the low plasma concentrations attained, these minor metabolites would not be anticipated to have physiological or pharmacological relevance.

Following oral and IV dosing, the ratios of dapoxetine to desmethyl dapoxetine were 9.82 and 17.8 respectively, and the ratios of dapoxetine to dapoxetine-N-oxide were 1.11 and 2.74 respectively. The ratios with oral dosing were ~2-fold lower than with IV dosing, indicating increased conversion during first-pass metabolism. The ratio of AUC_∞ for dapoxetine to didesmethyl dapoxetine was 289 for the oral dose, while it could not be calculated for the IV treatment. The dose-normalized oral: IV dapoxetine AUC_∞ ratio (that is oral bioavailability) was estimated to be 42%.

Dapoxetine was extensively metabolized to multiple metabolites through N-demethylation, naphthyl hydroxylation, N-oxidation, glucuronidation and sulfation. Unchanged dapoxetine and dapoxetine-N-oxide were the major circulating components in the plasma. Dapoxetine was eliminated primarily in the urine as conjugated metabolites; unchanged drug was below the LOQ in the urine. LC/MS analyses identified 14 metabolites in pooled urine samples. Most of the metabolites were glucuronide and sulfate conjugates, and M23 (OH-DED glucuronide No. 2) and M28 (OH-DDD-sulfate) were the most prevalent. Dapoxetine and 5 metabolites [M9 (3-DABP), M30 (OH-DED No. 1), M32 (OH-DDD No. 2), M34 (OH-DED No. 3) and M37 (OHDAP No. 2)] were identified by LC/MS and LC/MS/MS in faeces. The mass balance, metabolism and excretion data were similar in CYP2D6 poor (PM: n=2) and extensive metabolisers (EM: n=6).

Study F2X-LC-HIAC

This single-centre, single-dose, open-label study evaluated the absorption, distribution, metabolism and excretion of radio-labelled dapoxetine capsules (¹⁴C-dapoxetine 20 mg (50 µCi) or 40 mg (100 µCi)) in 7 Caucasian male subjects (mean age 41.7 years). The report indicated that most of the radioactivity was excreted in the urine as metabolized drug, but no PK data were provided for review.

Study C-2003-021

This study evaluated the PK and ECG pharmacodynamics of dapoxetine in 48 subjects. Subjects received 3 separate treatments: a) 2 x dapoxetine 120 mg tablets separated by 3 hours, b) 1 x moxifloxacin 400 mg tablet and c) 2 x placebo tablets separated by 3 hours.

The PK results showed that there were no detectable concentrations of R-dapoxetine, indicating there was no *in vivo* stereoconversion of S- to R-dapoxetine. The mean AUC_{∞} with dapoxetine 120 mg x 2 was ~3-4 times that reported in studies using dapoxetine 60 mg. The mean T_{max} was later than that reported in other studies because the administration of the 2 x 120 mg tablets involved the taking of one tablet followed 3 hours later by a second tablet (mean T_{max} 4.18 hours, versus 1.73 hours in study C-2002-043). Mean C_{max} and T_{max} for S-dapoxetine-N-oxide were 315 ± 91 ng/mL and 4.88 hours respectively after the first dapoxetine dose (~2 hours after the second dose). The mean terminal $t_{1/2}$ of S-dapoxetine-N-oxide was 20.2 hours. Mean AUC_{∞} of S-dapoxetine-N-oxide was 6390 ng.h/mL. The drug: metabolite ratio was 1.36.

Effect of food on dapoxetine PKs

Study C-2002-037

This single centre, randomised, open-label, single-dose, two-treatment, two-sequence, two-period crossover study investigated the effect of a high-fat meal²² on the PK of dapoxetine 60 mg in 29 male subjects (mean age 28.6 ± 9.1 years, 86.2% [n=25] Caucasians). Subjects received 1 x dapoxetine 60 mg tablet under fed (high-fat breakfast) and fasted conditions in two treatment periods.

After a high-fat meal, mean C_{max} for dapoxetine was modestly lower (398 versus 443 ng/mL) and occurred slightly later than in the fasting state (1.83 hours versus 1.30 hours). Food did not appear to have any significant effect on the elimination rate of dapoxetine or AUC values. The 90% CIs of the treatment ratios (A [fed]/B [fasted]) for the least squares (LS) mean values of area under the concentration -time curve to time t (last detectable concentration) (AUC_t) and AUC_{∞} were within the 80-125% range, at [103.74, 117.08%] and [104.99, 118.84%], respectively, indicating bioequivalence, while the lower limit of the 90% CI for C_{max} was slightly <80% at 77.6%. The upper limit of the 90% CI for C_{max} was 100.56%. This study was also evaluated in Section II.

Study F2X-LC-HIAE

This single-centre, randomised, open-label, two-way crossover study assessed the effect of food on the rate and extent of absorption of dapoxetine 40 mg (2 x 20 mg capsules) in 14 Caucasian subjects (mean age 38.6 ± 5.7 years). The effect of food on bioavailability was found to be minimal. Food decreased the dapoxetine rate of absorption, as reflected in a 35-minute delay (1.9 hours [fed] versus 1.3 hours [fasted], $p=0.01$) in T_{max} and 16% reduction in C_{max} (323ng/mL [fed] versus 386ng/mL [fast], $p=0.06$) in the presence of food; however, equivalence was established for the extent of absorption, as reflected by the AUC values, which appear to be comparable under both fed (1770 ng.h/mL) and fasted conditions (1660 ng.h/mL). $T_{1/2}$ values were similar for fed and fasted conditions (9.4-9.6 hours). Apparent clearance was 25.8 and 27.4 L/h for fed and fasted conditions, respectively. The apparent volume of distribution (V_d) was 330 and 350 L for fed and fasted conditions. This study is also evaluated in Section II.

²² 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4oz hashed brown potatoes, 8oz milk = 500-600kCal fat

Bioequivalence

Study C-2002-020-00

This single centre, randomised, open-label, single dose, three-treatment, six-sequence, three-period crossover study assessed the bioequivalence of 1 x 60 mg tablet to 2 x 30 mg capsules and 2 x 30 mg tablets of dapoxetine in 23 subjects (mean age: 26.7±6.0 years). The mean C_{max} values were 442-447 ng/mL across the treatments. T_{max} was 1.44-1.49 hours across the treatments. AUC_{∞} values were 2288-2511 ng.h/mL across the treatments. The PK for capsule and tablet treatments was bioequivalent with the ratios of C_{max} and AUC_{∞} for the above treatments falling within a usual acceptable range of [80,125%] (Table 3). This study was also evaluated in Section II.

Table 3: Pharmacokinetic Parameters from Study C-2002-020-00

Parameter	2x30 mg Dapoxetine capsules [A] (n=21)	2x30 mg Dapoxetine tablets [B] (n=21)	1x60 mg Dapoxetine tablet [C] (n=21)
C_{max}	445 (129)	442 (153)	447 (158)
T_{max}	1.49 (0.6)	1.44 (0.6)	1.44 (0.6)
$t_{1/2}$	17.4 (4.7)	16.8 (5.9)	17.6 (5.2)
AUC_t (ng.h/mL)	2288 (916)	2425 (1086)	2511 (1140)
AUC_{∞} (ng.h/mL)	2390 (988)	2496 (1089)	2616 (1227)

Parameter	Comparison	Ratio (%)	Power (%)	90% CI
$\ln AUC_{\infty}$	B/C	95.4	>99	[87.75, 103.61]
	C/A	107.4	>99	[98.82, 116.68]
$\ln AUC_t$	B/C	96.0	99	[87.94, 104.70]
	C/A	107.8	99	[98.77, 117.60]
$\ln C_{max}$	B/C	100.0	>99	[91.90, 108.82]
	C/A	99.4	>99	[91.38, 108.20]

The pivotal studies, C-2002-012 and C-2002-013 used 30 mg and 60 mg tablets of the same batch numbers as in this study. However, none of the formulations used in clinical studies were similar to the proposed commercial formulation. The sponsor has stated that such a bioequivalence study was not necessary as the formulations used in clinical studies were very similar to the proposed commercial formulation.

Study C-2004-009

This single-centre, open-label, randomised, four-way crossover study evaluated the bioequivalence of dapoxetine tablets produced with drug substance of different particle size in 36 subjects (mean age 27.1 years, Caucasian: n=24 (66.7%)). The results showed that the mean C_{max} values were similar (373-395ng/mL) among the different particle sizes. T_{max} was 1.12-1.33 hours across treatments, and not statistically significant between treatments except for between-treatment difference of 0.2 hours for treatments B and C ($p=0.01$) which was not considered to be clinically significant. The mean $t_{1/2}$ was 16.5-16.7 hours across treatments. AUC_{∞} values were 1820-1980 ng.h/mL. The 90% CI of AUC_{∞} and C_{max} of treatments A/C, B/C, A/D and B/D were within [80, 125%], indicating bioequivalence. AUC_{∞} for treatments A/C, B/C, A/D and B/D were [99.13, 111.43%], [100.21, 112.70%], [90.98, 102.32%] and [92.01, 103.43%], respectively. C_{max} for

treatments A/C, B/C, A/D and B/D were [99.89, 114.71%], [96.35, 110.72%], [93.83, 107.82%] and [90.56, 104.00%], respectively. This study was also evaluated in Section II.

Single and multiple-dosing studies

Study C-2001-004-A

This single-centre, double-blind, randomised, crossover, placebo-controlled, two-phase study evaluated the PK of dapoxetine, its effect on systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate, and safety after single and multiple doses in healthy men.

The PK analyses demonstrated that dapoxetine was rapidly absorbed after oral administration, with T_{max} at ~1.5-2 hours post-dose. C_{max} and AUC values increased proportionally at dosages up to 100 mg but increases were less than proportional at dosages >100 mg in both study phases. This may have been associated with the vomiting and diarrhoea that occurred in some subjects, or it may indicate saturation in the absorption of dapoxetine. Terminal $t_{1/2}$ for dapoxetine was 15-19 hours. Average plasma concentration (C_{avg}) of desmethyldapoxetine was 6-13 x lower, while C_{avg} of didesmethyl-dapoxetine was >100 x lower than C_{avg} of dapoxetine in single dosing. Metabolism of dapoxetine to desmethyldapoxetine and didesmethyl-dapoxetine did not appear to be saturated over the dose range studied, nor did it appear to change with repeated dosing. Desmethyl-dapoxetine AUCs were ~10 x smaller than dapoxetine AUCs while didesmethyl-dapoxetine AUCs were ~200 x smaller than dapoxetine AUCs in single-dosing, and this was similar with repeated dosing. The multiple-dose PK of metabolites were comparable to single-dose PK. Mean C_{avg} values for plasma desmethyldapoxetine were 6-9 x lower and C_{avg} for didesmethyl-dapoxetine were ≥ 100 x lower than for dapoxetine 80-120 mg in multiple-dosing. Mean C_{max} and $AUC_{120-144}$ for both metabolites plateaued at dapoxetine doses ≥ 100 mg. The mean terminal $t_{1/2}$ for both metabolites with multiple-dosing was ~18-21 hours. T_{max} for both metabolites was 2.5-4.2 hours post-dose.

Study F2X-LC-HIAA

This single-centre, open-label, crossover, sequential dose-escalation pilot study investigated the PK and PD of dapoxetine. The PK results showed that the mean $t_{1/2}$ of dapoxetine was 13.9 hours (12.1-15.4 hours). Clearance was 27.1 L/h (21.7-33.5 L/h). Volume of distribution (V_d) was 6.43 L/kg (5.37-7.58 L/kg). The results suggested that dapoxetine had linear pharmacokinetics and was eliminated by a non-saturable, first-order process. The plasma-concentration-versus-time profiles followed log-linear pharmacokinetics. The concentration of dapoxetine after multiple dosing could increase depending on the frequency of the dosing interval. The accumulation index was projected to be 1.06 for once daily (od) and 1.2 for twice daily (bd) administration. The concentration of desmethyldapoxetine was ~10% of the parent drug.

Study F2X-LC-HIAB

This single-centre, single-blind, placebo-controlled, multiple-dose escalation study investigated the PK and PD of dapoxetine in 22 subjects (mean age 37.1 years, Caucasian: n=21). The PK results showed that the $t_{1/2}$ was 16.0 ± 8.3 hours, V_d was 9.5 ± 5.9 L/kg and clearance (Cl) was 31.5 ± 11.2 L/h. The PK were non-saturable and first-order. Dapoxetine steady-state plasma-concentration-versus-time data were characterized by classic linear PK multi-compartmental models. C_{max} and AUC had a linear relationship with dose.

Study C-2004-010

This single-centre, randomised, single- and multiple-dose, open-label, two-treatment, two-period, crossover study assessed the dose proportionality and compared single- and multiple-dose PK of dapoxetine 30 and 60 mg in 42 subjects [mean age: 30.8 years, 20/42 (47.6%) Black, and 13/42 (31.0%) Caucasian]. The C_{max} for single and multiple dose of dapoxetine 30 mg was 297 and 349 ng/mL, respectively. The C_{max} for single and multiple dose of dapoxetine 60 mg was 498 and 596

ng/mL, respectively. The T_{\max} was similar with single and multiple doses of dapoxetine 30 and 60 mg (1.01-1.27 hours). The initial (disposition) and terminal $t_{1/2}$ values were 1.3 and 18.3 hours, respectively, for the 30 mg dose and 1.4 and 20.8 hours, respectively, for the 60 mg dose. AUC_t for single and multiple dose of dapoxetine 30 mg was 1110 and 1550 ng.h/mL, respectively. AUC_t for single and multiple dose of dapoxetine 60 mg was 2070 and 2950 ng.h/mL (Table 4). Dapoxetine PK was dose-proportional. The 90% CIs for AUC_{∞} and C_{\max} for single doses of dapoxetine 60/30 mg were [91.43, 103.57%] and [79.7, 94.23%], respectively. The 90% CIs for $\ln AUC_{0-24}$ and C_{\max} for multiple doses of dapoxetine 60/30 mg were [91.19, 101.45%] and [80.19, 91.94%], respectively. The 90% CIs for the ratio of AUC_{0-24} for dapoxetine following multiple dosing to AUC_{∞} after a single dose were [96.54-133.67%] for 30 mg and [98.05, 132.47%] for 60 mg. The ratio was not statistically different from 100% and the 90% CIs included 100%, indicating that dapoxetine followed time-invariant pharmacokinetics. There was modest accumulation with multiple-dosing (1.5x). Steady-state was achieved by the fourth dose.

Table 4: Study C-2004-010 pharmacokinetics results

:Parameter	Dapoxetine 30 mg		Dapoxetine 60 mg	
	Single dose	Multiple dose	Single dose	Multiple dose
C_{\max} (ng/mL)	297±130	349 ± 110	498 ± 180	596 ± 190
T_{\max} (h)	1.01 ± 0.34	1.03 ± 0.30	1.27 ± 0.44	1.07 ± 0.28
$t_{1/2}$ (h)	17.2 ± 5.5	19.8 ± 5.4	18.2 ± 7.4	20.9 ± 8.0
AUC_t (ng.h/mL)	1110 ±440	1550 ± 580	2070 ± 740	2950 ± 1100
AUC_{∞} (ng.h/mL)	1390 ± 610	Not relevant	2640 ± 1100	Not relevant

Pharmacokinetics in specific populations

Study C-2002-038 Effect of Age

This single-centre, open-label, single-dose, single-period, parallel group study compared the PK of dapoxetine in healthy elderly (≥ 65 years) and young men (18-45 years). Statistical analyses of C_{\max} , AUC_t , AUC_{∞} and T_{\max} for plasma dapoxetine showed no significant age-related differences. Dapoxetine was absorbed rapidly in both young and elderly men. C_{\max} values were 338 and 310 ng/mL in young and elderly men, respectively. T_{\max} was 1.28-1.29 hours in young and elderly men and $t_{1/2}$ was 17.8 hours in young men and 26.0 hours in elderly men. Dapoxetine AUC_{∞} was ~12% higher in the elderly subjects but it is unlikely that this difference is of clinical significance. Dapoxetine concentrations decreased to 5-6% of C_{\max} within 24 hours in young and elderly subjects, respectively, indicating that dapoxetine has a rapid elimination in both age groups.

Dapoxetine-N-oxide was the most abundant metabolite, with a mean AUC ~80% that of dapoxetine. The mean desmethyldapoxetine AUC was ~15% that of dapoxetine, and the mean didesmethylapoxetine AUC was only ~0.2% that of dapoxetine. Mean C_{\max} of each metabolite were significantly greater in the young than in the elderly group with differences of 50% (young: 20.8 versus 13.9 ng/mL, $p < 0.001$), 110% (young: 0.721 versus 0.344 ng/mL, $p = 0.011$), and 24% (young: 91.4 versus 73.6 ng/mL, $p = 0.005$) for desmethyldapoxetine, didesmethylapoxetine, and dapoxetine-N-oxide, respectively. Metabolite AUC values were also greater in the young than in the elderly group, although the differences were not statistically significant. Drug-to-metabolite ratios were consistently smaller in the young group, suggesting more metabolite formation in young men. Mean T_{\max} values were similar in both age groups for each metabolite, and ~1-2 hours longer than for the parent drug.

Study C-2002-056: CYP2D6 Effect of CYP2D6 metaboliser status

This was a multicentre, double blind, placebo-controlled, randomised, two-treatment, two-period study designed to investigate the PK of dapoxetine, and to evaluate the effects of dapoxetine on ECG pharmacodynamics in healthy adult male CYP2D6 poor metabolisers (PM) and extensive metabolisers (EM) (Table 5).

Table 5: Study C-2002-056 Mean values (SD) for PK parameters for dapoxetine 60 mg

Parameter	PM (n=13)	EM (n=15)
C _{max} (ng/mL)	467 ± 190	357 ± 140
T _{max} (h)	1.39 ± 0.61	1.88 ± 0.90
t _{1/2} (h)	21.9 ± 9.7	19.5 ± 5.2
AUC _t (ng.h/mL)	2520 ± 730	1890 ± 530
AUC _∞ (ng.h/mL)	2720 ± 850	2000 ± 580

The mean C_{max} and AUC for dapoxetine were slightly higher in PM versus EM; ~31% higher for C_{max} and 36% higher for AUC_∞. The ratio of AUC_∞ and C_{max} values in PM to EM was >100% and the 90% CI fell outside [80-125%], indicating that PM have higher AUC_∞ and C_{max} values than EM. The absorption of dapoxetine was rapid in both PM and EM with T_{max} at 1.39 hours and 1.88 hours, respectively (p=0.142). The mean t_{1/2} of dapoxetine was similar for PM and EM, 21.9 hours and 19.5 hours respectively. Dapoxetine concentrations had decreased to <5% of C_{max} by 24 hours for PM and EM, indicating that dapoxetine has a rapid elimination in PM and EM. Mean AUC_∞ /mean AUC₀₋₂₄ ratio was 1.38 and 1.30 for PM and EM, respectively, indicating minimal accumulation. Two-compartmental modelling with first order absorption and first order elimination indicated that the mean initial and terminal t_{1/2} for dapoxetine were 1.44 hours and 21.5 hours, respectively, for PM and 1.44 hours and 18.4 hours, respectively, for EM.

Mean C_{max} for desmethyldapoxetine were ~98% higher in PM (36.1±11 ng/mL) versus EM (18.2±8.9 ng/mL). AUC_∞ for desmethyldapoxetine was ~160% higher in PM (695±210 ng.h/mL) versus EM (266±160 ng.h/mL). T_{max} for desmethyldapoxetine was similar for PM and EM, 3.42 hours and 3.20 hours, respectively (p=0.449). The mean t_{1/2} of desmethyldapoxetine was 20.4 hours and 17.1 hours for PM and EM, respectively. The 90% CI for ratio of C_{max} and AUC_∞ values for PM/EM were outside [80, 125%], at [168.41, 267.16%] and [223.06, 359.65%], respectively, indicating that PM have a larger C_{max} and AUC_∞ than EM.

Mean C_{max} values for didesmethyl-dapoxetine were ~114% higher in PM (1.79±0.56 ng/mL) versus EM (0.835 ± 0.46 ng/mL). AUC_∞ values for desmethyldapoxetine were ~239% higher in PM (44.4±16 ng.h/mL) versus EM (13.1±12 ng.h/mL). T_{max} values for didesmethyl-dapoxetine were similar for PM and EM, 3.31 hours and 2.97 hours, respectively (p=0.858). The mean t_{1/2} of desmethyldapoxetine was 24.5 hours and 12.9 hours for PM and EM, respectively. The ratio of C_{max} (228.7%, [90% CI: 176.36, 296.48%]) and AUC_∞ (400%, [90% CI: 278.28, 574.28%]) of PM/EM was >100% and the 90% CI fell outside [80, 125%], indicating that the C_{max} and AUC_∞ values for didesmethyl-dapoxetine were larger in PM than in EM.

Mean C_{max} values for dapoxetine-N-oxide were ~14% higher in PM (79.4±16 ng/mL) versus EM (69.8±18 ng/mL). AUC_∞ values for dapoxetine-N-oxide were ~49% larger in PM versus EM. T_{max} values for dapoxetine-N-oxide were similar for PM and EM at 2.46 hours and 2.83 hours, respectively (p=0.259). The mean t_{1/2} of dapoxetine-N-oxide was 24.3 hours and 20.7 hours for PM and EM, respectively. The ratio of C_{max} (117.9%, [90% CI: 100.88, 137.67%]) and of AUC_∞

(153.1%, [90% CI: 126.32, 185.46%]) for PM/EM was >100% and the 90% CI fell outside [80%, 125%], indicating that PM had higher C_{\max} and larger AUC_{∞} values than EM.

The drug-to-metabolite ratios for desmethyldapoxetine (PM: 3.95 versus EM: 8.56) and didesmethyl-dapoxetine (PM: 67.3 versus EM: 239) were lower for PM versus EM consistent with reduced elimination of these metabolites in PM and suggesting that CYP2D6 may play a role in the metabolism of these two metabolites. The drug-to-metabolite ratios for dapoxetine-N-oxide, the predominant metabolite, were similar for the two groups (PM: 1.61 versus EM: 1.77).

Study C2003-018 (Mod 5.3.3.3): Effect of Renal impairment

This multi-centre, open-label, parallel-group study investigated the PK of a single dose of dapoxetine 60 mg tablet in male subjects with normal and impaired renal function. The protocol followed the TGA-adopted European Union (EU) guideline on pharmacokinetic evaluation in patients with impaired renal function.²³ Twenty two subjects were stratified into four groups:

- i) normal renal function with baseline creatinine clearance (CrCl) >80mL/min/ 1.73m² body surface area (BSA) (6 subjects: mean age 56.2 years, Caucasian: n=5),
- ii) mild renal impairment with CrCl 50-80mL/min/1.73m² (6 subjects: mean age 62.3, Caucasian: n=5),
- iii) moderate renal impairment with CrCl 30-50mL/min/1.73m² BSA (6 subjects: mean age 50.8 years, Caucasian: n=4), and
- iv) severe renal impairment with CrCl <30mL/min/1.73m² BSA (4 subjects: mean age 60.0 years, Caucasian: n=2).

Dapoxetine was well absorbed; T_{\max} was 1.09-1.33 hours and C_{\max} was 353-431 ng/mL across the groups (Table 6). AUC_{∞} was 2090-3820 ng.h/mL for normal to moderate renal impairment and 4530 ng.h/mL for severe renal impairment. Model-based $t_{1/2}$ was similar across the groups, initial $t_{1/2}$ was 1.58-2.97 hours and terminal $t_{1/2}$ was 18.7-35.3 hours without any obvious trend relating to decreasing renal function. Dapoxetine concentrations decreased to 4.5%, 9.7%, 7.1% and 10.7% of C_{\max} values 24 hours post-dose in normal, mildly, moderately and severely impaired renal function groups. There was no obvious accumulation with declining renal function. There was no significant correlation between creatinine clearance and C_{\max} ($p=0.43$) or AUC_{∞} ($p=0.15$) values for dapoxetine. Protein-binding was also analysed and found not to be altered in subjects with renal impairment versus healthy subjects (99.5-99.7% protein-bound).

Dapoxetine-N-oxide was the most abundant metabolite, with mean AUC_{∞} ~57-80% that of dapoxetine. The mean desmethyldapoxetine AUC_{∞} values were 9-17% that of dapoxetine. There was no clear trend with declining renal function. There was no significant correlation between creatinine clearance and C_{\max} or AUC_{∞} for dapoxetine-N-oxide and desmethyldapoxetine.

²³ EMEA. Committee for Medicinal Products for Human Use (CHMP), 23 June 2004. Note for Guidance on the Evaluation of the Pharmacokinetics of Medicinal Products in Patients with Impaired Renal Function CPMP/EWP/225/02.

Table 6: Study C-2003-018 Pharmacokinetics of dapoxetine and its metabolites in subjects with renal impairment.

Parameter	Normal renal function (n=6)	Mild renal impairment (n=6)	Moderate renal impairment (n=6)	Severe renal impairment (n=4)
C _{max} (ng/mL)	399 ± 120	386 ± 160	353 ± 190	431 ± 140
T _{max} (h)	1.09 ± 0.20	1.17 ± 0.41	1.33 ± 0.75	1.25 ± 0.29
t _{1/2} (h)	29.4 ± 8.3	39.5 ± 19	17.8 ± 4.1	28.4 ± 7.2
AUC _t (ng.h/mL)	2150 ± 620	3490 ± 780	2030 ± 440	4300 ± 2800
AUC _∞ (ng.h/mL)	2240 ± 630	3820 ± 770	2090 ± 430	4530 ± 3000
Urinary excretion (µg)	7.73 ± 9.7	25.6 ± 15	15.5 ± 11	36.3 ± 22
Renal clearance (mL/h)	4.10 ± 5.2	7.15 ± 3.8	7.32 ± 5.1	8.52 ± 1.9

Study C-2003-019 Effect of hepatic impairment

This multiple-centre, open-label, parallel-group study evaluated the PK of single dose of dapoxetine 60 mg tablet in subjects with normal and impaired hepatic function. The protocol followed the TGA-adopted EU guideline on pharmacokinetic evaluation in patients with impaired hepatic function.²⁴ No power calculations were performed. Twenty one subjects were stratified into four groups:

- i) normal hepatic function (6 subjects: mean age 50.0 years, Caucasian: n=3),
- ii) mild hepatic impairment with Child-Pugh A score 5-6 (6 subjects: mean age 52.5, Caucasian: n=6),
- iii) moderate hepatic impairment with Child-Pugh B score 7-9 (5 subjects: mean age 54.0 years, Caucasian: n=3), and
- iv) severe hepatic impairment with Child-Pugh C score 10-15 (4 subjects: mean age 52.8 years, Caucasian: n=3).

T_{max}, C_{max} and AUC_∞ were comparable in normal, mild and moderate hepatic impairment groups, but abnormal in the severe impairment group (Table 7). T_{max} was 1.46-1.60 hours in normal to moderate hepatic impairment and 2.25 hours in severe impairment. C_{max} was 277-470 ng/mL in normal to moderate hepatic impairment and 159 ng/mL in severe impairment. AUC_∞ values were 2060-3380 ng.h/mL in normal to moderate hepatic impairment, and 4710 ng.h/mL in severe impairment. Dapoxetine concentrations decreased to ~5% of C_{max} in normal and mild hepatic dysfunction, 7% in moderate impairment and 17% in severe impairment. Mean t_{1/2} was longer with declining hepatic function (mean t_{1/2} in normal subjects was longer in this study than in other Phase I studies because of a longer sampling interval performed in this study (120 hours versus 72 hours). Mean accumulation measured as ratio of AUC_∞/ AUC₀₋₂₄ indicated higher accumulation in severe dysfunction. Model-based analyses showed that the initial t_{1/2} for normal, mild, moderate and severe hepatic dysfunction were 1.39, 1.88, 1.96 and 2.79 hours, respectively and 23.9, 36.3, 36.4 and 98.2 hours, respectively for terminal t_{1/2}. Regression analyses using serum albumin and bilirubin indicated that there was a significant increase in AUC_∞ for dapoxetine, measured using unbound fraction, with declining hepatic function. Urinary excretion of dapoxetine was small (0.005-0.025%) and did

²⁴ EMEA. Committee for Medicinal Products for Human Use (CHMP), 17 February 2005. Guideline on the Evaluation of the Pharmacokinetics of Medicinal Products in Patients with Impaired Hepatic Function CPMP/EWP/2339/02.

not increase with declining hepatic function. Protein-binding was also analysed and found to be unaffected by hepatic impairment (99.3-99.7% protein-bound).

Table 7: Study C-2003-019 Mean (SD) values for dapoxetine PK parameters in 21 subjects with normal, mild, moderate and severe liver impairment.

Parameter	Normal liver function (n=6)	Mild liver impairment (n=6)	Moderate liver impairment (n=5)	Severe liver impairment (n=4)
C _{max} (ng/mL)	479 ± 190	277 ± 150	371 ± 140	159 ± 78
T _{max} (h)	1.46 ± 0.56	1.46 ± 0.33	1.60 ± 0.82	2.25 ± 0.87
t _{1/2} (h)	24.5 ± 2.7	37.2 ± 20	40.9 ± 12	91.7 ± 12
AUC _t (ng.h/mL)	2490 ± 660	1800 ± 1300	3030 ± 2000	3050 ± 1300
AUC _∞ (ng.h/mL)	2550 ± 680	2060 ± 1700	3380 ± 2400	4710 ± 1700
Urinary excretion (µg)	3.11 ± 1.3	9.06 ± 6.4	15.2 ± 11	12.6 ± 10
Renal clearance (mL/h)	1.29 ± 0.61	5.76 ± 4.4	4.85 ± 2.3	3.02 ± 2.9

In terms of metabolites, T_{max} for dapoxetine-N-oxide was similar across the groups (2.75-3.75 hours), but mean t_{1/2} was longer in severe hepatic dysfunction (86.6 hours) compared with that in normal to moderate dysfunction (30.1 – 35.0 hours). AUC_∞ for dapoxetine-N-oxide decreased with worsening hepatic dysfunction (662 ng.h/mL in severe dysfunction versus 2200 ng.h/mL in normal function). Renal clearance for dapoxetine-N-oxide appeared to increase with declining hepatic function (8.89 mL/h in severe dysfunction versus 2.82 mL/h in normal). Terminal t_{1/2} for desmethyldapoxetine was longer in moderate to severe liver impairment (38-91 hours) compared to normal/mild liver impairment (25– 28hours). Renal clearance for desmethyldapoxetine was unchanged. T_{max} for didesmethylapoxetine was longer (16.5 hours) in severe liver impairment versus normal to moderate liver impairment (2-4 hours) and AUC_t for didesmethylapoxetine was higher in moderate to severe liver impairment (21.4-25.7 ng/mL) versus normal to mild liver impairment (4.6-13.7 ng/mL). Renal clearance for didesmethylapoxetine declined with declining hepatic function (54.8 mL/h in severe dysfunction versus 313 mL/h). Drug: metabolite ratio for dapoxetine-N-oxide was higher in subjects with severe hepatic impairment and lower for desmethyldapoxetine and didesmethylapoxetine, suggesting alternative pathways for metabolism in severe hepatic dysfunction.

Study R096769-PRE-1001: Asian population

This multicentre, randomised, open-label, two-treatment, two-period crossover study compared the single-dose and multiple-dose dapoxetine PK between Japanese and Caucasian men; it also assessed the dose-proportionality of dapoxetine 30 and 60 mg doses in Japanese subjects, and the variability of dapoxetine PK in relationship to CYP2D6 gene variations.

Mean T_{max} for plasma dapoxetine was 0.985-1.27 hours in single- and multiple-dosing. The mean terminal t_{1/2} of dapoxetine was 14.0-17.2 hours. Non-body weight adjusted C_{max} and AUC of dapoxetine were observed to be slightly higher, outside bioequivalence criteria of [80-125%] in Japanese versus Caucasian men as Japanese subjects generally had lower body weight than Caucasian subjects which resulted in a higher dose based on mg/kg. After weight-adjustment, the results were equivalent, except for C_{max} of dapoxetine on Day 1 for the 60 mg dose. However, for weight-adjusted values for metabolites (dapoxetine-N-oxide, desmethyldapoxetine and didesmethylapoxetine), except for C_{max} and AUC₀₋₂₄ of dapoxetine-N-oxide on Day 1, the 90% CIs for the ratio of geometric means of Japanese versus Caucasian subjects for the single- and

multiple-dosing of dapoxetine 30 and 60 mg were not contained within the equivalence range of 80 to 125%. Steady-state was achieved after the fourth dose.

In terms of dose proportionality, dapoxetine AUCs increased linearly for 30 and 60 mg doses after single- and multiple-dosing. The low didesmethyl-dapoxetine plasma concentrations (the metabolic ratio to parent drug was 0.001-0.007) made it difficult to ascertain dose-proportionality. Dapoxetine-N-oxide and desmethyl-dapoxetine also increased in proportion to dose for C_{\max} and AUC values. The mean desmethyl-dapoxetine AUC and C_{\max} were <11% and <5% of those of dapoxetine respectively, and this relationship did not appear to vary by dose. Didesmethyl-dapoxetine AUC and C_{\max} were <0.7% and 0.3% of those of dapoxetine respectively, and this relationship did not appear to vary by dose. Dapoxetine-N-oxide AUC and C_{\max} were 98% and 40% of those of dapoxetine respectively, and this relationship did not appear to vary by dose. The total urine excretion across all quantified analytes (parent drug and metabolites) was generally <0.01% of the given dose in both ethnic groups.

Study C-2001-007 Hypertension

This double-blind, two-way crossover, placebo-controlled study evaluated the safety and tolerability, PK and effect on blood pressure of a single oral dapoxetine 100mg dose in 16 men with hypertension on a stable antihypertensive regimen [mean age: 49.1 years, 10/16 Black (62.5%)]. Fifteen of the subjects were CYP2D6 EMs. The PK results of these 15 subjects showed that the mean C_{\max} of dapoxetine, desmethyl-dapoxetine and didesmethyl-dapoxetine were 612.1, 23.0 and 0.626 ng/mL occurring at ~1.7, 2.8 and 3.0 hours, respectively. Elimination was biphasic with an initial rapid phase and a long terminal $t_{1/2}$. Terminal $t_{1/2}$ of dapoxetine, desmethyl-dapoxetine and didesmethyl-dapoxetine were ~28 hours, 25 hours and 9 hours, respectively. AUC_{∞} for dapoxetine was 4748.5 ng.h/mL which was ~13 x larger than for desmethyl-dapoxetine (412.1 ng.h/mL) and ~780x larger than for didesmethyl-dapoxetine (7.4 ng.h/mL). The PKs of dapoxetine in controlled hypertensive subjects were similar to those observed in the earlier studies in healthy subjects.

Drug interaction studies

Study C-2003-020 Warfarin

This single-centre, randomised, open-label, two-treatment, two-period, two-sequence crossover study investigated the effect of dapoxetine on warfarin PK and PD in 16 subjects (mean age 28.6 years, Caucasian: n=12 (75%)). Following administration of warfarin alone and in combination with dapoxetine, C_{\max} values for R- (1530 versus 1470 ng/mL) and S-warfarin (1570 versus 1500 ng/mL) were similar. T_{\max} values for both R- and S-warfarin were delayed by ~0.5 hours, ($p=0.135$ and 0.089 for R- and S-warfarin, respectively) when administered with dapoxetine. Compared with warfarin alone, co-administration with dapoxetine resulted in slightly longer terminal $t_{1/2}$ of R-warfarin (48.8 hours versus 50.4 hours) or S-warfarin (36 hours versus 37.8 hours), and larger mean AUC_{∞} values for R-warfarin (79800 versus 83600 ng.h/mL) and S-warfarin (49100 versus 52900 ng.h/mL). For R- and S-warfarin C_{\max} and AUC_{∞} values, the 90% CIs for the ratios of the means fell within 80-125%, indicating that dapoxetine did not significantly affect the PK of warfarin.

The mean baseline (pre-warfarin) prothrombin time (PT) and international normalised ratio (INR) were similar for warfarin alone and warfarin + dapoxetine treatment (PT: 11.7 and 11.8 seconds [s], respectively; INR 0.97 and 0.99, respectively). Mean maximum PT and INR (E_{\max}) values were slightly higher in dapoxetine + warfarin versus warfarin alone (E_{\max} PT 16.0 versus 15.3 s and E_{\max} INR 1.8 versus 1.6, respectively). In the presence of dapoxetine, T_{\max} to maximum effect on INR was non-significantly delayed by ~0.8 hours. PT and INR area under the effect curve from time zero to 144 hours ($AUEC_{0-144}$) values were slightly higher with dapoxetine + warfarin treatment versus warfarin alone ($AUECPT_{0-144}$ 1910 versus 1840 s x hr and the area under the effect curve for INR from zero to 144 hours ($AUECINR_{0-144}$) 181 versus 169, respectively). No subject had an INR >3.0 during the study. Mean PT and INR values were significantly higher at 36-96 hours following

warfarin + dapoxetine. The maximum difference reached 0.612 s for PT (90% CI 0.302-0.921, $p=0.0039$) and 0.133 for INR (90% CI 0.053-0.213, $p=0.0112$) at 36 hours post-dose. Following dapoxetine + warfarin, the mean AUECPT increased by 3.6% and AUECINR increased by 6.0%, with a maximum increase (upper limit of 90% CI) of 5.4% for PT and 8.1% for INR versus warfarin alone, which were not considered clinically significant. The 90% CIs for the ratios of the mean for PT and INR E_{\max} and AUEC (area under the PT/INR curve) values fell within 80-125%, suggesting that dapoxetine did not have any significant effect on the pharmacodynamic effects of warfarin.

Study C-2003-022 CYP3A4 substrate: Midazolam

This single-centre, randomised, open-label, two-treatment, two-period, crossover study investigated the effect of dapoxetine on midazolam pharmacokinetics in 24 healthy adult males (mean age: 27.7 years, 62.5% Caucasian). Midazolam is metabolized almost exclusively by CYP3A4.

Dapoxetine decreased the mean C_{\max} for midazolam by 21.7% and decreased the mean C_{\max} for hydroxymidazolam by 10.2%. Mean T_{\max} values for midazolam and hydroxymidazolam were similar following midazolam-only and midazolam + dapoxetine treatments, at ~0.82-0.88 hours. Mean terminal $t_{1/2}$ of midazolam following midazolam-only and midazolam + dapoxetine treatments were similar (5.46 versus 5.54 hours, respectively) but shorter for hydroxymidazolam following midazolam-only and midazolam + dapoxetine treatments (8.09 versus 5.64 hours). Dapoxetine decreased the mean midazolam AUC_{∞} values by 20.3% and decreased the mean hydroxymidazolam AUC_{∞} values by 8.1%. The mean \pm SD midazolam-to-hydroxymidazolam AUC_{∞} ratios were similar following midazolam-only and midazolam + dapoxetine treatments at 2.89 ± 1.2 and 2.52 ± 0.93 , respectively.

For midazolam, the 90% CIs for the AUC_{∞} and C_{\max} ratios comparing midazolam + dapoxetine to midazolam-only were [74.59, 88.31%]; $p<0.001$ and [74.39, 91.04%]; $p<0.003$, respectively, and they fell slightly outside the lower limit of 80%; although these differences were statistically significant they were not likely to be clinically relevant. For hydroxymidazolam, the 90% CIs for the ratios of AUC_{∞} and C_{\max} were within [80, 125%]. Dapoxetine did not significantly alter T_{\max} for midazolam or hydroxymidazolam.

Results of the above study suggested that dapoxetine did not inhibit the metabolism of midazolam by CYP3A4.

Study C-2003-023 CYP3A4 inhibitor: Ketoconazole

This single-centre, randomised, open-label, two-treatment, two-period crossover study investigated the effect of ketoconazole on PK of dapoxetine in 24 subjects (mean age 31.2 years, Caucasian: $n=16$ (66.7%)).

Co-administration of dapoxetine with ketoconazole increased the mean dapoxetine C_{\max} values (460 and 621 ng/mL after dapoxetine-only and dapoxetine + ketoconazole, respectively). Ketoconazole increased mean C_{\max} and AUC_{∞} for dapoxetine by 34.8% and 99.1%, respectively. C_{\max} values for dapoxetine after combination treatment were higher versus dapoxetine alone in 22 (92%) subjects; AUC_{∞} values were higher after combination treatment in all subjects. Although T_{\max} for dapoxetine was delayed by ~0.35 hours in ketoconazole + dapoxetine versus dapoxetine-only ($p=0.030$), the slight delay was not considered clinically significant. The estimated initial and terminal $t_{1/2}$ values for dapoxetine were 1.43 hours and 18.4 hours, respectively, for dapoxetine alone, and 1.32 hours and 20.7 hours, respectively, for ketoconazole + dapoxetine treatment. The 90% CIs for ratios of C_{\max} and AUC_{∞} values for dapoxetine after dapoxetine + ketoconazole versus dapoxetine-only were [124.48-144.86%] and [180.68-203.78%], and fell outside the 80-125% range, indicating that ketoconazole affected the PK of dapoxetine.

Dapoxetine concentrations decreased to 3.7 and 6.9% of C_{\max} by 24 hours for dapoxetine alone, and ketoconazole + dapoxetine, respectively, indicating that dapoxetine has a rapid elimination during

either treatment. Accumulation, measured as the ratio of AUC_{∞} to AUC_{0-24} , was 1.26 and 1.42 for the dapoxetine alone and the dapoxetine + ketoconazole treatments, respectively, indicating minimal accumulation.

The overall exposure of dapoxetine metabolites, desmethyldapoxetine and dapoxetine-N-oxide was increased in the presence of ketoconazole; however, ketoconazole did not appear to affect C_{max} of the metabolites. The 90% CI for the ratios of AUC_{∞} fell outside the [80-125%] range for desmethyldapoxetine [151.64, 202.61%] and dapoxetine-N-oxide [242.27 285.24%]. The 90% CI for ratios of C_{max} were within the [80, 125%] range for desmethyl-dapoxetine and dapoxetine-N-oxide.

Results from this study indicate that ketoconazole significantly affects the pharmacokinetics of dapoxetine and its metabolites.

Study C2003-024 CYP2D6 inhibitor: Fluoxetine

This single-centre, open-label, two-treatment, two-period sequential study investigated the effect of the potent CYP2D6 inhibitor fluoxetine on dapoxetine pharmacokinetics, and vice versa in 24 healthy adult males (mean age 29.4years, 58.3% Caucasian).

Co-administration with fluoxetine led to a statistically significant and clinically relevant increase in dapoxetine C_{max} (dapoxetine alone versus dapoxetine + fluoxetine; 427 versus 640 ng/mL). Fluoxetine increased mean C_{max} and AUC_{∞} for dapoxetine by 50% and 88%, respectively. T_{max} was similar for both treatments. The mean terminal $t_{1/2}$ values for dapoxetine were significantly prolonged following co-administration with fluoxetine (17.2 hours versus 25.1 hours).

C_{max} for desmethyldapoxetine was 19.6 ng/mL at 2.94 hours after dapoxetine alone and 32.3 ng/mL (64% higher) at 3.43 hours after fluoxetine + dapoxetine. $T_{1/2}$ was 18.4 hours for dapoxetine only treatment versus 23.1 hours for fluoxetine + dapoxetine treatment. Mean desmethyldapoxetine AUC_{∞} was 312 ng.h/mL for dapoxetine alone and 669 ng.h/mL (114% larger) for fluoxetine + dapoxetine. C_{max} for dapoxetine-N-oxide was 93.6 ng/mL at 2.55 hours after dapoxetine alone and 139 ng/mL (49% higher) at 2.41 hours after fluoxetine + dapoxetine. $T_{1/2}$ was 19.3 after dapoxetine alone and 24.1 hours after fluoxetine + dapoxetine. Mean dapoxetine-N-oxide AUC_{∞} was 1750 ng.h/mL for dapoxetine alone and 3020 ng.h/mL (73% larger) for fluoxetine + dapoxetine.

The 90% confidence intervals for C_{max} for dapoxetine, desmethyldapoxetine and dapoxetine-N-oxide were [138.61-164.58%], [149.82, 194.02%] and [137.64, 159.93%], respectively and for AUC_{∞} values were [174.41-227.94%], [194.80, 282.56%] and [159.50, 198.41%] respectively. Co-administration of fluoxetine did not affect T_{max} for dapoxetine significantly.

Dapoxetine concentrations decreased to 4% and 6% of C_{max} by 24 hours for dapoxetine alone, and fluoxetine + dapoxetine, respectively, indicating that dapoxetine has a rapid elimination in both treatments. The ratios of AUC_{∞} : AUC_{0-24} , were 1.25 and 1.48 for the respective dapoxetine only and dapoxetine + fluoxetine treatments, indicating minimal accumulation.

AUC_{∞} values for dapoxetine were 7-9 x larger than desmethyldapoxetine and 1.3-1.5 x larger than dapoxetine-N-oxide, and did not appear to be affected by co-administration with fluoxetine. Fluoxetine has not reached steady-state after 6 days of dosing and after addition of dapoxetine on Day 7 dosing of fluoxetine dosing, C_{max} for fluoxetine was slightly higher 197 (+11%) versus 177 ng/mL for fluoxetine alone and AUC_{0-24} was also slightly higher 4070 (+15%) versus 3550 ng.h/mL. Similar small increases in C_{max} and AUC_{∞} values were noted for its metabolite, norfluoxetine. The 90% CI for ratios of means of $\ln C_{max}$ and $\ln AUC_{0-24}$ for fluoxetine and norfluoxetine fell within [80, 125%], indicating that dapoxetine did not have a clinically relevant affect on PK of fluoxetine.

Study C-2002-025 substrate for CYP2C19: Omeprazole

This single-centre, open-label, two-treatment, two-period sequential study investigated the effect of omeprazole on dapoxetine PK in 24 subjects (mean age 25.9 years, 83.3% Caucasian). Omeprazole is extensively metabolised by CYP2C19 and CYP3A4. All subjects were CYP2C19 EM.

Co-administration with dapoxetine did not have a significant effect on AUC, C_{\max} , T_{\max} or $t_{1/2}$ of omeprazole and its metabolites. The effect of omeprazole on PK of dapoxetine was not evaluated in this study.

The mean (standard deviation [SD]) AUC_{∞} ratios for omeprazole-to-5-hydroxyomeprazole and for omeprazole-to-omeprazole sulfone were similar following omeprazole and omeprazole + dapoxetine treatments: 1.16 (1.1) versus 1.25 (1.1) and 1.42 (0.39) versus 1.39 (0.39), respectively. The 90% CIs for the ratios of C_{\max} and AUC_{∞} comparing omeprazole + dapoxetine and omeprazole were [86.22, 120.02%], and [100.02, 112.99%], respectively which fell within [80, 125%], suggesting that dapoxetine did not affect the PK of omeprazole. The 90% CIs for the ratios of C_{\max} and AUC_{∞} for omeprazole sulfone and C_{\max} and AUC_{∞} ratio for 5-hydroxy-omeprazole were within or just slightly out of [80, 125%].

Study C-2003-026 Alcohol

This single-centre, double-blind, randomised, four-treatment, four-period crossover study investigated the interaction between alcohol and dapoxetine in 24 subjects (mean age 25.5 years, all Caucasians).

Dapoxetine did not significantly affect the PK of ethanol; the 90% CI for C_{\max} and AUC_{∞} for ethanol fell within [80, 125%] with and without dapoxetine. C_{\max} values of ethanol when administered alone and with dapoxetine were 440 and 428 ng/mL, respectively. T_{\max} was 1.07-1.10 h. AUC_{∞} values for ethanol were 1020 and 970 ng.h/mL for ethanol and ethanol + dapoxetine, respectively.

Ethanol did not significantly affect the PK of dapoxetine and its metabolites. C_{\max} values of dapoxetine when administered alone and with ethanol were 492 and 531 ng/mL, respectively. T_{\max} was 1.35-1.47 hours. AUC_{∞} values for dapoxetine were 2600 and 2470 ng.h/mL for dapoxetine alone and ethanol + dapoxetine, respectively. The 90% CI for C_{\max} and AUC_{∞} for dapoxetine and dapoxetine-N-oxide fell within [80, 125%] with and without ethanol, indicating that ethanol did not affect PK of dapoxetine. The 90% CI for C_{\max} for desmethyldapoxetine fell within [80, 125%] while AUC_{∞} for desmethyldapoxetine was slightly out of the no-effect boundaries at [77.66, 105.10%].

Ethanol at 0.5 g/kg impaired several measures of attention, verbal recall and recognition with peak effect at 1.5 hours and resolved at 4 hours, consistent with known ethanol effect. Dapoxetine + ethanol treatment did not result in significant additional decline in above measures versus ethanol alone.

Study C-2003-027 PDE5 inhibitors: Tadalafil and Sildenafil

This single-centre, randomised, open-label, three-treatment, three-period, six-sequence crossover study investigated the effects of PDE5 inhibitors, tadalafil and sildenafil on the tolerability and PK of dapoxetine in 24 healthy male subjects (mean age 25.4 years, n=20 (83.3%) Caucasians).

Co-administration with tadalafil did not have statistically significant effects on the PKs of dapoxetine or its metabolites. The 90% CIs for the mean ratios of C_{\max} and AUC_{∞} for dapoxetine and its metabolites were within [80, 125%] for the comparison of dapoxetine alone and dapoxetine + tadalafil.

With regards to the effect of sildenafil on PK of dapoxetine, the 90% CIs for the mean ratios of C_{\max} for dapoxetine were within [80, 125%] for dapoxetine alone and dapoxetine + sildenafil treatments.

T_{\max} were comparable in both groups. However, the AUC_{∞} was 22% higher with sildenafil and 90% CI [106.90, 132.57] was slightly out of the no-effect boundary [80, 125%]. For PK of desmethyldapoxetine, there were no significant differences between dapoxetine alone and with sildenafil. For dapoxetine-N-oxide, the C_{\max} and AUC_{∞} values were within [80, 125%]. T_{\max} for dapoxetine-N-oxide was significantly prolonged (2.59 versus 3.55 hours, $p=0.008$), although unlikely to be clinically significant.

Dapoxetine concentrations decreased to ~5% of C_{\max} by 24 hours post-dose, indicating that dapoxetine has a rapid elimination when administered alone, or with PDE-inhibitors. The ratios of AUC_{∞} : AUC_{0-24} were 1.29, 1.26, and 1.30 for the dapoxetine alone, dapoxetine + tadalafil, and dapoxetine + sildenafil treatments, respectively, indicating minimal accumulation. There was no effect on $t_{1/2}$ of dapoxetine during co-treatment (mean terminal $t_{1/2}$ = 16.7 hours, 17.1 hours and 14.8 hours for dapoxetine alone, dapoxetine + tadalafil and dapoxetine + sildenafil, respectively).

Plasma concentrations of tadalafil and sildenafil in this study were comparable to published reports, suggesting that dapoxetine does not affect the pharmacokinetics of these two PDE5 inhibitors.

Study C-2003-029 substrate for CYP2C9: Glyburide

This single-centre, open-label, two-treatment, two-period, two-sequence, randomised crossover study investigated the effect of dapoxetine on glyburide PK and PD in 22 subjects (mean age 27.5 years, 59.1% Caucasian). Glyburide is metabolized primarily by CYP2C9. All subjects were CYP2C9 normal hydroxylators.

Co-administration of dapoxetine with glyburide did not have any significant effect on glyburide C_{\max} , AUC and mean terminal $t_{1/2}$ (6.25 versus 7.32 hours). The 90% CIs for the ratios of glyburide C_{\max} and AUC_{∞} for the two treatments were within [80, 125%]. Glyburide is metabolized primarily by CYP2C9, and the data suggest that dapoxetine does not inhibit CYP2C9 *in vivo*.

For glyburide pharmacodynamics, the mean minimum blood glucose concentration (C_{mingluc}) of glyburide was similar in the presence and absence of dapoxetine. The mean times to reach minimum glucose levels (T_{mingluc}), indicating the maximum effect of glyburide, were not significantly different. The mean area under the blood glucose concentration-time curve from Hour 0 up to 4 hours after glyburide dosing ($AUEC_{\text{gluc}(0-4)}$) and area under the blood glucose concentration-time curve from Hour 0 up to 24 hours after glyburide dosing ($AUEC_{\text{gluc}(0-24)}$) values were slightly higher in the presence of dapoxetine. With glyburide + dapoxetine, mean $AUEC_{\text{gluc}(0-4)}$ and $AUEC_{\text{gluc}(0-24)}$ were slightly higher in the presence of dapoxetine.

The 90% CIs for the ratios of $AUEC_{\text{gluc}(0-24)}$ of the two treatments were within [80, 125%], suggesting that the pharmacodynamics of glyburide were not affected by the co-administration of dapoxetine.

Plasma concentration-time profile for dapoxetine was performed on Day 6 of dapoxetine dosing. Mean C_{\max} was 430.7ng/mL and attained at 1.5 hours post-dose.

Study C-2003-042 substrate for CYP2D6: Desipramine

This single-centre, open-label, two-treatment, two-period, two-sequence randomised crossover study investigated the effect of dapoxetine on desipramine PK in 24 subjects (mean age 27.0 years, 66.7% Caucasian). Desipramine is a substrate for CYP2D6. Twenty-two subjects were CYP2D6 EMs, while two were CYP2D6 ultra-rapid metabolisers (UM).

Dapoxetine increased C_{\max} and AUC_{∞} of desipramine values by ~10.8% and 18.9%, respectively, suggesting that dapoxetine is a weak inhibitor of the CYP2D6 enzyme *in vivo*. After a single dose of desipramine, mean C_{\max} for desipramine was 23.2ng/mL at 5.44 hours; and after desipramine + dapoxetine dosing, mean C_{\max} for desipramine was 25.7ng/mL at 5.83 hours. AUC_{∞} was 687 ng.h/mL with desipramine alone and 817 ng.h/mL with desipramine + dapoxetine. Dapoxetine did

not affect the $t_{1/2}$ of desipramine. The 90% CIs for the ratios of C_{\max} and AUC_{∞} for the two treatments were slightly outside of [80, 125%], at [102, 129.31%] for C_{\max} and [115.79, 134.41%] for AUC_{∞} , indicating that dapoxetine has a modest effect on PK of desipramine. The effect of desipramine on dapoxetine PKs was not evaluated.

Plasma concentration-time profile for dapoxetine was performed on Day 6 of dapoxetine dosing. Mean C_{\max} was 356 ng/mL and was attained at 1.5 hours post-dose.

Study C-2004-017 Tamsulosin

This multi-centre, randomised, multiple-dose, double-blind, three-treatment, three-period, placebo-controlled crossover study investigated the safety of multiple doses of dapoxetine tablet in patients who were taking tamsulosin ≥ 0.4 mg for ≥ 6 weeks.

Tamsulosin does not affect PK of dapoxetine. After single and multiple doses of dapoxetine 30 mg, C_{\max} were 171 and 197 ng/mL, respectively. After single and multiple doses of dapoxetine 60 mg, C_{\max} were 319 ng/mL and 303 ng/mL, respectively. T_{\max} was ~ 1.5 hours after single and multiple dosing of dapoxetine. Dapoxetine AUC_{0-24} values were also similar after single and multiple doses of dapoxetine 30 mg and after 60 mg. Modest accumulation was noted after multiple doses of dapoxetine 30 mg (AUC_{0-24} Day 7: Day 1 ratio 1.64) and 60 mg (AUC_{0-24} Day 7: Day 1 ratio 1.11). The PK profiles of dapoxetine metabolites in the presence of tamsulosin were similar to the parent drug. The drug to metabolite AUC_{0-24} ratios were similar for single and multiple doses of dapoxetine 30 and 60 mg, indicating that metabolism of dapoxetine to metabolites was not affected in the presence of tamsulosin.

The PK of tamsulosin were also not altered in the presence of dapoxetine 30 and 60 mg. There was minimal accumulation of tamsulosin across the groups based on AUC_{0-24} Day 7: Day 1 ratio values of 1.01-1.15.

The orthostatic profile of dapoxetine 30 and 60 mg + tamsulosin was similar to that with tamsulosin + placebo. The mean maximum difference in orthostatic BP between dapoxetine 30 or 60 mg + tamsulosin versus placebo + tamsulosin on Days 1 and 7 was significant only for orthostatic DBP after dapoxetine 30 mg on Day 7. There was no dose-effect. In terms of differences from treatment baseline, there was no consistent difference from baseline seen in dapoxetine 30 or 60 mg + tamsulosin and placebo + tamsulosin groups. The change in standing SBP ($p = 0.004$) and DBP ($p = 0.049$) was significantly different across the treatment groups on Day 1. Pairwise comparison showed that the difference from baseline was significantly different for standing SBP for dapoxetine 30 mg + tamsulosin versus placebo + tamsulosin (-8.39 mmHg, $p = 0.002$), and standing DBP for dapoxetine 60 mg + tamsulosin versus placebo + tamsulosin ($+4.18$ mmHg, $p = 0.017$) on Day 1. However, these effects were not related to dose of dapoxetine.

Population PK studies

Studies C-2002-012 and C-2002-013 were two pivotal efficacy studies which also evaluated the population PK of oral dapoxetine 30 and 60 mg as needed (prn) in a subset of the study population ($n = 152$ in C-2002-012 and $n = 160$ in C-2002-013). The PK results from study C-2002-012 showed that C_{\max} values for dapoxetine 30 and 60 mg were 184.2 and 326 ng/mL, respectively at 1-2 hours post-dose. Dapoxetine concentrations decreased to $< 10\%$ by 32 hours. A population PK model was developed to describe the dapoxetine concentration-time data. The population estimates for CL/F (apparent clearance), V/F (apparent V_d for the central compartment), Q (apparent inter-compartmental clearance), V_{ss}/F (apparent V_d at steady-state) and K_a (first-order absorption constant) were 23.3 L/h, 23.5 L, 23.6 L/h, 356 L and 0.534 L/h, respectively. Comparison of post hoc estimates of the PK parameters between dapoxetine 30 and 60 mg doses indicated that CL/F in the 60 mg dose group (29.3 ± 13.6 L/h) was significantly higher than the 30 mg dose group (24.6 ± 12.7 L/h, $p = 0.03$). CYP2D6 genotype appeared to have an impact on apparent clearance ($p = 0.03$); the mean post hoc estimated clearance values were significantly lower in CYP2D6 PMs (19.6 ± 12.9

L/hr) than in CYP2D6 EMs (27.5 ± 13.1 L/hr). The relationship between age and CL/F and age and V/F reached statistical significance ($p=0.041$ and $p=0.038$, respectively). However, age explained only ~0.82% of the inter-individual variability for CL/F and 1.57% for V/F. Furthermore, CL/F decreased by <12%, and V/F increased by <24% of the population mean for each decade increase in age. The V/F values between the dose groups were not significantly different.

The PK results in C-2002-013 were also similar, demonstrating that C_{\max} was 191.1 and 341.7 ng/mL at 1-2 hours post-dose. The population estimates for CL/F, V/F, Q, Vss/F and K_a were 24.6 L/h, 23.5 L, 24.3 L/h, 373 L and 0.567 L/h, respectively. Post hoc estimates of CL/F, Vss/F, Q and K_a did not appear to have a significant relationship with CYP2D6 genotype, race, age and body weight.

Summary of PK studies

- Dapoxetine is a short-acting drug. T_{\max} is ~1.5-2 hours post-dosing. Initial (disposition) $t_{1/2}$ is approximately 1.5 hours. Terminal $t_{1/2}$ is approximately 19 h. C_{\max} for dapoxetine after a single 30 mg dose is ~300 ng/mL and after a single 60 mg dose is approximately 430 ng/mL. AUC_{∞} for dapoxetine 30 mg is ~1500 ng.h/mL, and for 60 mg is ~2400 ng.h/mL. PK of dapoxetine are dose-proportional for single- and multiple-dosing up to 100 mg but less than dose proportional at doses >100 mg. There is modest accumulation with multiple-dosing (~1.5x). Steady-state is achieved by the fourth dose. Dapoxetine concentrations decrease to <5% C_{\max} within 24 hours and there is minimal accumulation. Clearance is 27.1 L/hour (21.7-33.5 L/hour). V_d is 6.43 L/kg (5.37-7.58 L/kg). Dapoxetine was >99% protein-bound. Absolute oral bioavailability of dapoxetine was 42%.
- Dapoxetine is extensively metabolized to multiple metabolites following oral dosing and there is evidence of pre-systemic first-pass metabolism after oral administration. Approximately 59.6% and 23.1% of the dose are excreted in urine and faeces, respectively, within 168 hours following oral dosing. Dapoxetine is eliminated primarily in the urine as glucuronide and sulfate conjugates; unchanged drug is below LOQ in the urine. Parent drug and 5 metabolites are identified in faeces. The major metabolites are N-dapoxetine-oxide (pre-dominant), desmethyldapoxetine and didesmethyl-dapoxetine. The mean T_{\max} of desmethyldapoxetine and didesmethyl-dapoxetine are ~2.8 and 3.0 hours, respectively. Elimination is biphasic with an initial rapid Phase and a long terminal $t_{1/2}$. Terminal $t_{1/2}$ of desmethyldapoxetine and didesmethyl-dapoxetine are 25 hours and 9 hours, respectively. Mean AUC_{∞} for dapoxetine-N-oxide is ~57-80% that of dapoxetine. AUC_{∞} for dapoxetine are ~10 x larger than for desmethyldapoxetine and >200 x larger than for didesmethyl-dapoxetine. The mean terminal $t_{1/2}$ for both metabolites with multiple-dosing is ~18-21 h. T_{\max} for both metabolites is 2.5-4.2 hours post-dose. Dapoxetine-N-oxide is weakly active at the serotonin uptake transporter in vitro transporter studies. Desmethyldapoxetine showed equivalent activity to dapoxetine in a limited number of assays in serotonin reuptake, and didesmethyl-dapoxetine has approximately half the potency in serotonin reuptake assays. However, due to the low plasma concentrations attained, these minor metabolites are unlikely to have clinical significance.
- Food does not appear to have a significant effect on PK of dapoxetine. Mean C_{\max} was ~10-16% lower while mean AUC was ~10% higher after a high fat meal as demonstrated in studies C-2002-037-01 and F2X-LC-HIAE. Food decreased the dapoxetine rate of absorption, as reflected in a 35-minute delay in T_{\max} , however equivalence was established for the extent of absorption, as reflected by the comparable AUC values, under both fed and fasted conditions. $T_{1/2}$, apparent clearance and V_d values were similar at ~10 hours, ~26-27 L/h and 330-350 L under fed and fasted conditions as demonstrated in F2X-LC-HIAE.
- Bioequivalence between dapoxetine tablets and capsules in the Phase II and III studies was established in study C-2002-020-00, with the 90% CIs for ratios of AUC and $\ln C_{\max}$ of the tablets versus capsules falling within the standard bioequivalence criteria of [80, 125%]. Bioequivalence of

dapoxetine tablets produced with drug substance of different particle sizes ranging from DL50 28 to 131µm was evaluated and found to be bioequivalent in C-2004-009. Two of the four pivotal studies, C-2002-012 and C-2002-013 used the 30 mg and 60 mg tablets studied in the bioequivalence study C-2002-020-00.

- Drug interactions: Co-administration with ketoconazole (CYP3A4 inhibitor) moderately increased exposure to dapoxetine and its metabolites. Fluoxetine (CYP2D6 inhibitor) moderately affects the PK of dapoxetine and its metabolites. Dapoxetine has a modest effect on PK of desipramine (substrate for CYP2D6), while dapoxetine did not affect the PK of substrates for CYP2C9 (glyburide), CYP2C19 (omeprazole) and CYP3A4 (midazolam). Dapoxetine does not appear to have any significant effect on the PK and PD effect of warfarin. PDE5 inhibitors (tadalafil and sildenafil) do not affect the PKs of dapoxetine; plasma concentrations of tadalafil and sildenafil in this study were comparable to published reports, suggesting that dapoxetine does not affect the pharmacokinetics of these two PDE5 inhibitors.
- Dapoxetine does not affect the PK or PD effects of tamsulosin. Dapoxetine does not affect the PK of ethanol and its respective metabolites, and vice versa, but appears to result in additive neurological side-effects of both drugs.
- Age does not appear to have a significant effect on the PK of dapoxetine (study C-2002-038). The C_{max} and AUC values of dapoxetine and its metabolites were moderately increased in CYP2D6 poor metabolisers (PM) compared to the extensive metabolisers (EM) in study C-2002-056-01. PK of dapoxetine was not affected in mild to moderate renal impairment but there was an increase in AUC (up to 50%) in severe renal impairment as demonstrated in study C2003-018. However, there was no significant correlation between creatinine clearance and C_{max} and AUC_{∞} values for dapoxetine and its metabolites. There was a 2-3-fold increase in $t_{1/2}$, 2-fold increase in T_{max} , 3-fold decrease in C_{max} and 1.5-2-fold increase in AUC values for dapoxetine in severe hepatic impairment versus normal to moderate hepatic dysfunction (study C-2003-019). Protein binding was not affected in renal and hepatic impairment. Similar PK findings were noted for its metabolites. Study C-2001-007 demonstrated that the PKs of dapoxetine in hypertensive subjects were similar to that observed in healthy normotensive subjects.

Efficacy

Overview

Efficacy of dapoxetine was evaluated in two dose-finding Phase II studies: GP-PE-98-01 and C-2001-008-02; four efficacy Phase III studies: C-2002-012, C-2002-013, R096769-PRE-3001 in European subjects and R09769-pre-3003 in Asian-Pacific subjects; one withdrawal Phase III study: R-06769-PRE-3002 in American and Canadian subjects; and one extension study: C-2002-014; involving 6404 male subjects with premature ejaculation (PE).

According to the DSM-IV-TR, premature ejaculation (PE) was defined as "...the persistent or recurrent onset of orgasm and ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it."²⁵ The condition must also cause at least moderate distress or interpersonal difficulty (as defined by a subject's response to "Personal Distress" and "Relationship Distress" questions in the Ejaculation Questionnaire). It cannot be due exclusively to the direct effects of a substance, hence experiencing levels of psychological distress that are similar to those experienced by men with erectile dysfunction and who are likely to seek, as well as benefit, from treatment.

The inclusion criteria in the efficacy studies were heterosexual men aged 18-65 years, in a stable and monogamous sexual relationship for ≥ 6 months and with a history of PE in $>50\%$ of

²⁵ DSM IV-TR: Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision.

intercourse experiences over the previous 6 months for Phase II studies and $\geq 75\%$ for Phase III studies. Participants had to have an average intravaginal ejaculatory latency time (IELT) ≤ 2 minutes (min) and a diagnosis of PE as defined in the DSM IV-TR. Subjects must be in good health, without history of erectile dysfunction, and not taking any antidepressants, anti-impotence medications and CYP P450 inducers. Subjects must also be normotensive; if hypertensive, BP must be controlled to $\leq 180/100$ mmHg. Partners had to use contraception. During the study, participants were instructed to take the study drug at 1-3 hours prior to sexual intercourse for it to coincide with T_{\max} , and no more than 1 dose per 24 hours (except for GP-PE-98-01 in which the interval was 12 hours, because of the lower dose used). The subjects and their partners were expected to attempt sexual intercourse ≥ 2 x per week.

The primary efficacy parameter in these studies was IELT, defined as the average duration of intercourse attempts since the baseline clinic visit where ejaculation was recorded as occurring intravaginally or before penetration.

Depending on the study, participants and their partners were also asked to complete various patient-reported outcome (PRO) measures such as Sexual Function Inventory [SFI] and Symptom Severity Impression [SSI], PE subscale from the Golombok-Rust Inventory of Sexual Satisfaction [GRISS] and Premature Ejaculation Questionnaire [PEQ] Form A, assessment of global impression of change (GIC), perception of firmness of erections, perception of distress and medication helpfulness questionnaire (MHQ). In all studies that measured IELT, the duration of sexual intercourse after dosing was measured using a stopwatch controlled by the partner and recorded in an event log. These comprised the secondary objectives. The PRO measures are rated on 4- to 7-point scales.

Currently, there is no consensus as to what level of IELT constitutes a meaningful improvement in PE. While IELT may be viewed as an indicator of pharmacologic activity, the clinical relevance of achieving a given level of IELT or a given level of change in IELT is likely to differ from individual to individual. Therefore, to contextualize the improvement in IELT seen with dapoxetine, it is necessary to examine the relationships between IELT and responses to participant and partner PRO measures. Two observational studies (no treatment), one conducted in the U.S. (C-2004-004) and the other conducted in the EU (R96769-PRE-3004) were performed in 2004 after feedback from the FDA USA regarding the validity of the use of IELT and PRO measures in the definition of PE in Phase III studies C-2002-012 and C-2002-013. Better ratings on key participant-reported measures (participant perceptions of control over ejaculation, satisfaction with sexual intercourse and personal distress) were found to accompany increases in IELT in observational studies C-2004-004 and R96769-PRE-3004. These findings imply that the pharmacologic effects of dapoxetine on IELT may lead to improvements that have meaning to participants.

A definition of a responder that is “ ≥ 2 -category increase in control over ejaculation and ≥ 1 -category decrease in personal distress” was developed based on findings in observational studies C-2004-004 and R96769-PRE-3004 that evaluated the inter-relationships between IELT and the PRO measures of control over ejaculation, distress related to ejaculation, satisfaction with sexual intercourse, and interpersonal difficulty related to ejaculation. The analysis indicated that among men with PE, control is central to their perception of the negative impact of PE, and also has a substantial direct effect on feelings of distress related to ejaculation and satisfaction with intercourse. In contrast, IELT was found not to have a direct effect on more distal aspects of PE such as distress, satisfaction, and interpersonal difficulty, but plays an indirect role on these outcome measures through the perception of control.

Efficacy data were analysed using analysis of covariance (ANCOVA), Cochran-Mantel-Haenszel, analysis of variance (ANOVA), logistic regression and Spearman rank analysis.

Dose finding studies

Study GP-PE-98-01

This multicentre, double-blind, randomised, placebo-controlled, three-period crossover study (GP-PE-98-01) evaluated the efficacy, dose-response relationship and safety of dapoxetine 20 and 40 mg capsules prn in the treatment of PE in 157 subjects over 4 weeks (Table 8).

Table 8: Details of Study GP-PE-98-01

No. subjects, Age, Gender	Diagnosis, Inclusion & exclusion criteria	Test product, Dosage regimen, Administration route, Formulation, Treatment duration	Evaluation criteria	Results	Adverse reactions/ Safety
157M Mean age: 37.1 (19 to 60) 125 Caucasian, 13 Black, 19 Others Multicentre (US)	IELT ≤ 2 min in 50% intercourse	Placebo prn Dapoxetine 2x10mg capsules prn (20 mg total dose) Dapoxetine 2x 20 mg capsules prn (40 mg total dose) All treatments were for 12 weeks (4 weeks per treatment)	Primary: IELT Secondary: PRO measures	A dose-response improvement was seen in IELT [2.22 (2.62), 2.70 (2.69) and 3.31 (4.09) min for placebo, dapoxetine 20 and 40 mg, respectively] participant's control over ejaculation and satisfaction with sexual intercourse, participant's and partner's SSI and GIC ratings for dapoxetine 20 and 40 mg, and both were superior to placebo.	TEAEs were reported by 12.7%, 15.9% and 17.0% of placebo, dapoxetine 20 and 40 mg groups, respectively. Most were mild in severity and treatment-related. The most common AEs reported more frequently with dapoxetine versus placebo were headache, nausea, dizziness, diarrhoea, nervousness and somnolence. No dose effect noted in this study.

After screening and a two-week lead-in period, participants were randomised into one of six treatment sequences with placebo and dapoxetine 20 and 40 mg treatments. Subjects were allowed to take up to 6 doses of study drug during each 4-week treatment period. Enrolment of up to 150 men was planned to allow completion of ≥ 80 participants, as this would yield $\geq 87\%$ power to detect a 1-minute (min) difference in IELT between any two dose levels, using a within-participants SD=2 min in IELT and a 2-sided $\alpha \leq 0.048$ level t-test. A total of 157 subjects were randomised (mean age: 37.1 years, 79.6% Caucasian). The mean (SD) baseline IELT time for all participants was 1.34 (1.07) min and was similar across the three assigned treatments [placebo: 1.55 min, dapoxetine 20 mg: 1.21 min and dapoxetine 40 mg: 1.24 min]. A total of 128 subjects completed the study. Twenty-nine participants (18.5%) discontinued prematurely. The discontinuation rate was similar among the three treatments: dapoxetine 20 mg (11/145, 7.6%), dapoxetine 40 mg (10/141, 7.1%), and placebo (8/142, 5.6%). The most common reason for discontinuation was lost to follow-up across all three groups (5-8 discontinuations per group (3.5-5.5%)). There were no discontinuations due to AEs during dapoxetine 20 mg or placebo treatments; only 2/141 subjects (1.4%) discontinued due to AEs during dapoxetine 40 mg treatment.

Primary efficacy results

The primary efficacy parameter was IELT. At endpoint, the mean (SD) IELT was 2.22 (2.62), 2.70 (2.69) and 3.31 (4.09) min for the placebo, dapoxetine 20 and 40 mg treatment periods (overall

$p=0.0007$). IELT was significantly increased with both dapoxetine doses compared with placebo ($p=0.042$ for dapoxetine 20 mg, $p=0.0001$ for 40 mg), but there was no significant difference between the 20 and 40 mg doses.

Secondary efficacy results

Secondary efficacy parameters included the duration of all intercourse attempts, SSI, GIC, control of ejaculation and satisfaction with sexual intercourse. Mean (SD) values for duration of all intercourse attempts were 2.26 (2.64) min for placebo, 2.82 (2.79) min for dapoxetine 20 mg, and 3.30 (4.02) min for dapoxetine 40 mg (overall $p=0.0009$). Relative to placebo, the duration of all intercourse attempts was significantly longer with both dapoxetine doses ($p=0.029$ for dapoxetine 20 mg, $p=0.0002$ for dapoxetine 40 mg), and not significant between the two doses.

Mean (SD) scores for participant GIC were 0.24 (1.02) for placebo, 0.75 (1.10) for dapoxetine 20 mg, and 0.91 (1.17) for dapoxetine 40 mg (overall $p<0.0001$). Mean scores were significantly better for both dapoxetine treatments versus placebo for the comparison of each active treatment to placebo ($p<0.0001$), while the difference between the two dapoxetine doses was similar.

Mean (SD) scores for the participant's response to satisfaction with sexual intercourse were 3.19 (1.81) for placebo, 3.48 (1.81) for dapoxetine 20 mg, and 3.69 (1.83) for dapoxetine 40 mg (overall $p=0.002$). Mean scores were significantly better for both dapoxetine treatments versus placebo ($p=0.0457$ for dapoxetine 20 mg, $p=0.0004$ for dapoxetine 40 mg) and not significantly different between the two dapoxetine doses.

Mean (SD) scores for the participant's response to control over ejaculation were 0.87 (1.13) for placebo, 1.07 (1.38) for dapoxetine 20 mg and 1.41 (1.65) for dapoxetine 40 mg (overall $p<0.0001$). The scores were significantly better for dapoxetine 40 mg versus placebo ($p<0.0001$), but not for dapoxetine 20 mg versus placebo ($p=0.0977$). The difference between the two dapoxetine treatments was significant ($p=0.0083$).

Participant SSI ratings of "none" or "mild" were provided by 2.6% of participants at baseline, and 7.3%, 16.7% and 22.3% of participants following treatment with placebo, dapoxetine 20 and 40 mg, respectively. Mean (SD) scores for the SSI were 2.34 (0.62) for placebo, 2.23 (0.78) for dapoxetine 20 mg, and 2.00 (0.85) for dapoxetine 40 mg. Statistical analysis was not performed on SSI.

In terms of partner's PRO assessments, the GIC was significantly better for both dapoxetine treatments versus placebo. The percentage of partners indicating improvement in the participant's PE condition via the GIC responses of "slightly better" to "much better" was 35.7% for placebo, 54.8% for dapoxetine 20 mg and 52.9% for dapoxetine 40 mg. Mean (SD) scores for partner GIC were 0.30 (1.00) for placebo, 0.82 (1.12) for dapoxetine 20 mg, and 0.76 (1.23) for dapoxetine 40 mg (overall $p=0.0001$). Mean scores were significantly better for both dapoxetine treatments relative to placebo ($p<0.0001$ for dapoxetine 20 mg, $p=0.0007$ for dapoxetine 40 mg), while the scores were similar between the two dapoxetine doses.

Partner SSI ratings of "none" or "mild" were provided by 10.1% of partners at baseline, and 11.5%, 35.9%, and 29.5% of partners following placebo, dapoxetine 20 and 40 mg treatments, respectively. Mean (SD) scores for partner-rated SSI were 2.20 (0.72) for placebo, 1.82 (0.85) for dapoxetine 20 mg, and 1.95 (0.91) for dapoxetine 40 mg. No statistical analysis was performed.

Similarly, no statistical analysis was performed on the partner's PE questionnaire. For partner responses to the three questions in the PEQ control domain, there was a consistent trend that favoured dapoxetine 40 mg over 20 mg, and both dapoxetine treatments were favoured over placebo. There were no obvious differences in the partner responses to the four questions from the satisfaction domain across the treatment groups.

In summary, dapoxetine 20 and 40 mg were significantly superior to placebo in IELT, participant's control over ejaculation and satisfaction with sexual intercourse, and

participant's and partner's SSI and GIC ratings. There was a trend towards greater improvement with the higher dose in the primary and secondary efficacy parameters but the differences between dapoxetine 20 and 40 mg were not significant. Although the improvements in the primary and secondary efficacy parameters seen with dapoxetine 20 mg were significantly superior to placebo, the magnitude of the improvements was small and of uncertain clinical significance.

Study C-2001-008-02

This multicentre, double-blind, randomised, placebo-controlled, dose-finding six-sequence study evaluated the efficacy of dapoxetine 60 and 100 mg capsules prn in the treatment of PE in 166 subjects over 2 weeks (Table 9). After a 2-week baseline period, participants were randomised into treatment sequences with placebo and dapoxetine 60 and 100 mg. Participants were allowed to take up to 8 doses of study drug during each 2-week treatment period. A sample size of 93 subjects completing all three treatment periods was determined sufficient to detect a 1.0-min difference in mean IELT between the best- and worst-performing treatments with 80% power, where the best treatment was defined as that having the longest mean IELT. The sample-size calculation was based on an F-test assuming SD=2.18 min and $p \leq 0.05$. To be most conservative, the mean IELT of the second-best treatment was assumed to fall at the midpoint between the mean scores of the best and worst treatments. The SD estimate was derived from results from study GP-PE-98-01.

Table 9: Details of Study C-2001-008-02

No. subjects, Age, Gender	Diagnosis Inclusion & exclusion criteria	Test Product, Dosage regimen, Administration route, Formulation, Treatment duration	Evaluation criteria	Results	Adverse reactions/ Safety
166M Mean age: 40.3 (23 -64) 133 Caucasian, 7 Black, 26 Other US	IELT ≤ 2 min in 50% intercourse	Treatment A: Dapoxetine capsules 60 mg prn Treatment B: Dapoxetine capsules 100mg prn Treatment C: Placebo prn 2 weeks per treatment Up to 8 doses of the assigned study drug in each 2-week treatment period 1-2 hours before sexual intercourse. Minimum of 3-day washout between treatments	Primary: IELT Secondary: PRO measures	Dapoxetine 60 & 100 mg were superior to placebo in increasing IELT [2.06 (2.32) min for placebo, 2.93 (2.60) min for dapoxetine 60 mg, and 3.20 (2.76) min for dapoxetine 100mg] and improving control over ejaculation and satisfaction of sexual intercourse. There was no significant difference between dapoxetine 60 and 100mg in nearly all the primary and secondary efficacy criteria. The improvement in participant's perception of control over ejaculation, sexual satisfaction, symptom severity and global impression of change was also reflected in the partner's scores.	TEAEs were reported by 17%, 28% and 40% and considered to be treatment-related in 6.2%, 21.5% and 31.6% of placebo, dapoxetine 60 and 100mg, respectively. The most common AEs were nausea, dizziness, diarrhoea, insomnia, headache and nervousness. Most were mild-moderate in severity. A possible dose-related effect was noted. 10 subjects discontinued due to AEs and 9 were from dapoxetine 100mg group. Overall, dapoxetine 60 mg was better tolerated than 100mg.

A total of 166 subjects (mean age: 40.3 years, 80.1% Caucasian) were randomised. Thirty six participants (21.7%) discontinued prematurely. More participants discontinued during treatment

with dapoxetine 100mg (20/155, 12.9%) than with dapoxetine 60 mg (8/144, 5.6%) or placebo (8/145, 5.5%). The most frequent reason for early termination was adverse effects (AEs) (9/155, 5.8%) for the dapoxetine 100mg treatment. There were no discontinuations due to AEs during dapoxetine 60 mg treatment and only 1/145 participants (0.7%) during placebo treatment. For the dapoxetine 60 mg and placebo treatments, the most common reason for discontinuation was loss to follow-up.

Primary efficacy results

The primary efficacy endpoint was IELT and the mean (SD) baseline IELT for all participants was 1.01 (0.51) min, and was similar across the treatment groups. IELT was significantly increased with both doses of dapoxetine versus placebo for all participants ($p < 0.0001$ for the comparison of each active treatment to placebo). The mean (SD) values for IELT at endpoint were 2.06 (2.32) min for placebo, 2.93 (2.60) min for dapoxetine 60 mg, and 3.20 (2.76) min for dapoxetine 100 mg. There was no significant difference in the IELT obtained with the two dapoxetine treatments ($p = 0.23$). Mean (SD) IELT was significantly increased from baseline after the first dose of each dapoxetine treatment compared with placebo; 0.33 (0.97) min for placebo, 1.52 (3.20) min for dapoxetine 60 mg, and 1.39 (1.99) min for dapoxetine 100mg; ($p = 0.01$ for 60 mg and $p = 0.025$ for 100mg).

Secondary efficacy results

The secondary efficacy criteria were a series of PRO measures reported by participant and partner regarding aspects of sexual functioning, including perceptions of ejaculatory control, erectile function, sexual satisfaction, interest in sexual intercourse, SSI, GIC, medication helpfulness and duration of sexual intercourse.

Mean (SD) values for duration of all intercourse attempts were significantly longer with both dapoxetine doses [2.08 (2.31) min for placebo, 3.08 (2.72) min for dapoxetine 60 mg, and 3.59 (3.39) min for dapoxetine 100mg (overall $p < 0.0001$)] and was significantly longer for dapoxetine 100 than 60 mg ($p = 0.0174$). Mean (SD) changes from baseline in the duration of all intercourse attempts were 1.07 (2.24) min for placebo, 2.10 (2.65) min for dapoxetine 60 mg and 2.58 (3.27) min for dapoxetine 100mg. For the first intercourse attempt after randomisation, mean (SD) changes from baseline were 0.43 (1.07) min for placebo, 1.92 (3.82) min for dapoxetine 60 mg, and 1.78 (3.54) min for dapoxetine 100mg (overall $p = 0.0275$). Relative to placebo, the duration of the first intercourse attempt after randomisation was significantly longer with both doses of dapoxetine treatment ($p = 0.017$ for 60 mg and $p = 0.029$ for 100mg), and the difference between the two dapoxetine treatments was not significant ($p = 0.83$).

In terms of participant's PRO measures, there were significant improvements in perception of control over ejaculation, satisfaction with sexual intercourse, interest in sexual intercourse, duration of sexual intercourse, satisfaction with sexual relationship, SSI, GIC and MHQ. The difference between the two dapoxetine dosages was not significant except for perception of duration of sexual intercourse in which the 100mg was significantly longer than 60 mg. There was no significant difference in the perception of distress across the treatment groups.

In terms of partner's PRO measures, the scores for perception of participant's control over ejaculation, satisfaction with sexual intercourse, perception of interest and duration in sexual intercourse, satisfaction with sexual relationship, SSI, GIC, perception of medication helpfulness were significantly greater for the two dapoxetine treatments versus placebo ($p \leq 0.01$) and generally similar between the two dapoxetine doses. There was no significant difference in perception of participant's distress.

Improvements in IELT were accompanied by increases in participant's perceptions of control over ejaculation, satisfaction with sexual intercourse and GIC. Within- and between-group effect sizes were also computed. Within-group effect sizes for IELT and key PRO endpoints for the placebo,

dapoxetine 60 and 100mg treatments, respectively, were 2.06, 3.76, and 4.29 min for IELT, 0.70, 1.69, and 1.89 for scores on participant perception of control over ejaculation, and 0.25, 0.68, and 0.81 for scores on participant perception of satisfaction with sexual intercourse.²⁶ Between-group effect sizes for IELT and key PRO endpoints for the dapoxetine 60 and 100mg treatments, respectively, were 0.39 and 0.52 for IELT, 0.64 and 0.74 for scores on participant perception of control over ejaculation, and 0.39 and 0.50 for scores on participant perception of satisfaction with sexual intercourse.²⁷

In summary, this dose-finding study demonstrated that dapoxetine 60 and 100mg were superior to placebo in increasing IELT and improving control over ejaculation and satisfaction with sexual intercourse. There was no significant difference between dapoxetine 60 and 100mg in nearly all the primary and secondary efficacy criteria. The improvement in participant's perception of control over ejaculation, sexual satisfaction, SSI and GIC was also seen in the partner's scores.

Pivotal Phase III studies

Dapoxetine 30 mg and 60 mg were used in the pivotal Phase III studies, as the results from the dose-finding studies showed that the treatment effect of 20 mg was small and the tolerance of 100 mg was poor with higher incidence of AEs and withdrawal rate.

Study C-2002-012

This pivotal, multicentre, double-blind, parallel, placebo-controlled, randomised study evaluated the efficacy of oral dapoxetine 30 and 60 mg tablets prn in 1294 males with PE for 12 weeks (Table 10).

After a 2-week screening period, the participants were stratified into two groups by baseline mean IELT, ≤ 1 or > 1 min, and randomised equally into either placebo, dapoxetine 30 or 60 mg treatment groups. Follow-up visits were conducted at the end of baseline, and at Weeks 4, 8 and 12. A total of 1294 subjects (87.0% Caucasian), with mean age of 40.7 years and mean (SD) baseline IELT 0.92 (0.49) min, were randomised to placebo (n=440), dapoxetine 30 mg (n=429) and 60 mg (n=425) groups. A total of 941 subjects (placebo: n=339 (77.0%), dapoxetine 30 mg: n=316 (73.7%), dapoxetine 60 mg: n=286 (67.3%)) completed the study. A sample size of 900 subjects (300 per group) was considered sufficient to detect a 1.0 min difference between best- and worst-performing treatments with 98% power, where the best treatment was defined as the treatment having the highest IELT. Moreover, the same sample size could detect 0.68 min difference between best and worst performing treatments with 80% power. With respect to pairwise comparisons, 300 participants per group could detect a 1.0 min difference with $> 99\%$ power, and a 0.61 min difference with 80% power. Overall, the most common reasons for early termination were lost to follow-up (85/1294, 6.6%), withdrawal of consent (83/1294, 6.4%), personal reason (73/1294, 5.6%) and AEs (62/1294, 4.8%). The proportion of participants discontinuing early due to AEs was higher in the dapoxetine 60 mg group (39/425, 9.2%) compared with the dapoxetine 30 mg (21/429, 4.9%) and placebo (2/440, 0.5%) groups.

²⁶ Within-group effect was the magnitude of change based on the difference in mean score measured at follow-up and baseline; the variability was measured using the standard deviation of the population at baseline.

²⁷ Between-group effect sizes were computed relative to placebo to evaluate the magnitude of treatment benefit based on the difference in mean change score between the treatment and placebo groups; the variability was measured using the standard deviation of the change score for the placebo group.

Table 10: Details of Study C-2002-012

No. subjects, Age, Gender	Diagnosis, Inclusion & exclusion criteria	Test product, Dosage regimen, route, Formulation, Treatment duration	Evaluation criteria	Results	Adverse reactions/ Safety
1294 male subjects (placebo: n=440; dapoxetine 30 mg: n=429; dapoxetine 60 mg: n=425) Mean age: 40.7 (18 to 76) 1126 Caucasian, 79 Black, 89 Others US 24 Jun 2003 to 1 Jun 2004	IELT \leq 2min in 75% intercourse	Placebo prn Dapoxetine tablet 30 mg prn Dapoxetine tablet 60 mg prn All treatments were for 12 weeks	Primary: IELT Secondary: PRO measures	Dapoxetine 30 and 60 mg showed significant improvement in IELT and control over ejaculation and satisfaction with sexual intercourse compared with placebo, and the 60 mg dose was superior to the 30 mg dose. Mean (SD) values for IELT at study endpoint were 1.66 (2.087), 2.86 (3.588), and 3.36 (3.973) min for placebo, dapoxetine 30 and 60 mg, respectively (overall $p < 0.0001$). Significant improvements were seen from the first dose and sustained over 12 weeks. Subgroup analyses using baseline average IELT \leq 1min and $>$ 1min showed similar results.	TEAEs were reported by 36%, 49% and 60% of placebo, dapoxetine 30 and 60 mg groups, respectively. Treatment-related AEs were reported by 10.2%, 30.2% and 48.0% of placebo, dapoxetine 30 and 60 mg groups, respectively, and mostly affected the GIT or CNS systems. Most were mild-moderate in severity. SAEs in $<$ 1% of all treatment groups. Nausea, diarrhoea & dizziness were the most common AEs, likely to be treatment-related, tend to be dose-related and occurred at first dose. No suicidal ideation, few CVS AEs, small numbers with sexual dysfunction and withdrawal symptoms were noted.

Efficacy results

Mean (SD) values for primary efficacy parameter, IELT at endpoint, were 1.66 (2.087), 2.86 (3.588), and 3.36 (3.973) min for placebo, dapoxetine 30 and 60 mg, respectively (overall $p < 0.0001$). Both dapoxetine 30 and 60 mg treatments showed significant improvement in PE compared with placebo ($p < 0.0001$ for both dapoxetine doses), and the 60 mg dose was superior to the 30 mg dose ($p = 0.03$). For change from baseline in IELT at study endpoint, mean (SD) values were 0.73 (1.968), 1.96 (3.484), and 2.47 (3.884) minutes for placebo, dapoxetine 30 and 60 mg, respectively (overall $p < 0.0001$). Relative to placebo, change from baseline in IELT was significantly longer with both dapoxetine treatments ($p < 0.0001$). IELT was also significantly longer ($p = 0.033$) for dapoxetine 60 versus 30 mg.

Significant increases were seen for both dapoxetine doses from the first dose. Mean (SD) changes from baseline in IELT associated with the first dose were 0.40 (1.647), 1.21 (3.283), and 1.78 (4.594) min for placebo, dapoxetine 30 and 60 mg, respectively ($p < 0.0001$). IELT was significantly increased with the first dose for both dapoxetine treatments versus placebo ($p < 0.0001$ for dapoxetine 60 mg versus placebo, $p = 0.0155$ for 30 mg versus placebo). The mean change was also significantly increased for dapoxetine 60 versus 30 mg ($p = 0.0067$). Significant increases were seen for both dapoxetine doses in Weeks 4-12 ($p < 0.0001$ for all comparisons). IELT was significantly increased for dapoxetine 60 versus 30 mg at each time point (Week 4, $p = 0.0021$; Week 8, $p = 0.0225$; Week 12, $p = 0.0055$) and onset of action was seen within 30 mins of dosing (Table 11).

Table 11: Mean IELT by Time from Dosing

Time from Dosing (hours)	Mean (SD) IELT minutes		
	Placebo	Dapoxetine 30 mg	Dapoxetine 60 mg
0 – <0.5	1.79 (2.021) n=27	2.57 (2.265) n=26	3.61 (5.485) n=28
0.5 – <1	1.66 (1.605) n=81	2.40 (2.287) n=86	3.36 (3.172) n=76
1 – <2	1.57 (1.800) n=401	2.71 (3.120) n=376	3.15 (3.690) n=352
2 – <3	1.55 (1.792) n=370	2.75 (3.346) n=366	3.51 (4.067) n=332
3 – <4	1.91 (2.755) n=134	3.09 (3.747) n=121	4.06 (4.142) n=116
≥4	1.62 (1.403) n=83	2.28 (2.113) n=82	3.63 (4.047) n=74

Secondary efficacy results (participant reported measure)

Results of secondary endpoints were also significantly better for both doses of dapoxetine versus placebo for participant perception of control over ejaculation, satisfaction with sexual intercourse ($p<0.0001$ for overall comparison and for comparison of each dapoxetine dose group versus placebo for the PROs mentioned). Mean (SD) scores for change in participant perception of control over ejaculation from baseline to study endpoint were 0.56 (0.92), 1.26 (1.08), and 1.33 (1.20) for placebo, dapoxetine 30 mg and 60 mg treatments, respectively ($p<0.0001$). Relative to placebo, mean change scores were significantly greater for both dapoxetine treatments ($p<0.0001$), but not significant between both doses. Percentages of participants rating their control over ejaculation during sexual intercourse as “fair” to “very good” were 3.6%, 3.3%, and 3.5% at baseline, and 25.8%, 55.1%, and 56.5% at study endpoint for the placebo, dapoxetine 30 and 60 mg treatments, respectively. Relative to placebo, the change in the percentages of participants who had improvement in their control over ejaculation was significant for both dapoxetine doses ($p<0.0001$) but similar between both dapoxetine dose groups.

Mean (SD) scores for change in participant perception of satisfaction with sexual intercourse from baseline to study endpoint were -0.02 (1.11), 0.47 (1.17) and 0.56 (1.23) for placebo, dapoxetine 30 and 60 mg, respectively ($p<0.0001$). Relative to placebo, mean change scores were significantly greater for both dapoxetine treatments ($p<0.0001$), but not significant between both dapoxetine treatments. Percentages of participants rating their satisfaction with sexual intercourse as “fair” to “very good” were 52.6%, 54.8% and 55.3% at baseline and 55.3%, 72.1% and 78.0% at study endpoint for the placebo, dapoxetine 30 and 60 mg treatments, respectively.

Mean (SD) scores for change in participant’s SSI from baseline to study endpoint were -0.34 (0.70), -0.82 (0.89), and -0.83 (0.94) for placebo, dapoxetine 30 and 60 mg, respectively ($p<0.0001$) but similar between both dapoxetine treatments. SSI ratings of “mild” to “none” were provided by 0%, 0%, and 0.2% of participants at baseline, and by 12.1%, 31.5% and 32.7% of participants at study endpoint for the placebo, dapoxetine 30 and 60 mg treatments, respectively. Relative to placebo, the change in the percentages of participants who had improvement in SSI was significant for both dapoxetine doses ($p<0.0001$), but similar between both dapoxetine dose groups.

Mean (SD) scores for participant GIC at study endpoint were 0.29 (0.85) for placebo, 0.95 (1.07) for dapoxetine 30 mg and 1.15 (1.09) for dapoxetine 60 mg ($p<0.0001$). Mean scores were significantly better for both dapoxetine treatments versus placebo ($p<0.0001$), and also significantly

better ($p=0.0091$) for dapoxetine 60 versus 30 mg at study endpoint. Percentages of participants indicating improvement in GIC at study endpoint were 24.5%, 60.4%, and 66.4% for placebo, dapoxetine 30 and 60 mg, respectively. Relative to placebo, the percentages of participant indicating improvement was significantly higher with both dapoxetine dose groups ($p<0.0001$) but similar between both dose groups.

Partner reported measures

Mean (SD) scores for change in partner perception of satisfaction with sexual intercourse from baseline to study endpoint were 0.10 (1.03), 0.55 (1.10), and 0.57 (1.14) for placebo, dapoxetine 30 and 60 mg, respectively ($p<0.0001$). Relative to placebo (28.3%), the percentage of partners who perceived improvement in satisfaction with sexual intercourse was significantly ($p<0.0001$) greater for both dapoxetine 30 mg (48.4%) and 60 mg (49.4%) treatments ($p<0.0001$) and similar between both doses.

Effect of baseline IELT on efficacy results

Subgroup analyses were performed on participants assigned to the stratum of baseline average IELT ≤ 1 min and IELT > 1 min. Results showed that IELT was significantly increased for both doses of dapoxetine compared with placebo for participants assigned to the stratum of baseline average IELT ≤ 1 min and for those assigned to the stratum of baseline average IELT > 1 min. For the subgroup with baseline average IELT ≤ 1 min, IELT at study endpoint was 1.95x, 3.88x and 4.53x higher than at baseline for placebo, dapoxetine 30 and 60 mg, respectively. Relative to placebo, IELT was significantly longer with both dapoxetine treatments ($p<0.0001$). For subgroup with baseline average IELT > 1 min, IELT at study endpoint was 1.69x, 2.61x and 3.21x higher than baseline for placebo, dapoxetine 30 and 60 mg, respectively. Relative to placebo, IELT was significantly longer with both dapoxetine treatments ($p<0.0001$ and $p=0.0005$ for the respective comparison of dapoxetine 60 and 30 mg versus placebo).

In summary, dapoxetine 30 and 60 mg showed significant improvement in IELT and control over ejaculation and satisfaction with sexual intercourse compared with placebo, and the 60 mg dose was superior to the 30 mg dose. Significant improvements were seen from the first dose and sustained over 12 weeks. Subgroup analyses using baseline average IELT ≤ 1 min and > 1 min showed similar results.

Study C-2002-013

This was another pivotal multicentre, double-blind, parallel, placebo-controlled randomised study which examined the efficacy of dapoxetine 30 and 60 mg in 1320 males with PE over 12 weeks (Table 12). It followed the same study design, power calculations and statistical analyses as study C-2002-012. A total of 1320 males with mean age 40.4 years, predominantly Caucasians (86.6%) with mean baseline IELT 0.90 (0.47) min, were randomised to placebo ($n=430$), dapoxetine 30 and 60 mg ($n=445$ in each group) and 1017 completed the study (placebo: $n=333$ [77.4%], dapoxetine 30 mg: $n=360$ [80.9%], dapoxetine 60 mg: $n=324$ [72.8%]). The common reasons for study termination were lost to follow-up, withdrawal of consent, personal reasons and AEs. Of note, AEs was the most common reason for study termination in the dapoxetine 60 mg group.

Table 12: Details of Study C-2202

No. subjects, Age, Gender	Diagnosis, Inclusion & exclusion criteria	Test product, Dosage regimen, Administration route, Formulation, Treatment duration	Evaluation criteria	Results	Adverse reactions/ Safety
1320 male subjects (placebo: n=430; dapoxetine 30 mg: n=445; dapoxetine 60 mg: n=445) Mean age: 40.4 (18 to 77) 1143 Caucasian, 78 Black, 99 Others US 17 Jun 2003 to 8 Jun 2004	IELT ≤ 2 min in 75% intercourse	Placebo prn Dapoxetine tablet 30 mg prn Dapoxetine tablet 60 mg prn All treatments were for 12 weeks	Primary: IELT Secondary: PRO measures	Dapoxetine 30 & 60 mg prn were superior to placebo in improving IELT and secondary parameters such as control over ejaculation and satisfaction with sexual intercourse. Mean (SD) IELT at endpoint: 1.84 (2.335), 2.70 (3.386) and 3.28 (3.404) min for placebo, dapoxetine 30 and 60 mg, respectively. Dapoxetine 60 mg was significantly superior to 30 mg in IELT and most of the secondary PRO parameters. Improvement in IELT was noted from the first dose.	TEAE were reported by 33%, 47% & 56% of the placebo, dapoxetine 30 and 60 mg groups, respectively. Most of the AEs were of mild-moderate in severity, and treatment-related. Nausea, headache, dizziness and diarrhoea were the most common AEs. Nausea, dizziness and diarrhoea appeared dose-related and often started with the first dose. Infrequent mood-related and CVS AEs were noted. Impotence was reported in ~3% of subjects on dapoxetine. <1% SAEs were reported in all groups. More subjects in dapoxetine 60 mg discontinued due to AEs versus 30 mg & placebo. Nausea was the most common AE for discontinuation. No withdrawal symptoms were noted.

Primary efficacy results

Dapoxetine 30 and 60 mg showed significant improvement in IELT compared with placebo, and the 60 mg dose was superior to the 30 mg dose. Mean (SD) values for IELT at endpoint were 1.84 (2.335), 2.70 (3.386) and 3.28 (3.404) min for placebo, dapoxetine 30 and 60 mg, respectively ($p < 0.0001$). Dapoxetine 30 and 60 mg treatment significantly increased IELT compared with placebo for all participants ($p < 0.0001$ for both), and dapoxetine 60 mg was superior to 30 mg ($p = 0.007$). For the change from baseline in IELT at study endpoint, mean (SD) values were 0.96 (2.249), 1.79 (3.311), and 2.38 (3.296) min for placebo, dapoxetine 30 and 60 mg, respectively ($p < 0.0001$). Relative to placebo, change from baseline in IELT was significantly longer with both dapoxetine treatments ($p < 0.0001$ for both), while it was significantly longer for dapoxetine 60 versus 30 mg ($p = 0.007$). Mean (SD) changes from baseline in IELT associated with the first dose were 0.57 (1.827), 1.13 (2.665), and 1.35 (2.778) min for placebo, dapoxetine 30 and 60 mg, respectively (overall $p = 0.004$). Significant increases in IELT were seen from the first dose, and subsequent evaluations at Weeks 4-12. ($p < 0.0001$ for overall comparison from first dose to Week 12). IELT was significantly longer with each dapoxetine treatment versus placebo ($p = 0.0014$ for dapoxetine 60 mg, $p = 0.0169$ for dapoxetine 30 mg for the first dose, $p < 0.0001$ for each comparison of dapoxetine versus placebo at Weeks 4-12). IELT was also significantly increased for dapoxetine 60 mg versus 30 mg at each time point except for the first dose (Week 4, $p = 0.0012$; Week 8, $p = 0.0004$; Week 12, $p = 0.0036$).

Secondary efficacy results (participant reported measures)

Results of secondary criteria were significantly better for both doses of dapoxetine versus placebo ($p < 0.0001$ for all) for participant perception of control over ejaculation, satisfaction with sexual intercourse, severity of PE and GIC and partner perception of satisfaction with sexual intercourse. Mean (SD) scores for change in participant perception of control over ejaculation from baseline to endpoint were 0.63 (0.97), 1.16 (1.05), and 1.41 (1.16) for the placebo, dapoxetine 30 and 60 mg treatments, respectively (overall $p < 0.0001$). The mean change in control scores were significantly greater for both dapoxetine treatments versus placebo ($p < 0.0001$ for both), and significantly greater for dapoxetine 60 versus 30 mg ($p = 0.0039$). Mean (SD) scores for change in participant perception of satisfaction with sexual intercourse from baseline to endpoint were 0.06 (1.05), 0.45 (1.14) and 0.62 (1.24) for placebo, dapoxetine 30 and 60 mg, respectively (overall $p < 0.0001$). Relative to placebo, mean change scores were significantly greater for both dapoxetine treatments ($p < 0.0001$ for both), but not significant between the two doses. Mean (SD) scores for change in SSI from baseline to endpoint were -0.36 (0.71) for placebo, -0.65 (0.89) for dapoxetine 30 mg, and -0.96 (0.90) for dapoxetine 60 mg (overall $p < 0.0001$). Both dapoxetine treatments were associated with significantly lower SSI versus placebo ($p < 0.0001$ for both), and the SSI scores for dapoxetine 60 mg were significantly lower than the 30 mg dose ($p < 0.0001$). Mean (SD) scores for participant GIC at endpoint were 0.37 (0.86), 0.88 (1.00), and 1.22 (1.11) for placebo, dapoxetine 30 and 60 mg, respectively ($p < 0.0001$). Mean scores were significantly better for both dapoxetine treatments relative to placebo ($p < 0.0001$ for both), and significantly better for dapoxetine 60 versus 30 mg ($p < 0.0001$).

Partner reported measures

Mean (SD) scores for change in partner perception of satisfaction with sexual intercourse from baseline to endpoint were 0.04 (0.96), 0.41 (1.06), and 0.57 (1.14) for placebo, dapoxetine 30 and 60 mg, respectively (overall $p < 0.0001$). The mean change in scores was significantly greater for the two dapoxetine treatments versus placebo ($p < 0.0001$ for both), but similar between the two doses. For other efficacy measures, namely medication helpfulness as per participant's and partner's assessment, partner's ratings for GIC, SSI and perception of participant's control over ejaculation, and duration of all intercourse events, both dapoxetine treatments showed significantly greater scores versus placebo ($p < 0.0001$), and the scores for dapoxetine 60 mg were significantly greater than for 30 mg ($p < 0.01$). There was no significant change in participant perception of firmness of erections. The effects of dapoxetine could be seen within 30 min of dosing.

Effect Size

Between-group effect sizes for IELT, participant's perception of control over ejaculation and satisfaction with sexual intercourse for the dapoxetine 30 and 60 mg treatments, respectively, were 0.37 and 0.63 for IELT, 0.55 and 0.80 for control over ejaculation and 0.37 and 0.53 for satisfaction with intercourse. Between-group effect sizes indicated that dapoxetine treatment led to moderate changes in IELT and participant perception of satisfaction with sexual intercourse, and moderate to large changes in participant perception of control over ejaculation.

Subgroup efficacy analysis

In the subgroup analysis, results showed that IELT was significantly increased for both doses of dapoxetine versus placebo for the strata of average baseline IELT ≤ 1 min and IELT > 1 min. For the subgroup with average baseline IELT ≤ 1 min, IELT at study endpoint was 2.27x, 3.25x and 4.17x higher than at baseline for placebo, dapoxetine 30 and 60 mg, respectively ($p < 0.0001$ and $p = 0.0092$ for the respective comparison of dapoxetine 60 and 30 mg versus placebo). For subgroup with IELT > 1 min, IELT at study endpoint was 1.94x, 2.77x and 3.19x higher than at baseline for placebo, dapoxetine 30 mg and dapoxetine 60 mg, respectively ($p < 0.0001$ and $p = 0.0057$ for the respective comparison of dapoxetine 60 and 30 mg versus placebo). Similar findings were noted in

perceptions of control over ejaculation and satisfaction with sexual intercourse. Improvements over time were also noted for subgroup analyses with average baseline IELT ≤ 1 min and IELT > 1 min.

In summary, dapoxetine 30 and 60 mg prn were superior to placebo in improving IELT and secondary parameters such as control over ejaculation and satisfaction with sexual intercourse. Mean (SD) IELT at endpoint were 1.84 (2.335), 2.70 (3.386) and 3.28 (3.404) min for placebo, dapoxetine 30 and 60 mg, respectively. Dapoxetine 60 mg was significantly superior to 30 mg in IELT and most of the secondary PRO parameters. Improvement in IELT was noted from the first dose and was maintained over 12 weeks of treatment.

Study R096769-PRE-3001 European subjects

Another pivotal, multicentre, multinational (conducted outside of USA), placebo-controlled, double-blind, randomised parallel group study evaluated the efficacy and safety of dapoxetine 30 and 60 mg prn in men with PE over 24 weeks (Table 13). The primary objective was to demonstrate that dapoxetine 30 or 60 mg prn could prolong IELT versus placebo. The secondary objectives were to assess the proportion of subjects who had ≥ 2 -category increase in control over ejaculation and ≥ 1 -category decrease in personal distress (classified as responder), or ≥ 1 -category decrease in personal distress, or ≥ 1 -category increase in satisfaction with sexual intercourse. Other secondary objectives were to assess the effect of dapoxetine treatment versus placebo on changes in the following efficacy evaluations captured at each 4-weekly visit: GIC (subject and partner), control over ejaculation (subject and partner), satisfaction with sexual intercourse (subject and partner), SSI (subject and partner), personal distress (subject and partner), interpersonal difficulty (subject and partner), medication helpfulness question (subject and partner), satisfaction with sexual intercourse (recorded on the event log), change in average IELT, the number of all intercourse attempts recorded in the event log, and average duration of all intercourse attempts. A 1-week withdrawal assessment (WA) period following the double-blind treatment Phase assessed the effects of abrupt discontinuation of study drug as measured by the Discontinuation Emergent Signs and Symptoms (DESS) checklist.

Table 13: Details of Study R096769-PRE-3001

No. subjects, Age, Gender	Diagnosis, Inclusion & exclusion criteria	Test product, Dosage regimen, route, Formulation, Treatment duration	Evaluation criteria	Results	Adverse reactions/ Safety
1162 male subjects (placebo: n=385; dapoxetine 30 mg: n=388; dapoxetine 60 mg: n=389) Mean age: 40.0 (18 to 68) 979 Caucasian, 15 Black, 168 Others 22 countries 6 Dec 2004 to 31 Oct 2006	Men with IELT ≤ 2 min in 75% intercourse	Placebo prn Dapoxetine tablet 30 mg prn Dapoxetine tablet 60 mg prn All treatments were for 24 weeks; additional 7 days on same treatment or switch to placebo	Primary: IELT Secondary: ≥ 2 -category increase in control over ejaculation & ≥ 1 -category decrease in personal distress (classified a responder), or ≥ 1 -category decrease in personal distress, or ≥ 1 -category increase in satisfaction with sexual intercourse. Other: other PRO measures, MINI, BDI-II, SIGH-A, SIG-MA, BARS, IIEF, DESS	Dapoxetine 30 & 60 mg prn were superior to placebo in prolonging IELT, improving responder rates (defined as ≥ 2 -category increase in control over ejaculation and ≥ 1 -category decrease in personal distress), decreasing personal distress by ≥ 1 -category and improving sexual satisfaction by ≥ 1 -category. Average IELT increased from baseline of ~ 0.9 min to 1.9, 3.1 and 3.5 min in placebo, dapoxetine 30 & 60 mg groups respectively, at Week 24, which was similar to results at Week 12. The effect of treatment increased over time, with most increase by Week 12. Similar results were seen when subjects were stratified into baseline IELT ≤ 1 min and > 1 min, with greater improvements seen in baseline > 1 min stratum.	TEAEs were reported by 38.4%, 56.2% & 68.1% of placebo, dapoxetine 30 and 60 mg groups. The most common AEs reported were nausea, headache, dizziness & diarrhoea. First dose effect was noted. A higher % of subjects from dapoxetine 60 mg group discontinued due to AEs, mostly due to nausea. $\sim 1\%$ SAEs were reported, of note a syncopal AE with sinus arrest 28 sec in a subject after first dose of dapoxetine 60 mg. More supraventricular ectopy & increased BP noted in dapoxetine groups. No deleterious effect on suicidality, mood, libido was observed. A slightly higher incidence of erectile dysfunction (2.0%) as well as dizziness (2.2%) and vomiting (2.2%) was seen during WA period

Discontinuation Emergent Signs and Symptoms (DESS), Mini International Neuropsychiatric Interview (M.I.N.I.); revised Beck Depression Inventory (BDI-II); Structured Interview Guide for the Hamilton Anxiety Scale (SIGH-A) Structured Interview Guide for the Montgomery-Asberg Depression Rating Scale (SIG-MA); Barnes Akathisia Rating Scale (BARS); and International Index of Erectile Function Questionnaire (IIEF).

The study consisted of a screening visit and a 4-week baseline period, a 24-week double-blind treatment Phase, a 1-week double-blind WA Phase with the same treatment or placebo during the WA period, a follow-up visit ~ 1 week later (Week 25), and a post-study telephone contact (~ 2 weeks after completion of the WA period or upon early study termination). The total duration of the study was ~ 31 weeks. The planned sample size was 1300 subjects, which would give an evaluable sample size of 258 subjects per group (n=774) in order to detect a difference in mean average IELT $\geq +1$ min between the placebo and dapoxetine 60 mg groups, with 90% power at a 2-sided $\alpha=0.05$, assuming a common SD=3.5 min, and a drop-out rate of 40%. For the first key secondary efficacy variable (that is, ≥ 2 -category increase in control over ejaculation and ≥ 1 -category decrease in Personal Distress), the response rates for this variable in Study R096769-PRE-3002 were 47.6% in the dapoxetine 60 mg prn group and 21.7% in the placebo group. Assuming that these same response rates would be observed in this study, the planned sample size would have $>90\%$ power to

detect a difference of 25.9% between dapoxetine 60 mg and placebo groups. This sample size selection was not powered for comparison of the two dapoxetine doses. A total of 1162 subjects, predominantly Caucasian (n=979, 84%) with mean age of 40 years were randomised to placebo (n=385), dapoxetine 30 mg (n=388) and 60 mg (n=389) groups, and comprised the ITT analysis set. A total of 618/1162 subjects completed the treatment period [placebo: n=189 (49%), dapoxetine 30 mg: n=222 (57%), dapoxetine 60 mg: n=207 (53%)], and 550/618 subjects entered the WA period, which was completed by 549 subjects. The most common reason for discontinuation was subject choice (n=281, [24%]) with a higher percentage from the placebo group (31%) than either of the dapoxetine groups (21% in each group). Of these 281 subjects, 102 subjects withdrew due to insufficient response and 179 withdrew due to personal reason. Of the subjects withdrawing due to insufficient response, a higher number withdrew from the placebo group (n=56) than in the dapoxetine 30 (n=25) and 60 mg groups (n=21). Of the 179 subjects who withdrew due to personal reasons, a similar number of subjects in each treatment group withdrew (62, 56 and 61 subjects in the placebo, dapoxetine 30 and 60 mg groups, respectively). A higher percentage of subjects withdrew due to AE(s) in the dapoxetine 30 (4%) and 60 mg groups (8%) than in the placebo group (1%). The rate of withdrawal for reasons of 'Lost to Follow-up' and 'Other' was similar across the three groups. Of note, the sponsor suspended randomising new subjects for six weeks following the report of a case of syncope associated with sinus arrest with asystole in this study. Due to this suspension/interruption, 9% of subjects withdrew from the study, resulting in a large overall drop-out rate.

Mean average IELT for the ITT analysis set was 0.877 min, with 62% of subjects reporting a baseline average IELT \geq 1 min. At baseline, 94% of subjects reported having poor or very poor control over ejaculation, 68% reported "quite a bit" or "extreme" personal distress related to PE, and 59% reported having poor or very poor satisfaction with sexual intercourse. A similar percentage of subjects reported moderate baseline interpersonal difficulty in the placebo (24%) and dapoxetine 30 (26%) and 60 mg groups (23%). At baseline, 82% of partners reported that respective subjects had poor or very poor control over ejaculation. Partners reported less personal distress related to PE (44%) than subjects (68%). The percentage of partners reporting poor or very poor satisfaction with sexual intercourse (57%) was similar to that reported by subjects (59%). There were no apparent differences between treatment groups in the distribution of baseline partner PRO responses.

Primary efficacy results

Average (SD) IELT increased from baseline of ~0.9 (0.50) min to 1.9 (2.89), 3.1 (4.88) and 3.5 (3.80) min in placebo, dapoxetine 30 and 60 mg groups respectively, at Week 24, which was similar to the results at Week 12 ($p < 0.001$ for both dapoxetine groups versus placebo) (Table 14). A significant increase in the average IELT in each dapoxetine dose group versus placebo was observed at all time points, beginning at first dose, and was maintained at all subsequent time points (all $p < 0.001$), with most of the increase by Week 12. Similar results were obtained for subjects in each IELT stratum. There was a significant ($p < 0.001$) interaction between treatment and time, indicating that the effect of the treatment, as measured by average IELT, increased over time.

Table 14: Primary efficacy results over time

	----- PLACEBO -----			-- DPX 30 MG PRN --			-- DPX 60 MG PRN --		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
Average IELT (min)									
Baseline	382	0.9	0.51	385	0.9	0.50	387	0.9	0.49
Week 4	332	1.6	2.38	356	2.5	4.12	347	2.9	3.45
Week 8	280	1.9	2.96	303	3.0	4.98	287	3.4	3.35
Week 12	238	2.0	3.40	264	3.5	5.08	249	3.8	3.98
Week 16	221	2.2	3.19	240	3.6	5.48	229	3.8	3.80
Week 20	195	2.3	3.40	221	3.5	4.16	214	3.9	3.88
Week 24	182	2.3	3.27	218	3.3	4.07	198	3.9	3.65
End point (trt wk12)	339	1.9	3.11	363	3.2	4.61	355	3.5	4.04
End point (trt)	339	1.9	2.89	363	3.1	4.88	355	3.5	3.80

Results of the key secondary endpoints were consistent with those of the primary efficacy analyses.

Responder rate

At Week 24, there were significantly more responders (subjects who had ≥ 2 -category increase in control over ejaculation and ≥ 1 -category decrease in personal distress) in the dapoxetine 30 mg (25.3%) and 60 mg groups (37.1%) versus the placebo group (13.0%, $p < 0.001$). A significantly greater percentage of subjects responded in each of the dapoxetine groups versus placebo from Weeks 4 to 24 (5.8-17.3% [$n=20-39$] for placebo, 18.4-32.6% [$n=66-86$] for dapoxetine 30 mg, 26.6-39.4% [$n=93-216$] for dapoxetine 60 mg, $p=0.003$ for dapoxetine 30 mg versus placebo at Week 16, all other comparisons $p = 0.001$). In the ≤ 1 min stratum, the percentage of subjects who responded at Week 24 was 8.5% ($n=18$), 21.6% ($n=49$) and 34.6% ($n=74$) in the placebo, dapoxetine 30 mg and 60 mg groups, respectively (overall $p < 0.001$); in the > 1 min stratum these results were 19.7% ($n=26$), 31.8% ($n=42$) and 40.9% ($n=56$), respectively ($p < 0.001$). Similar results were seen for Week 12.

Other secondary efficacy results

A significantly larger proportion of subjects in both dapoxetine groups experienced improvement in personal distress scores (≥ 1 -category decrease) compared with placebo ($p < 0.001$ for both doses) at Week 12 (46.1%, 63.1% and 67.4% in the placebo dapoxetine 30 mg and 60 mg groups respectively) and Week 24 (47.8%, 60% and 68.6%, respectively). A significantly greater percentage of subjects with ≥ 1 -category decrease in distress were noted in each of the dapoxetine groups versus placebo from Weeks 4 to 24 ($p < 0.001$), except for the response in the dapoxetine 30 mg group at Week 24 ($p = 0.136$). Similar results were seen in subjects in the ≤ 1 min IELT stratum for Weeks 4-24. For subjects in the ≤ 1 min IELT stratum, the percentage of subjects who had ≥ 1 -category decrease in personal distress at Week 24 was 40.8% (87/213), 57.7% (131/227) and 68.2% (146/214) in the placebo, dapoxetine 30 mg and 60 mg groups, respectively ($p < 0.001$). The differences from placebo were significant for each dapoxetine group. Similar results were seen at Week 12. For the subjects in the > 1 min IELT stratum, the percentage of subjects with ≥ 1 -category decrease in distress was generally higher in each of the dapoxetine groups than the placebo group at Weeks 4-24. At Week 24, the percentage of subjects who had ≥ 1 -category decrease in personal distress was significantly higher in the dapoxetine 30 mg (216/360, 60.0%) and 60 mg groups (242/353, 68.6%) than in the placebo group (166/347, 47.8%) ($p < 0.001$).

In addition, significantly more subjects experienced improvement in satisfaction score after treatment with dapoxetine 30 or 60 mg versus placebo ($p < 0.001$ for both comparisons). At Week 24, there was a significantly higher percentage of subjects who had ≥ 1 -category increase in satisfaction with sexual intercourse in the dapoxetine 30 (48.5%, 174/359) and 60 mg groups (55.8%, 197/353) than in the placebo group (35.7%, 124/347) ($p < 0.001$). Similar results were obtained at Week 12. A significantly greater percentage had ≥ 1 -category increase in satisfaction

with sexual intercourse in each dapoxetine dose group. The percentage of subjects who had ≥ 1 -category increase in satisfaction with sexual intercourse at Week 24 was 28.6% (61/213), 44.1% (100/227) and 54.7% (117/214) in the placebo, dapoxetine 30 mg and 60 mg groups, respectively (overall $p < 0.001$). The differences from placebo were significant for each dapoxetine group ($p < 0.001$ for both). Similar results were seen for Week 12. For the > 1 min IELT stratum, although the percentage of subjects with ≥ 1 -category increase in satisfaction was generally higher in each dapoxetine dose group than the placebo group at Weeks 4-24, there were significant differences between the dapoxetine groups and the placebo group only at Weeks 4-12. At Week 12, the percentage of subjects who had ≥ 1 -category increase in satisfaction with sexual intercourse was 36.4% (48/132), 56.8% (75/132) and 55.5% (76/137) in the placebo, dapoxetine 30 and 60 mg groups, respectively. The differences were significantly greater for both dapoxetine groups versus placebo ($p < 0.001$ for both). Similar results were seen in the ≤ 1 min stratum.

Significant improvements compared with placebo were seen for other secondary efficacy variables for both dapoxetine doses. At Week 24, a higher percentage of subjects in the 30 mg (57.7%, 207/359) and 60 mg (72.4%, 255/352) dapoxetine groups responded as being at least slightly better in GIC compared with the placebo group (32.0%, 111/347). At Week 24 endpoint, a higher percentage of subjects in the 30 mg (30.9%, 111/359) and 60 mg (40.4%, 143/354) dapoxetine groups perceived ≥ 2 -category increase in control over ejaculation compared with the placebo group (15.0%, 52/347) ($p < 0.001$). The percentage of subjects who reported very poor or poor satisfaction with sexual intercourse at baseline and shifted to fair, good, or very good satisfaction at endpoint was greater in dapoxetine 30 mg (30%) and 60 mg (36%) groups than in the placebo group (19%). The percentage of subjects who reported “moderate” to “extreme” interpersonal difficulty at baseline and shifted to “none” or “a little bit” of difficulty at endpoint was greater in the dapoxetine 30 (25%) and 60 mg (26%) groups than in the placebo group (20%). At Week 24, a higher percentage of subjects in the 30 mg (37.3%) and 60 mg (44.0%) dapoxetine groups than in the placebo group (17.1%) rated the helpfulness of the medication as “good” to “excellent”. Similar results were obtained at Week 12 for the above mentioned PROs. The improvements in the above mentioned PROs were significantly greater in both dapoxetine groups compared with placebo ($p < 0.001$) at all time points.

In terms of partner’s PROs, the change from baseline in partner scores for Satisfaction with Sexual Intercourse were significantly greater ($p < 0.001$ for both dapoxetine groups versus placebo) at Week 24. Additionally, there were statistically greater decreases from baseline in scores in the dapoxetine 60 mg group than in the placebo group at all post-baseline time points for the partner Personal Distress outcome measure and for most time points for the partner Interpersonal Difficulty outcome measure. For the partner’s rating of the subject’s Control Over Ejaculation and SSI, the change in scores was significantly greater in the dapoxetine groups versus the placebo group ($p < 0.001$).

In summary, dapoxetine 30 mg and 60 mg prn were superior to placebo in prolonging IELT, improving responder rates (defined as ≥ 2 -category increase in control over ejaculation and ≥ 1 -category decrease in personal distress), decreasing personal distress by ≥ 1 -category and improving sexual satisfaction by ≥ 1 -category. The effect of treatment increased over time, with maximum increases by Week 12 with efficacy maintained until Week 24. Similar results were seen when subjects were stratified into baseline IELT ≤ 1 min and > 1 min, with greater improvements seen in baseline > 1 min stratum.

Study R096769-PRE-3003

The multicentre, placebo-controlled, double-blind, randomised parallel-group study evaluated the efficacy and safety of dapoxetine 30 and 60 mg prn in men with PE from Asian-Pacific regions/countries, including Australia for 12 weeks (Table 15). The study consisted of a screening visit and a 4-week baseline period, a 12-week double-blind treatment Phase with an end of treatment or early

termination visit, and a post-study telephone contact (~2 weeks after discontinuation to assess new and existing AEs).

Table 15: Details of Study R096769-PRE-3003

No. subjects, Age, Gender	Diagnosis, Inclusion & exclusion criteria	Test product, Dosage regimen, Administration route, Formulation, Treatment duration	Evaluation criteria	Results	Adverse reactions/ Safety
<p>1067 male subjects (placebo: n=357; dapoxetine 30 mg prn: n=354.; dapoxetine 60 mg prn: n=356.)</p> <p>Mean age: 40.9 (20 - 82)</p> <p>85 Caucasian, 982 Other*</p> <p>*Other included 979 Asians</p> <p>9 countries in Asia and Australia</p> <p>12 Apr 2005 to 22 Jun 2006</p>	Men with IELT \leq 2min in 75% sexual intercourse	<p>Placebo prn</p> <p>Dapoxetine tablet 30 mg prn</p> <p>Dapoxetine tablet 60 mg prn</p> <p>Treatment duration: 12 weeks</p>	<p>Primary efficacy: IELT at endpoint</p> <p>Secondary efficacy: responders (proportion of subjects with \geq2-category increase in control & \geq1-category decrease in distress from baseline), \geq1-category decrease in distress from baseline, \geq1-category increase in satisfaction in intercourse, other PRO measures</p>	<p>Dapoxetine 30 & 60 mg prn were significantly superior to placebo in prolonging IELT (at first dose, at endpoint and at Weeks 4-12), improving responder rates, decreasing personal distress by \geq1-category and improving sexual satisfaction by \geq1-category. Average IELT increased from 1.1min at baseline to 2.42, 3.85 & 4.23min in placebo, dapoxetine 30 & 60 mg groups, respectively at the endpoint ($p<0.001$). The proportion of responders were 37.2% (n=125), 34.7% (n=114) for dapoxetine 60 & 30 mg compared to 21.7% (n=74) for placebo ($p<0.001$). The effect of treatment increased over time. Similar results were seen in subgroup analyses for baseline IELT \leq1min and $>$1min stratum and country/ region.</p>	<p>No new safety issues identified in this population of Asian men. The most common AEs reported by subjects on dapoxetine were nausea and dizziness. No noteworthy mood-related, cardiovascular safety issues or sexual side effects were demonstrated.</p> <p>Dapoxetine 30 and 60 mg significantly prolonged IELT compared with placebo in men with PE from Asian Pacific countries. One accidental drowning death occurred & alcohol was involved.</p>

The primary efficacy endpoint was the average IELT at study endpoint. Secondary endpoints included responder to treatment (that is, 2-category improvement in control over ejaculation and 1-category decrease in distress over time to ejaculation as defined in Section 8, based on two observational studies), Control over Ejaculation, Personal Distress, and Satisfaction with Sexual Intercourse.

A sample size of 370 subjects per group (n=1110) would detect a difference of +1 min (SD=3.5 min) in mean average IELT between placebo and active treatment with 90% power and 2-sided $\alpha=0.05$, assuming a 30% discontinuation rate. Assuming the same responder rates as seen in R096769-PRE-3002 (47.6% in the dapoxetine 60 mg prn group and 21.7% in the placebo group), the above sample size would provide $>90\%$ power to detect a difference of 25.9% between the dapoxetine 60 mg prn and placebo groups. In addition, ≥ 600 subjects were to be of self-assigned Asian ethnicity as follows: 300 subjects of Chinese ethnicity, 100 subjects of Taiwan-Chinese ethnicity, and 200 subjects of Korean ethnicity; the remaining 510 subjects were recruited either in these three regions/countries or in other Asian-Pacific regions/ countries, including Australia.

A total of 1067 subjects (mean age: 40.9 years, 92% Asian) were randomised to placebo (n=357), dapoxetine 30 mg prn (n=354), and dapoxetine 60 mg prn (n=356) groups, and comprised the intent-to-treat (ITT) analysis set. The mean baseline IELT was 1.06 min, with 45% of subjects having IELT ≤ 1 min. In each treatment group, 90% of subjects reported poor or very poor “Control over Ejaculation”. Subjects also reported high levels of Personal Distress (75% with ratings of “quite a bit” or “extremely distressed”) and low levels of Satisfaction with Sexual Intercourse (78% with ratings of Very Poor or Poor satisfaction).

A total of 858 (80%) subjects completed the study. The percentage of subjects who discontinued early was greater in the dapoxetine groups than in the placebo group. Subject choice was the reason for most study discontinuations (11-12% in all groups). A greater percentage of subjects discontinued due to AE(s) in the dapoxetine groups (2% in the dapoxetine 30 mg and 5% in the dapoxetine 60 mg group) compared with the placebo (<1%) group.

Primary efficacy results

The efficacy results demonstrated a significant prolongation in average IELT for dapoxetine 30 mg and 60 mg compared with placebo at first dose, study endpoint (the primary efficacy variable), and at Weeks 4, 8 and 12 (Table 16). Average (SD) IELT increased from ~1.1 (0.46) min at baseline to 4.2 (3.97) min and 3.9 (3.95) min in dapoxetine 60 mg and 30 mg groups respectively at the study endpoint, compared with 2.4 (2.05) min in the placebo group ($p < 0.001$ for overall comparison and comparison of each dapoxetine group versus placebo). Mean (SD) IELT values after the first dose were 1.8 (1.71), 2.7 (2.68) and 3.0 (3.2) min for placebo, dapoxetine 30 and 60 mg respectively ($p < 0.001$ for overall comparison and comparison of each dapoxetine group versus placebo). A significant increase in average IELT in both dapoxetine groups versus placebo was observed for each time point from Week 4 onwards ($p < 0.001$ for all). The magnitude of between-treatment differences in the changes in average IELT increased from Weeks 4 to 12. The mean values for placebo, dapoxetine 30 and 60 mg groups for Weeks 4-12 were 2.0-2.5 min, 3.1-4.0 min and 3.4-4.3 min respectively. Significant increases in the changes from baseline in the average IELT were seen in each dapoxetine dose group versus placebo at Weeks 4-12 (LS means for dapoxetine 30 mg versus placebo: 1.07-1.42, LS means for dapoxetine 60 mg versus placebo: 1.32-1.79, $p < 0.001$ for all).

Table 16: Response over Time

	----- PLACEBO -----			-- DPX 30 MG PRN --			-- DPX 60 MG PRN --		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
Average IELT (min)									
BASELINE	357	1.0	0.47	354	1.1	0.45	356	1.1	0.48
WEEK 4	341	2.0	1.59	333	3.1	2.97	329	3.4	3.40
WEEK 8	312	2.4	2.46	309	3.5	3.32	299	3.8	3.44
WEEK 12	295	2.5	2.11	281	4.0	4.00	278	4.3	3.97
END POINT (TRT)	342	2.4	2.05	333	3.9	3.95	331	4.2	3.97

Note: End Point (trt) Refers to the last postbaseline observation during the Treatment Period.

Subgroup analyses according to stratum of baseline IELT ≤ 1 min and > 1 min showed similar results as above with significant improvements seen in each subgroup for each dapoxetine dose versus placebo from Weeks 4 to 12 ($p \leq 0.004$). In general, subjects included in the baseline average IELT > 1 min stratum had greater numerical increases in IELT over time compared to subjects with baseline average IELT ≤ 1 min stratum. Similar results were noted when analysed according to region/ country. There was a significant ($p < 0.001$) interaction between treatment and time, indicating that the effect of the treatment, as measured by average IELT, increased over time.

Responder rate (≥ 2 -category improvement in control over ejaculation and ≥ 1 -category decrease in distress over time to ejaculation)

The treatment benefit of dapoxetine indicated by the increase in IELT was supported by results of three key secondary evaluations. The proportions of treatment responders were significantly ($p < 0.001$) greater with dapoxetine 60 mg (37.2%) and 30 mg (34.7%) compared to placebo (21.7%). Responder rates in the baseline average IELT > 1 min stratum were numerically greater (dapoxetine 30 mg: 21.3-37.4%, dapoxetine 60 mg: 26.4-45.5%, placebo: 14.3-25.6%) and significant at all time points ($p < 0.017$) compared with the baseline average IELT ≤ 1 min stratum (30 mg: 21.2-32.5%, 60 mg: 22.4-33.8%, placebo: 11.8-19.4%, $p = 0.009-0.035$ at all time points). In terms of decreased Personal Distress, 191 (56.0%), 219 (66.6%), and 245 (72.7%) of the subjects reported ≥ 1 -category decrease in Personal Distress scores from baseline to endpoint in the placebo, dapoxetine 30 and 60 mg groups, respectively ($p < 0.001$). Significantly higher proportions of subjects in dapoxetine 60 and 30 mg groups versus placebo experienced improvement in Personal Distress score after 12 weeks ($p < 0.001$ for 60 mg, $p = 0.007$ for 30 mg). The difference between dapoxetine 60 and 30 mg was small (6.1%, $p = 0.071$). The percentage of subjects with > 1 min baseline average IELT stratum who improved were significantly greater at all time points (30 mg: 55.7-69.9%, 60 mg: 68.3-79.9%, placebo: 44.4-63.4%, $p < 0.001-0.009$) compared with subjects in the baseline average IELT ≤ 1 min stratum. A smaller percentage of subjects in the baseline average IELT ≤ 1 min stratum showed significant improvements at all time points (30 mg: 53.4-65.1%, 60 mg: 51.3-67.7%, placebo: 37.5-50.4%, $p = 0.004-0.054$).

In terms of improvement in Satisfaction With Sexual Intercourse, there were 197 (57.8%), 228 (69.3%) and 225 (75.9%) subjects who reported ≥ 1 -category increase in Satisfaction with Sexual Intercourse scores from baseline to endpoint in the placebo, dapoxetine 30 mg and 60 mg groups respectively ($p < 0.001$). Significantly higher percentages of subjects in dapoxetine 60 mg and 30 mg groups versus placebo experienced improvement in Satisfaction scores at 12 weeks ($p < 0.001$ for 60 mg, $p = 0.002$ for 30 mg). The difference between the dapoxetine 60 and 30 mg groups was small (6.6%, $p = 0.05$). The percentage of subjects in the > 1 min baseline average IELT stratum who showed improvement were significantly greater at all time points with dapoxetine versus placebo (30 mg: 65.0-73.6%, 60 mg: 69.2-81.2%, placebo: 46.0-61.6%, $p < 0.001-0.002$). For the ≤ 1 min baseline average IELT stratum, a smaller percentage of subjects showed significant improvement at all time points, including endpoint (30 mg: 57.5-65.9%, 60 mg: 59.9-73.8%, placebo: 43.4-59.7%, $p = 0.004-0.050$). A dose-related trend was consistently observed across all endpoints in IELT and the three key secondary endpoints, and other secondary endpoint measures. These observed effects were evident irrespective of baseline IELT and were consistent across all regions/countries in the Asia/Pacific region including China-Chinese, Korea, and Taiwan-Chinese; suggesting that Asian men also respond to dapoxetine treatment.

Other secondary efficacy results

The other secondary efficacy analyses included changes from baseline in the responses to the PRO measures of Control Over Ejaculation, Satisfaction With Sexual Intercourse, SSI, Personal Distress, and Interpersonal Difficulty as well as MHQ, clinical GIC, the number of satisfactory events based on the event log, and the average duration of all intercourse attempts. For all PROs, mean changes from baseline were significantly greater in the dapoxetine groups than the placebo group at all time points ($p = 0.007$ to < 0.001). Similar results were obtained with country/ region analyses.

At Week 12, higher proportions in the dapoxetine 30 (71.4%) and 60 mg (79.2%) groups reported at least a slightly better response in clinical GIC compared with the placebo group (52.8%, $p < 0.001$) and the improvement was significantly greater in the dapoxetine groups than the placebo group at the Week 4-12 time points ($p < 0.001$).

At endpoint, higher proportions in the dapoxetine 30 (37.7%) and 60 mg (40.5%) groups responded as having ≥ 2 -category increase in control over ejaculation compared with the placebo group (25.8%, $p < 0.001$).

At endpoint, greater proportions in the dapoxetine groups (30 mg: 41.3%, 60 mg: 40.9%) than the placebo group (29.0%) rated their satisfaction with sexual intercourse as good or very good ($p < 0.001$).

At endpoint, greater proportions in the dapoxetine groups (30 mg: 42.9%, 60 mg: 45.4%) reported lower SSI than the placebo group (30.5%, $p < 0.001$).

At endpoint, the proportions who reported that they were not at all or a little bit distressed were higher in the dapoxetine groups (30 mg: 47.4%, 60 mg: 46.6%) than the placebo group (34.3%) and the proportions who reported that they were quite a bit or extremely distressed were lower in the dapoxetine groups than the placebo group.

At endpoint, the proportions who reported no or only a little bit of interpersonal difficulty were slightly higher in the dapoxetine groups (30 mg: 51.1%, 60 mg: 57.2%) than the placebo group (44.6%, $p < 0.001$).

At endpoint, the proportions who reported good to excellent "Medication helpfulness" were slightly higher in the dapoxetine groups (30 mg: 45.9%, 60 mg: 49.8%) than the placebo group (31.4%, $p < 0.001$).

At the first evaluable event associated with the study drug, there was a significantly higher proportion of subjects with satisfactory sexual experiences based on event log in the dapoxetine 30 mg (34.8%) and 60 mg groups (37.5%) than the placebo group (21.6%, $p < 0.001$).

In summary, dapoxetine 30 mg and 60 mg prn were significantly superior to placebo in prolonging IELT (at first dose, at endpoint and at Weeks 4-12), improving responder rates, decreasing personal distress by ≥ 1 -category and improving sexual satisfaction by ≥ 1 -category. The effect of treatment increased over the 12 week treatment duration. Similar results were seen in subgroup analyses for baseline IELT ≤ 1 min and > 1 min stratum and country/ region.

Other efficacy studies

Study R096769-pre-3002

This was a placebo-controlled, double-blind, randomised, parallel-group study conducted in 1238 men with PE in USA and Canada, with the primary objective of assessing possible withdrawal effects as measured by Discontinuation Emergent Signs and Symptoms (DESS) after abrupt cessation of chronic administration of dapoxetine 60 mg (62 days of once daily followed by 7 days of placebo), as compared to continuous (69 days) dosing of dapoxetine 60 mg once daily (Table 17).²⁸ One of the secondary objectives of the randomised placebo-controlled trial was to evaluate the efficacy of dapoxetine 60 mg prn or 60 mg once daily in 1238 men with PE in USA and Canada for 9 weeks. Because this was predominantly a safety study, subjects enrolled in this study were not required to meet the inclusion criteria for IELT (that is, IELT ≥ 2 min in 75% of the sexual intercourse events recorded during baseline) as in subjects enrolled in other Phase III efficacy studies. Despite this, the definition of PE used in the current study resulted in a population of subjects that was very similar to the Phase III studies with $> 90\%$ of subjects reporting very poor or poor baseline control over ejaculation. . The mean age was 41 years, and predominantly (80%)

²⁸ DESS – Discontinuation Emergent Signs and Symptoms. The instrument includes 43 items. The identified signs and symptoms are placed into 1 of 4 categories: new symptom; old symptom, but worsened; old symptom, but improved; and old symptom but unchanged, with a final category of symptom not present. The number of symptoms rated as "new" or "old, but worse" is summed to indicate the impact of discontinuation of therapy.

Caucasian. They were randomised to placebo (n=245), dapoxetine 60 mg prn (n=491) and dapoxetine 60 mg once daily (n=502).

Table 17: Details of Study R096769-pre-3002

No. subjects, Age, Gender	Diagnosis, Inclusion & exclusion criteria	Test product, Dosage regimen, Administration route, Formulation, Treatment duration	Evaluation criteria	Results	Adverse reactions
1238 male subjects (placebo: n=245; dapoxetine 60 mg prn: n=491.; dapoxetine 60 mg once daily: n= 502 Mean age: 41.0 (19 - 72) 986 Caucasian, 139 Black, 113 Others US, Canada 8 Nov 2004 to 30 Aug 2005	Subjects with PE	Placebo Dapoxetine tablet 60 mg Treatment: 62 days of dapoxetine once daily; 62 days of dapoxetine prn; or placebo once daily and prn; additional 7 days on dapoxetine (same dosing regimen) or switch to placebo	Safety: DESS Efficacy parameters: PRO measures for Control Over Ejaculation, Satisfaction With Sexual Intercourse, SSI, Clinical GIC, Medication Helpfulness, Personal Distress, and Interpersonal Difficulty.	Withdrawal effects as measured by DESS were rare (n=8). Efficacy: In all 3 treatments there was a time-dependent increase in Satisfaction with Sexual Intercourse and Control Over Ejaculation and a time-dependent decrease in Personal Distress, Interpersonal Difficulty and SSI. Improvement in sexual functioning as measured by PROs was greater in both the dapoxetine once daily and prn groups, versus placebo. The average PRO response was slightly higher in the dapoxetine 60 mg prn group versus once daily group, likely because sexual activity coincided with T _{max} of dapoxetine when taken prn compared to when taken once daily	AEs were reported by 44.1%, 61.3% & 62.5% of the placebo, dapoxetine 60 mg prn and dapoxetine 60 mg once daily groups during treatment period and by 16.8%, 13.1%, 18.8%, 23.6% & 26.5% of the placebo/placebo, dapoxetine 60 mg prn/placebo, dapoxetine 60 mg prn/prn., dapoxetine 60 mg once daily/ placebo, and dapoxetine 60 mg once daily/ once daily treatment sequence during WA period. The most common AEs during treatment and WA period were nausea, dizziness, headache, diarrhoea & insomnia. More subjects on dapoxetine versus placebo withdrew due to AEs; nausea being the most common AE for this. No clear pattern on suicidality was seen. No increase in accidental injury or akathisia was seen. Dizziness was the most common CVS and CNS AE. 5 cases of syncope were reported, all resolved with no sequelae. Slightly higher % of orthostatic hypotension was seen with dapoxetine versus placebo. No increase in sexual dysfunction was seen. <1% SAEs were reported.

The efficacy criteria were PRO for Control Over Ejaculation, Satisfaction With Sexual Intercourse, SSI, Clinical GIC, Medication Helpfulness, Personal Distress, and Interpersonal Difficulty. Baseline scores were similar across the three groups. For all PROs, both dosing regimens of dapoxetine (prn and once daily.) were significantly better than placebo at Weeks 4 and 9 (p<0.001) (Table 18). The percentage of subjects who reported “very poor” or “poor” control over their ejaculation at baseline, and “fair” to “very good” control at endpoint was greater in the dapoxetine groups (prn: n=274 [64%]; once daily: n=264 [59%]) than the placebo group (n=97, 44%); the difference between dapoxetine and placebo was significant for both dapoxetine treatments

($p < 0.001$). The percentage of subjects who reported “very poor” or “poor” satisfaction with sexual intercourse at baseline, and “fair” to “very good” satisfaction with sexual intercourse at endpoint was greater in the dapoxetine groups (prn: $n=183$ [42%]; once daily: $n=169$ [38%]) than the placebo group ($n=69$, 31%); the difference between dapoxetine and placebo was significant for both dapoxetine treatments ($p = 0.014$). The percentage of subjects who reported being “moderately” to “extremely” distressed at baseline, and “not at all” and “a little bit” distressed at endpoint was greater in the dapoxetine groups (prn: $n=218$ [51%]; once daily: $n=210$ [47%]) than the placebo group ($n=39$, 31%); the difference between dapoxetine and placebo was significant for both dapoxetine treatments ($p < 0.001$). The percentage of subjects who reported high levels of interpersonal difficulty at baseline and low levels at endpoint was greater in the dapoxetine groups (prn: $n=165$ [38%] once daily: $n=166$ [37%]) than the placebo group ($n=63$, 29%); the difference between dapoxetine and placebo was significant for dapoxetine prn ($p < 0.001$) and marginally significant for dapoxetine once daily ($p = 0.054$). The percentage of subjects who reported high levels of SSI at baseline and low levels at endpoint was greater in the dapoxetine groups (prn: $n=221$ [51%]; once daily: $n=204$ [46%]) than the placebo group ($n=65$, 29%). The difference between dapoxetine and placebo was significant for both dapoxetine treatments ($p < 0.001$). In terms of subject-assessed GIC, a higher percentage of subjects in the dapoxetine groups (prn: $n=178$ [41.3%]; once daily: $n=174$ [39.1%]) reported that their PE was better or much better compared with the placebo group ($n=46$, 20.8%) at endpoint. Subject-assessed GIC was significantly better than placebo for both dapoxetine treatments ($p < 0.001$) at Weeks 4 and 9. At endpoint, a higher percentage of subjects in the dapoxetine groups (prn: $n=225$ [52.4%]; once daily: $n=212$ [47.6%]) rated the helpfulness of the medication as “good” to “excellent” compared with the placebo group ($n=63$, 28.4%). Subjects’ assessments of the helpfulness of medication were significantly better than placebo for both dapoxetine treatments ($p < 0.001$) at Weeks 4 and 9.

Table 18: Scores from Baseline over Time

Baseline and Follow-up Questions: Values in Item Scores From Baseline Over Time (MITT Analysis Set)									
	----- PLACEBO -----			-- DPX 60 MG PRN --			--- DPX 60 MG QD ---		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
Control over ejaculation									
Baseline	221	0.6	0.59	431	0.6	0.61	447	0.7	0.65
Week 4	210	1.4	0.96	381	2.1	1.10	395	2.0	1.13
Week 9	169	1.6	1.03	317	2.3	1.09	334	2.2	1.15
End point (trt)	221	1.6	1.02	431	2.1	1.13	447	2.1	1.15
Satisfaction with sexual intercourse									
Baseline	221	1.5	0.79	431	1.4	0.83	447	1.3	0.90
Week 4	210	1.8	1.01	381	2.5	1.03	395	2.3	1.04
Week 9	169	2.0	0.98	317	2.6	1.07	334	2.5	1.09
End point (trt)	221	2.0	1.01	431	2.5	1.11	447	2.4	1.11
Personal distress									
Baseline	221	2.8	0.82	431	2.8	0.81	447	2.9	0.82
Week 4	210	2.2	0.99	381	1.6	0.99	396	1.6	1.11
Week 9	168	2.0	1.06	318	1.4	1.02	337	1.5	1.11
End point (trt)	221	2.0	1.05	431	1.5	1.05	447	1.6	1.11
Interpersonal difficulty									
Baseline	221	1.8	1.14	431	1.7	1.06	447	1.8	1.14
Week 4	210	1.2	1.10	381	0.9	0.98	396	0.9	1.01
Week 9	169	1.2	1.01	318	0.7	0.93	337	0.9	1.00
End point (trt)	221	1.1	1.04	431	0.8	1.00	447	0.9	1.05
Symptom severity impression									
Baseline	221	2.4	0.62	431	2.4	0.61	447	2.4	0.61
Week 4	210	2.0	0.78	381	1.5	0.88	396	1.5	0.88
Week 9	169	1.8	0.80	318	1.3	0.89	337	1.4	0.93
End point (trt)	221	1.8	0.79	431	1.5	0.92	447	1.5	0.92

Note: Endpoint (trt) refers to the last post-baseline observation during the Treatment Period.

In all three treatment groups there was a time-dependent increase in Satisfaction with Sexual Intercourse and Control Over Ejaculation and a time-dependent decrease in Personal Distress, Interpersonal Difficulty and SSI. Improvement in sexual functioning as measured by PROs was greater in dapoxetine once daily and prn groups, compared to the placebo group. In general, average PRO response was slightly higher in the dapoxetine 60 mg prn group versus once daily group, likely because the sexual activity coincided with T_{max} of dapoxetine when taken prn at 1-3 hours before sexual activity compared to when taken once daily.

Study C-2002-014

This multicentre, open-label extension study of studies C-2002-012 and C-2002-013 evaluated the long-term safety and efficacy of dapoxetine therapy in 1774 adult males with PE for 9 months (Table 19). After participation in the above studies, subjects were allowed to enter this trial within 30 days and provided with a supply of dapoxetine 60 mg tablets to be taken on prn basis at ~1-3 hours prior to intercourse. The dose could be decreased to 30 mg after the first month if 60 mg was poorly tolerated, and to stay at 30 mg for the remainder of the study. Participants who did not tolerate the 30 mg dose of dapoxetine were to be discontinued from the study. Participants were evaluated for safety and efficacy at Months 1, 2, 3, 6, and 9.

Table 19: Details of Study C-2002-014

No. subjects, Age, Gender	Diagnosis, Inclusion & exclusion criteria	Test product, Dosage regimen, Administration route, Formulation, Treatment duration	Evaluation criteria	Results	Adverse reactions
1774 male subjects Mean age: 41.1 (18-77) 1571 Caucasian, 96 Black, 107 Other US 16 Sep 2003 to 14 Apr 2005	Adult males with premature ejaculation who completed C-2002-012 or C-2002-013	Dapoxetine tablets 60 mg prn Dose reduction to dapoxetine 30 mg prn (for the remainder of time) was allowed after the first month Treatment duration: 9 months	Efficacy: PRO measures Safety: AE reporting, vital signs, ECG, laboratory tests	After 1 month of treatment with dapoxetine, participants previously assigned placebo in C-2002-012 & C-2002-013 noted significant improvements from baseline (p<0.0001) in satisfaction with sexual intercourse, control over ejaculation, SSI & medication helpfulness that were comparable with the efficacy results for participants who initially received dapoxetine 60 mg in the double-blind studies, and these significant improvements were maintained up to endpoint. Efficacy was also maintained for the duration of this study for all participants regardless of previous dapoxetine dose.	AE(s) were reported by 56.7% participants with an onset date in this study and similar regardless of previous assigned treatments in C-2002-012 and C-2002-013. No suicidal ideation. Few subjects had new onset depression & euphoria. Few had sexual dysfunction. Few had asymptomatic CK rises. No change in BP noted. SAEs included 1x seizure, 2x syncope, 1x stroke and 1 case of cardiomyopathy & SVT. Overall, no new safety concerns were identified.

A total of 1774 subjects (mean age: 41.1 year, 89% Caucasians) were treated; 615, 607 and 552 from placebo, dapoxetine 30 mg and 60 mg groups from the previous studies. Of these, 962 completed the study. A total of 1250 participants received dapoxetine for ≥6 months; 962 received dapoxetine for ≥9 months; and 654 received dapoxetine treatment for ~12 months including the

duration of previous studies. The main reasons for early withdrawal were lack of efficacy (12.8%) and lost to follow-up (9.9%). Discontinuation due to lack of efficacy was reported more frequently in this study than in the previous double-blind Phase III studies. Eleven percent (total n=194/1774) of the participants had a dose reduction from 60 to 30 mg; of these 71 subjects had prior placebo treatment, another 71 subjects had prior dapoxetine 30 mg treatment and 52 subjects had prior dapoxetine 60 mg treatment, before entering this extension study. AEs were reported as the reason for dose reduction for 192/ 194 participants, and nausea (45.9%) was the most common AE cited for dose reduction.

After 1 month of treatment with dapoxetine in this extension study, participants previously assigned placebo in the double-blind studies noted significant improvements from baseline ($p < 0.0001$) in satisfaction with sexual intercourse, control over ejaculation, SSI and medication helpfulness that were comparable with the efficacy results for participants who initially received dapoxetine 60 mg in the double-blind studies, and these significant improvements were maintained up to endpoint. Efficacy was also maintained for the duration of this study for all participants regardless of previous dapoxetine dose.

Summary of efficacy

- The primary efficacy criterion used in dose-finding and efficacy trials is IELT. Because there is no definitive cut-off for IELT for diagnosis of premature ejaculation (PE) and there is some overlap in the duration of IELT for men with PE and men without PE, IELT alone is not sufficient to assess the response in treatment for PE. IELT is used in conjunction with PRO measures, that is, ≥ 2 -category increase control over ejaculation and ≥ 1 -category decrease in personal distress, to define a responder to treatment in the newer pivotal Phase III trials, namely studies R096769-PRE-3001 and R096769-PRE-3003. PRO measures such as scores for control over ejaculation and satisfaction in sexual intercourse were used as key secondary variables in earlier Phase III studies C-2002-12 and C-2002-013 to assess treatment response in addition to IELT.
- In terms of exposure, participants were instructed to take the study drug at 1-3 hours prior to sexual intercourse for it to coincide with T_{max} , and no more than 1 dose per 24 hours (except for GP-PE-98-01 in which the interval was 12 hours, because of the lower dose used). The subjects and their partners were expected to attempt sexual intercourse ≥ 2 x per week.
- Study GP-PE-98-01 was a dose-finding study which evaluated the efficacy of dapoxetine 20 and 40 mg in 157 middle-aged subjects who were predominantly Caucasian and had a mean (SD) baseline IELT 1.34 (1.07) min, in the treatment of PE over 4 weeks. A dose-response improvement was seen in mean (SD) IELT at endpoint [2.22 (2.62), 2.70 (2.69) and 3.31 (4.09) min for placebo, dapoxetine 20 and 40 mg, respectively]. The primary efficacy results were supported by significant improvements in participant's control over ejaculation and satisfaction with sexual intercourse, participant's and partner's SSI and GIC ratings.
- In another dose-finding study (C-2001-008-02) which involved 166 middle-aged predominantly Caucasian subjects with mean (SD) baseline IELT 1.01 (0.51) min over 2 weeks, dapoxetine 60 mg and 100mg were superior to placebo in increasing mean (SD) IELT [2.06 (2.32) min for placebo, 2.93 (2.60) min for dapoxetine 60 mg, and 3.20 (2.76) min for dapoxetine 100mg], and improving control over ejaculation and satisfaction of sexual intercourse. There was no significant difference between dapoxetine 60 and 100mg in nearly all the primary and secondary efficacy criteria. The improvement in participant's perception of control over ejaculation, sexual satisfaction, SSI and GIC was also reflected in the partner's scores. Dapoxetine 30 mg and 60 mg were used in the pivotal Phase III studies, as the treatment effect of 20 mg was small and the tolerance of 100mg was poor with higher withdrawal rates.
- Studies C-2002-012 and C-2002-013 were pivotal studies. C-2002-012 evaluated the efficacy of dapoxetine 30 and 60 mg prn in 1294 middle-aged predominantly Caucasian subjects with mean

(SD) baseline IELT 0.92 (0.49) min, in the treatment of PE over 12 weeks. Dapoxetine 30 and 60 mg treatment resulted in significant improvement in mean (SD) IELT at endpoint [1.66 (2.087), 2.86 (3.588), and 3.36 (3.973) min for placebo, dapoxetine 30 and 60 mg, respectively], control over ejaculation and satisfaction with sexual intercourse compared with placebo, and the 60 mg dose was superior to the 30 mg dose. C-2002-013 evaluated the efficacy of dapoxetine 30 and 60 mg prn in 1320 predominantly Caucasian subjects with mean (SD) baseline IELT of 0.90 (0.47) min, in the treatment of PE over 12 weeks. Dapoxetine 30 and 60 mg prn resulted in significant improvement in mean (SD) IELT [1.84 (2.335), 2.70 (3.386) and 3.28 (3.404) min for placebo, dapoxetine 30 and 60 mg, respectively], control over ejaculation and satisfaction with sexual intercourse at endpoint. Dapoxetine 60 mg was significantly superior to 30 mg in IELT and most of the secondary PRO parameters. In both studies, improvement in IELT was noted from the first dose. Significant improvements were seen from the first dose and sustained over 12 weeks. Subgroup analyses using baseline average IELT ≤ 1 min and > 1 min showed similar results.

- Studies R096769-PRE-3001 and R096769-PRE-3003 were carried out in European and Asian subjects to confirm the efficacy and safety of dapoxetine in other ethnic groups. In both studies, 90-94% of the patients reported having ‘poor or very poor’ control over ejaculation, and 68% reported “quite a bit” or “extreme” personal distress related to PE at baseline. R096769-PRE-3001 was a study conducted in 1162 European subjects with PE which demonstrated that dapoxetine 30 mg and 60 mg prn were superior to placebo in prolonging IELT; average (SD) IELT increased from baseline of ~ 0.9 (0.50) min to 1.9 (2.89), 3.1 (3.88) and 3.5 (1.69) min in placebo, dapoxetine 30 and 60 mg groups respectively, at Week 24 ($p < 0.001$). Dapoxetine also significantly improved responder rates defined as ≥ 2 -category increase in control over ejaculation and ≥ 1 -category decrease in personal distress (37.1%, 25.3% and 13% in dapoxetine 60 mg, 30 mg and placebo groups respectively). Unfortunately, there was a large drop-out rate due to one subject suffering a 28-second sinus pause associated with a consequent vasovagal syncope event. Another Phase III (Study R096769-PRE-3003) involving 1067 subjects of Asian/ Pacific origin also demonstrated that both dapoxetine 30 mg and 60 mg prn were significantly superior to placebo in prolonging IELT [average (SD) IELT increased from ~ 1.1 (0.46) min at baseline to 4.2 (3.97), 3.9 (3.95) and 2.4 (2.05) min at endpoint in dapoxetine 60 mg, 30 mg and placebo groups, respectively ($p < 0.001$)] and improving responder rate [37.2%, 34.7% and 21.7%, respectively ($p < 0.001$)]. In both studies, the effect of treatment increased over time. At endpoint, the proportions who reported that they were not at all or a little bit distressed were higher in the dapoxetine groups (30 mg: 47.4%, 60 mg: 46.6%) than the placebo group (34.3%) and the proportions who reported that they were quite a bit or extremely distressed were lower in the dapoxetine groups than the placebo group. Similar results were seen in subgroup analyses for baseline IELT ≤ 1 min and > 1 min stratum and country/ region.
- Results of the safety study R096769-PRE-3001 demonstrated that efficacy of dapoxetine 60 mg prn was maintained for up to 24 weeks. Results of another study C-2002-014, which was a 9-month extension study of pivotal, 12-week, Phase III studies C-2002-012 and C-2002-013 demonstrated that the efficacy of dapoxetine 30-60 mg prn for treatment of PE was maintained for up to 12 months.

Safety

Safety of dapoxetine was evaluated in all clinical studies involving over 700 subjects in the Phase I studies and over 6000 subjects with PE in the Phase II and III studies. In addition to usual safety evaluations in Phase I studies, specific attention was given to the effect of various doses of dapoxetine on BP and QTc interval because of increased incidence of dizziness and, rarely, syncope in subjects receiving dapoxetine.

Special studies to evaluate effect on BP and ECG

Effect on BP

C-2001-004-A

This study was described under *Pharmacokinetics*.

Dapoxetine did not have a clinically relevant effect on SBP, DBP, heart rate, MAP, or double product (heart rate * SBP) after single or multiple doses. Small differences between dapoxetine and placebo in mean SBP (maximal difference in Phase A: 7.2 mmHg and in Phase B: 13.1 mmHg) or DBP (maximal difference in Phase A: 7.9 mmHg and in Phase B: 12.3 mmHg) were observed, generally in the first 8 hours post-dose. Higher values were seen more often with dapoxetine than placebo, however these differences were intermittent, and not clinically relevant. These higher BP readings with dapoxetine were also demonstrated with ambulatory BP monitoring in both Phases of the study. The maximal statistically significant difference using ambulatory BP monitoring was 4.4 mmHg for mean SBP and 3.3 mmHg for mean DBP in Phase A. The maximal statistically significant difference in ambulatory BP monitoring was 7.0 mmHg for mean SBP and 8.1 mmHg for mean DBP. There was no obvious dose or time relation with these differences. In Phase A, no dapoxetine-treated subject had two consecutive BP measurements that were ≥ 30 mmHg (systolic) or ≥ 15 mmHg (diastolic) higher than placebo, an event that would have stopped dose escalation. In Phase B, the comparison of mean SBP and DBP values between Days 1 and 6 did not show any clinically relevant differences. Most analyses showed no significant differences between dapoxetine and placebo in SBP and DBP. When statistically significant differences were present, they were not dose-related and not considered clinically meaningful.

All AEs were mild or moderate and most were considered to be treatment-related. Two subjects withdrew in Phase B because of mild-to-moderate treatment-related gastrointestinal tract (GIT) and/or CNS AEs, one after a single 120 mg dose, and one after 2 x 120 mg doses. More subjects reported AEs during dapoxetine versus placebo treatment (61.9% versus 20.9% in Phase A; 87.1% versus 34.4% in Phase B). More subjects reported AEs at the higher dapoxetine doses (40%, 40%, 81.8% and 81.8% with 60, 100, 140 and 160 mg dapoxetine in Phase A; 72.7%, 90% and 100% with 80, 100 and 120 mg in Phase B). Nausea was the most common AE (Phase A: dapoxetine versus placebo: 31% versus 0%; Phase B: 52% versus 12.5%). Other common AEs in dapoxetine-treated subjects in Phase A were diarrhoea (23.8%) and vomiting (14.3%), and none of these AEs were reported during placebo treatment. Other common AEs in Phase B were headache (dapoxetine versus placebo: 25.8% versus 6.3%), somnolence (22.6% versus 9.4%) and dizziness (19.4% versus 0%). More subjects reported headaches (80mg: n=2, 100mg: n=2, 120 mg: n=4) and dizziness (80mg: n=0, 100mg: n=1, 120 mg: n=5) at higher doses. During multiple-dosing, the percentage of subjects reporting AEs was highest during the initial days of treatment; for example. 5-6 subjects in all dose groups complained of nausea on Day 1 versus 0-1 subjects on Day 5.

Study C-2001-007

This study was also described under *Pharmacokinetics*.

Because of isolated hypertensive episodes reported in the early dapoxetine studies, this study was designed to determine if significant increases in blood pressure after dapoxetine dosing could be elicited in a population considered "at risk" that is, treated hypertensive patients. Study C-2001-004 had not demonstrated significant rises in BP in subjects receiving dapoxetine 60-160 mg. Subjects in C-2001-007 must have had sitting BP <160/100mmHg. Subjects were randomised to 1 of two treatment sequences (dapoxetine then placebo, or placebo then dapoxetine) in 1:1 ratio. Evaluation of BP effect consisted of the calculation of AUC for BP and double product (heart rate * SBP) values measured after dosing during treadmill exercise (pre-exercise through the end of Stage II

Bruce protocol).²⁹ Changes in vital signs during sexual activity were considered comparable to Stage II Bruce protocol. Additional vital sign data from ambulatory blood pressure monitoring (ABPM) were evaluated: peak, 24-hour average, average daytime (0800–2000), average night-time (2000–0800), 0–4 hour average, 4–12 hour average, and load for SBP and DBP readings (defined as the percentage of readings >140/90 during the day and 120/80 during the night). A single 100 mg dose of dapoxetine had no statistically or clinically significant effects on blood pressure or heart rate relative to placebo treatment during treadmill exercise in these subjects. During the exercise testing, mean changes in vital signs from pre-exercise to the end of Stage II were comparable for both treatments. Mean SBP increased by 12 and 11 mmHg for dapoxetine and placebo, respectively, whereas mean DBP decreased by 6 and 3 mmHg, respectively. Average heart rate increased by 22 and 23 beats per minute (bpm) for dapoxetine and placebo, respectively.

However, mean BP data collected during ABPM (SBP, DBP and MAP) were slightly higher for dapoxetine compared with placebo. The between-treatment differences were small in magnitude, generally <5 mmHg, but were statistically significant during 3 intervals: 24 hours average, daytime (0–12 hours average), and 4–12 hours average.

More subjects experienced AEs with dapoxetine compared to placebo, namely nausea, diarrhoea, hypertension, dizziness, somnolence, headache and GIT disorder. Most AEs were considered as drug-related. Nausea and diarrhoea were the most frequent AEs associated with dapoxetine. The AEs were generally transient, self-limited, and mild to moderate in severity. Overall, changes in ECG intervals were comparable for dapoxetine and placebo. Mean increases of 1.06 and 0.06 milliseconds (ms) from pre-study values were observed in QTc interval at T_{max}. At 3 hours post-dose, there were mean decreases (from pre-study values) in QTc of 0.88 and 0.56 ms for dapoxetine and placebo, respectively. However, these results should be interpreted with caution due to very small numbers of hypertensive patients evaluated in this study.

Effect on ECG

Study C-2002-056-01

This study evaluated the effects on ECG pharmacodynamics after single dose dapoxetine 60 mg in healthy men who were CYP2D6 EM (n=15) and PM (n=13). The ECGs were evaluated independently in a blinded fashion by cardiologists at a central laboratory. QT interval (uncorrected), QT interval with Bazett's correction (QTcB), QT interval with Frederica's correction (QTcF), and subject- and study-specific corrections were reported. Changes in QTc from baseline, at each time point, T_{max} and the maximum change from baseline were to be estimated using the following definitions of baseline; that is, a) the pre-dose QTc value on the day of treatment (treatment baseline), and b) the average of the pre-dose QTc values across both treatment periods for a subject (study baseline). The actual QTc at each time point, maximum QTc, and average QTc value over the 24 hours assessment period were also evaluated. The number of subjects with QTc ≥500 ms, ≥480 ms and ≥450 ms and change in QTc (QTc - QTc_{baseline}) values ≥60 ms and ≥30 ms were also examined. Treatment effects were assessed using ANOVA. In addition, a 90% CI was calculated for placebo-corrected QT/QTc at T_{max}.

The 90% CI for the placebo-corrected dapoxetine QTc values at T_{max} included zero for CYP2D6 EM and PM, suggesting that dapoxetine did not prolong the QTc interval. Pairwise comparisons of QT and QTc intervals were similar for dapoxetine and placebo, and for PM and EM at each time point. Isolated occurrences of statistically significant QT and QTc differences were observed after dapoxetine and placebo doses, but no treatment-emergent pattern was observed. There was no difference observed in the mean average QTc interval between dapoxetine and placebo treatments

²⁹ The Bruce protocol is a diagnostic test used in the evaluation of cardiac function, developed by Robert A. Bruce. The protocol, involving a treadmill, has been widely adopted protocol and extensively validated.

evaluated over a 24 hour period. After dapoxetine or placebo treatment, PM tended to have a shorter mean QTc than EM group. The absence of an increase in QTc above placebo and lower QTc values in the PM group who had modestly higher dapoxetine exposure versus EM group, indicated that dapoxetine did not increase the QTc interval. No subject had QTc ≥ 480 ms. The number of subjects with QTc ≥ 450 ms was 1 in each metaboliser group after dapoxetine treatment and 3 in EM group after placebo. The number of subjects with QT changes ≥ 30 ms at any time from baseline (treatment and study) was similar or lower for the dapoxetine and placebo treatments in both metaboliser groups. The PM group did not have a greater number of outliers than the EM group. For the mean maximum increase in QTcB values, there were no differences observed between the dapoxetine and placebo treatments in EM and placebo treatment in PM; the mean maximum increase in QTcB values was 5-8 ms shorter after dapoxetine in PM than after placebo.

Study C-2002-043

This single centre, randomised, open-label, single dose, placebo- and positive-controlled (moxifloxacin 400mg), crossover study evaluated the ECG pharmacodynamics of dapoxetine (60 mg and 120 mg) in 48 subjects (mean age 27.5 years, 60.4% Caucasian). The study was performed in accordance with CPMP guidelines and 45 subjects completed the study.³⁰ Assuming an intra-individual SD=12 ms for the change in QTc interval over baseline, a sample size of 40 subjects would allow detection of 9 ms difference between two treatments with 90% power. The 90% CI for the placebo-corrected moxifloxacin QTc values at T_{max} did not include 0 and the lower bound of the 90% CI was >0 for any of the correction methods used, indicating that moxifloxacin prolongs the QTc interval compared to placebo. In contrast, the 90% CI for the placebo-corrected dapoxetine QTc values included 0 or the upper bound of the 90% CI was slightly <0 , indicating that dapoxetine does not prolong the QTc interval. The mean average QTc interval based on the AUC₀₋₂₄ was 5 ms greater for moxifloxacin than for placebo. The mean average QTc interval over time from 0.5-24 hours was 5-6 ms greater for moxifloxacin than for placebo. Whether based on AUC or calculated as the mean value over time, no difference was observed in the mean average QTc interval between dapoxetine treatments and placebo, or between the two dapoxetine doses.

The number of QTc outliers (that is, QTc ≥ 500 , ≥ 480 and ≥ 450 ms and QTc values ≥ 60 and ≥ 30 ms from baseline) was, in most cases, greater for moxifloxacin than either dapoxetine treatment or placebo treatment for all QT correction methods used. Additionally, in most cases, the number of QTc outliers during the dapoxetine treatments was similar to or less than placebo treatment, and the 120 mg dapoxetine dose did not have a greater number of outliers than the 60 mg dose. Based on pairwise comparisons, QTc was significantly higher at more time points for moxifloxacin versus placebo than for either dapoxetine treatment versus placebo.

The incidence of AEs was higher in the dapoxetine 60 mg (41.3%) and 120 mg (58.7%) compared with moxifloxacin (19.1%) and placebo (25.5%). Nausea was the most common AE with an incidence of 19.6%, 45.7%, 6.4% and 6.4% in the dapoxetine 60 mg, dapoxetine 120 mg, moxifloxacin and placebo treatments, respectively. Other common AEs during either dapoxetine treatment were vomiting, headache, diarrhoea, dizziness, abdominal pain, rhinitis and flatulence, usually more frequent with the higher 120 mg dose. Two subjects discontinued due to AE(s): 1 subject had a 6-beat, non-sustained ventricular tachycardia (VT) at ~2 hours after receiving moxifloxacin 400mg, and 1 subject had abnormal ejaculations that began ~15 hours after receiving dapoxetine 120 mg treatment and lasted ~37 days.

³⁰ EMEA. ICH E14. The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs, 25 May 2005. Note for guidance on the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs (CHMP/ICH/2/04).

Study C-2003-021

This study was also described under *Pharmacokinetics*.

AE incidence was higher in subjects treated with dapoxetine compared with moxifloxacin and placebo (79.5%, 31.3% and 32.6% with dapoxetine, moxifloxacin and placebo respectively) with nausea being the most common AE (47.7%, 4.2% and 2.2% respectively). Other common AEs during dapoxetine treatment were diarrhoea, dizziness, vomiting, abdominal pain and asthenia. A probably drug-related severe AE relating to nausea occurred in 1 subject that started 20 min after the second dose of dapoxetine and lasted 4 min. One subject had vasovagal syncope 2 hours after the first dapoxetine dose at 2 hours post-dose during blood collection, which was considered as a moderately severe AE and possibly drug-related. Administration of the second dose of dapoxetine 120 mg was delayed by 1 hours, and occurred without incident.

Safety in Phase I studies

Safety results of PK studies

Eight subjects were treated in study C-2002-051 which involved the administration of oral ¹⁴C-dapoxetine 60 mg and IV dapoxetine 30 mg. Six subjects (75%) reported AE(s) in both treatments. The most common AEs in the oral dapoxetine 60 mg group were pruritus (n=4, 50%) and headache (n=3, 37.5%). None of the pruritus reports was considered to be drug-related. Other common AEs after oral dapoxetine were nausea and vomiting. The most common AE in the dapoxetine 30 mg IV group was headache (n=2, 25%).

Study F2X-LC-HIAC evaluated the PK of radiolabelled dapoxetine 20 and 40 mg capsules in 6 subjects. AE(s) were reported by 1 subject who received dapoxetine 20 mg and two subjects who received dapoxetine 40 mg. AEs included arrhythmia, constipation, diarrhoea, asthenia, headache, neck pain, pain, nausea, dizziness, yawn, and taste perversion. Common drug-related AEs were headache, dizziness, nausea, yawn, and asthenia.

Twenty-nine subjects were enrolled in C-2002-037-01 which assessed the effect of food on the PK of dapoxetine. The proportion of subjects reporting AE(s) after dapoxetine treatment was 44.8% and 34.5% under fasting and fed conditions, respectively. Nausea was the most common AE after fasting (24.1%) and fed (13.8%) treatment periods. Other common AEs were headache (fasting: 17.2%, fed: 10.3%), dizziness (fed: 10.3%), and vomiting (fasting: 6.9%).

Fourteen subjects were enrolled in F2X-LC-HIAE which investigated the effect of food on the PK of dapoxetine 40 mg. AE(s) were reported by 8 (57.1%) subjects in each treatment group. Headache (dapoxetine: n=6, placebo: n=1), dizziness (dapoxetine: n=4, placebo: n=2), nausea (dapoxetine: n=2, placebo: n=0), and yawn (dapoxetine: n=2, placebo: n=0) were noted in more subjects following dapoxetine administration versus placebo.

Twenty-three subjects were enrolled in study C2002-020-00 which examined the bioequivalence of dapoxetine tablets versus capsules. AE incidence was similar in all treatment groups (69.6%, 65.2% and 75% after 2 x 30 mg dapoxetine capsules, 2 x dapoxetine tablets and 1x 60 mg tablet respectively). Nausea was the most commonly reported AE (43.5%, 43.5% and 45.8%, respectively). Other common AEs were headache, dizziness, diarrhoea, abdominal pain, vomiting, dysphagia and somnolence. Three subjects (1 from each treatment) had isolated incidences of asymptomatic first degree AV block (PR interval 208-224 ms), which were self-limiting.

Study C-2004-009 evaluated the bioequivalence of dapoxetine tablets produced with drug substance of various particle sizes in 36 subjects. The number of AEs was similar across the 4 treatment groups; 18/34 (52.9%), 17/35 (48.6%), 17/36 (47.2%) and 16/35 (45.7%) subjects in treatments using particle size ranging from DL50 28 to 131µm. One subject withdrew after sustaining a scalp laceration following a fall due to dizziness after taking dapoxetine. The most common AEs were

nausea, dizziness and diarrhoea. Other common AEs included asthenia, headache, vomiting, somnolence, abnormal thinking, yawn and acne. No significant drug-related orthostatic effect was noted. Two subjects had a creatine phosphokinase (CK) rise; 1 subject had a CK rise from 172 U/L at baseline to 460 U/L at Day 32 (study completion), CK peaked at 1108 U/L at Day 40 before decreasing, while another subject had a CK rise from 208 U/L at baseline to 593 U/L at Day 32 (study completion), CK peaked at 603 U/L at Day 35, before decreasing. There was no mention of whether this was considered as drug-related.

Study F2X-LC-HIAA examined the PK of dapoxetine in a dose-escalation regimen starting from 5mg up to 120 mg, in 4 subjects. Dapoxetine was generally well tolerated at 5-60 mg. Most of the AEs were considered to be drug-related, such as hypertension, pallor, vasodilation, agitation, anxiety, nervousness, increased reflexes, tremor, rhinitis, skin disorder, sweating, chills, fever and abnormal blurred vision. One subject withdrew due to hypertension while on 80 mg dose (he tolerated the 30 mg dose), and the BP returned to baseline at 9.6 hours. This subject also experienced tremor, fever, nervousness, increased reflexes and CK rise (from 107 to 320 U/mL) after dapoxetine 80 mg. Another subject receiving the 120 mg dose also had transient hypertension up to 163/93 mmHg. Based on this, a maximum of 60 mg was considered as a safe dose. In addition, dapoxetine had no effect on pulmonary function or pulmonary artery pressure (animal toxicology studies have shown increases in pulmonary artery pressures).

F2X-LC-HIAB was a dose-escalation study which investigated the PK and PD of dapoxetine 5-40 mg in 20 subjects. There were 3 severe AEs: 1 subject had a severe headache that lasted 20 min (dapoxetine 10mg), and another subject had severe anxiety that lasted 5 hours (dapoxetine 10 mg) and a severe headache that lasted 2.3 hours (placebo). Incidence of AEs was not related to dapoxetine dose (59.1%, 100%, 50% and 25% in the placebo, 10/30 mg, 5/20 mg and 40 mg groups respectively). The most frequent AEs were asthenia (4 subjects on placebo, 1 on 5 mg, 2 on 10 mg, and 1 on 30 mg) and headache (5 subjects on placebo and 2 on 10mg). One subject experienced 7 episodes of mild-moderate palpitations and 3 episodes of mild arrhythmia at the 10mg dose. None of these episodes were considered to be drug-related, as the same subject also experienced 1 episode of palpitation and 1 episode of arrhythmia while on placebo. Other AEs considered to be drug-related were anorexia, constipation, anxiety, apathy, dizziness, euphoria, nervousness, paraesthesia, somnolence, pruritis, sweating, photophobia, taste perversion, rhinitis, rash and breast pain. CK elevation was noted for two subjects; one had CK rise from 79 to 369 U/mL after 5 days of dapoxetine 5mg daily and the other had CK rise (values not given) after 7 days of dapoxetine 10mg daily.

Study F2X-LC-HIAF evaluated the PD effect of single (5-20 mg) and multiple dosing of dapoxetine 5mg bd, 10mg bd and 20 mg once daily in 20 subjects. AE(s) were reported by 9 (45.0%), 3 (60.0%), 4 (80.0%), and 3 (60.0%) subjects while receiving placebo, dapoxetine 5, 10 and 20 mg, respectively. Headache was the most common AE occurring with dapoxetine and placebo, followed by diarrhoea and rash. AEs considered to be drug-related were headache (n=5), diarrhoea (n=3), nausea (n=1), anorexia (n=1) and euphoria (n=1). Seven subjects (dapoxetine 10mg bd: n=3, placebo: n=4) had transient ALT rises, which were not considered as clinically significant.

Study C2004-010-02 assessed dose-proportionality and compared single- and multiple-dose PK of dapoxetine 30 mg and 60 mg in 42 healthy adult males. AEs were reported by 11/42 subjects (26.2%) during single-dosing and 19/42 subjects (45.2%) during multiple-dosing of dapoxetine 30 mg. AEs were reported by 17/42 (40.5%) subjects during single and multiple dosing with dapoxetine 60 mg. Diarrhoea was the most common AE, reported by 4 (9.5%) and 5 (11.9%) during the single-dose Phase and 8 (19.0%) and 4 (9.5%) subjects during the multiple-dose Phase with dapoxetine 30 and 60 mg, respectively. One subject receiving dapoxetine 60 mg experienced syncope (severe AE) which resolved without sequelae. Other common AEs were dizziness, nausea,

headache, somnolence, flatulence, dyspepsia, nervousness, rhinitis, pharyngitis, anorexia, abdominal pain, asthenia, palpitation and vasodilatation. Orthostatic safety assessments did not reveal any significant orthostasis with single- and multiple doses of dapoxetine 30 and 60 mg. Seven subjects had CK rise compared to baseline, and one of them was considered as a laboratory AE. Five subjects had alanine transaminase (ALT) and aspartate transaminase (AST) rises compared to baseline, and one of them was considered as a laboratory AE.

Safety results of drug-drug interaction studies.

Study C-2003-020 evaluated the drug interaction between warfarin and dapoxetine in 16 males. The incidence of AEs was higher in subjects treated with dapoxetine + warfarin (68.8%) compared to warfarin (18.8%) or dapoxetine (37.5%). The most common AEs during dapoxetine-only treatment included nausea (n=4, 25%) and dizziness (n=3, 18.8%). The most common AEs during warfarin + dapoxetine included dizziness (n=5, 31.3%) and somnolence (n=3, 18.8%). Dizziness did not appear to be related to changes in vital signs.

Study C-2003-022 evaluated the drug interaction between midazolam and dapoxetine in 24 males. AEs were reported by 18/24 subjects (75%) with midazolam, 17/24 subjects (70.85%) with dapoxetine, and 21/24 subjects (87.5%) with dapoxetine + midazolam. The most common AE was nausea [dapoxetine only: n=10, (41.7%) and dapoxetine + midazolam: n=1, (4.2%)], and all nausea AEs were considered to be related to dapoxetine. Somnolence was the most common AE following midazolam, seen in 14 (58.3%) subjects after midazolam alone and 18 (75%) subjects following midazolam + dapoxetine. All events of somnolence were considered not related to dapoxetine. Other common AEs were headache, asthenia, vomiting, diarrhoea, twitching, depersonalization, dizziness and pruritus. All except asthenia were considered related to dapoxetine. One subject had CK rise from a normal baseline to 4905 IU/L and 1 subject had a small rise in AST from 36 U/L at baseline to 71 U/L after 6 days of dapoxetine 60 mg treatment.

Study C-2003-023 evaluated the drug interaction between dapoxetine and ketoconazole in 24 subjects. Twenty-one of 24 subjects (87.5%) reported 91 AEs. The highest incidence occurred during ketoconazole + dapoxetine treatment (83.3%) versus dapoxetine alone (58.3%) and ketoconazole alone (37.5%). Nausea was the most common AE (66.7%, 25% and 0% respectively), followed by dizziness (n=5 for dapoxetine only, n=1 for ketoconazole only, n=7 for combination) and diarrhoea (n=4 for dapoxetine only, n=0 for ketoconazole only, n=6 for combination). Other common AEs included vomiting, headache, asthenia and somnolence.

Study C-2002-024 evaluated the drug interaction between fluoxetine and dapoxetine in 24 subjects. The highest incidence of AEs occurred during dapoxetine-only treatment (16/24, 66.7%) compared to fluoxetine alone (11/23, 47.8%) and fluoxetine + dapoxetine (8/22, 36.4%). Nausea was the most common AE, 41.7% (n=10) with dapoxetine only treatment, 17.4% (n=4) with fluoxetine alone and 4.5% (n=1) with fluoxetine + dapoxetine. All reports of nausea were considered to be treatment-related. Dizziness was the next most common, 16.7% (n=4) with dapoxetine only treatment, 4.3% (n=1) with fluoxetine alone and 13.6% (n=3) with fluoxetine + dapoxetine. Other common treatment-related AEs included vomiting, headache, diarrhoea, asthenia, somnolence, insomnia, vasodilatation, rhinitis and cough.

Study C-2003-025 evaluated the drug interaction between omeprazole and dapoxetine. The incidence of AEs was 33.3%, 13.6% and 27.3% during dapoxetine only, omeprazole only and dapoxetine + omeprazole treatment respectively. The most frequent AE following dapoxetine was nausea (16.7%), which occurred at a higher incidence in the dapoxetine-only treatment (16.7%) than in either the omeprazole-only or dapoxetine + omeprazole treatments (4.5% in each treatment group). Other common AEs were headache, somnolence, and diarrhoea. One subject had elevated CK at baseline and rose to 752 U/L at the end of study.

Study C-2003-026 evaluated the drug interaction between ethanol and dapoxetine in 24 males. Incidence of AEs was 28.6%, 75%, 52.2% and 38.1% with ethanol alone, dapoxetine + ethanol, dapoxetine alone and placebo respectively. Somnolence was the most common AE (9.5%, 30%, 13% and 9.5% respectively). Other common AEs were headache, nausea, abnormal thinking, alcohol tolerance, asthenia, chills, euphoria, neurosis and blurred vision.

Study C-2003-027 evaluated the drug interaction between dapoxetine and PDE5 inhibitors, namely tadalafil and sildenafil in 24 subjects. AEs were reported by (43.5%, 43.5% and 47.8% after dapoxetine alone, dapoxetine + tadalafil and dapoxetine + sildenafil respectively). Nausea and diarrhoea were the most common AEs. Diarrhoea was the most frequent AE with dapoxetine-only treatment (21.7%), and nausea was the most frequent AE with dapoxetine + tadalafil (26.1%) and dapoxetine + sildenafil (21.7%). Other common AEs were headache, dizziness and vomiting. Review of subjects with dizziness did not show any significant drop in BP to <100/-, except in 1 subject about 3 hours post-treatment with dapoxetine + sildenafil. Two subjects had BP decreasing to ~70-78/50mmHg during dapoxetine + tadalafil although they were not reported as AEs. Small CK rises up to 342 IU/L in 3 subjects were noted.

Study C-2003-029 investigated the drug interaction between dapoxetine and glyburide in 22 subjects. AEs were reported by 63.2% during the glyburide-only treatment, 54.5% during the dapoxetine-only treatment, and 70.0% during glyburide + dapoxetine treatment. The most frequent AEs were nervousness (15.8%, 4.5% and 25% respectively) and nausea (0, 27.3% and 10% respectively). Dizziness was reported in 2, 1 and 5 subjects during glyburide-only, dapoxetine-only treatment and glyburide + dapoxetine treatment Phases. Other common AEs included diarrhoea, vomiting, sweating and hypoglycaemia.

Study C-2003-042 evaluated the drug interaction between dapoxetine and desipramine in 24 subjects. AEs were reported by 43.5% during desipramine-only treatment, 62.5% during dapoxetine-only treatment Phase, and 43.5% during desipramine + dapoxetine treatment. Nausea was the most frequent AE, occurring in 37.5% in dapoxetine-only treatment, no subjects in desipramine + dapoxetine treatment and 4.3% in desipramine-only treatment. Other common AEs included somnolence, headache, diarrhoea, asthenia, dizziness and tremor. Two subjects had asymptomatic transient CK rises up to 797 U/L.

Study C-2004-017 evaluated the potential drug interaction and safety of single and multiple dosing of dapoxetine in 56 subjects who were taking tamsulosin for ≥ 6 weeks. One subject discontinued due to hypotension on Day 1 of placebo + tamsulosin treatment and another subject discontinued due to dizziness, headache and fatigue on Day 1 and headache on Day 2 after taking dapoxetine 30 mg + tamsulosin. There was an apparent dose-effect with regards to the incidence of AEs; 23.2% for dapoxetine 60 mg + tamsulosin, 10.9% for dapoxetine 30 mg + tamsulosin, and 5.4% for placebo + tamsulosin. The most common AEs were diarrhoea, dizziness, headache and nausea. Two subjects reported AEs relating to orthostatic hypotension during dapoxetine 30 mg + tamsulosin treatment. The same subjects also experienced AEs with dapoxetine 60 mg + tamsulosin; 1 had vasovagal at 8h post-dose and the other had palpitations. Three subjects reported dizziness during dapoxetine 60 mg + tamsulosin, 3 during dapoxetine 30 mg + tamsulosin, and 1 during placebo + tamsulosin. There was no dose-effect in the incidence of orthostatic hypotension (defined as decrease in SBP ≥ 20 mmHg, DBP ≥ 10 mmHg and increase in HR ≥ 20 bpm); 16% (n=9) each in dapoxetine 60 mg + tamsulosin, and placebo + tamsulosin, and 20% (n=11) in dapoxetine 30 mg + tamsulosin treatment on Day 1 and 8.9% (n=5), 13% (n=7) and 11% (n=6) for placebo + tamsulosin, dapoxetine 30 mg + tamsulosin and dapoxetine 60 mg + tamsulosin, respectively.

Safety results of PK studies in specific populations.

Age

In study C-2002-038 which evaluated the PK and safety of single dose of dapoxetine 60 mg in healthy elderly and young men, ~50-55% of subjects in both age groups reported AEs. No age-related pattern was seen in the AEs. Diarrhoea, abdominal pain, nausea and headache were the most common AEs in both age groups.

CYP2D6 PM and EM status

Study C-2002-056-01 evaluated the PK of a single dose of dapoxetine 60 mg in 13 healthy subjects who were CYP2D6 PM and 15 subjects who were CYP2D6 EM. One severe AE was reported, that is, ventricular tachycardia (VT) occurred after placebo treatment, which resulted in discontinuation of one PM. The proportion of subjects reporting AE(s) after dapoxetine 60 mg was 84.6% for PM (11/13 subjects) and 62.5% for EM (10/16 subjects), and after placebo was 64.3% for PM (9/14 subjects) and 33.3% for EM (5/15 subjects). Drug-related AEs were reported in 61.5% of PM (8/13 subjects) and 43.8% of EM (7/16 subjects) after dapoxetine 60 mg. Nausea, headache, diarrhoea, abdominal pain, dizziness, euphoria, and flatulence were the common AEs after dapoxetine treatment. A comparable number of CYP2D6 PM and EM reported nausea, headache, abdominal pain, dizziness, and euphoria after dapoxetine treatment; diarrhoea was only reported by EM (n=3) and flatulence was only reported by PM (n=2) after dapoxetine 60 mg. The number of subjects reporting AEs after dapoxetine 60 mg, overall and drug-related, was similar between the PM and EM groups. One PM had possibly drug-related laboratory AEs: CK increased from 126 to 1379 IU/L and AST increased from 16 to 58 IU/L, which normalised 10 days later. QTc intervals were similar for dapoxetine and placebo, and for PM and EM at each time point.

Renal impairment

Study C2003-018 evaluated the PK of a single dose of dapoxetine 60 mg in 22 subjects with normal and varying degrees of impaired renal function. Incidences of AEs appeared higher in the severe renal impairment group; 33.3% (2/6) in normal renal function group, 16.7% (1/6) each in mild and moderate renal impairment groups, and 75% (3/4) in severe renal impairment group. Most AEs (12/19) were possibly or probably drug-related, namely headache, nausea, vomiting, sweating, pallor, hypertension and hypotension.

Hepatic impairment

Study C-2003-019 evaluated the PK of single dose of dapoxetine 60 mg in 21 subjects with normal and varying degrees of hepatic impairment. There was no specific trend with AE incidence of 66.7%, 33.3%, 40 % and 75 % in normal, mild, moderate and severe hepatic impairment respectively. Most AEs (15/21) were considered to be possibly or probably drug-related, namely nausea, diarrhoea, raised ALT, headache, dry mouth and left-sided pain. Two subjects had small rises in ALT which were considered as AEs, from 41 to 61 IU/L and from 26 to 72 IU/L, which were self-limiting. One subject with severe hepatic impairment had increased QTc interval from 402 to 507 ms.

Asian population

Study R096769-pre-1001 evaluated the single and multiple-dose PK of dapoxetine in 44 healthy Japanese and 44 Caucasian men. Overall, 80% of Caucasian and 86% of Japanese subjects experienced AEs. Nausea was the most frequent AE (Caucasians versus Japanese; 55% versus 59%). Other common AEs included diarrhoea (32%, versus 36%), dizziness (32% versus 36%), headache (23% versus 16%), and somnolence (18% versus 30%). The percentage of Caucasian and Japanese subjects who reported nausea was greater with dapoxetine 60 versus 30 mg treatment. The frequency of dizziness was greater in the Japanese taking dapoxetine 60 mg. Other less common AEs reported more frequently by Japanese versus Caucasian subjects included upper abdominal

pain (11% versus 0%), abdominal pain (5% versus 0%), fatigue (7% versus 0%), and shoulder pain (5% versus 0%). AEs that were reported more frequently by Caucasian versus Japanese subjects included flatulence (9% versus 2%), cold sweats (5% versus 0%), and muscle tightness (7% versus 2%). Two subjects had cardiovascular AEs (1 with syncope and 1 with arrhythmia). The subject with asymptomatic arrhythmia, reported during Holter monitoring on Days 4 and 8, was considered as having had a probable drug-related AE and led to the subject's discontinuation from the study. Two Japanese subjects had self-limiting CK rises that were clinically significant, one after dapoxetine 30 mg with CK rise ~7.8x the upper limit of normal (ULN) and another after dapoxetine 60 mg with CK rise ~20 x ULN, but they were not reported as AEs and these subjects were not discontinued. Two subjects (Caucasian: n=1 and Japanese: n=1) had transient QTcF prolongations at 453-469 ms after dapoxetine 30 and 60 mg which were not present at baseline.

Safety results in efficacy studies

Of the 6,404 subjects in the Phase II and III placebo-controlled studies and the 1,774 subjects who enrolled in the open-label extension study, 1361 received at least 180 days of treatment and 378 received at least 360 days of treatment. In addition to standard AEs, special attention was given to AEs relating to: a) cardiovascular system (CVS), in particular syncope and arrhythmias, b) CNS, in particular to suicidality, mood and affect, accidental injuries to suggest a temporal relationship with the administration of dapoxetine. Questionnaires and an independent assessment of AE data were employed, c) genitourinary tract (GUT), in particular sexual dysfunction, d) bleeding and e) withdrawal syndrome – measured by Discontinuation Emergent Signs and Symptoms (DESS) checklist.

Safety results of Phase II dose-finding studies

Study GP-PE-98-01

This study evaluated the efficacy and dose-response relationship of dapoxetine 20 and 40 mg capsules prn in the treatment of PE in 157 subjects. Treatment-emergent AEs (TEAEs) were reported by 12.7% (18/142), 15.9% (23/145), and 17.0% (24/141) of participants during treatment with placebo, dapoxetine 20 and 40 mg, respectively. Common AEs reported more frequently with dapoxetine than with placebo were headache (0.7%, 3.4% and 2.7% for placebo, dapoxetine 20 and 40 mg, respectively), nausea (1.4%, 0.7% and 2.8%, respectively), dizziness (0.7%, 0% and 2.8%), diarrhoea, nervousness and somnolence. The incidences of headache were 0.7% (n=1) for placebo, 3.4% (n=5) for dapoxetine 20 mg and 2.8% (n=4) dapoxetine 40 mg. The incidences of nausea were 1.4% (n=2) for placebo, 0.7% (n=1) for dapoxetine 20 mg and 2.8% (n=4) for dapoxetine 40 mg. The incidences of dizziness were 0.7% (n=1) for placebo, 0 for dapoxetine 20 mg and 2.8% (n=4) for dapoxetine 40 mg. These common AEs occurred throughout the treatment periods and were not limited to a first dose effect. Most AEs were mild in severity and treatment-related. The occurrence of moderate and severe AEs was similar during treatment with dapoxetine 20 mg or 40 mg. No deaths were reported. Two participants discontinued due to AE relating to mild diarrhoea during the 40 mg treatment period. A non-treatment related SAE was reported in 1 participant who underwent knee surgery for an old injury. In terms of noteworthy accidental injury, one participant taking dapoxetine 40 mg prn experienced 3 episodes of injury burns over 7 days, followed by another episode of injury burns ~3 weeks later while the participant was receiving dapoxetine 20 mg prn (nil further explanations were provided). Another subject had a fall while on dapoxetine 20 mg. In terms of sexual dysfunction, 3 subjects reported impotence during dapoxetine treatment (dapoxetine 20 mg: n=2, 40 mg: n=1) versus 1 during placebo treatment. One of them was considered as severe and all were considered to be treatment-related.

Study C-2001-008-02

This study evaluated the efficacy and dose-response relationship of dapoxetine 60 mg and 100mg prn versus placebo in the treatment of PE in 166 subjects. TEAEs were reported by 17% (25/145),

28% (40/144), and 40% (62/155) and considered to be treatment-related in 6.2% (9/145). The incidence of TEAEs (17%, 28% and 40% in placebo, dapoxetine 60 mg and 100mg groups, respectively) and treatment-related AEs (6.2%, 21.5% and 31.6%, respectively) suggested a possible dose effect. The most common AEs were nausea (0.7%, 5.6% and 16.1%, respectively), dizziness (0%, 2.1% and 7.7%), diarrhoea, insomnia, headache and nervousness. These common AEs occurred predominantly with the first dose of dapoxetine 60 or 100mg administered (Table 20). Most AEs were mild to moderate in severity and judged to be treatment-related.

Table 20: TEAEs with incidence $\geq 2\%$

All Adverse Events With Incidence $\geq 2\%$ During Any Treatment Period Number (%) of Treated Participants			
Body System COSTART Term	Placebo (n=145)	Dapoxetine 60 mg (n=144)	Dapoxetine 100 mg (n=155)
Nausea	1 (0.7%)	8 (5.6%)	25 (16.1%)
Dizziness	0	3 (2.1%)	12 (7.7%)
Diarrhea	1 (0.7%)	7 (4.9%)	10 (6.5%)
Insomnia	1 (0.7%)	6 (4.2%)	9 (5.8%)
Headache	0	6 (4.2%)	9 (5.8%)
Nervousness	0	5 (3.5%)	5 (3.2%)
Vomiting	0	0	5 (3.2%)
Dyspepsia	0	4 (2.8%)	3 (1.9%)
Somnolence	1 (0.7%)	4 (2.8%)	2 (1.3%)
Upper respiratory tract infection	1 (0.7%)	3 (2.1%)	2 (1.3%)
Rhinitis	1 (0.7%)	6 (4.2%)	1 (0.6%)

Note: AEs in this table are sorted by decreasing incidence during the dapoxetine 100-mg treatment period. A participant may be reported in more than 1 COSTART category.

Ten participants (10/166, 6.0%) discontinued due to AEs: 1/145 (0.7%), 0 and 9/155 (5.8%) in placebo, dapoxetine 60 and 100mg treatments respectively. Common AEs that led to discontinuation were nausea, vomiting, nervousness, diarrhoea and sweating. All AEs that led to study discontinuation were graded as moderate to severe, resolved without intervention and were considered to be treatment-related. Of note, one subject had a syncopal episode with head-striking at ~7h after the first dose of dapoxetine 100mg. Two non-treatment related SAEs (snake bite and subsequent cellulitis) were reported in one participant. There were no deaths reported.

One laboratory AE was reported (mildly abnormal post-treatment elevation in ALP to 120 and GGT to 64IU/L that resolved on re-test in 1 participant).

Overall, results from this Phase II dose-finding study suggested that dapoxetine 60 mg prn was better tolerated than dapoxetine 100 mg prn.

Phase III efficacy studies

An overview of the incidence of AEs in the Phase III studies is found in Table 21.

Table 21: TEAEs in Phase III Studies

System Organ Class Preferred Term	Placebo (N=1857) n (%)	DPX 30 mg p.r.n. (N=1616) n (%)	DPX 60 mg p.r.n. (N=2106) n (%)	DPX 60 mg q.d. (N=502) n (%)	Total DPX (N=4224) n (%)
Total no. subjects with adverse events	651 (35.1)	760 (47.0)	1270 (60.3)	341 (67.9)	2371 (56.1)
Gastrointestinal disorders	141 (7.6)	290 (17.9)	681 (32.3)	149 (29.7)	1120 (26.5)
Nausea	41 (2.2)	178 (11.0)	467 (22.2)	86 (17.1)	731 (17.3)
Diarrhoea	32 (1.7)	56 (3.5)	145 (6.9)	47 (9.4)	248 (5.9)
Dry mouth	13 (0.7)	20 (1.2)	55 (2.6)	17 (3.4)	92 (2.2)
Vomiting	7 (0.4)	16 (1.0)	49 (2.3)	9 (1.8)	74 (1.8)
Nervous system disorders	162 (8.7)	247 (15.3)	500 (23.7)	143 (28.5)	890 (21.1)
Dizziness	40 (2.2)	94 (5.8)	230 (10.9)	75 (14.9)	399 (9.4)
Headache	89 (4.8)	91 (5.6)	185 (8.8)	56 (11.2)	332 (7.9)
Somnolence	10 (0.5)	50 (3.1)	98 (4.7)	18 (3.6)	166 (3.9)
Disturbance in attention	10 (0.5)	7 (0.4)	17 (0.8)	13 (2.6)	37 (0.9)
Infections and infestations	208 (11.2)	194 (12.0)	228 (10.8)	57 (11.4)	479 (11.3)
Nasopharyngitis	43 (2.3)	51 (3.2)	61 (2.9)	17 (3.4)	129 (3.1)
Influenza	27 (1.5)	34 (2.1)	47 (2.2)	10 (2.0)	91 (2.2)
Upper respiratory tract infection	58 (3.1)	33 (2.0)	46 (2.2)	12 (2.4)	91 (2.2)
Psychiatric disorders	68 (3.7)	89 (5.5)	212 (10.1)	92 (18.3)	393 (9.3)
Insomnia	28 (1.5)	34 (2.1)	83 (3.9)	44 (8.8)	161 (3.8)
Anxiety	10 (0.5)	17 (1.1)	42 (2.0)	11 (2.2)	70 (1.7)
General disorders and administration site conditions	58 (3.1)	79 (4.9)	170 (8.1)	75 (14.9)	324 (7.7)
Fatigue	23 (1.2)	32 (2.0)	86 (4.1)	46 (9.2)	164 (3.9)
Irritability	14 (0.8)	2 (0.1)	24 (1.1)	18 (3.6)	44 (1.0)
Investigations	75 (4.0)	62 (3.8)	116 (5.5)	41 (8.2)	219 (5.2)
Blood pressure orthostatic	8 (0.4)	0	12 (0.6)	11 (2.2)	23 (0.5)
Reproductive system and breast disorders	46 (2.5)	60 (3.7)	88 (4.2)	16 (3.2)	164 (3.9)
Erectile dysfunction	29 (1.6)	37 (2.3)	54 (2.6)	6 (1.2)	97 (2.3)
Vascular disorders	36 (1.9)	24 (1.5)	68 (3.2)	39 (7.8)	131 (3.1)
Orthostatic hypotension*	13 (0.7)	6 (0.4)	26 (1.2)	24 (4.8)	56 (1.3)
Skin and subcutaneous tissue disorders	32 (1.7)	31 (1.9)	63 (3.0)	27 (5.4)	121 (2.9)
Hyperhidrosis	4 (0.2)	13 (0.8)	25 (1.2)	15 (3.0)	53 (1.3)
Eye disorders	17 (0.9)	12 (0.7)	28 (1.3)	16 (3.2)	56 (1.3)
Vision blurred	7 (0.4)	1 (0.1)	11 (0.5)	10 (2.0)	22 (0.5)

* Includes the following verbatim terms that coded to the MedDRA SOC, "Vascular Disorders": orthostatic hypotension, orthostatic hypotensive event, orthostadichypotension, orthostatic hypotensive, asymptomatic orthostatic hypotension, and orthostatic blood pressure.

Studies included: C-2002-012, C-2002-013, R096769-PRE-3001, R096769-PRE-3002 and R096769-PRE-3003.

Table 21 (cont):

	PLACEBO	DPX 30 MG	DPX 60 MG	DPX 60 MG	Total Dpx
System Organ Class	(N=1857)	PRN	PRN	QD	(N=4224)
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)
Total no. subjects with adverse events	342 (18.4)	487 (30.1)	987 (46.9)	276 (55.0)	1750 (41.4)
Gastrointestinal disorders	70 (3.8)	205 (12.7)	541 (25.7)	124 (24.7)	870 (20.6)
Nausea	21 (1.1)	130 (8.0)	371 (17.6)	72 (14.3)	573 (13.6)
Diarrhoea	16 (0.9)	40 (2.5)	104 (4.9)	32 (6.4)	176 (4.2)
Dry mouth	7 (0.4)	16 (1.0)	45 (2.1)	12 (2.4)	73 (1.7)
Nervous system disorders	95 (5.1)	178 (11.0)	391 (18.6)	99 (19.7)	668 (15.8)
Dizziness	28 (1.5)	69 (4.3)	188 (8.9)	55 (11.0)	312 (7.4)
Headache	45 (2.4)	58 (3.6)	124 (5.9)	32 (6.4)	214 (5.1)
Somnolence	7 (0.4)	39 (2.4)	76 (3.6)	13 (2.6)	128 (3.0)
Psychiatric disorders	31 (1.7)	54 (3.3)	144 (6.8)	56 (11.2)	254 (6.0)
Insomnia	11 (0.6)	20 (1.2)	55 (2.6)	25 (5.0)	100 (2.4)
General disorders and administration site conditions	26 (1.4)	51 (3.2)	102 (4.8)	48 (9.6)	201 (4.8)
Fatigue	13 (0.7)	21 (1.3)	56 (2.7)	29 (5.8)	106 (2.5)
Vascular disorders	21 (1.1)	21 (1.3)	58 (2.8)	36 (7.2)	115 (2.7)
Orthostatic hypotension	10 (0.5)	6 (0.4)	23 (1.1)	24 (4.8)	53 (1.3)

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Studies included: C-2002-012, C-2002-013, R096769-PRE-3001, R096769-PRE-3002 and R096769-PRE-3003.

Study C-2002-012

This was a pivotal placebo-controlled efficacy study which evaluated the use of dapoxetine 30 and 60 mg prn in 1294 males with PE. A total of 309 (69.9%), 276 (64.0%) and 269 (63.3%) participants in the placebo, dapoxetine 30 and 60 mg groups, respectively were exposed to study drug for ≥ 85 days, and took a mean of 22-23.4 doses of drug/ placebo. No deaths occurred during this study. SAE(s) were reported in 4 (0.9%), 2 (0.5%), and 3 (0.7%) participants in the placebo, dapoxetine 30 and 60 mg groups, respectively; all were associated with an intercurrent illness, pre-existing condition or accident, and were assessed as non-treatment related. Incidence of early withdrawal due to AE(s) was higher in dapoxetine groups (0.5%, 4.9% and 8.7% in the placebo, dapoxetine 30 and 60 mg groups, respectively) and nausea was the most common AE for early withdrawal (0%, 1.2% and 3.3%, respectively).

Dapoxetine-treated patients reported higher incidence of TEAEs (36%, 49% and 60% in the placebo, dapoxetine 30 and 60 mg groups, respectively) and treatment-related AEs (10.2%, 30.2% and 48%, respectively); the majority of these AEs affected GIT and CNS systems and were of mild to moderate severity. Nausea (2.7%, 9.3% and 19.8% in placebo, dapoxetine 30 mg and 60 mg groups, respectively), diarrhoea (1.6%, 4.6% and 7.3%), dizziness (0.9%, 2.8% and 5.4%) and headache (2.7%, 5.3% and 4.9%) were the most common AEs reported during dapoxetine treatment. Other common AEs which occurred more frequently with dapoxetine versus placebo treatment were: impotence, asthenia, dyspepsia, somnolence, insomnia, vomiting and dry mouth (Table 22). Nausea, diarrhoea, dizziness and insomnia appeared dose-related and often started with the first dose of dapoxetine administered. Severe AEs were reported by 2.3% (10/442), 2.3% (10/431), and 4.2% (18/425) of participants with placebo, dapoxetine 30 and 60 mg treatments respectively.

Severe AEs considered to be dapoxetine-related were accidental injury, diarrhoea, vomiting, nausea, pain, headache, agitation, anorgasmia, impotence, dizziness and myalgia.

In terms of AEs relating to mood and affect, they were reported infrequently. There was no suicidal ideation. Nine participants reported depression: 1 (0.2%), 3 (0.7%) and 5 (1.2%) in the placebo, dapoxetine 30 and 60 mg groups, respectively. Of note, 4/8 subjects who reported depression while taking dapoxetine had no prior history of depression. Three participants reported euphoria which was determined by the investigator to be possibly or probably drug-related: 2 in the dapoxetine 30 mg group and 1 in the 60 mg group. For all the participants who reported accidental injury, 13 (2.9%) in the placebo group, 22 (5.1%) in the dapoxetine 30 mg group, and 14 (3.3%) in the dapoxetine 60 mg group, the AEs were assessed as not related to study medication, and no AEs potentially suggesting suicidal ideation were noted. With one exception of an AE relating to hand injury, no AEs with a temporal relationship to accidental injuries were identified that might potentially indicate an impairment of participants' alertness.

Table 22: Treatment-related AEs - Study C-2002-012

COSTART Term	Placebo (n=442)	Dapoxetine 30 mg (n=431)	Dapoxetine 60 mg (n=425)
Nausea	5 (1.1%)	37 (8.6%)	82 (19.3%)
Diarrhea	3 (0.7%)	15 (3.5%)	30 (7.1%)
Dizziness	3 (0.7%)	12 (2.8%)	23 (5.4%)
Headache	8 (1.8%)	20 (4.6%)	18 (4.2%)
Impotence	5 (1.1%)	11 (2.6%)	15 (3.5%)
Somnolence	1 (0.2%)	15 (3.5%)	14 (3.3%)
Asthenia	2 (0.5%)	4 (0.9%)	13 (3.1%)
Dyspepsia	4 (0.9%)	6 (1.4%)	13 (3.1%)
Insomnia	0	7 (1.6%)	12 (2.8%)
Vomiting	0	5 (1.2%)	9 (2.1%)
Dry mouth	1 (0.2%)	9 (2.1%)	6 (1.4%)

In terms of CVS AEs, there was no evidence of hypotensive or cardiac effects with dapoxetine. Few participants in any treatment group experienced CVS AE(s) such as ECG abnormalities, palpitations, syncope, tachycardia and ventricular extrasystoles: 11 (2.5%), 8 (1.9%), and 19 (4.5%) participants in the placebo, dapoxetine 30 mg and 60 mg treatment groups respectively and most were mild-moderate in severity. At termination, a similar number of subjects in the placebo and dapoxetine treatment groups had QT/QTc >500 ms or an increase from screening by >60 ms. Scatter plots showed no trends between dapoxetine concentrations and QTc. Few participants in any treatment group reported abnormal bleeding: 2, 4 and 7 in the placebo, dapoxetine 30 and 60 mg groups respectively.

With respect to GUT AEs, impotence was reported in 6 (1.4%), 13 (3.0%) and 16 (3.8%) subjects receiving placebo, dapoxetine 30 and 60 mg treatments, respectively, and 8 subjects from dapoxetine groups discontinued due to impotence.

In terms of assessing for withdrawal syndrome, there was no difference in the number of participants from the treatment groups who reported AE(s) after the last dose or within 30 days of the last dose; 41 (9.3%), 36 (8.4%), and 37 (8.7%) in the placebo, dapoxetine 30 and 60 mg groups, respectively.

Twenty-three participants.9 (2.0%) in the placebo group, 9 (2.1%) in the dapoxetine 30 mg group, and 5 (1.2%) in the dapoxetine 60 mg group had CK increase reported as an AE. One subject was discontinued early after receiving 12 doses of dapoxetine 30 mg because of a CK increase that was assessed as severe (from 450 U/L at screening to 1087 U/L; range, 0-198 U/L).

Study C-2002-013

This pivotal efficacy study evaluated the use of dapoxetine 30 and 60 mg prn in 1320 males with PE. Patients treated with dapoxetine reported higher incidence of TEAEs (33%, 47% and 56% in the placebo, dapoxetine 30 and 60 mg groups, respectively) and treatment-related AEs (11.4%, 25.4% and 40.4%, respectively). Overall, most of the AEs were of mild-moderate in severity and most of the AEs reported in the dapoxetine groups were assessed as treatment-related. Nausea (1.2%, 8.1% and 20.4% in placebo, dapoxetine 30 mg and 60 mg groups, respectively), headache (5.3%, 6.5% and 8.5%), dizziness (0.7%, 3.1% and 7%) and diarrhoea (1.2%, 3.1% and 6.3%) appeared dose-related. Nausea, dizziness, diarrhoea, somnolence, nervousness, insomnia and anxiety also demonstrated first-dose effect. Nausea, dizziness, headache, diarrhoea, somnolence and asthenia were mostly treatment-related AEs, which occurred more frequently in the dapoxetine groups compared to the placebo group (Table 23).

Table 23: All reported AEs in $\geq 2\%$ of participants in Study C-2002-013

COSTART Term	Placebo (n=430)	Dapoxetine 30 mg (n=445)	Dapoxetine 60 mg (n=445)
Nausea	5 (1.2%)	36 (8.1%)	91 (20.4%)
Headache	23 (5.3%)	29 (6.5%)	38 (8.5%)
Dizziness	3 (0.7%)	14 (3.1%)	31 (7.0%)
Diarrhea	5 (1.2%)	14 (3.1%)	28 (6.3%)
Somnolence	1 (0.2%)	13 (2.9%)	18 (4.0%)
Impotence	7 (1.6%)	12 (2.7%)	17 (3.8%)
Asthenia	4 (0.9%)	10 (2.2%)	17 (3.8%)
Rhinitis	9 (2.1%)	14 (3.1%)	16 (3.6%)
Nervousness	0	4 (0.9%)	15 (3.4%)
Insomnia	3 (0.7%)	16 (3.6%)	14 (3.1%)
Anxiety	3 (0.7%)	5 (1.1%)	13 (2.9%)
Upper respiratory tract infection	21 (4.9%)	22 (4.9%)	13 (2.9%)
Accidental injury	4 (0.9%)	6 (1.3%)	12 (2.7%)
Dyspepsia	5 (1.2%)	12 (2.7%)	10 (2.2%)
Sinusitis	4 (0.9%)	9 (2.0%)	9 (2.0%)
Pain	11 (2.6%)	6 (1.3%)	4 (0.9%)
Pharyngitis	3 (0.7%)	11 (2.5%)	2 (0.4%)

AEs relating to mood and affect were infrequent. There was no suicidal ideation reported. One subject in the dapoxetine 30 mg group and 6 in the 60 mg group reported euphoria. In terms of accidental injury, 4 (0.9%), 6 (1.3%) and 12 (2.7%) were reported in the respective placebo, dapoxetine 30 and 60 mg groups, and none of them was assessed to be drug-related. No temporal relationship to the accidental injuries was identified that might potentially indicate impairment of participants' alertness. CVS AEs were reported infrequently. Tachycardia was reported as AE in 2, 3 and 7 subjects in placebo, dapoxetine 30 and 60 mg groups, respectively; and 1 subject from each dapoxetine group discontinued due to tachycardia. All the tachycardia AEs in the dapoxetine groups were considered drug-related. However, there was minimal objective documentation such as heart

rate and ECG when these AEs were reported. In terms of QTc changes, the maximum mean positive difference for QTcB between pre-dose and at 1-2 hours and 4-8 hours post-dose was 7.1 ms for placebo, 3.9 ms for dapoxetine 30 mg and 4.2 ms for dapoxetine 60 mg, while for QTcF, the maximum mean positive difference between pre-dose and at 1-2 hours and 4-8 hours post-dose was <5 ms in all three groups. No participant had a treatment-emergent absolute QT or QTcB or QTcF >500ms at 1-2 or 4-8h post-dose.

Impotence was reported in 7 (1.6%), 12 (2.7%) and 17 (3.8%) subjects in placebo, dapoxetine 30 and 60 mg groups respectively. Of these, 1 and 5 subjects from dapoxetine 30 and 60 mg groups respectively discontinued due to impotence. There were no obvious bleeding abnormalities noted. No withdrawal syndrome was observed.

No deaths were reported. SAEs were reported in 4 (0.9%), 1 (0.2%) and 2 (0.4%) participants in the placebo, dapoxetine 30 and 60 mg groups, respectively; all but one in the placebo group were associated with an intercurrent illness or other condition, and were assessed as not treatment related.

Early terminations due to AE(s) occurred in 1.4%, 3.1% and 10.3% of participants in the placebo, dapoxetine 30 and 60 mg groups respectively and nausea was the most common AE for early termination (0.2%, 1.3% and 4.3%, respectively).

Genotyping analysis indicated that 92.1% (1216/1320) of participants were CYP2D6 EMs and 6.6% (87/1320) were CYP2D6 PMs. Due to the small numbers of PMs, it was difficult to assess the relationship between any differences in the AEs and CYP genotype.

R096769-PRE-3001

This pivotal efficacy and safety placebo-controlled study evaluated the use of dapoxetine 30 and 60 mg prn in 1162 European subjects. AEs were reported by 38.4% (148/385), 56.2% (218/388) and 68.1% (265/389) of subjects in the placebo, dapoxetine 30 and 60 mg groups, respectively. The most common AEs reported are consistent with the GIT and CNS AEs of the SSRI class of drugs such as nausea (2.9%, 16.5% and 30.6%, respectively), headache (8.3%, 6.4% and 13.6%), dizziness (2.6%, 7.7% and 13.4%) and diarrhoea (1.6%, 3.9% and 11.3%) (Table 24). These AEs also tend to occur at higher frequency after the first dose of dapoxetine compared to placebo.

The percentage of subjects who discontinued treatment due to AE(s) was highest in the dapoxetine 60 mg group (1.3%, 3.9% and 8.2% in the placebo, dapoxetine 30 and 60 mg groups, respectively). AEs that led to most discontinuations were nausea (placebo: n= [0.3%], dapoxetine 30 mg: n=4 [1.0%] and dapoxetine 60 mg: n=10 [2.6%]). There was a low incidence of SAEs (~1%) across treatment groups, and most of these AEs were not dapoxetine-related and resolved without sequelae.

Mood, anxiety, incidence of akathisia, and sexual side effects were assessed by administration of questionnaires described under *Efficacy*. Mood-related AEs were reported by 5.7% (n=22), 9.0% (n=35) and 12.1% (n=47) of subjects in the placebo, dapoxetine 30 and 60 mg groups respectively. In particular, insomnia and anxiety were more common with dapoxetine (~7% for insomnia and ~3% for anxiety) versus placebo (~3% for insomnia, 0.5% for anxiety). AE data as well as the SIG-MA and BDI-II questionnaires showed no evidence of treatment-emergent suicidality with dapoxetine. Similarly, there was no evidence of effects of anxiety or akathisia, as measured by the HAM-A and BARS respectively. The percentage of subjects who reported an accidental injury was 1.8% (n=7), 2.8% (n=11) and 2.3% (n=9) in the placebo, dapoxetine 30 and 60 mg groups respectively. Most of them were mild-moderate in severity, did not result in study discontinuation, and not treatment-related. Dizziness was the most common AE reported under CNS and CVS AE. The rates of CNS-related AEs excluding dizziness for placebo, dapoxetine 30 and 60 mg groups were 3.9%, 12.6% and 15.4% respectively. The AEs with the highest incidence (dizziness, somnolence and fatigue) were reported by a greater proportion of subjects in the dapoxetine 30 (4-8%) and 60 mg (7-13%) groups than the placebo group (1-3%). The rates of CVS AEs (excluding

dizziness) were 3.1%, 4.9% and 8.5% for placebo, dapoxetine 30 and 60 mg groups respectively and increased BP was the most common AE, occurring at a higher incidence in dapoxetine 60 mg group (3.1%) versus placebo and dapoxetine 30 mg (0.3-0.5%). Four syncopal AEs were reported in dapoxetine 60 mg group and 1 in the placebo group. Of note, 1 subject had a syncopal episode with 28 s of sinus arrest occurring at 1h 5 min after dapoxetine 60 mg on Day 1; and he was withdrawn. Holter monitoring was also performed for 3h after the first dose in all subjects for further CVS safety evaluation. The Holter results indicated a similar incidence of abnormalities across treatment groups. There were slightly more subjects (~23-24%) in the dapoxetine 60 mg group with unifocal and multifocal supraventricular ectopy versus 20-22% in the dapoxetine 30 mg group and 19% in the placebo group. Single-beat ventricular ectopy (predominantly unifocal) was also slightly more commonly reported in subjects in the dapoxetine 30 and 60 mg groups (25.2-27.1%) versus the placebo group (21.6%). There was no evidence of deleterious effects on sexual functioning as measured by IIEF and the incidence of GUT AEs was similarly low across treatment groups, with 3.1%, 3.1% and 4.9% of subjects in the placebo, dapoxetine 30 and 60 mg groups, respectively. The incidences of abnormal bleeding were extremely low and similar across the groups.

Table 24: TEAEs reported in $\geq 2\%$ of subjects in Study R096769-PRE-3001

Dictionary-derived Term	PLACEBO (N=385) n (%)	DPX 30 MG PRN (N=388) n (%)	DPX 60 MG PRN (N=389) n (%)
Total no. subjects with adverse events	148 (38.4)	218 (56.2)	265 (68.1)
Nausea	11 (2.9)	64 (16.5)	119 (30.6)
Headache	32 (8.3)	25 (6.4)	53 (13.6)
Dizziness	10 (2.6)	30 (7.7)	52 (13.4)
Diarrhoea	6 (1.6)	15 (3.9)	44 (11.3)
Somnolence	4 (1.0)	15 (3.9)	28 (7.2)
Insomnia	12 (3.1)	10 (2.6)	27 (6.9)
Fatigue	8 (2.1)	22 (5.7)	26 (6.7)
Nasopharyngitis	13 (3.4)	21 (5.4)	24 (6.2)
Dry mouth	2 (0.5)	9 (2.3)	17 (4.4)
Influenza	10 (2.6)	18 (4.6)	16 (4.1)
Anxiety	2 (0.5)	11 (2.8)	12 (3.1)
Blood pressure increased	1 (0.3)	2 (0.5)	12 (3.1)
Erectile dysfunction	8 (2.1)	8 (2.1)	12 (3.1)
Vomiting	2 (0.5)	5 (1.3)	12 (3.1)
Dyspepsia	5 (1.3)	6 (1.5)	10 (2.6)
Hyperhidrosis	2 (0.5)	7 (1.8)	10 (2.6)
Abdominal pain	1 (0.3)	3 (0.8)	9 (2.3)
Asthenia	1 (0.3)	9 (2.3)	4 (1.0)
Back pain	6 (1.6)	8 (2.1)	4 (1.0)

Discontinuation of dapoxetine treatment did not cause SSRI withdrawal syndrome. During the WA period, subjects who were switched to placebo after receiving dapoxetine 30 or 60 mg for 24 weeks reported a slightly higher incidence of headache (~4.0%) compared with subjects who received dapoxetine continuously for 25 weeks [1-2%]. There was also a slightly higher incidence of erectile

dysfunction (2.0%) as well as dizziness (2.2%) and vomiting (2.2%) when switched to placebo compared to continuous dapoxetine (0% for all events).

Study R096769-PRE-3003

This randomised, placebo-controlled study evaluated the efficacy and safety of dapoxetine 30 and 60 mg prn in 1067 men with PE from Asian-Pacific regions over 12 weeks.

AEs were reported by 17.9% (64/357), 33.3% (118/354), and 49.7% (177/356) of subjects in the placebo, dapoxetine 30 and 60 mg groups, respectively. The most common AEs were nausea, dizziness, somnolence, headache, vomiting, diarrhoea; all consistent with GIT and CNS effects of the SSRI class of medications. Compared with the dapoxetine 30 mg dose, 60 mg was associated with a higher incidence of nausea (60 mg versus 30 mg: 26.4% versus 10.5%), dizziness (18.8% versus 10.5%), somnolence (6.2% versus 3.4%), and headache (4.8% versus 3.4%) (Table 25). The percentage of subjects who reported AEs after the first dose was higher in the dapoxetine groups (30 mg: 9.0%, 60 mg: 18.0%), than the placebo group (5.0%); nausea, dizziness, and somnolence being the most frequent first-dose AEs.

Table 25: TEAEs in $\geq 1\%$ of subjects in Study R096769-PRE-3003

	PLACEBO (N=357)	DPX 30 MG PRN (N=354)	DPX 60 MG PRN (N=356)
Preferred Term	n (%)	n (%)	n (%)
Total no. Subjects With Adverse Events*	64 (17.9)	118 (33.3)	177 (49.7)
Nausea	7 (2.0)	37 (10.5)	94 (26.4)
Dizziness	14 (3.9)	37 (10.5)	67 (18.8)
Somnolence	2 (0.6)	12 (3.4)	22 (6.2)
Headache	7 (2.0)	12 (3.4)	17 (4.8)
Vomiting	0	1 (0.3)	9 (2.5)
Diarrhoea	3 (0.8)	7 (2.0)	6 (1.7)
Flushing	1 (0.3)	2 (0.6)	4 (1.1)
Palpitations	1 (0.3)	0	4 (1.1)
Upper respiratory tract infection	5 (1.4)	3 (0.8)	4 (1.1)
Nasopharyngitis	3 (0.8)	7 (2.0)	1 (0.3)

Note: Percentages calculated with the number of subjects in each group as denominator. Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.

* Subject 010305 (in the dapoxetine 30 mg group) had a non-serious, mild adverse event of aching legs (preferred term: pain in extremity) prior to and on the same day of the first dose. Since the onset time was unknown, the event was considered as a treatment-emergent adverse event.

A low percentage of subjects discontinued due to AE(s) (dapoxetine 60 mg: n=18 [5.1%], 30 mg: n=6 [1.7%] and placebo: n=1 [0.3%]). Nausea and dizziness were the most frequent AEs resulting in early discontinuation from the dapoxetine 60 mg group (9 and 6 subjects, respectively), while two subjects discontinued early in the dapoxetine 30 mg group because of dizziness. No subject in the placebo group discontinued early due to nausea or dizziness.

SAEs were uncommon (3 subjects each in placebo and dapoxetine 30 mg groups) and all were judged to be non-treatment related. One 45-year-old Korean subject without a history of depression from the dapoxetine 30 mg group died due to accidental drowning that involved alcohol consumption. The death occurred 12 days after the last dose and was not considered to be drug-related. He had taken 19 doses of study drug during the course of the study.

The incidence of CNS AEs was 5.0%, 13.8% and 24.2% in the placebo, dapoxetine 30 and 60 mg groups, respectively. Dose-related effects were observed with some CNS AEs, namely dizziness (60 mg versus 30 mg: 18.8% versus 10.5%) and somnolence (6.2% versus 3.4%). The frequency of

dizziness and somnolence in this study was higher than that seen in other Phase III studies possibly due to higher drug exposure due to lower body weights in this population, cultural factors and greater sensitivity to mild neurocognitive changes. There were no reports of suicidal ideation or suicide. The overall incidence of mood-related AEs was very low. The incidence of accidental injury AEs was low; 1, 2 and 1 subjects in the placebo, dapoxetine 30 and 60 mg groups respectively.

The incidence of CVS AEs also appeared to be dose-related: 72 (20.2%), 40 (11.3%) 17 (4.8%) subjects in the dapoxetine 60 and 30 mg, and placebo groups, respectively. The most common CVS AE was dizziness (18.8%, 10.5%, and 3.9%, respectively), although some of the dizziness might not be of cardiac origin. No subjects reported syncope in this study. However, a higher percentage of subjects in the dapoxetine 60 mg group (14.3%) than in the dapoxetine 30 mg (5.6%) and placebo group (2.0%) reported possible prodromal symptoms for syncope after the first dose. The most frequent possible prodromal symptoms were nausea (8.4%, 3.4% and 0.6% in the 60 mg, 30 mg and placebo groups, respectively) and dizziness (7.9%, 2.8% and 1.4%, respectively). Evaluation of Holter data indicated an absence of clinically important effects of dapoxetine on cardiac rhythm. Two cases of non-sustained VT were detected during Holter monitoring in subjects who received placebo and one in a subject who received dapoxetine 30 mg; no VT was recorded in subjects taking dapoxetine 60 mg. Except for a slightly higher incidence of multifocal supraventricular ectopy in the dapoxetine groups (19% in each dose group versus 14.6% in the placebo group), the incidences of other subtypes of supraventricular and ventricular ectopy were similar across the groups in this study. There were no significant abnormal bleeding events.

Thirteen subjects had GUT AEs with a slightly greater percentage of subjects from the dapoxetine groups (60 mg: n=7 (2.0%), 30 mg: n=4 (1.1%)) versus the placebo group (n=2, 0.6%). No treatment-emergent effects on the domains of erectile function, orgasmic function or libido were observed based on IIEF.

One subject in the dapoxetine 30 mg group, discontinued on Day 46 due to possibly drug-related elevation in ALT (from baseline of 32U/L to 180U/L on Day 29) and AST (from baseline 33U/L to 141U/L on Day 29), which normalised spontaneously about 1 month later.

Safety results from other Phase III studies

Study R96769-PRE-3002- Withdrawal effects

This was a placebo-controlled, double-blind, randomised parallel-group study conducted in men with PE in USA and Canada. The primary objective was to assess the possible withdrawal effects as measured by the Discontinuation Emergent Signs and Symptoms (DESS) checklist after abrupt cessation of chronic administration of dapoxetine 60 mg. The study consisted of a screening visit and 7-day baseline period, a 69-day double-blind treatment Phase (62 days of double-blind treatment followed by a second randomisation on Day 63 to the same treatment or placebo for 7 days) with an end of treatment visit on Day 70 or at the time of early termination, a follow-up visit 7 days after study discontinuation, and a post-study telephone contact (~14 days after discontinuation to assess new and existing AEs). The total duration was 91 days (13 weeks).

In addition to usual safety assessment using AE reporting, laboratory, vital signs and physical findings, mood, anxiety, incidence of akathisia and sexual side effects were assessed using the M.I.N.I., BDI-II, MADRS, HAM-A, BARS and IIEF.^{31,32,33,34,35,36} Holter monitoring was

³¹ M.I.N.I. - Mini International Neuropsychiatric Interview

³² Beck Depression Inventory (BDI, self-reported) - assesses depressive symptomatology in psychiatrically diagnosed subjects and in normal populations of adolescents and adults.

³³ Montgomery-Asberg Depression Rating Scale (MADRS, observer rated) - a 10-item scale to measure depression, with each item being rated on a scale of 0 to 6. It covers the core symptoms of depression with the exception of motor retardation.

performed at 30 min prior to first dose until 3 hours post-dose. The primary objective, which is the incidence of discontinuation syndrome as measured by DESS, was analysed by means of logistic regression. Withdrawal effects as measured by DESS were rare, regardless of treatment sequence. Overall, 8 subjects had discontinuation syndrome during the WA period: 2 (1.3%), 1 (0.6%), 1 (0.7%), 2 (1.4%) and 2 (1.3%), in the dapoxetine 60 mg once daily/placebo, dapoxetine 60 mg once daily/once daily, dapoxetine 60 mg prn/placebo, dapoxetine 60 mg prn/prn, and placebo/placebo treatment sequences, respectively. The mean scores and mean changes from baseline in DESS scores were similar in all treatment sequences. Changes from baseline in DESS scores were similar in magnitude in subjects who received either dapoxetine treatment (once daily or prn) continuously for 69 days and in subjects who were switched to placebo after receiving dapoxetine (once daily or prn). Thus, there is no evidence of withdrawal effects (based on DESS) when dapoxetine treatment (once daily or prn) is abruptly discontinued.

Consistent with the lack of withdrawal effects based on DESS, AE data generally showed little indication of withdrawal symptoms with dapoxetine treatment. However, the slightly higher incidence of mild or moderate insomnia and dizziness (6.1% and 4.8%) in subjects in the dapoxetine 60 mg once daily/placebo sequence compared to dapoxetine 60 mg once daily/once daily (2.4% and 1.2%) suggests that the occurrence of generally mild withdrawal symptoms following discontinuation of daily dosing of dapoxetine cannot be excluded.

In terms of AE reporting, AEs were reported by 44.1% (n=108), 61.3% (n=301) and 62.5% (n=314) of subjects in the placebo, dapoxetine 60 mg prn and dapoxetine 60 mg once daily groups during the treatment period and by 16.8% (28/167), 13.1% (20/153), 18.8% (30/160), 23.6% (39/165) and 26.5% (44/166) of subjects in the placebo/placebo, dapoxetine 60 mg prn/placebo, dapoxetine 60 mg prn/prn, dapoxetine 60 mg once daily/placebo, and dapoxetine 60 mg once daily/once daily treatment sequence during the WA period (Table 26). During the treatment period, the most common AEs were nausea, dizziness, headache, diarrhoea, fatigue and insomnia. Most AEs were mild or moderate in severity, and reported more frequently in the dapoxetine groups than the placebo group. Common AEs during the WA period included diarrhoea, headache, insomnia, nausea, irritability and dizziness. The type and frequency of treatment-emergent and early discontinuation AEs observed for dapoxetine were similar to those reported for dapoxetine in previous Phase III studies.

³⁴ Hamilton Anxiety Scale (HAM-A) (observer-rated) - clinical interview assessment tool for anxiety that includes 14 items that assess anxious mood, tension, fears, insomnia, intellectual functioning, depressed mood, somatic symptoms, and behaviour. Higher scores represent higher levels of anxiety.

³⁵ Barnes Akathisia Rating Scale (BARS, observer-rated) - an instrument to assess akathisia. The instrument includes 4 items that address observed motor movements, subject awareness of restlessness, subject distress related to restlessness, and a global clinical assessment.

³⁶ International Index of Erectile Function Questionnaire (IIEF, self-reported) - a 15-item instrument to assess severity of ED in men.

Table 26: TEAEs in $\geq 2\%$ of subjects in Study R96769-PRE-3002

	PLACEBO	DPX 60 MG PRN	DPX 60 MG QD
	(N=245)	(N=491)	(N=502)
Preferred Term	n (%)	n (%)	n (%)
Total no. subjects with adverse Events	108 (44.1)	301 (61.3)	314 (62.5)
Nausea	4 (1.6)	75 (15.3)	78 (15.5)
Dizziness	7 (2.9)	50 (10.2)	59 (11.8)
Headache	15 (6.1)	40 (8.1)	42 (8.4)
Diarrhoea	5 (2.0)	30 (6.1)	40 (8.0)
Fatigue	7 (2.9)	22 (4.5)	37 (7.4)
Insomnia	9 (3.7)	32 (6.5)	31 (6.2)
Orthostatic hypotension ^a	8 (3.3)	22 (4.5)	24 (4.8)
Somnolence	2 (0.8)	18 (3.7)	16 (3.2)
Nasopharyngitis	7 (2.9)	6 (1.2)	14 (2.8)
Dry mouth	7 (2.9)	20 (4.1)	13 (2.6)
Disturbance in attention	2 (0.8)	7 (1.4)	11 (2.2)
Blood pressure orthostatic ^b	7 (2.9)	10 (2.0)	9 (1.8)
Influenza	2 (0.8)	13 (2.6)	8 (1.6)
Irritability	4 (1.6)	11 (2.2)	8 (1.6)
Upper respiratory tract infection	9 (3.7)	14 (2.9)	8 (1.6)
Anxiety	4 (1.6)	12 (2.4)	7 (1.4)
Erectile dysfunction	6 (2.4)	4 (0.8)	6 (1.2)
Flushing	0	10 (2.0)	4 (0.8)

Note: Percentages calculated with the number of subjects in each group as denominator.

Incidence is based on the number of subjects experiencing at least 1 adverse event, not the number of events.

^a Includes the following verbatim terms that coded to the MedDRA SOC, "Vascular Disorders": orthostatic hypotension, orthostatic hypotensive event, orthostadichypotension, orthostatic hypotensive, asymptomatic orthostatic hypotension, and orthostatic blood pressure drop.

^b Includes the following verbatim terms that coded to the MedDRA SOC, "Investigations": orthostatic event, asymptomatic orthostasis, orthostatic blood pressure changes, and asymptomatic orthostatic event.

There was no difference in the frequency of AEs reported between the dapoxetine once daily and prn groups, indicating that dapoxetine when dosed either once daily or prn has a similar safety profile. There were no deaths reported and a low incidence of SAEs (placebo: n=1; dapoxetine 60 mg prn n=2; dapoxetine 60 mg once daily: n=7). A total of 9.6% of subjects in each dapoxetine group (prn: n=47, once daily: n=48) and 2.0% (n=5) of placebo-treated subjects discontinued due to AE(s). Nausea and dizziness were the most frequent AEs resulting in early discontinuation in the dapoxetine 60 mg prn and once daily groups.

In terms of mood-related AEs, no pattern of treatment-emergent suicidality with dapoxetine was seen. One subject in the dapoxetine 60 mg prn/placebo group reported suicidal ideation that was accompanied by a moderate stress reaction to a psychosocial event that began on Day 31 and resolved on Day 76. One subject in the dapoxetine 60 mg once daily group reported suicidal dreams on Day 39. The subject decided to discontinue on Day 40 and did not enter the WA period. He reported no further suicidal dreams after study discontinuation. Consistent with the AE data, scores on the suicidality item of the BDI-II and MADRS questionnaires also showed no evidence of treatment-emergent suicidal ideation associated with dapoxetine treatment. An external assessment

of blinded narratives using the method characterized at Columbia University for evaluation of suicidality narratives showed that the rates of possibly suicide-related AEs were similar across the groups (2.4-3.2%) and did not suggest a clear safety signal for dapoxetine and suicidality.

Four (1.6%) subjects in the placebo group reported AEs that were considered due to accidental injury compared with 11 (2.2%) subjects in the dapoxetine prn group, and 10 (2.0%) subjects in the dapoxetine once daily group, while 2 (1.2%) subjects in the dapoxetine 60 mg once daily/placebo treatment sequence, 3 (1.8%) subjects in the dapoxetine 60 mg once daily/once daily treatment sequence, and no subjects who received placebo or dapoxetine 60 mg prn during the WA period. AE data and scores on the HAM-A and BARS questionnaires showed no evidence of treatment-emergent anxiety or akathisia with dapoxetine.

In terms of CVS AEs, dizziness was the most common AE and occurred more frequently with dapoxetine compared to placebo during treatment period [dapoxetine prn: n=50/491 (10.2%), dapoxetine once daily: n=59/502 (11.8%), placebo: n=7/245 (2.9%)] and WA period (placebo/placebo: n=1/167 (0.6%), dapoxetine 60 mg prn/placebo: n=2/153 (1.3%), dapoxetine 60 mg prn/prn: n=4/160 (2.5%), dapoxetine 60 mg once daily/placebo: n=8/165 (4.8%), dapoxetine 60 mg once daily/once daily: n=2/166 (1.2%)). Five subjects reported syncope or vasovagal episodes during the study. Of these, 3 experienced loss of consciousness varying from 15 sec to 1 min, meeting the protocol-specified definition of syncope. The other two subjects did not lose consciousness. All cases of syncope resolved spontaneously with no further reports of syncope in 2/5 subjects who continued the study. Two subjects with syncope had sinus arrest 5.0-5.2 seconds after taking the first dose of dapoxetine 60 mg. Another two subjects had a pause of 1.06-1.47 seconds. The fifth subject had supraventricular tachycardia. In addition, in another subject who reported orthostatic hypotension, a 2.3 s sinus pause was noted on the first day. All these abnormalities occurred within 40-60 min post-first dose. Holter monitoring performed on the first dose day to assess CVS safety showed a slightly higher percentage of abnormalities in the dapoxetine group (598/991, 60.3%) than in the placebo group (134/245, 54.7%). The most frequent abnormalities were supraventricular arrhythmias (placebo: n=102/245, 41.6%, dapoxetine: n=485/991, 48.9%) and ventricular arrhythmias (placebo: n=63/245 (25.7%), dapoxetine: n=256/991 (25.8%)). The supraventricular arrhythmias were mainly uni- and multifocal, while the ventricular arrhythmias were mainly single-beat and unifocal. Three cases of VT were detected during Holter monitoring, all in the dapoxetine group. All cases were asymptomatic and non-sustained (<30 sec), and were not reported as AEs by the investigator. The morphology of the QRS complexes during these episodes of VT suggested an autonomic mechanism, and that these episodes of VT were thus unlikely to be related to treatment with dapoxetine. There was a slightly higher percentage of subjects with JNC-7³⁷ defined orthostatic hypotension in the dapoxetine-treated group than the placebo group (placebo n=19/245 (7.8%), dapoxetine: n=117/988 (11.8%)). The incidence of change from baseline in QTcF of 30-60ms and QTcF >60ms was similar in all groups (~4.0-4.2% for Δ QTcF 30-60ms and 0-0.5% for Δ QTcF 60ms).

In terms of GUT AEs, there was no evidence of a treatment-emergent effect on sexual functioning/erectile dysfunction based on IIEF questionnaire scores and AE data.

Study C-2002-014- Long term safety of dapoxetine

This is an extension study of pivotal, 12-week Phase III studies C-2002-012 and C-2002-13 involving 1774 subjects up to 9 months. Subjects previously randomised to placebo and dapoxetine 30 mg prn in the above studies were administered dapoxetine 60 mg prn in this open-labelled study. AE(s) were reported by 56.7% (1006/1774) participants with an onset in this study: 58.5%

³⁷ Orthostatic hypotension was considered to be present if there was a supine to standing SBP decrease of >20mmHg or DBP decrease >10mmHg.

(360/615) whose prior treatment was placebo, 55.7% (338/607) whose prior treatment was dapoxetine 30 mg, and 55.8% (308/552) whose prior treatment was dapoxetine 60 mg. Similar to the Phase III controlled studies, most AEs were of mild-moderate severity; AEs were severe in 79 (4.5%) participants; and this did not appear to be affected by prior treatment in the controlled studies (placebo: 4.4%, dapoxetine 30 mg: 4.0% and dapoxetine 60 mg: 5.1%). Nausea (n=273, 15.4%), diarrhoea (n=98, 5.5%), upper respiratory tract infection (URTI) (n=97, 5.5%), dizziness (n=92, 5.2%), headache (n=86, 4.8%) and accidental injury (n=86, 4.8%) were the most common AEs reported, and, except for accidental injury and URTI, they were generally considered possibly or probably drug-related. The type and rate of AEs were consistent with those seen in C-2002-012 and C-2002-013. The percentage of participants who reported AE(s) with an onset in this study and the percentage reporting the most common AEs with an onset in this study tended to be highest in participants who were previously assigned to placebo in C-2002-012 and C-2002-013 studies, and lowest in those continuing on dapoxetine 60 mg. Based on AEs with onset in this study and ongoing AEs from the controlled studies, the incidence of specific AEs was similar for all three prior treatment groups. The most common AEs reported and the proportion of participants reporting these AEs were consistent across the other analyses: participants who reported a specific AE in this study but not in the previous Phase III study; participants who reported a specific AE in the previous studies but not in this study; and AEs reported by participants in the previous studies and in this study. Participants previously assigned placebo tended to report the common AEs associated with dapoxetine for the first time in this study, while participants continuing on dapoxetine 60 mg tended to have more of these specific AEs ongoing from the prior study and tended not to report them as new onsets in this study.

No deaths were reported. Twenty-five (1.4%) participants experienced SAEs; mainly (22/25) associated with an intercurrent illness, pre-existing condition or accident, and assessed as not drug-related. Four SAEs were reported by 3 participants that were not reported in the controlled studies: 1 case of seizure in a participant without history of seizures and occurred 4 days after the last dose, 1 case of cardiomyopathy and SVT in a participant with extensive pre-existing congenital heart disease and occurred 35 days after the last dose, and 1 case of stroke in a participant with significant risk factors. Three (0.2%) participants had SAEs that were considered possibly or probably treatment-related (the subject with seizure and another two with syncope).

A total of 119 (6.7%) participants discontinued early due to AE(s). Nausea was the most common AE for early termination, cited by 29 (1.6%) participants.

In terms of CNS AEs, no suicidal ideation or attempts were reported during this study. The number of participants who reported new onset of depression or euphoria in this study was small and the narratives were brief, making it difficult to draw any conclusion about the role dapoxetine has on mood and affect. Ten participants reported depression: 3 with prior placebo treatment, 2 with prior dapoxetine 30 mg treatment, and 5 with prior dapoxetine 60 mg treatment. Nine of them had no prior history of depression. Seven of the depression AEs were considered by the investigator to be not drug-related, 2 were possibly drug-related and 1 was probably drug-related. One of the depression AEs resulted in early termination. Five of the subjects required drug treatment for depression. Seven participants reported euphoria AEs which were all considered to be possibly or probably drug-related, 3 of them reported an onset in previous study C-2002-013 while 4 participants reported new onset euphoria in study C-2002-014: 2 with prior placebo treatment and 2 with prior dapoxetine 60 mg treatment, and 2 of them had a dose reduction because of the euphoria. None of the subjects discontinued due to euphoria and the duration of AEs varied from 32 to 205 days. A 38-year-old Caucasian male with a prior history of depression and bipolar disorder diagnosed in 1996, experienced psychosis and anxiety on Day 30. He was previously enrolled in the placebo group in study C-2002-012. The AE started while on dapoxetine 60 mg, were moderate in severity, and resolved with residual effects after 14 days. The subject was withdrawn early from the study. The participant was commenced on oral olanzapine and sertraline to treat the AE, starting on

the day of its onset. While in study C-2002-014, the participant was dispensed 30 doses of dapoxetine 60 mg, of which 17 doses were returned over 43 days. The investigator considered the AE not to be treatment-related.

Eighty-six participants (4.8%) reported accidental injury; 80 (4.5%) at dapoxetine 60 mg and 6 (3.1%) after a dose reduction to 30 mg. The accidental injury was judged as not drug-related for 85/86 participants. One participant had an accidental injury (mild abrasions on forehead) subsequent to a syncope, which was assessed as a possibly drug-related SAE. Five cases were observed to have a temporal relationship to the accidental injuries potentially indicating an impairment of the participants' alertness.

Only 1.8% (n=32) experienced CVS AEs of special interest. Two participants had the dapoxetine dose reduced from 60 to 30 mg because of irregular heart beat and palpitations. No significant abnormal bleedings were observed.

In terms of GUT AEs, 1.4% (n=24) and 0.8% (n=15) experienced impotence and abnormal ejaculation, with similar distribution across prior assigned treatment groups.

The AEs (type and percentages) were similar between the 1648 CYP2D6 EMs and 118 CYP2D6 PMs.

No clinically relevant mean changes were observed between baseline and termination for laboratory tests, vital signs, ECGs or physical examination findings. Twenty-four participants (1.4%) had CK increase reported as an AE, with similar distribution across groups based on prior treatment assignment. Participants with CK>5x or >10x ULN were asymptomatic and had no significant renal impairment. Over the course of all dapoxetine exposure (starting from prior controlled studies), there was no difference in SBP and DBP as well as heart rate for the three prior treatment groups (trend analysis). There was also no indication of a dapoxetine treatment effect in the shift analyses of SBP, DBP or heart rate results for all participants who entered the study.

Hence, no new safety concerns attributed to longer-term use of dapoxetine prn were observed in this study.

Syncope

In light of the increased incidence of syncope in the dapoxetine group versus placebo group (0.25% versus 0.04%), the sponsor investigated this further by performing:

1. three ECG studies which evaluated the effect of dapoxetine on QT interval which have been discussed previously
2. orthostatic profiles in subjects exposed to dapoxetine which have also been discussed previously
3. Holter monitor studies in 3353 subjects in Phase III studies for the first 3 hours in studies R96769-PRE-3001, R96769-PRE-3002 and R96769-PRE-3003 which evaluated the incidence of ventricular and supraventricular ectopics and runs, as well as AV blocks. There was an increased incidence of ventricular and supraventricular single ectopic beats, however, these were generally considered as clinically benign. The incidence of ventricular tachycardia was similar between placebo and dapoxetine treatment groups.

Analyses of syncope in the dapoxetine clinical program revealed several factors associated with syncope following dapoxetine dosing:

- a) location of the subject at the time of the event,
- b) first versus subsequent exposure to dapoxetine,
- c) temporal relationship to dosing, and
- d) dose level (30 versus 60 mg).

The majority of cases occurred in the study centre (onsite) versus in the home environment (offsite). In the dapoxetine group, 11 cases of adjudicated syncope occurred at the study site, while 4 cases occurred offsite, despite the fact that the majority of dapoxetine doses were taken offsite (e.g., at home). Of the 37 cases of interest, there was no recurrence of events observed in 25 subjects who continued in the dapoxetine program. The number and percentage of subjects with adjudicated syncope is greater with the first dose (0.19%) compared to subjects with a subsequent dose (0.08%). When syncope incidence was adjusted for the number of doses taken, the number and percentage of subjects with adjudicated syncope following the first dose (1.917 per 1000 doses) was substantially greater than that observed for each subsequent dose (0.017 per 1000 doses). The percentage of subjects with adjudicated syncope occurring with the first dose in the onsite setting is greater than that occurring with subsequent doses administered onsite (0.28% versus 0.18%, respectively). However, the percentage of subjects with adjudicated syncope occurring with the first dose in the offsite setting is similar to the offsite subsequent dose incidence (0.05% versus 0.06%, respectively). Many of the episodes of syncope occurred within the first 3 hours after the first dose of dapoxetine correlating with T_{max} and activities such as orthostatic manoeuvres and venepuncture around the time of T_{max} may have contributed to many of the cases. The incidence of syncope observed with the 30 mg dose level was lower than that observed with the 60 mg dose level.

Accidental injury

The incidence rates of accidental injury in the five Phase III studies combined were 1.8%, 2.7%, 2.2% and 3.0% for placebo, dapoxetine 30 mg prn, dapoxetine 60 mg prn and dapoxetine 60 mg daily treatment groups, respectively. None of the accidental injury AEs were associated with suicidality. In the extension study C-2002-014, the incidence rates of accidental injury-related AEs were 4.2%, 5.8% and 6.7% in subjects whose prior treatment was placebo, dapoxetine 30 and 60 mg, respectively. The occurrence of neurocognitive-related AEs may also put patients at risk for accidental injury. An analysis of the association between neurocognitive-related AEs and accidental injury-related AEs showed no indication of an association. Two placebo-treated subjects and 20 dapoxetine-treated subjects reported both accidental injury AEs and neurocognitive-related AEs during the seven Phase II and III placebo-controlled studies. The occurrence of accidental injury AEs was not significantly associated with that of the neurocognitive-related AEs in either the placebo ($p \geq 0.650$) or the dapoxetine ($p = 0.697$) treatment groups. In the dapoxetine treatment groups, based on Fisher's two-sided exact test, the probability of having 20 subjects with both an accidental injury AE and a neurocognitive-related AE was 0.697, indicating that there was a large probability to observe this number due to random chance given that the observed total numbers of 755 (out of 4538) subjects and 110 (out of 4538) subjects who reported neurocognitive-related AEs and accidental injury AEs respectively.

Depression, euphoria and suicidality

Combined safety analysis of the mood-related AEs in the five Phase III studies revealed that there was no clear increase in the incidence of depression based on AEs with terms such as "depression", "depressed mood" and "major depression" in dapoxetine-treated subjects versus placebo. The incidence rates of "depression" were 0.3% (6/1857) in the placebo group versus 0.4% (17/4224) in combined dapoxetine group (0.2% (3/1616) in dapoxetine 30 mg prn group, 0.5% (10/2106) in dapoxetine 60 mg prn group, 0.8% (4/502) in dapoxetine 60 mg once daily group. The incidence rates of "depressed mood" were 0.3% (5/1857) in the placebo group versus 0.4% (16/4224) in the combined dapoxetine group (0.2% (4/2106) in the dapoxetine 30 mg prn group, 0.5% (10/2106) in the dapoxetine 60 mg prn group and 0.4% (2/502) in the dapoxetine 60 mg once daily group. The incidence rates of "major depression" were 0% in the placebo group versus 1/4224 ($<0.1\%$) in the combined dapoxetine group (0 in the dapoxetine 30 mg prn and 60 mg once daily groups, 1/2106 in the dapoxetine 60 mg prn group). In terms of euphoria, combined safety analysis of the Phase III studies revealed that the incidence rates were 0% for placebo group versus 0.4% (17/4224) in the

combined dapoxetine group (0.2% (3/1616) in the dapoxetine 30 mg prn group, 0.5% (11/2106) in the dapoxetine 60 mg prn group and 0.6% (3/502) in the dapoxetine 60 mg once daily group. From the review of brief narratives of the small number of individual cases in the uncontrolled long-term study C-2002-014, there appears to be a temporal relationship in the incidence of depression and euphoria in subjects with no prior history of depression or euphoria, however many cases were not considered to be drug-related by the investigators. The incidence rates of depression and euphoria in C-2002-014 were 0.56% (10/1774) and 0.4% (7/1774).

R096769-PRE-3001 and R096769-PRE-3003 included a prospective assessment to investigate concerns related to the risk of drug-associated suicidality, the suicidality items from two validated questionnaires, MADRS and BDI-II. Overall, the scores on the suicidality item of the BDI-II and MADRS questionnaires showed no pattern of treatment-emergent suicidality or other psychiatric symptoms with dapoxetine. An external assessment of blinded narratives using the method characterized at Columbia University for evaluation of suicidality narratives showed that the rates of possibly suicide-related AEs were similar across the groups and did not suggest a clear safety signal for dapoxetine and suicidality. No suicide attempts or ideation was reported in C-2002-014

Overdose and potential for abuse

No AEs of overdoses were reported. Subjects were advised not to take more than 1 dapoxetine dose during a 24-hour period. No other information on overdose is available. Instructions for the management of overdose are provided in the proposed product label.

No pattern of misuse or overdose of dapoxetine was observed in the clinical studies.

Summary of safety

Phase I studies

- More subjects reported AEs during dapoxetine versus placebo treatment. Most AEs were mild to moderate in severity, and considered to be possibly or probably related to dapoxetine. The AEs attributed to dapoxetine were mostly related to gastrointestinal (GIT) and central nervous systems (CNS). A dose effect was seen. Nausea was the most common AE (affecting ~20-40% of subjects). The most frequently reported AEs in a dapoxetine treatment period during a Phase I study across all doses were nausea (36.7%), diarrhoea (20.1%), dizziness (18.3%), and headache (14.7%); incidences (% of subjects) of these AEs during a placebo treatment period were 2.8%, 0.7%, 1.4%, and 5.5%, respectively.
- In multiple-dosing, the percentage of subjects reporting AEs was highest during the initial days of treatment. No SAEs related to dapoxetine and deaths were reported in all Phase I studies. Only a few subjects withdrew due to AEs. Occasional CK and transaminases rises were noted in Phase I studies.
- Special attention was also given to BP effect and QTc interval in view of the increased incidence of dizziness, occasional report of increased BP, and rarely, syncope in Phase III studies. C-2001-004 showed slightly higher SBP and DBP values up to 13mmHg during single-dosing of dapoxetine 60-160 mg and multiple-dosing of dapoxetine 80-120 mg, but the increases were intermittent and not dose-related. C-2001-007 assessed the BP effect of dapoxetine 100mg in stable treated hypertensive subjects who exercised on treadmill up to the end of Stage II Bruce protocol, and the results showed that dapoxetine had no statistically or clinically significant effect on BP or heart rate relative to placebo. ECG studies [C-2002-043 and C-2002-021] did not show any trend of QTc interval prolongation associated with dapoxetine treatment.
- Although co-administration of dapoxetine with warfarin led to a slight increase (~5-10%) in AUC of R- and S-warfarin enantiomers and slight increase (~5%) in effect on PT and INR,

these changes were unlikely to be clinically significant as demonstrated by lack of increased bleeding events. Co-administration of midazolam with dapoxetine reduces the exposure to midazolam by ~20%, but the AE incidence in subjects treated with midazolam alone, dapoxetine alone and dapoxetine; + midazolam were similar (~70-80%); the most common AE for dapoxetine was nausea and for midazolam was somnolence.

- The increase in dapoxetine exposure when co-administered with a CYP3A4 inhibitor such as ketoconazole (AUC increased by 99%) was also associated with an increased incidence of AE reporting during ketoconazole + dapoxetine treatment versus dapoxetine alone. Despite the higher C_{max} (by 50%) and AUC_{∞} (by 88%) during co-administration of a CYP 2D6 inhibitor such fluoxetine with dapoxetine, there was no increased incidence of AEs.
- Co-administration of dapoxetine with omeprazole (CYP2C19 substrate) and glyburide (CYP2C9 substrate) was not associated with new or increased incidence in AEs. There was minor additive impairment when ethanol was co-administered with dapoxetine, especially noted in the Digit Vigilance Speed and Digit Symbol Substitution Test, but no new AEs were reported. Co-administration with desipramine did not appear to affect the safety profile of dapoxetine. Co-administration of dapoxetine with PDE inhibitors such as sildenafil and tadalafil did not reveal any additive AEs. Tamsulosin did not have any significant effect on orthostatic profile, although more subjects reported dizziness during co-treatment with dapoxetine compared with tamsulosin + placebo.
- No specific safety concerns were noted in elderly subjects. Although there were small increases in exposure in CYP2D6 PMs, PMs had a similar QTc interval to EMs and overall the QTc effects after dapoxetine were similar to those after placebo treatment. The safety profile of dapoxetine was similar in CYP2D6 PM and EM. Safety profile in Japanese versus Caucasian subjects was similar despite a modest increase in exposure to dapoxetine (~10-20%) in the Japanese, which was likely related to lower body weight of Japanese compared to Caucasian subjects. The incidence of AEs was significantly higher in dapoxetine-treated patients with severe renal and hepatic impairment and it should be avoided in these conditions.

Phase II & III studies

- Over 40% of subjects taking dapoxetine 30-60 mg tablets prn reported AEs compared to placebo (13-38%). Most were mild to moderate in severity and usually treatment-related. SAEs were uncommon ~1%.
- Nausea was the most common AE which was treatment-related (~10-30%), and its incidence increased with increasing dose of dapoxetine. Nausea was the most common AE leading to discontinuation. Other GIT AEs included vomiting and diarrhoea. Dizziness and headache were the common CNS AEs. They were usually considered to be treatment-related and also had a dose effect.
- No increase suicidal ideation was seen. Few (<1%) reported new onset of depression or euphoria. It is noteworthy that subjects with a history of depression were excluded in the studies. In Phase III studies, mood-related AEs were seen in 3.6% (66/1857) placebo subjects and 9.1% (383/4224) for all dapoxetine subjects (30 and 60 mg); the most common being insomnia, anxiety and irritability. There was no trend to increase accidental injuries and no definite temporal relationship could be seen in most of the accidental injuries reported.
- Syncope occurred infrequently but after a sinus arrest of 28 s after first dose of dapoxetine 60 mg in a subject in Study R096769-PRE-3001, a warning was issued to exclude subjects with a history of cardiogenic syncope.

- No significant sexual dysfunction was observed. Although higher GUT AEs were reported in all dapoxetine groups 3.9% (166/4224) versus 1.8% (34/1857) placebo group in Phase III studies (the most common being erectile dysfunction and reduced libido), IIEF results did not confirm this.
- No abnormal bleeding was seen and there were no clinically relevant changes in laboratory parameters.
- No withdrawal effect was seen based on DESS. However, there was a ~3% higher incidence of dizziness and insomnia in subjects who ceased dapoxetine 60 mg abruptly in study R096769-PRE-3002.
- No new safety concerns were seen with longer-term use of dapoxetine up to 12 months.

Clinical Summary and Conclusions

- Dapoxetine is a short-acting drug which is readily absorbed and metabolized, hence suitable for use on an “as required” basis for treatment of premature ejaculation. It has dose-proportional pharmacokinetics. Its metabolism is inhibited by CYP3A4 and CYP2D6, but there is minimal interaction between dapoxetine and drugs which are metabolized by various CYP450 isoforms. There is minimal food effect. There is no significant difference observed in pharmacokinetics in different age and race groups. An increase in dapoxetine exposure is noted in subjects with severe renal and hepatic impairment. A statement was provided by the sponsor about the similarity of the active substance between trial and proposed commercial formulation, its dissolubility profile and stability to support the decision that further bioequivalence studies were deemed unnecessary.
- The efficacy of dapoxetine has been demonstrated in four pivotal studies performed in >6000 subjects showing that IELT is significantly prolonged and associated with improvement in perception of control over ejaculation, satisfaction in sexual intercourse and reduction in personal distress. These improvements are also supported by partner perception of satisfaction in sexual intercourse and reduction in partner’s distress, and the couple’s perception of medication helpfulness. From the Phase III studies, the improvement in IELT was ~1.5-2 min longer in duration than placebo. The increase in mean score for control over ejaculation (which is essential for perceived improvement in PE) was generally <1-category point overall when compared to placebo. The proportion of subjects who were classified as responders (improvement in control over ejaculation by ≥ 2 categories and personal distress by ≥ 1 category) was ~24% higher than placebo at most. The proportion of subjects who had improvement in personal distress or sexual satisfaction by ≥ 1 -category was ~25% at the maximum. It is noteworthy that there was a moderate placebo effect of ~30% and the improvements in the active treatment groups appeared modest when each variable was viewed in isolation. However, with a composite of efficacy variables showing improvement in a complex disease such as PE, it would appear that a proportion of subjects with PE benefited from dapoxetine. Moreover, the efficacy of dapoxetine was also demonstrated in subgroup analyses in subjects with baseline stratum IELT ≤ 1 min versus >1 min, and different ethnic groups and geographical regions. Approximately ~13% of subjects in the extension study (C-2002-014) involving 1774 subjects ceased due to lack of efficacy.
- In terms of safety, besides the well-known AEs associated with SSRIs, syncope is a concern. Although the incidence was low, it occurred at a higher incidence in subjects taking dapoxetine versus placebo (0.25% versus 0.04%). Given that it tended to occur within 1h after the first dose and in association with sinus pauses, it is likely to be neuro-cardiogenic in origin. The sinus pauses were significant, lasting between 5-28 seconds. Additional ECG studies to investigate for QTc prolongation in association with dapoxetine use, and study C-2004-017 to investigate for potential interaction between dapoxetine and tamsulosin in the

orthostatic profile were conducted. No QTc prolongation and no significant effect on orthostatic profile were demonstrated. Perhaps more careful screening of subjects resulted in lack of reports of syncope in the latest study R096769-pre-3003, although prodromes for syncope such as nausea and dizziness were still reported.

- SSRI have also been associated with increased incidence of suicidality. The sponsor responded by including suicidality as one of the safety variables in their newer Phase III studies [R096769-PRE-3001, R096769-PRE-3003 and R096769-PRE-3002]. No increase in suicidality was noted. An external assessment of blinded narratives using the method characterised at Columbia University for evaluation of suicidality narratives was obtained for all of the possibly suicide-related adverse events in the clinical program, and there was no clear signal that dapoxetine was associated with suicide. There was a drowning death in a Korean subject which occurred 12 days after the last dose and it was considered accidental and unrelated, in the context of alcohol use. In addition, unlike other SSRI, dapoxetine is a short-acting drug and only taken on a prn basis for treatment with PE. This may lead to lower likelihood of increased risk of suicidality.
- In terms of long-term safety data, according to TGA-adopted European Commission guidelines for assessment of long-term safety of a new drug for use in a non-life-threatening condition, a minimum of 100 subjects should be exposed to the drug for ≥ 12 months.³⁸ Thus far, 378 subjects have been exposed to dapoxetine for ≥ 360 days, which would meet the requirement of the guidelines. No new safety concerns were identified in study C-2002-014, which was of the longest duration.

The sponsor agreed that there is no generally accepted IELT criterion as a primary efficacy parameter for PE based on literature review. A review of published studies found that average IELT among men with PE ranged from 1 to 3 minutes.^{39,40,41} Rowland et al suggested an IELT criterion for PE of < 2 minutes in $\geq 75\%$ of sexual intercourse attempts over the previous 6 months, arguing that the frequency of IELT episodes as well as a minimum duration of time should be considered in the definition of PE.⁴¹ Waldinger et al proposed statistically-derived IELT cut-offs of 1 min for 'definite' PE and 1.5 min for 'probable' PE, based on 0.5 to 2.5 percentiles of stopwatch-assessed IELT in a multinational survey.^{42,43} In the general population, available evidence suggests that self-reported IELT varies on average from about 5 to 16 min with substantial differences across geographic regions.^{41,42,44} Because IELT does not fully characterize the PE condition, multiple outcome measures, including IELT, perceived control over ejaculation, and an element of impact of the condition (for example, distress/bother, interpersonal difficulty) have been advocated as

³⁸ pp. 121-125 of Rules Governing Medicinal Products in the European Union 1998 (3C) – 3CC5A, November 1994. The Extent of Population Exposure to Assess Clinical Safety for Medicines Intended for Long-Term Treatment of Non-Life-Threatening Conditions. <http://www.tga.gov.au/docs/pdf/euguide/vol3c/3cc5aen.pdf>.

³⁹ Patrick DL, Althof S, Pryor J, et al. Premature ejaculation: an observational study of men and their partners. *J Sex Med.* 2005;2:358-367.

⁴⁰ Waldinger MD, Hengeveld MW, Zwinderman AH, et al. An empirical operationalization study of DSM-IV diagnostic criteria for premature ejaculation. *Int J Psychiatr Clin Pract.* 1998a; 2:287-293.

⁴¹ Rowland DL, Cooper SE, Schneider M. Defining premature ejaculation for experimental and clinical investigations. *Arch Sex Behav.* 2001;30:235-253.

⁴² Waldinger MD, Quinn P, Dilleen M, et al. A multinational population survey of intravaginal ejaculation latency time. *J Sex Med.* 2005a;2:492-497.

⁴³ Waldinger MD, Zwinderman AH, Olivier B, Schweitzer DH. Proposal for a definition of lifelong premature ejaculation based on epidemiological stopwatch data. *J Sex Med.* 2005b; 2:489-507.

⁴⁴ Montorsi F. Prevalence of premature ejaculation: a global and regional perspective. *J Sex Med.* 2005;2(Suppl 2):96-102.

endpoints for treatment.^{45,46} The sponsor submitted the results of another observational study, R096769-PRE-3004 which investigated the correlation between IELT and PRO measures in European subjects to demonstrate the reproducibility of the above primary and secondary efficacy measures, including the sponsor's definition of treatment responder (that is subjects with ≥ 2 -category increase in control over ejaculation and ≥ 1 -category decrease in personal distress after receiving treatment) in other ethnic groups and geographical regions. In addition, review of meeting minutes with health authorities in various European countries revealed that they also recognized the lack of a suitable definition of PE and agreed that the use of IELT as the primary efficacy criterion and the sponsor's definition of treatment responder as a secondary efficacy criterion as being suitable for the Phase III studies. The criticism of both observational studies C-2004-004 and R09769-PRE-3004 is that the subjects were classified as having PE based on clinical judgement using the DSM-IV-TR criteria, hence the study group of interest included subjects with IELT ≤ 2 min and > 2 min. The number of subjects classified as having PE who had IELT ≤ 2 min was small (less than 100 in each study and constituted ~ 30 -40% of the subjects classified as having PE).

Improvement in IELT was small and might not be clinically significant. The improvement in IELT was ~ 1.5 -2 min longer in duration than placebo in the Phase III studies. The increase in mean score for control over ejaculation (which is essential for improvement in PE) was generally less than 1-category point overall when compared to placebo. The proportion of subjects who were classified as responders (improvement in control over ejaculation by two categories and personal distress by 1 category) was $\sim 24\%$ higher than placebo at the maximum. The proportion of subjects who had improvement in personal distress or sexual satisfaction by 1-category was $\sim 25\%$ at the maximum. It is noteworthy that there was a moderate placebo effect of $\sim 30\%$ and the improvements in the active treatment groups appeared modest when viewed in isolation. However, with a composite of variables showing improvement in the known complexity of PE, it would appear that a proportion of subjects with PE benefited from dapoxetine.

In terms of syncope, although the incidence was low, it occurs at a higher incidence in subjects taking dapoxetine versus placebo (0.25% versus 0.04%). Additional ECG studies to investigate for QTc prolongation in association with dapoxetine use, and study C-2004-017 to investigate for potential interaction between dapoxetine and tamsulosin in the orthostatic profile were conducted. No QTc prolongation and no significant effect on orthostatic profile were demonstrated to explain the aetiology of the syncope. Review of the ECG studies and Holter monitor results did not reveal any bradycardic episodes, increase in first and second degree AV blocks or increase in ventricular ectopics. There was an increase in ventricular and supraventricular single ectopics in dapoxetine group versus placebo group, however, ventricular and supraventricular single ectopics are generally considered clinically benign. Given that it tends to occur within 3 hours after the first dose and in association with sinus pauses, it is likely to be neurocardiogenic in origin. To help understand the potential magnitude of an increased risk of syncope, the number-needed-to-harm (NNH) was calculated. The NNH is the number of individuals who would need to be treated with dapoxetine to observe one *additional* case of syncope relative to the background risk. Data from the dapoxetine clinical development program indicate that the NNH is 10,000 for 30 mg and 556 for 60 mg in the Phase III studies. The occurrence of syncope as well as potential adverse sequelae resulting from syncope can be minimized through key educational programs including:

- 1) education regarding known and established risk factors for syncope;
- 2) instruction regarding the precipitating circumstances around the occurrence of syncope that was observed in the clinical dapoxetine program; and

⁴⁵ Rowland DL. Treatment of premature ejaculation: selecting outcomes to determine efficacy. *Bull Int Soc Sex Impot Res.* 2003;32:261-270.

⁴⁶ McMahon C. The etiology and management of premature ejaculation. *Nat Clin Pract Urol.* 2005;2:426-433.

3) actions to minimize progression of possibly prodromal symptoms to loss of consciousness. In the dapoxetine clinical development program, educational actions were instituted in mid-2005 after the case report of a subject with a 28s sinus pause. After educational measures such as instructions to maintain adequate hydration, avoid standing up quickly, assume a recumbent position if the patient feels light-headed, dizzy, sweaty, shaky, clammy, or nauseated, were implemented and physicians were educated on how to counsel their patients, no further syncopal events occurred in the program.

However, it is difficult to ascertain how successful the educational programs would be and whether the guidelines would be adhered to in the clinical setting.

In terms of suicidality associated with SSRI, the sponsor responded by including suicidality as one of the safety variable in their newer Phase III studies [R096769-PRE-3001, R096769-PRE-3003 and R096769-PRE-3002] performed after the initial rejection analysing the suicidality data in studies. No increase in suicidality was noted. An external assessment of blinded narratives using the method characterised at Columbia University for evaluation of suicidality narratives was obtained for all of the possibly suicide-related adverse events in the clinical program, and there was no clear signal that dapoxetine was associated with suicide. There was a drowning death in a Korean subject which occurred 12 days after the last dose and it was considered accidental and unrelated, in the context of alcohol use. In addition, unlike other SSRI, dapoxetine is a short-acting drug and only taken on a prn basis for treatment with PE. Hence, it is unlikely to lead to increased risk of suicidality.

Accidental injuries were a concern and were included as one of the safety variables analysed in the newer Phase III studies. The incidence rates of accidental injury in the five Phase III studies combined were 1.8%, 2.7%, 2.2% and 3.0% for placebo, dapoxetine 30 mg prn, dapoxetine 60 mg prn and dapoxetine 60 mg daily. None of the accidental injury AEs were associated with suicidality. In the extension study C-2002-014, the incidence rates of accidental injury-related AEs were 4.2%, 5.8% and 6.7% in subjects whose prior treatment was placebo, dapoxetine 30 and 60 mg, respectively. An analysis of the association between neurocognitive-related AEs and accidental injury-related AEs showed no indication of an association. However, higher rates of accidental injuries have been observed with SSRIs suggesting it is possible that accidents would be more common among patients experiencing drug-related effects such as somnolence, disturbance in attention and fatigue.

In terms of mood-related AEs, there was a slightly higher incidence in dapoxetine-treated subjects (9.1% versus 3.6%) and the most common were insomnia and anxiety. There was no increased incidence of depression in the short-term placebo-controlled Phase III studies, but there was a small number with new onset of depression in the uncontrolled long-term study C-2002-014. It is noteworthy that subjects with a history of depression were excluded in the studies, and hence safety of dapoxetine in these subjects has not been established.

Although there was a small increase in AEs relating to sexual dysfunction, this was not confirmed on IIEF questionnaire. Overall the incidence of AEs relating to sexual dysfunction was low in the Phase III studies (3.9% all dapoxetine groups combined versus 1.8% placebo).

More studies were conducted to assess the risk-benefit in the Asian population as the studies were predominantly performed in Caucasian population. There were also concerns regarding the slightly higher exposure of dapoxetine. The sponsor subsequently organised study R096769-PRE-1001 which investigated the PK of dapoxetine in Japanese versus Caucasian subjects, and study R096769-PRE-3003 which investigated the efficacy of dapoxetine in the treatment of PE in predominantly Asian subjects. The PK results revealed an increase in exposure by ~10-20% in Japanese subjects mainly due to the lower body weight. The efficacy study results confirmed the efficacy of dapoxetine 30 and 60 mg prn in the treatment of PE and there were no new concerns in the safety profile. Slightly more dizziness AEs were reported but no syncope was reported.

General comments

Potential for off-label use is acknowledged. A Risk Management Plan has been put forward for use in Europe by the sponsor to manage this as well as the ongoing review of the incidence of syncope.

There was a wide range between the minimum and the maximum increases seen in IELT after treatments with placebo (0-25 min) and dapoxetine 30 and 60 mg prn (0-38 min) in the PE subjects studied. There was also considerable overlap seen in the improvement in IELT in dapoxetine and placebo groups. Results of subgroup analyses using baseline IELT stratum ≤ 1 min versus > 1 min placebo were reviewed to see if it is possible to define which subjects with PE would benefit most from the use of dapoxetine 30 and 60 mg prn after 12-24 weeks of treatment. The results of subgroup analyses according to baseline IELT stratum ≤ 1 min versus > 1 min confirmed the primary efficacy analyses, and it would appear that subjects with baseline IELT > 1 min appeared to receive greater improvement with the use of dapoxetine 30 and 60 mg prn. However, similar to the primary efficacy analyses, the results showed that a large number of subjects would fail to derive benefit based on IELT prolongation and responder rate, and the placebo group appeared to achieve similar IELT results as dapoxetine 30 and 60 mg groups in some subjects. Approximately 50-80% of subjects who received dapoxetine failed to meet the criteria for responder rate compared to 75-95% of subjects who received placebo.

Because PE is a non-life-threatening condition, the use of any drug to treat this disease ideally should have minimal adverse reactions. Currently, in addition to GIT AEs (26.5% in all dapoxetine groups versus 7.6% in placebo group) and CNS AEs (21.1% in all dapoxetine groups versus 8.7% in placebo group) commonly associated with SSRIs, there are other concerns such as syncope, accidental injuries and sexual dysfunction. When this is taken into consideration together with the variable improvements in IELT and responder rates (and many would appear not to derive any clinically significant benefit from dapoxetine), it is difficult to justify the use of dapoxetine in subjects with PE. On the other hand, there were subjects with PE and associated personal distress and relationship difficulties who derived marked improvement in IELT, control of ejaculation and reduction in personal distress in the Phase III studies evaluated. Hence, it is also difficult to justify rejecting the approval of dapoxetine use in this subgroup of patients with PE. Review of subgroup analyses according to baseline IELT stratum of < 1 min versus ≥ 1 min did not help to provide more information into which subjects were the most likely to derive benefit. It is possible that further data analysis of primary and secondary efficacy parameters based on baseline IELT in ascending tenth percentiles might provide more information, although the numbers in each percentile group might be too small to provide statistical significance.

Bearing in mind the small risk of syncope, accidental injuries and possible mood-related AEs, only a selected population of patients with PE would be suitable for the use of dapoxetine. Many subjects with PE would be excluded based on numerous risk factors for syncope such as a history of neurocardiogenic syncope, cardiovascular disorders (outflow obstruction, arrhythmias), diseases (such as Parkinson's disease and diabetes) and medications (anti-Parkinsonian medications) which affect the autonomic system, concurrent antihypertensive medications and risk factors for psychiatric disorders. There was concern that even if dapoxetine was approved for use in the treatment of PE in carefully selected subjects after baseline assessment by urologists, in consultation with general practitioners, cardiologists and psychiatrists, the risk of leakage of drug use exists and the risk of potentially serious adverse events outweighs the small benefit that may be derived from the use of dapoxetine. Moreover, many subjects or clinicians may not follow through a thorough assessment prior to commencement of dapoxetine.

Recommendation

The evaluator believed that based on the current available data submitted, Priligy 30 mg and 60 mg cannot be approved for the treatment of premature ejaculation even in carefully selected male subjects aged 18-64 years who have the following:

- i) persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the patient wishes,
- ii) marked personal distress or interpersonal difficulty as a consequence of premature ejaculation, and
- iii) poor control over ejaculation.

It is difficult to identify which patients will benefit the most from the drug. Because of the adverse reaction profile, even with careful screening, it would not justify the exposure of many patients with PE to the potentially serious adverse effects.

Hence, it would be more prudent to reject the drug at this stage.

Supplementary Clinical Evaluation

The sponsor identified certain key concerns which were raised in the clinical evaluation report and addressed those issues. The initial issue raised in the TGA report is in **bold font** followed by the sponsor's summary of response (in '*italics*') and the evaluator's comments on the sponsor's responses follow in 'normal font'.

1. The proportion of subjects meeting the responder definition was considered low, and only a marginal difference was observed in response between dapoxetine and placebo-treated subjects.

The sponsor argued that the difference in proportion of subjects meeting the definition of at least a 2 category improvement in Control over ejaculation, and at least one category improvement in Personal Distress related to timing of ejaculation was substantial. The sponsor mentioned that the percentage of subjects who met the stringent response criteria was 18.1%, 30.8% and 40.2% in placebo, dapoxetine 30 mg and 60 mg groups, respectively.

However, the sponsor has not clearly stated from where these figures were derived. The above responder rate analysis was only done in two of the four Phase III studies. Study R096769-3001 in 1162 European subjects showed response rates of 13%, 25.3% and 37.1% in placebo, dapoxetine 30 mg and 60 mg groups, respectively; however study R096769-PRE-3003 in 1067 subjects from Asian-Pacific regions showed greater placebo response with response rates of 21.7%, 34.7% and 37.2% in placebo, dapoxetine 30 mg and 60 mg groups, respectively.

The sponsor also stressed that the response rates based on the stringent definition of at least a 2 category improvement in Control over ejaculation, and at least one category improvement in Personal Distress related to timing of ejaculation were conservative and would not include the broader population of patients who experience lesser degrees of benefit. The sponsor further stated that patient-reported CGI of change (CGIC), which was measured as a secondary efficacy endpoint in all Phase III studies at all follow-up visits, showed better results in dapoxetine-treated subjects compared with placebo-treated subjects (see table below).

CGIC Summary at Week 12 (LPOCF)*; Studies Pooled: C-2002-012, C-2002-013, R096769-PRE-3001, R096769-PRE-3002 and R096769-PRE-3003

CGIC Response Outcome	Placebo n (%)	Priligy 30 mg n (%)	Priligy 60 mg n (%)
No Change or Worse**	1076 (64.0%)	564 (37.9%)	535 (28.3%)
Slightly Better	357 (21.2%)	467 (31.4%***	618 (32.7%***
Better	185 (11.0%)	305 (20.5%)	441 (23.3%)
Much Better	64 (3.8%)	151 (10.2%)	295 (15.6%)
Total	1682 (100%)	1487 (100%)	1889 (100%)

* LPOCF is last post-baseline observation carried forward

** No Change or Worse includes No Change, Slightly Worse, Worse or Much Worse

*** At least Slightly Better CGIC response rate: Placebo (36%), Priligy 30 mg (62.1%) and Priligy 60 mg (71.7%) with p-value <0.0001 for Priligy 30 mg versus placebo and Priligy 60 mg versus placebo.

The sponsor provided additional information to validate the importance of CGIC as an important efficacy measure and its ability to relate to multiple domains of PE, including IELT and satisfaction with sexual intercourse, as well as control over ejaculation and distress related to timing of ejaculation. In brief, results of the validity tests suggested that CGI scores would be expected to be at least moderately correlated with measures of similar concept such as changes in control over ejaculation, distress related to ejaculation and PE severity (correlation co-efficient of 0.73, 0.61 and 0.63 for change in control, distress and severity, respectively)⁴⁷. The results provided suggest that improvements in CGI would correspond to improvements in IELT (those who are slightly better appear to have at least 1 minute greater change in IELT than those with no change, while those who are better or much better have an approximately 3-6 minute greater change), control of ejaculation, personal distress and severity.

The evaluator noted that the additional efficacy analysis with special emphasis on CGIC and its correlation with improvements in IELT, control, distress and severity suggested that dapoxetine does appear to lead to clinically relevant improvement in some patients with PE.

2. Subgroup analysis did not identify a more responsive subgroup of men with PE. It was suggested that further exploratory analyses using more strictly defined baseline IELT categories (that is, tenth percentiles) could be more informative as to which patients are most likely to respond to treatment.

The sponsor agreed that further classification of men with PE by baseline IELT severity would be informative if more responsive subgroups of subjects could be identified. However, as stated in the clinical evaluation report, the sponsor has confirmed that using tenth percentiles as subgroups would result in relatively narrow baseline IELT categories (approximately 12 seconds) with an insufficient number of subjects in each category to provide reliable results. However, they have conducted additional analyses of efficacy of IELT and PRO data classified by baseline IELT categories of <0.5, >0.5 to 1, >1 to 1.5 and >1.5 to 2 minutes; this analysis showed that the effects of dapoxetine 30 mg and 60 mg were always superior to placebo in the subgroups defined above, although the results suggested that subjects with greater baseline IELT values had greater increase in IELT and improvements in PRO measures at study endpoint compared with those with lesser IELT values at baseline. However, the above results should be interpreted with caution as the number of patients with baseline IELT >1.5 to 2 minutes was much smaller than the other subgroups. Overall, these additional subgroup analyses based on baseline IELT values did not reveal a more responsive group to dapoxetine treatment.

The sponsor also stated that the effects of dapoxetine treatment are experienced soon after initiation of treatment with significant improvements in IELT and CGI over placebo at first follow-up visit at Week 4. This would enable each patient and his physician to determine not only the clinical relevance of his response to dapoxetine treatment but also help determine if further treatment is required or not. This would help minimise drug exposure. In order to minimise drug exposure in subjects unresponsive to treatment, an appropriate statement was proposed for the Product Information.

Although the additional exploratory analysis failed to identify subgroup of patients that may respond to dapoxetine treatment, inclusion of such a statement in the PI would help address concerns raised in the earlier clinical report by minimising drug exposure and subsequent risks associated with dapoxetine in non-responders.

⁴⁷ Convergent or discriminant validity was assessed by computing the Spearman correlation co-efficient between CGI and patient-reported measures at study endpoint.

3. The effect of dapoxetine on the primary outcome parameter of IELT was noted as highly variable between subjects and with overlap between dapoxetine and placebo-treated subjects.

The sponsor accepted the fact that the IELT results were highly variable but stressed the clinical significance of changes in other PRO measures, including the CGIC. Furthermore, in order to provide further guidance to physicians on clinical relevance of treatment effect of dapoxetine, the sponsor proposed additions to the Clinical Trials section of the PI:-

The additions to the PI seem to address the concerns raised about high variability in IELT response and also provide more clinically relevant guidelines for the prescribing physician.

4. Is the efficacy of dapoxetine 60 mg statistically significantly different from 30 mg?

The sponsor suggested that although dapoxetine 60 mg did not always lead to statistically significantly greater improvement compared to 30 mg dose, the results indicated a trend suggesting the same. Changes to the PI were proposed to address this issue.

These changes to the PI sufficiently address the concerns regarding no statistical significant difference in efficacy between dapoxetine 30 mg and 60 mg by ensuring that only patients with insufficient response and acceptable side effects would be exposed to the higher dose of 60 mg.

5. Although SSRI class-related safety issues were addressed by the three additional dapoxetine Phase III studies conducted subsequent to the NDA submitted to the US FDA in 2004, the TGA remains concerned about CNS and mood-related AEs, AEs of sexual dysfunction, accidental injury AEs and AEs suggestive of SSRI withdrawal effects.

The sponsor's main response to the evaluator's safety concerns stressed the fact that emergence of most dapoxetine AEs occurred in a predictable time-frame shortly after drug administration (over half of the AEs were reported within the first 4 weeks of treatment and were generally mild to moderate in severity), enabling the individual patient to determine tolerability to dapoxetine treatment soon after its initiation, and consider further treatment based on his response.

The onset of dapoxetine AEs was evaluated in approximately 3500 patients in studies R096769-PRE-3001, -3002 and -3003, who were administered the first dose of study drug at the study centre, permitting accurate documentation of time of onset and resolution of AEs for the large majority (approximately 95%) of subjects who reported AEs with the initial dose. A total of 24 (2.4%), 60 (8.1%) and 262 (15.1%) subjects treated with placebo, dapoxetine 30 mg and 60 mg, respectively, reported the most common CNS and GI dose-dependent AEs observed in the clinical development program (dizziness, headache, nausea or somnolence) on Day 1. The time of onset of these AEs approximates that of T_{max} (1.3 hours) with mean duration of approximately 1.3 hours (see table below).

Dose Dependent Adverse Events Onset and Duration in Phase 3 Studies
(Dapoxetine: Intent-to-Treat Analysis Set)

	--- PLACEBO --- (N=987)	--- DPX 30 MG --- (N=742)	--- DPX 60 MG --- (N=1738)
First dose to AE time (h)			
N	24 (2.4%)	60 (8.1%)	262 (15.1%)
Mean (SD)	1.29 (1.280)	1.49 (1.993)	1.18 (1.400)
Median	1.00	1.00	0.92
Range	(0.1;6.5)	(0.0;14.3)	(0.0;13.5)
AE duration (h)			
N	21 (2.1%)	55 (7.4%)	234 (13.5%)
Mean (SD)	0.86 (0.889)	1.55 (2.050)	1.46 (1.671)
Median	0.58	1.00	1.00
Range	(0.0;3.5)	(0.0;11.2)	(0.0;11.5)

First Dose AE: Subjects with AE onset time from First Dose to AE Onset, both First Dose and AE Onset have non-missing value

AE Duration: Time from AE Onset to AE Ending.

Studies included: R096769-PRE-3001, R096769-PRE-3002 and R096769-PRE-3003.

Only AEs with onset time after first dose time on the same day were considered.

Source: table5_3.rtf generated by table5_3.sas and table5_3_1.rtf generated by table5_3_1.sas

The risk of injury accompanying syncope is an identified risk in the dapoxetine RMP, but the sponsor claims that it was manageable through enhanced pharmacovigilance and additional risk minimisation activities; this was demonstrated by the absence of further reports of episodes of syncope following implementation of risk minimisation efforts during the course of two of the dapoxetine Phase III studies (R096679-PRE-3001 and -3003).

Patient education regarding risk of syncope and accidents are adequately highlighted in the modified PI. The blister packaging was designed so the subjects are continually reminded of measures to prevent syncope and accompanying accidents with every dose administration. Priligy labelling and proposed packaging also contain similar precautionary statements

The modifications to the proposed Priligy PI adequately address concerns regarding AEs associated with dapoxetine including risks of syncope and accidental injury and it is recognised that since dapoxetine is administered only on an on-demand basis, each patient that experiences intolerable AEs should be able to discontinue treatment.

6. Syncope: Based on the assessor's report, we understand safety concerns related to syncope include the higher incidence of syncope observed with dapoxetine compared with placebo, and the lack of identifiable risk factors for vasovagal syncope.

A search of the dapoxetine clinical database for all AE terms and MedDRA preferred terms that might reflect a syncopal event revealed 37 cases of potentially relevant cases of syncope (including cases of interest of syncope and vasovagal syncope, even though loss of consciousness may not have occurred). In the majority of cases (9 of 15 adjudicated syncope and 19 of 30 cases of interest in dapoxetine group) for which vital sign measurements or ECG recordings were obtained during or shortly after syncopal event, there was a decrease in heart rate, blood pressure or both. Furthermore, in cases when the duration of loss of consciousness was recorded, it was generally brief and associated with spontaneous recovery (consistent with a vasovagal mechanism). Review of the individual narratives suggested that other causes of syncope seen in clinical practice (such as those related to structural heart disease, atrial tachyarrhythmias, neurologic causes, etc) were not suspected or observed in any of the clinical cases. All of the seven cases of interest of syncope (5 adjudicated) who were wearing a Holter monitor at the time of the syncopal event had bradycardia with or without sinus arrest, suggesting vasovagal aetiology and none of these 7 subjects had VT during their syncopal episodes. Of the seven cases with Holter monitoring at the time of the

syncopal episode, 3 of them had sinus arrest; a 43 year old white male and 32-year old white male were discontinued from further dapoxetine treatment following a syncopal episode after the first dose of dapoxetine and had normal vital signs and ECG at follow-up visits. However, a 23-year old white male with severe syncope (and sinus arrest) after first dose of dapoxetine recovered and continued in the study receiving further dapoxetine doses without incident.

The occurrence of cardiac arrhythmia was examined in 3353 patients in the Phase III placebo-controlled studies R096769- Pre-3001, PRE-3002 and –PRE-3003 to explore its potential contribution to the occurrence of syncope. Holter ECG monitoring was performed beginning 10 to 30 minutes before and ending 3 hours after the first dose of study drug. Nine cases of non-sustained VT occurred during Holter monitoring in the Phase III studies: 0.2% (2/950), 0.3% (2/715) and 0.3% (5/1688) in placebo, dapoxetine 30 mg and 60 mg groups, respectively. All cases were asymptomatic, 5 cases were monomorphic (unifocal) and 4 were polymorphic (multifocal). Review of the narratives suggested that no symptomatic or sustained tachyarrhythmias were detected.

No prolongation of cardiac repolarisation was observed in the 3 thorough QT/QTc studies.

To evaluate the possibility that orthostatic hypotension could potentially contribute to the occurrence of syncope, measurement of vital signs (supine and standing) in response to orthostatic challenge within 15 minutes to 3 hours of dosing on first day was performed as part of the cardiovascular safety evaluation in the three Phase III studies (3001, -3002 and -3003). Compared with placebo, dapoxetine-treated patients showed slightly higher incidence of orthostatic hypotension (JNC-7-criteria)⁴⁸ and orthostatic SBP (<20 mmHg) after dosing on Day 1, while incidence of orthostatic DBP change (<10 mmHg) was similar. Shift table analysis for orthostatic hypotension and evaluation of orthostatic SBP and DBP changes by category/ limits of change showed no apparent differences between placebo and dapoxetine groups. The number of subjects who had a decrease in heart rate during orthostatic manoeuvres was low and similar in placebo and dapoxetine groups and more subjects had increased heart rates suggesting reflex tachycardia response.

The majority of the cases of interest (of syncope) (22/37) showed one or more of the typical prodromal symptoms such as dizziness or lightheadedness, nausea, blurred vision, headaches, palpitations, paraesthesia and pallor either before or at the time of syncopal episode; nausea and dizziness were the most frequently reported pre-syncopal symptoms. AEs that could reflect prodromal symptoms generally emerged approximately 1.5 hours following dapoxetine dose, which was consistent with the time the syncope occurred in most cases. Hence, these symptoms appear in a predictable timeframe following dapoxetine administration and may provide a basis for counselling patients regarding recognizing symptoms and taking actions, such as lying down, so that the symptoms do not progress to actual loss of consciousness.

The incidence of syncope appeared to be highest during the Phase I studies and the majority of these cases occurred during a study site visit rather than an offsite setting. The sponsor further stated that various procedures such as vital sign measurements, orthostatic manoeuvres, ECG/ Holter monitoring (in Phase III studies) and venepuncture (in Phase I studies) may have contributed to vasovagal syncope. Review of the narratives of the six cases of syncope which occurred following off-site dosing with dapoxetine showed that all of them had at least one of the risk factors for vasovagal syncope (during defaecation, micturition, cough; decreased cardiac preload conditions such as dehydration; alcohol; other medications that may reduce orthostatic tolerance).

⁴⁸ JNC-7: In the seventh report of the US National Institutes of Health Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, orthostatic hypotension was defined as decrease in SBP of >20mmHg and/or in DBP of >10mmHg on standing.

Furthermore, none of the subjects who reported syncope had a recurrent syncopal event, including 19 subjects who continued in the study following a syncopal event post-dosing. Review of the duration, outcome and potential triggering circumstances for each of the 37 cases of interest showed that the duration of most of the reported cases ranged from few seconds to 2 minutes and was associated with spontaneous recovery. Of the 15 patients with adjudicated syncope (and loss of consciousness), 5 patients experienced injuries from the syncope, but all of these recovered spontaneously and did not lead to any long-term harm. Of the 37 cases of interest, 14 were discontinued from the study and 23 completed the study per protocol.

The sponsor stated that patient education regarding recognition of prodromal symptoms, as well as specific actions that can be implemented when these symptoms occur represents an opportunity to minimize the progression to loss of consciousness. Furthermore, an analysis of the number or percentage of subjects with syncope before and after implementation of mandatory patient instructions for minimizing syncope incidence suggested that these measures may be useful in minimizing the risk of syncope associated with dapoxetine treatment.

Priligy packaging is also a key component of the Risk Management Plan (RMP) and includes the statements on the blister packages to remind patients of measures to reduce the risk. The RMP also proposed two post-approval studies to be conducted in the EU, which may serve to identify additional risks.

The occurrence of syncope and potential adverse sequelae resulting from syncope can likely be minimized through key educational programs for health care providers regarding:-

- known and established risk factors for syncope,*
- precipitating circumstances around the occurrence of syncope that were observed in the clinical dapoxetine program,*
- actions to minimize progression of possibly prodromal symptoms to loss of consciousness,*
- caution that patients with underlying severe cardiac impairment may be at higher risk for syncope and other cardiac events.*

Overall, analysis provided by sponsor suggests that a vasovagal mechanism is the most likely aetiology of syncope in dapoxetine-treated patients. Furthermore, the sponsor suggests that vasovagal syncope is manageable through patient education/ instruction regarding recognition of prodromal symptoms and implementation of measures to prevent progression to loss of consciousness have been included in the modified PI. Furthermore, the instructions on the blister packages will remind patients of measures to reduce the risk of syncope every time they take the drug. The sponsor has also provided draft protocols of two post-marketing studies to further characterise safety and use of dapoxetine. All these measures taken by the sponsor help to address the safety concerns regarding syncope raised in the earlier TGA clinical evaluation report.

7. Depression: Patients with clinical depression were excluded in the Phase III studies for dapoxetine. We understand that the TGA is concerned of the risk of suicide in depressed patients who may use dapoxetine.

Patients with clinical depression were excluded from the main Phase III studies. To manage risk of possible dapoxetine use in men with undiagnosed depression, or in depressed men currently undergoing psychiatric treatment, appropriate information for both health care providers and patients has been developed in the PI and the Consumer Medicine Information (CMI).

To warn physicians of possible risk with dapoxetine treatment and to help prevent the use of dapoxetine in patients taking medicines with other serotonergic properties, or in patients with depressive symptoms, contraindications and labelling precautions are specified in the proposed PI for Priligy.

The above modifications to the proposed PI for Priligy help to address some of the concerns regarding depression raised in the earlier TGA evaluation report.

8. Emergence of cognitive impairment when ethanol is co-administered with dapoxetine.

The sponsor has addressed concerns regarding safety risks associated with concomitant use of dapoxetine with alcohol by recommending to avoid alcohol while taking Priligy and has made substantial changes to the product labelling including warnings of the potential safety risks.

The changes made to the Priligy PI adequately address safety concerns regarding concomitant administration of alcohol with Priligy.

9. Possible interactions with recreational drugs

Although interactions studies were not conducted with recreational drugs, possible pharmacodynamic interactions and potential toxicities of dapoxetine in combination with recreational drugs were discussed. Due to potential effects between dapoxetine and recreational drugs, the sponsor has taken the approach of recommending against use of dapoxetine with recreational drugs and has made substantial changes to the proposed Priligy PI to enhance the warning for the potential safety risks.

The changes made to the Priligy PI adequately address concerns regarding concomitant administration of recreational drugs with dapoxetine.

10. The effects of dapoxetine on PDE5I pharmacokinetics

Safety concerns regarding concomitant treatment of dapoxetine with PDE5Is such as sildenafil and vardenafil, especially those of orthostatic hypotension, were addressed by adding warnings in the Priligy PI.

These warnings in the Priligy PI should help to address concerns regarding concomitant administration of dapoxetine with PDE5Is.

11. No established bioequivalence between formulations used in clinical studies and the proposed commercial formulation.

The sponsor has clarified that the drug formulation used during Phase II and III studies was of the same dosage form (composition) as the one intended for commercialization (oral film-coated tablets) and each batch was manufactured according to the same manufacturing process, at a similar scale, and under same conditions as the proposed commercial formulations. The only difference was the modification of the debossing image present on the tablets.

The response was considered satisfactory.

12. Occasional CK and transaminase rises observed in Phase I studies

Although isolated cases of elevated CK and transaminases were observed in the Phase I studies, a comprehensive analysis of CK and transaminase data from the Phase III studies did not suggest any relation between dapoxetine use and elevations of these laboratory parameters.

The new analysis submitted by the sponsor suggests that the incidence of elevated CK and transaminases was low and similar in the placebo and dapoxetine groups.

13. Incidence of AEs in patients with severe renal and hepatic impairment: The reviewer notes that the incidence of AEs was significantly higher in dapoxetine-treated patients with severe renal and hepatic impairment and it should be avoided in these conditions.

The sponsor has addressed these concerns by including additional Precautions in the proposed PI.

The changes to PI adequately addressed the concerns raised by the clinical evaluator.

Conclusion

Dapoxetine is a drug specifically developed for the on-demand treatment of PE and is the first oral medication (tablet) to be approved for this condition (approval granted in New Zealand, Finland, Sweden, Portugal, Austria, Germany, Italy, Spain, Argentina, Mexico, Uruguay, Malaysia, Philippines and Korea and currently under review in the Middle East, Asia Pacific, North America and Latin America. In the USA, in accordance with US Regulations, the applicant submitted a “Letter of Intent” in response to the Action Letter, notifying the Agency of its intent to amend the New Drug Application (1 November 2005); thus the file remains open.

Dapoxetine has been extensively evaluated in five randomised, placebo-controlled Phase III clinical trials involving more than 6,000 men with PE and their partners. Dapoxetine is a unique, short-acting, selective serotonin reuptake inhibitor (SSRI) designed to be taken only when needed. The short half-life means that the males could probably take this medication when required, instead of being exposed to chronic dosing in order to build up the typical level in the body like that of the traditional SSRIs. It can be taken 1–3 hours before sexual intercourse is anticipated, rather than every day.

The concerns regarding efficacy, safety and other concerns raised in the earlier TGA clinical evaluation report have been adequately addressed in this submission. Although no new data were submitted, reanalysis of some of the efficacy and safety results and substantial changes to the proposed PI for Priligy provide a favourable risk-benefit profile for the drug in the treatment of PE. Furthermore, the two post-marketing studies should help define the patient population likely to benefit and also monitor safety. The extensive Risk Management Plan should help address the concerns regarding syncope and other AEs associated with dapoxetine treatment.

Recommendation

It is recommended that Priligy be approved for the treatment of premature ejaculation in male subjects aged 18-64 years who have the following:

- i) Persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the patient wishes,
- ii) marked personal distress or interpersonal difficulty as a consequence of premature ejaculation, and
- iii) poor control over ejaculation.

This approval is subject to incorporation of suggested changes to the proposed PI and regular updates on the results of the post-marketing studies, which are to be initiated in Europe.

V. **Pharmacovigilance Findings**

There was no Risk Management Plan evaluated with the initial application as it was not a requirement at the time of submission. It was, however, considered in the supplementary evaluation and was the subject of one of the concerns addressed by the sponsor as follows:

Risk Management Plan

Off label use, misuse and abuse as performance enhancers (that is, leakage of drug)

The sponsor has described the potential for off-label use, misuse and abuse of dapoxetine in 5 distinct populations of concern: Men without PE, adolescents, men with or without PE who abuse prescription drugs, illicit drugs or alcohol, men with co-morbidities that conflict with PI precautions and contraindications and men who may use excessive doses of dapoxetine. They have further summarised pertinent elements of the RMP for monitoring safety concerns in each of these specified populations.

Effectiveness of education programs and whether recommendations for syncope risk minimization would be adhered to in the clinical setting.

The effectiveness of the educational programs will be examined in the two proposed post-marketing studies. Furthermore, the sponsor has taken considerable measures for managing this potential risk of syncope, including appropriate information for both health care providers and patients in the PI, CMI and patient brochure. An enhanced package design with a multi-fold blister pack will provide a reminder to patients regarding prodromal symptoms and effective measures to reduce the risk of syncope as they take each dose. Specific measures within the PI designed to reinforce the concept of minimizing risk through education and recognition of symptoms that might be prodromal and actions to reduce the risk of progression to actual loss of consciousness were outlined.

The evaluator noted that the modified RMP with plans for further postmarketing studies was now acceptable.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

Approval was recommended from a chemistry, quality control and bioavailability aspect. Five bioavailability studies were conducted that demonstrated: absolute bioavailability was approximately 40%, food did not affect extent of absorption but slightly lowered the peak levels of dapoxetine and increased half life from 1.3 to 1.8 hours, 2x 30 mg and 60 mg tablets are bioequivalent and bioequivalence was seen between two different particle sizes of dapoxetine. It was noted from these bioavailability studies that 9% of subjects vomited after taking dapoxetine. No objections were raised by the Pharmaceutical Subcommittee (PSC) of the ADEC to registration but it was recommended that terminal elimination half lives for poor and extensive metabolisers be included in the PI. The sponsor is proposing for the carton labels to contain a warning statement on use with alcohol (no more than two drinks per day), "may cause dizziness or fainting", "what to do if feeling faint" and "avoid driving or operating machinery".

Nonclinical

The nonclinical submission involved primary and supplementary evaluation phases in which the evaluator had not supported the registration of Priligy in either evaluation report. The first evaluation report noted that dapoxetine led to central nervous system effects typical of an SSRI, increased blood pressure (at levels less than clinical C_{max}), disturbed cardiac conduction (at a low NOEL of 2) and contractile function. In guinea pigs at 9 times clinical C_{max} , dapoxetine led to shortened QTc interval, lengthened PR and QRS interval, bundle branch block, AV block and abolished cardiac contraction. Plasma protein binding was very high and absorption and clearance were rapid with wide tissue distribution, including through the blood brain barrier. Metabolism was through CYP3A4, CYP2D6 and FMO1 with the major metabolite having weak activity. Dose proportionality was seen in all species.

Repeat dose studies at subclinical exposures showed severe toxicities in the CNS (hyperactivity, aggressiveness, vocalisation, sleeping time, appetite suppression), liver (enzyme induction, vacuolation, inflammation, centrilobular hypertrophy, fatty change, necrosis/degeneration, hepatic porphyria) and kidney (tubular degeneration, nephritis, fibrosis, cysts, abscesses, hydronephrosis, urolithiasis), along with some effects in the respiratory and lymphoid organs. Dapoxetine was not seen to be carcinogenic in a 2 year rat study, but a 6 month topical study in transgenic mice showed a weak carcinogenic effect. No effects on male fertility, sperm count or motility were observed nor effects on female fertility or postnatal development. However male fertility studies used an unknown relative exposure margin which was likely to be low ($<2 \times$ AUC and 70% of C_{max} in humans). No teratogenicity was seen but delayed ossification was observed in rats and rabbits. Limited efficacy was seen in the non-clinical studies, as expected, given that dapoxetine is a short

lasting drug and that adaptive changes require chronic inhibition of serotonin reuptake. High multiples of drug exposures were not achieved in the studies which casts doubt on the predictive value of negative findings.

The second evaluation report, which contained three genotoxicity studies, did not address the concerns raised by the evaluator in the first report and therefore led to the submission not being supported for registration.

Clinical

Evaluator's Recommendations

The clinical data relies on 29 Phase I studies (n=785), 8 Phase II and III studies (n=6404 (n=654 for 12 months)) of which dapoxetine includes 4538 subjects and two observational studies. The supplementary data did not include any new studies, but included one volume of responses to the issues raised in the first evaluation report. The clinical evaluator recommended rejection in the primary evaluation report and then recommended approval in the supplementary evaluation report. Issues noted by the evaluator in the first report included:

- Modest efficacy, suitability of IELT as a primary efficacy endpoint and the question of who would benefit?.
- Adverse effects of SSRIs.
- Syncope, sexual dysfunction, suicidality, mood related adverse events, accidental injury.
- Data in Asian populations.
- Off label use.

Following the supplementary data evaluation, there were no outstanding concerns from the clinical evaluator following re-analysis of some issues, changes to the PI, risk minimisation proposals and a post-marketing study to define the patient population likely to benefit. A Risk Management Plan was proposed to address safety concerns.

Pharmacology

The pharmacology studies which were conducted in healthy males, 18-45 years, showed:

Dapoxetine inhibited serotonin reuptake in *ex vivo* platelets by 25% and in a dose dependent manner with peak effect occurring after 2-3 hours and lowered serotonin in whole blood to 80%.

Dapoxetine is short acting, T_{max} 1.5-2 hours, $t_{1/2}$ 12-19 hours, 1.5 x accumulation with modest dosing, concentrations decrease to <5% C_{max} within 24 hours, clearance is 27L/hr, V_d 6.43L/kg, >99% protein bound, absolute bioavailability of 42%.

Dapoxetine has linear pharmacokinetics (PK), undergoes first pass metabolism, is extensively metabolised to multiple metabolites and is primarily eliminated in the urine. The major metabolite is N-dapoxetine-oxide which is weakly active. Food does not have a significant effect on dapoxetine.

$T_{1/2}$ was longer in elderly men (17.8 versus 26 hours) and exposure slightly higher (12%). Exposure was increased in CYP2D6 poor metabolisers versus extensive metabolisers by 36%. The PK were not affected in mild to moderate renal impairment but AUC increased by 50% in severe renal impairment. In severe hepatic impairment, there was increased exposure (2 fold) with prolonged $t_{1/2}$ and T_{max} compared to normal to moderate hepatic impairment.

Ketoconazole (CYP3A4 inhibitor) significantly increased exposure to dapoxetine (AUC +100%), whereas fluoxetine (CYP2D6 inhibitor) had moderate effects on dapoxetine (AUC +88%).

Tadalafil did not affect the PK of dapoxetine but sildenafil had a slight effect (AUC +22%), but the

reverse was not tested for either drug. Dapoxetine had a modest effect on the PK of desipramine (AUC +19%, CYP2D6), but did not significantly affect the PK of glyburide (CYP2C9), omeprazole (CYP2C19), midazolam (AUC -20%, CYP3A4), warfarin (PK or pharmacodynamics), tamsulosin (PK but -8.4/+4.2mmHg on Day 1) or ethanol (and vice versa) but increased neurological effects.

The PK in hypertensive subjects were similar to normotensive subjects and a population PK analysis showed clearance was greater on 60 mg versus 30 mg dapoxetine.

Efficacy

The clinical trials used subjects who were heterosexual males, 18-65 years, in a stable sexual relationship for ≥ 6 months and a history of PE in $>50\%$ of intercourse experiences over the previous 6 months for Phase II studies or $>75\%$ for Phase III studies. Subjects had premature ejaculation (PE) based on DSM-IV-TR criteria along with moderate distress or interpersonal difficulty, which was not due to a substance. They also had to be in good health, without erectile dysfunction, normotensive and not taking antidepressants, erectile dysfunction treatments or CYP450 inducers. Dapoxetine was taken 1-3 hours prior to sexual intercourse to coincide with t_{max} with a maximum one dose per 24 hours. Partners were to be on contraception and sexual intercourse was expected to be attempted ≥ 2 times / week. The primary efficacy endpoint was the Intravaginal Ejaculatory Latency Time (IELT) which measured the average duration of intercourse attempts since baseline clinic visit, where ejaculation was recorded as occurring intravaginally or before penetration by the partner using a stopwatch and event log. Subjects were required to have a baseline time of ≤ 2 minutes. A number of secondary measures were used that included participant and partner reported outcomes rated on a 0-4 or 0-7 point scale, such as Sexual Function Inventory (SFI), Symptom Severity Impression (SSI), PE subscale from the Golombok-Rust Inventory of Sexual Satisfaction (GRISS) and Premature Ejaculation Questionnaire (PEQ), global impression of change (GIC), perception of erection firmness, distress and medication helpfulness questionnaire (MHQ). Two important secondary measures were control of ejaculation (0-4 point scale) and satisfaction with sexual intercourse (0-4 point scale), since observational studies showed these correlated with improvements in IELT.

Study GP-PE-98-01: This was a multicentre, double blind, randomised, placebo controlled, three way crossover trial in 157 subjects with PE for 4 weeks to assess a 20 versus 40 mg dose prn. The results were statistically significantly greater on dapoxetine compared to placebo but not between dapoxetine doses (Table 27). Secondary endpoints were mostly supportive for dapoxetine but there was no difference between doses.

Table 27: IELT at baseline and Week 4 results		Week 4		
Mean(SD)	Baseline	Placebo	20 mg	40 mg
IELT, minutes	1.34 (1.07)	2.22(2.62)	2.70 (2.69)	3.31 (4.09)
Difference from previous column	-	+0.88	+0.48	+0.61

Study C-2001-008-02: This was a multicentre, double blind, randomised, placebo controlled dose finding study in 166 subjects with PE for 2 weeks to assess a 60 versus 100mg dose prn. The results were statistically significantly greater on dapoxetine compared to placebo but not between dapoxetine doses (Table 28). Secondary endpoints were mostly supportive for dapoxetine but generally no dose response.

Table 28 : IELT at baseline and Week 2 results		Week 2		
Mean(SD)	Baseline	Placebo	60 mg	100 mg
IELT, minutes	1.01 (0.51)	2.06(2.32)	2.93 (2.60)	3.20 (2.76)
Difference from previous column	-	+1.05	+0.87	+0.27

Study C-2002-012: This was a multicentre, double blind, randomised, placebo controlled study in 1294 males with PE for 12 weeks to assess a 30 and 60 mg dose prn. Subjects were stratified based on baseline IELT of ≤ 1 min or > 1 min. A total of 941 subjects completed the study (6.6% loss to follow-up, 6.4% withdrawal of consent, 5.6% personal reasons, 4.8% adverse events). The results were statistically significantly greater on dapoxetine compared to placebo and 60 mg was statistically better than 30 mg (Table 29). Improvement was seen from the first dose. Secondary endpoints were mostly supportive for dapoxetine over placebo, including participant reported outcomes (control of ejaculation, satisfaction with intercourse, SSI, GIC) and partner reported outcomes (satisfaction with intercourse, medication helpfulness, GIC, SSI, control of ejaculation and duration of intercourse), but no change in erection firmness. An analysis of baseline IELT ≤ 1 min and > 1 min showed similar results overall and both doses of dapoxetine were significantly greater than placebo.

Table 29: IELT at baseline and Week 12 results		Week 12		
Mean(SD)	Baseline	Placebo	30 mg	60 mg
IELT, minutes	0.94 (0.49)	1.66 (2.08)	2.86 (3.59)	3.36 (3.97)
Difference from previous column	-	+0.72	+1.20	+0.50
Baseline IELT ≤ 1 min	0.60-0.62	1.21 (1.35)	2.33 (3.84)	2.72 (3.31)
Control of Ejaculation	0.35-0.37	0.90 (0.85)	1.63 (1.08)	1.71 (1.17)
Difference from previous column	-	+0.53	+0.73	+0.10
Satisfaction with sexual intercourse	1.64-1.65	1.58 (1.03)	2.13 (1.10)	2.18 (1.06)
Difference from previous column	-	-0.06	+0.54	+0.05
Baseline IELT > 1 min	1.40-1.46	2.38 (2.75)	3.81 (2.86)	4.49 (4.75)
Control of Ejaculation	0.54-0.60	1.18 (1.06)	1.89 (1.13)	1.89 (1.14)
Difference from previous column	-	+0.64	+0.67	-0.02
Satisfaction with sexual intercourse	1.76-1.80	1.82 (1.08)	2.28 (1.03)	2.44 (1.06)
Difference from previous column	-	+0.06	+0.44	+0.14

Study C-2002-013: This was a multicentre, double blind, randomised, placebo controlled study in 1320 males with PE for 12 weeks to assess a 30 and 60 mg dose prn. A total of 1017 subjects

completed the study with terminations due to loss to follow-up, withdrawal of consent, personal reasons and mainly adverse events. The results were statistically significantly greater on dapoxetine compared to placebo and 60 mg was statistically better than 30 mg (Table 30). Improvement was seen from the first dose. Secondary endpoints were mostly supportive for dapoxetine over placebo, including participant reported outcomes (control of ejaculation, satisfaction with intercourse, SSI, GIC) and partner reported outcomes (satisfaction with intercourse, medication helpfulness, GIC, SSI, control of ejaculation and duration of intercourse), but no change in erection firmness. An analysis of baseline IELT ≤ 1 min and > 1 min showed similar results overall and both doses of dapoxetine were significantly greater than placebo.

Table 30: IELT at baseline and Week 12 results		Week 12		
Mean(SD)	Baseline	Placebo	30 mg	60 mg
IELT, minutes	0.90 (0.47)	1.84 (2.34)	2.70 (3.39)	3.28 (3.40)
Difference from previous column	-	+0.94	+0.86	+0.58
Baseline IELT ≤ 1 min	0.60-0.63	1.36 (1.95)	2.05 (3.22)	2.63 (3.18)
Control of Ejaculation	0.37-0.41	0.96 (0.88)	1.41 (1.03)	1.77 (1.14)
Difference from previous column	-	+0.59	+0.44	+0.33
Satisfaction with sexual intercourse	1.54-1.71	1.59 (1.05)	1.92 (0.99)	2.33 (1.04)
Difference from previous column	-	+0.05	+0.29	+0.28
Baseline IELT > 1 min	1.36-1.37	2.66 (2.69)	3.77 (3.39)	4.37 (3.50)
Control of Ejaculation	0.51-0.56	1.33 (1.01)	1.86 (1.08)	2.02 (1.09)
Difference from previous column	-	+0.77	+0.58	+0.11
Satisfaction with sexual intercourse	1.64-1.78	1.96 (1.04)	2.26 (1.04)	2.40 (1.01)
Difference from previous column	-	+0.19	+0.43	0

Study R096769-PRE-3001: This was a multicentre, double blind, randomised, placebo controlled study in 1162 European males with PE for 24 weeks to assess a 30 and 60 mg dose prn. Besides the standard endpoints, this study also assessed the responder rate as proportion of subjects who had a ≥ 2 category increase in control over ejaculation and ≥ 1 category decrease in personal distress. 618 subjects completed the study and 550 entered a one week withdrawal period. Terminations were due to insufficient response (8.7%), personal reasons (15.3%), adverse events (4-8% dapoxetine versus 1% placebo), loss to follow-up and other reasons. The results were statistically significantly greater on dapoxetine compared to placebo (Table 31). Improvement was seen from the first dose. Responder rate was 13% placebo, 25% 30 mg and 37% 60 mg which was statistically greater on dapoxetine. Responders rates were also significantly greater on dapoxetine based on IELT of ≤ 1 min and > 1 min. Secondary endpoints were mostly supportive for dapoxetine over placebo, including participant reported outcomes (control of ejaculation, ≥ 1 category increase in satisfaction with intercourse, > 1 category decrease in personal distress, GIC) and partner reported outcomes

(satisfaction with intercourse, SSI, control of ejaculation and partner personal distress). An analysis of baseline IELT ≤ 1 min and >1 min, showed both doses of dapoxetine were significantly greater than placebo with those with baseline >1 min having better results.

Table 31: IELT at baseline and Week 24 results		Week 24		
	Baseline	Placebo	30 mg	60 mg
IELT, mean (SD), minutes	0.88 (0.50)	1.9 (2.89)	3.1 (4.88)	3.5 (3.80)
Difference from previous column	-	+1.02	+1.20	+0.40
Control of ejaculation (%) (+2 category increase)	-	15	31	40
Difference from previous column	-	-	+16%	+9%
Satisfaction with sexual intercourse (%) (+1 category increase)	-	29	44	55
Difference from previous column	-	-	+15%	+11%

Study R096769-PRE-3003: This was a multicentre, double blind, randomised, placebo controlled study in 1067 Asian/Pacific males with PE for 12 weeks to assess a 30 and 60 mg dose prn. Besides the standard endpoints, this study also assessed the responder rate as above. 858 subjects completed the study. Terminations were due to subject choice (12%), adverse events (2-5% dapoxetine versus $<1\%$ placebo). The results were statistically significantly greater on dapoxetine compared to placebo (Table 32). Improvement was seen from the first dose. Responder rate was 22% placebo, 35% 30 mg and 37% 60 mg which was statistically greater on dapoxetine. Responder rates were also significantly greater on dapoxetine based on IELT of ≤ 1 min and >1 min. Secondary endpoints were mostly supportive for dapoxetine over placebo, including control of ejaculation, ≥ 1 category increase in satisfaction with intercourse, >1 category decrease in personal distress, GIC, satisfaction with intercourse, SSI, medication helpfulness and interpersonal difficulty. An analysis of baseline IELT ≤ 1 min and >1 min showed both doses of dapoxetine were significantly greater than placebo with those with baseline >1 min having better results.

Table 32: IELT at baseline and Week 12 results		Week 12		
	Baseline	Placebo	30 mg	60 mg
IELT, mean (SD) minutes	1.06 (0.46)	2.4 (2.05)	3.9 (3.95)	4.2 (3.97)
Difference from previous column	-	+1.34	+1.50	+0.30
-----Baseline IELT \leq 1min	0.56-0.62	3.61 (2.00)	3.91 (3.93)	3.25 (3.63)
-----Baseline IELT >1min	1.40-1.44	3.07 (3.65)	4.58 (3.81)	5.04 (4.06)
Control of ejaculation (%) (+2 category increase)	-	26	38	41
Difference from previous column	-	-	+12%	+3%
Satisfaction with sexual intercourse (%) (+1 category increase)	-	58	69	76
Difference from previous column	-	-	+11%	+7%

Study R096769-PRE-3002: This was a multicentre, double blind, randomised, placebo controlled study in 1238 North American males with PE to assess a 60 mg daily dose for 62 days followed by 7 days placebo versus 69 days of 60 mg daily. This safety study was designed to assess withdrawal effects and subjects were not required to meet the IELT inclusion criterion of ≤ 2 min for PE, however >90% had poor to very poor control over ejaculation. Outcomes such as control over ejaculation, satisfaction with intercourse, SSI, GIC, medication helpfulness, personal distress and interpersonal difficulty were statistically better on dapoxetine than placebo at weeks 4 and 9. In general, dapoxetine prn dosing showed better results than dapoxetine daily dosing.

Study C-2002-014: This open label study assessed long term efficacy and safety from two earlier studies in 1774 males for 9 months using prn dosing 1-3 hours prior to intercourse. A total of 962 completed the study with terminations mainly due to lack of efficacy (12.8%) and loss to follow-up (9.9%). 654 men received >12months total treatment. 11% reduced dose from 60 mg to 30 mg nearly all due to adverse events with nausea being most common (46%). Efficacy was maintained for dapoxetine subjects.

Safety

The clinical program comprised 700 subjects in Phase I studies and over 6000 subjects in Phase II and III studies. Specific studies examined blood pressure and QTc interval.

Phase I studies showed adverse events were greater on dapoxetine than placebo with most being mild to moderate but with a dose response seen. The most common adverse events were nausea (20-40%), diarrhoea, vomiting, headache, dizziness, taste perversion, yawn, pain, asthenia, constipation, anorexia, somnolence, vasodilation, anxiety, euphoria, agitation, nervousness, sweating, pruritus, chills, fever and blurred vision. Arrhythmia and first degree AV block were reported. Adverse effects from one study included diarrhoea (20%), dizziness (18%), headache (15%) compared to small percentages in placebo subjects. No serious adverse events or deaths were reported. Two subjects had hypertension on high doses. CK rises were seen in some (for example, peaks of 1108 U/L, 603 U/L, 320 U/L, 369 U/L) and transaminase rises were also seen.

Drug interaction studies showed combination with ketoconazole led to increased adverse events and ethanol led to increased impairment on digit testing. Tadalafil and sildenafil did not lead to increased adverse events and neither did combined use with tamsulosin in terms of orthostatic hypotension, however there was increased dizziness. The other drug interaction studies in general did not show an increase in adverse events when combined with dapoxetine.

Special studies examining blood pressure showed slightly increased blood pressure with dapoxetine up to 13/12mmHg using doses up to 160 mg but did not appear to be dose-related. In hypertensive men, blood pressure difference to placebo following treadmill exercising was about +2/-3mmHg and heart rate did not appear to be altered. ECG studies did not show dapoxetine causing an increase in QTc interval. No age related pattern of adverse events was seen. Adverse events were higher in 2D6 poor metabolisers than extensive metabolisers and higher on dapoxetine than placebo. Adverse events were higher in severe renal impairment and in severe liver impairment. Safety was similar between Japanese and Caucasian populations, although two Japanese subjects had CK rises of 7.8 x ULN and 20 x ULN.

The Phase II and III studies noted higher rates of adverse events on dapoxetine than placebo which were dose dependent with the most common being nausea which was also the most common leading to discontinuation. In the Phase III studies, the percentages of adverse events overall for placebo, 30 mg and 60 mg dapoxetine are in Attachment 1, but noting that overall dizziness is 5 x higher, psychiatric disorders are 2.7 x higher, anxiety is 4 x higher, insomnia 2.6 x higher, fatigue 3.4 x higher, vascular disorders 1.7 x higher, erectile dysfunction is 1.6 x higher, orthostatic hypotension is 1.7 x higher and hyperhidrosis 6 x higher on dapoxetine 60 mg than placebo.

Some percentages of events noted for placebo, 30 mg and 60 mg dapoxetine were as follows:

- Study 012: depression (0.2, 0.7, 1.2), accidental injury (2.9, 5.1, 3.3), cardiovascular (2.5, 1.9, 4.5)
- Study 013: euphoria (0, 0.2, 1.3), accidental injury (0.9, 1.3, 2.7)
- Study 3001: accidental injury (1.8, 2.8, 2.3), mood related (5.7, 9, 12.1), cardiovascular (3.1, 4.9, 8.5, mainly increased blood pressure), ectopics on Holter monitoring (19, 20-22, 23-24)
- Study 3002: mood related (8.2, 14.9, 13.5), cardiovascular (11, 21, 20.5, mainly dizziness), urogenital and sexual function (2.4, 3.3, 3.6), accidental injury (1.6, 2.2, 2).
- Study 3003: prodromal symptoms for syncope (2, 5.6, 14.3), CNS (5, 13.8, 24.2), cardiovascular (4.8, 11.3, 20.2, mainly dizziness).

Study 3002, with Holter monitoring, showed slightly higher supraventricular arrhythmias on dapoxetine than placebo (49 versus 42%) and 3 cases of VT on dapoxetine were considered unlikely to be related.

Suicidal ideation did not appear increased and new onset depression or euphoria was <1%. Mood related adverse events were seen in 9.1% of dapoxetine versus 3.6% of placebo subjects with the most common being anxiety, insomnia and irritability. Depression was seen in 0.3% placebo versus 0.4% of dapoxetine combined and there may be a temporal relationship in the incidence of depression and euphoria in subjects with no prior history. There were no overdoses. Accidental injuries were slightly greater on dapoxetine at 2.5% versus 1.8% on placebo. Syncope occurred in 0.25% of dapoxetine versus 0.04% of placebo subjects which was greater with first dose than subsequent doses. Holter monitoring in three of the Phase III studies showed increased incidence of ventricular and supraventricular ectopic beats. One subject had a sinus arrest of 28 s after first dose of 60 mg dapoxetine. Sexual dysfunction overall was 3.9% dapoxetine versus 1.8% placebo. No abnormal bleeding or laboratory changes were noted. No withdrawal effect was seen on prn dosing but slightly higher insomnia and dizziness were seen with daily dosing and there was a slight

increase in dizziness and insomnia leading to discontinuation. Long term safety indicated use up to 12 months did not raise additional concerns.

Risk-Benefit Analysis

Delegate Considerations

FDA Issued PDUFA Action Letter

The FDA PDUFA Action Letter stating that dapoxetine was not-approvable for the PE indication in October 2005 for the registration of dapoxetine was based on a smaller dataset than has been evaluated by the TGA. Since the FDA issued PDUFA Action Letter in October 2005, the sponsor has conducted further studies that were submitted to the TGA for evaluation but were not considered by the FDA. These included:

- Phase I PK study in Japanese and Caucasian subjects
- Phase I drug interaction study with tamsulosin
- Observational study in 1115 subjects to further characterise Intravaginal Ejaculatory Latency Time (IELT) and provide further evidence on the reliability of participant reported outcome measures.
- Three Phase III studies examining personal distress, interpersonal difficulty, treatment responders, mood, anxiety, akathisia, sexual function (IIEF), SSRI withdrawal, suicidality, cardiovascular safety, Holter monitoring and syncope.

Efficacy

The primary efficacy endpoint of IELT has some difficulties as an efficacy endpoint in PE studies. It lacks consensus on what constitutes a meaningful improvement in PE, it is unclear whether an IELT of <2 minutes is appropriate to define premature ejaculation, there is potential for men without premature ejaculation to be included in the arbitrary cut-off of 2 minutes and a given change in IELT varied highly amongst individuals, as seen by large standard deviations in the results. Observational studies indicated that improvements in IELT corresponded with improvements in perceptions of control over ejaculation, satisfaction with intercourse and personal distress. Therefore to address the problems with IELT, a responder definition was constructed of ≥ 2 category increase in control over ejaculation (0-4 point scale) and ≥ 1 category decrease in personal distress (0-4 point scale). The responder rates are intended to support the efficacy of dapoxetine along with other secondary endpoints.

In terms of IELT across the Phase III studies, the results firstly showed that the baseline IELT was about 0.88-1.06 minutes across all groups. With placebo, this increased by 0.72-1.34 minutes, indicating a significant placebo response rate. With dapoxetine, the IELT difference from placebo was 0.86-1.5min for the 30 mg dose. With the 60 mg dose the difference from 30 mg was 0.30-0.58 minutes for a total gain over placebo of 1.44-1.8 minutes at the maximum dose, which were statistically significant results compared to placebo. However, these results are of modest gain and of questionable clinical significance and when looking at the range of results, the wide standard deviations imply that some subjects would receive negligible benefit.

When examining the control over ejaculation, it can be seen that there is a significant placebo response rate of about 0.53-0.77 points. With 30 mg dapoxetine, the mean placebo subtracted gain is of 0.44-0.73 and when 60 mg dapoxetine is used, the gain over 30 mg is of -0.02 to 0.33. Again these are modest improvements on a 4 point scale. When examining satisfaction with sexual intercourse, it can be seen that there isn't much of a placebo response rate with change of about -0.06 to +0.19 points. When 30 mg dapoxetine is used, the mean placebo subtracted gain is of 0.29-0.54 and when 60 mg dapoxetine is used, the gain over 30 mg is of 0 to 0.28. These results are also of modest benefit on a 4 point scale.

Studies 3001 and 3003 show that the percentage of men who had a 2 category gain in control of ejaculation using placebo subtracted results was 12-16% for dapoxetine 30 mg and a further 3-9% for dapoxetine 60 mg. The same studies using a one category gain in satisfaction with sexual intercourse showed 11-15% gain with dapoxetine 30 mg over placebo and a further 7-11% gain with 60 mg dapoxetine. These studies showed a significant placebo response rate and modest efficacy from dapoxetine. The responder rates in these studies showed a placebo response rate of 13-22% versus 25-35% with 30 mg dapoxetine and 37% with 60 mg dapoxetine. The sponsor provided a pooled analysis that also used study 3001 but this study did not pre-specify for inclusion of subjects based on IELT time of ≤ 2 min. The pooled results were nevertheless similar with responder rates of 18% placebo, 31% dapoxetine 30 mg and 40% dapoxetine 60 mg. Although the responder rate criteria are a more difficult measurement, statistically significant results were still obtained, but again the clinical benefit is modest, in light of the placebo response rate. Secondary endpoints generally showed improvement with dapoxetine over placebo. Overall, the results showed high variability amongst subjects, which sometimes overlapped with placebo subjects, as seen by the large standard deviations. This was seen for the primary and secondary endpoints and suggests that the diagnostic criteria for PE may not be tight, the rating tools not highly specific or further study is needed to identify a more responsive group of subjects.

The sponsor has performed some post-hoc analyses by baseline IELT and participant reported outcomes using IELT cut-offs of <0.5 min, 0.5-1min, 1-1.5min and 1.5-2min to identify if certain groups would benefit more from dapoxetine. This showed that groups with greater baseline IELT had a greater increase in IELT and improvement in participant reported outcomes compared with those with lesser IELT values at baseline. However this is a post-hoc analysis which requires confirmation in a subsequent predefined study and overall the results did not identify a more responsive group. Given that a response to dapoxetine was seen within 4 weeks, the sponsor has proposed to include a PI statement advising the treating doctor to assess if continuing treatment is appropriate after this time.

Dose response

Some studies indicated a statistically significant dose response for 60 mg over 30 mg dapoxetine but this was not seen in all studies as agreed by the sponsor in the supplementary data. The sponsor therefore proposes to modify the PI to only use the 60 mg dose when 30 mg is insufficient and side effects are acceptable. However a dose response was also seen for adverse effects, therefore it is questionable whether a higher dose should be allowed given that a clear additional clinical benefit has not been demonstrated.

Syncope and cardiac conduction

The clinical trials showed syncope was >6 x higher on dapoxetine than placebo. A review by the sponsor identified 37 potentially relevant cases of syncope of which the majority had a decrease in heart rate, blood pressure or both which appeared to suggest a vasovagal mechanism. Of these, 7 cases who were wearing a Holter monitor were of particular interest. This showed 3 subjects experienced sinus arrest (two with 5 second pause and bradycardia and the third with a sinus arrest and 28 second period of asystole with ventricular and supraventricular ectopics and bradycardia), another experienced prolonged sinus pauses (longest RR of 4.59 s), another with ventricular and supraventricular ectopics and two with sinus bradycardia (44 and 55 bpm). These all occurred in otherwise healthy males with premature ejaculation. In practice, men would not be wearing a Holter monitor nor monitored as in a clinical trial and could have other risk factors for syncope or cardiovascular diseases (noting these subjects were excluded from the trials), especially in older males, that may increase their risk. In the clinical studies, ectopics and supraventricular arrhythmias were slightly higher on dapoxetine, along with increased blood pressure. A review of arrhythmias in the trial programme showed 9 cases of non-sustained VT occurring in 0.2%, 0.3% and 0.3% of placebo, 30 mg and 60 mg groups, all asymptomatic. A review of hypotension cases

showed an increase in orthostatic hypotension (8.6% placebo, 9.5% on 30 mg and 10.4% on 60 mg) and an increase in orthostatic systolic BP (3.9% placebo, 4.9% on 30 mg and 5.8% on 60 mg). ECGs did not detect QTc prolongation.

Syncopal events were associated with prodromal symptoms which may forewarn men to take precautionary measures. However, combination use with alcohol or other drugs may increase the risk of orthostatic hypotension or syncope which could then be potentially serious. While the syncopes were associated with spontaneous recovery, 5 of the 15 adjudicated cases were associated with injuries which were recoverable and 14 of the 37 cases discontinued. Despite the likely vasovagal aetiology, there is some concern from non-clinical findings regarding cardiac arrhythmia. Studies in guinea pigs showed dapoxetine leads to severe disturbances in cardiac conduction and contractile function at a low No Observed Adverse Effect Level of only 2 based on animal:human C_{max} . Other non-clinical findings included shortened QTc interval, lengthened PR and QRS interval, bundle branch block, AV block and abolished cardiac contraction which were observed at 9 times human exposure margins, however the next dose level tested where no effects were seen was at 2 times human exposure, thus leaving a deficiency in the exposure assessment. Although the sponsor has cited other studies in which these cardiac / ECG effects were not seen, these studies in question used exposure margins that were <0.5 of human exposure and are therefore inadequate to dismiss concerns on cardiac conduction for men. It is therefore unknown if at moderately higher doses, conduction effects could occur (for example with misuse, off-label). The sponsor is proposing to address the concern with syncope through PI / CMI warnings, package warnings, educational programs and a Risk Management Plan. However, it is unclear if these proposals will be effective.

Misuse and off-label use

There is concern for potential off label use and misuse of dapoxetine with recreational drugs and alcohol at doses greater than approved, at a frequency of greater than once per 24 hours or in an older population for which there is no data to demonstrate its efficacy or safety. Although this is beyond the intended use of the product, it needs to be considered that there is potential for such use in practice. Combination with tadalafil did not affect the dapoxetine PK but combination with sildenafil led to a 22% increase in exposure. Whilst this is relatively small, there is potential for orthostatic intolerance and the effects of dapoxetine on PDE5 inhibitors have not been assessed. The sponsor has identified the potential for off-label use associated with five distinct populations: men without PE, adolescents, men who are also abusing prescription drugs, illicit drugs or alcohol, men with co morbidities and men who use excessive amounts of dapoxetine. There is a lack of data in these groups except an interaction study with alcohol which showed an exacerbation of neurological effects which could lead to increased somnolence or decreased alertness. The potential for a pharmacodynamic interaction between dapoxetine and recreational drugs is discussed in the supplementary evaluation. These effects could result from drugs with serotonergic activity (leading to arrhythmia, serotonin syndrome) or drugs with sedative properties (leading to somnolence or further dizziness). The sponsor has proposed to address this with PI / CMI warnings and their Risk Management Plan, however it is unknown if these proposals would be effective.

Nonclinical toxicities and male fertility

In general, the repeat dose studies tested dapoxetine and its main metabolites at exposure levels that were frequently low compared to the dose in humans. This is inadequate for assessing drug safety for a product that could be used long term in relatively healthy males since it limits the ability of the non-clinical studies to reveal potential toxicity. Some safety concerns seen in the non-clinical data, for example, CNS, hepatic and renal effects were at exposures that were less than or close to human exposure. Clinically, CNS effects were seen by way of adverse events such as anxiety, dizziness, somnolence, insomnia, nervousness and euphoria and renal effects by way of haematuria only being reported in dapoxetine-treated subjects and not placebo-treated subjects. The hepatic and renal

findings may reflect the large doses of dapoxetine given to animals, the respiratory findings may reflect gastric lavage irritation and lymphoid findings may reflect non-specific toxicity, but this cannot be certain, especially given the low exposure margin. Male fertility has also not been adequately assessed, again due to low exposures in animal studies and therefore this remains a potential risk for men, despite the negative findings on sperm count and motility seen. Ossification problems were also seen in animal studies.

Tumour promotion

There remains some doubt on the carcinogenic potential of dapoxetine, even though it was not genotoxic. The studies in animals used inadequate exposures to dapoxetine that were <0.7 (mice) or <1.8 (rats) of clinical exposure which raises doubt on the carcinogenic safety of dapoxetine in men when given long term, despite no treatment related increases in tumour incidence in rats. A study in mice using topical dermal application of dapoxetine showed an increase in the incidence of papillomas, however the non-clinical evaluator considered this may reflect irritancy rather than carcinogenicity as such. The sponsor submitted supplementary data that comprised two additional genotoxicity studies which further supported the lack of genotoxicity, however this does not override the deficiency in the exposure margin in the carcinogenicity data, nor the concern in relation to tumour promotion from the dermal study.

Accidental Injuries

Accidental injuries were higher on dapoxetine than placebo at 1.4x greater with a large variety of causes, some serious. It is possible that dizziness, syncope or changes in alertness or sleep may be related. The sponsor is proposing to address this through risk minimisation activities including patient education in PI/CMI and blister packaging. On a prn dosing this may be minimised, but those using the drug regularly or misusing could be further affected.

Suicidality

SSRIs have been associated with suicidality however no cases were reported in the clinical programme with dapoxetine. There were, however, higher rates of mood-related adverse events on dapoxetine such as euphoria and anxiety. Depression rates were similar to placebo and there were no overdoses. Whilst the prn dosing and short half-life do not indicate a concern from this data, there nevertheless remains an overall concern given that men with depression were excluded from the trials, dapoxetine is an SSRI and that SSRIs have been associated with suicidality. The studies also used essentially healthy males aged 18-64 years who were not taking antidepressants. There is concern therefore on whether dapoxetine would be efficacious and safe in the wider population such as those taking antidepressants, with psychiatric diagnoses such as depression or at risk of suicide. The sponsor proposes to address this through warnings in the PI.

Other safety issues

Neurological and gastrointestinal adverse events were common and occurred in a dose dependent manner. On Day 1 of treatment, the most common AE of dizziness, headache, nausea or somnolence occurred in 2.4% placebo, 8.1% 30 mg and 15.1% 60 mg which correlated with T_{max} . Sexual dysfunction did not appear to be greater but erectile dysfunction was noted to be slightly higher and genitourinary events slightly higher. A post-hoc analysis of CK and liver transaminases showed the risk to be low and similar to placebo. There did not appear to be any withdrawal effects from prn dosing and no increase in abnormal bleeding or laboratory changes.

Age

Only limited data is available in males older than 65 years to ascertain safety or efficacy in this age group, however the sponsor is not proposing registration for males older than 64 years. The PK data indicated slightly higher exposure and for a longer period than younger males, therefore further

assessment is needed in this area. Given that somnolence and dizziness may be more common in the elderly then further study is needed.

Data issues, further study

A total of 378 subjects have been exposed to dapoxetine for >12 months which fulfils the TGA-approved European guideline on long term exposure, however more subjects exposed for this duration or longer would have been useful.³⁸ The sponsor is conducting two post-marketing studies to help define the patient population most likely to benefit from dapoxetine and also to monitor safety further. One of these is a trial in 12,000 men for 12 weeks to compare dapoxetine with alternate care treatments. Such data would have been useful as part of this registration since it may address the concerns with the IELT measurement, wide variation in individual responses, significance of clinical results and uncertainty on the population most likely to benefit. There are also no post-marketing data available, which would have been helpful with concerns over safety, misuse or off-label use.

Summary

A disease which is non life-threatening requires a high standard of safety and clear demonstration of clinically meaningful efficacy with good internal and external validity and risks that should be manageable through the use of the PI / CMI. For dapoxetine, the efficacy has been modest and of uncertain clinical benefit in an otherwise healthy male population even though it has been of statistical significance over placebo. The wide variability in individual response and concerns with the IELT endpoint need further investigation and a more responsive group of subjects should be identified. The known and potential safety issues discussed above, including those from non-clinical data, are of concern and the extensive proposals to manage them through PI/CMI warnings, blister warnings, risk minimisation activities, education programmes and further trials appear to be in excess of what would be expected for the treatment of premature ejaculation. It is also unknown how successful these proposals would be in practice. It is acknowledged that there are no TGA approved treatments for premature ejaculation and that other products are being used off-label. However, when the benefits are balanced against the known and potential risks from this SSRI, in the context of a condition which is non life-threatening, the Delegate was inclined to view the efficacy findings as not outweighing the safety concerns; the risk/benefit balance of dapoxetine was considered unfavourable at the time. The Delegate proposed to reject the submission based on the efficacy and safety of the product not being satisfactorily established for the reasons stated above in the Risk / Benefit Discussion.

The Delegate requested that the sponsor address the following issues in their Pre-ACPM (previously ADEC) response:

- An update on clinical trials planned or underway to further investigate efficacy and safety.
- Any further non-clinical studies to address the concerns raised by the non-clinical evaluator.
- A summary of post-market activities planned for Australia to minimise risk from dapoxetine, including from misuse or off-label use.
- Why males ≥ 65 years not been assessed in clinical trials?

The Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC) was asked by the Delegate to address the following issues:

- Is the efficacy demonstrated clinically meaningful?
- Is the safety profile of dapoxetine acceptable for premature ejaculation?
- Does the efficacy benefit outweigh the safety concerns in this population?

- Are the non-clinical findings and deficiencies of significant concern?
- Do the sponsor's PI/CMI warnings, risk minimisation activities, blister labelling and educational programmes adequately address the safety concerns for dapoxetine?
- Could the product be approvable with further restrictions?

Advisory Committee Considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended approval of Priligy 30 mg tablets for the indication:

PRILIGY is indicated for the treatment of premature ejaculation (PE) in men 18 to 64 years of age, who have all of the following:

- *Persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the patient wishes; and*
- *marked personal distress or interpersonal difficulty as a consequence of PE; and*
- *poor control over ejaculation*

In making this decision, the Committee accepted that satisfaction experienced by the patients in the clinical trial could be interpreted as clinically meaningful, although the clinical benefit appears to be modest. The Committee strongly encouraged implementation of a stringent Risk Management Plan to address the safety concerns and the potential for abuse and off-label use. The ACPM noted the dose response effect for syncope and recommended the inclusion of a boxed warning concerning syncope associated with Priligy. The PI and CMI documents must clearly state that a double dose is not to be taken due to the increased risks and lack of additional benefit.

The Committee recommended rejection of the registration of the 60 mg tablets on the grounds that there remain safety concerns at this dose with no consistent additional significant benefit demonstrated. The sponsor subsequently withdrew the application to register the 60 mg tablets.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Priligy film-coated tablets containing dapoxetine 30 mg (as hydrochloride) for the indication:

Priligy is indicated for the treatment of premature ejaculation (PE) in men 18 to 64 years of age, who have all of the following:

- *an intravaginal ejaculatory latency time (IELT) of less than two minutes; and*
- *persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the patient wishes; and*
- *marked personal distress or interpersonal difficulty as a consequence of PE; and*
- *poor control over ejaculation.*

The product was approved with the following specific conditions of approval:

1. The implementation in Australia of the Dapoxetine Risk Management Plan (RMP) dated 22 July 2010 Version 2, as agreed with the TGA and its Office of Product Review.
2. The sponsor is to submit reports of the following clinical trials / reports to the TGA for evaluation as Category 1 submissions when they are completed:
 - a. The PAUSE Study (Premature Ejaculation - Actual Use Safety and Effectiveness Study)
 - b. The COUPLE Study (Concomitant Use of Priligy in Men Treated for Erectile Dysfunction)
 - c. The PRILIGY Usage Patterns in Selected Populations study

- d. The report of the IMMP study in New Zealand (Priligy Intensive Medicines Monitoring Programme)
- e. The PASSION Study (The Asia Pacific Flexible Dose Study of Dapoxetine and Patient Satisfaction in Premature Ejaculation Therapy).

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

PRILIGY[®]

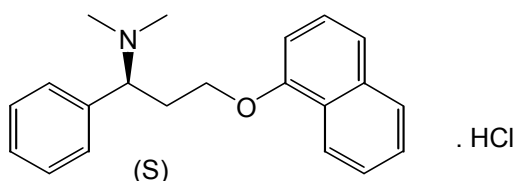
PRODUCT INFORMATION

SYNCOPE: Patients on PRILIGY need to be made aware that they could experience syncope at any time with or without prodromal symptoms during their treatment with PRILIGY. Syncope characterized as loss of consciousness has been reported in clinical trials and is considered medicinal product-related. A dose-response relationship is suggested. Prodromal symptoms (such as nausea, dizziness or light headedness) often preceded the syncope. Patients should be counselled about the importance of maintaining adequate hydration, and about how to recognise and act upon prodromal signs and symptoms (see **PRECAUTIONS**) to decrease the likelihood of serious injury associated with falls due to loss of consciousness. Patients must not take more than one tablet once every 24 hours due to increased risk.

NAME OF THE MEDICINE

Dapoxetine hydrochloride

Dapoxetine hydrochloride has the following chemical structure:



C₂₁H₂₃NO.HCl

MW: 341.88

CAS: 129938-20-1

DESCRIPTION

Dapoxetine hydrochloride belongs to the pharmacotherapeutic group of selective serotonin reuptake inhibitors (SSRIs).

PRILIGY is available as 30 mg tablets. Each PRILIGY 30 mg film-coated tablet contains 30 mg of dapoxetine base (as hydrochloride). Inactive ingredients: lactose, cellulose-microcrystalline, croscarmellose sodium, silica-colloidal anhydrous, magnesium stearate, hypromellose, glycerol triacetate, titanium dioxide, iron oxide black, iron oxide yellow.

Dapoxetine hydrochloride is a white to slightly yellow powder. It is freely soluble in methanol, propylene glycol, some organic solvents (eg. N,N-dimethylformamide) and slightly soluble in ethanol. The solubility of dapoxetine hydrochloride in aqueous media is a function of the pH (soluble at pH 3.9, sparingly soluble at pH 2.1 and insoluble at pH >7.0).

The chemical name is (+)-(S)-N, N-dimethyl-(α)-[2-(1-naphthalenyloxy) ethyl]-benzenemethanamine hydrochloride.

PHARMACOLOGY

Pharmacodynamics

Mechanism of action

Dapoxetine inhibits the serotonin transporter. The mechanism of action of dapoxetine in premature ejaculation is presumed to be linked to the inhibition of neuronal reuptake of serotonin and the subsequent potentiation of the neurotransmitter's action at pre- and post-synaptic receptors.

Human ejaculation is primarily mediated by the sympathetic nervous system. The ejaculatory pathway originates from a spinal reflex centre, mediated by the brain stem, which is influenced initially by a number of nuclei in the brain (medial preoptic and paraventricular nuclei). In the rat, dapoxetine inhibits the ejaculatory expulsion reflex by acting at a supraspinal level with the lateral paragigantocellular nucleus (LPGi) as a necessary brain structure for the effect. Post ganglionic sympathetic fibres that innervate the seminal vesicles, vas deferens, prostate, bulbourethral muscles, and bladder neck cause them to contract in a coordinated fashion to achieve ejaculation. Dapoxetine modulates this ejaculatory reflex in rats, causing an increase in pudendal motoneuron reflex discharge (PMRD) latency.

Pharmacokinetics

Absorption

Dapoxetine is rapidly absorbed with maximum plasma concentrations (C_{max}) occurring approximately 1-2 hours after tablet intake. The absolute oral bioavailability of dapoxetine is approximately 40% (range 15-76%). Following single oral doses of 30 mg and 60 mg in the fasted state, peak plasma concentration of dapoxetine were 297 ng/ml after 1.01 hours, and 498 ng/ml after 1.27 hours, respectively.

Ingestion of a high fat meal modestly reduced the C_{max} (by 10%) and modestly increased the AUC (by 12%) of dapoxetine and slightly delayed the time for dapoxetine to reach peak concentrations; however, the extent of absorption was not affected by consumption of a high fat meal. These changes are not clinically significant. PRILIGY can be taken with or without food.

Distribution

Greater than 99% of dapoxetine is bound *in vitro* to human plasma proteins. The active metabolite desmethyldapoxetine is 98.5% protein bound. Dapoxetine appears to have a rapid distribution with a mean steady state volume of distribution of 162 L. Following intravenous administration in humans, mean estimated initial, intermediate, and terminal half-life values for dapoxetine were 0.10, 2.19, and 19.3 hours respectively.

Metabolism

In vitro studies suggest that dapoxetine is cleared by multiple enzyme systems in the liver and kidneys, primarily CYP2D6, CYP3A4, and flavin monooxygenase 1 (FMO1). Following oral dosing in a clinical study designed to explore the metabolism of ^{14}C -dapoxetine, dapoxetine was extensively metabolised to multiple metabolites primarily through the following biotransformational pathways: N-oxidation, N-demethylation, naphthyl hydroxylation, glucuronidation and sulfation. There was evidence of presystemic first-pass metabolism after oral administration.

Intact dapoxetine and dapoxetine-N-oxide were the major circulating species in the plasma. *In vitro* functional and binding studies showed that dapoxetine-N-oxide was only weakly active at the serotonin transporter. Additional metabolites include desmethyldapoxetine and didesmethylapoxetine, which account for less than 3% of the circulating medicinal product-related material. *In vitro* functional studies indicate that desmethyldapoxetine is equipotent to dapoxetine and didesmethylapoxetine has approximately 50% of the potency of dapoxetine. The unbound AUC of desmethyldapoxetine is ~40-50% of the free exposure of dapoxetine. The unbound (C_{max}) of desmethyldapoxetine is estimated to be 15-20% of dapoxetine C_{max} in the absence of intrinsic or extrinsic factors that may change exposure levels. The half-life of desmethyldapoxetine is similar to that of dapoxetine.

Excretion

The metabolites of dapoxetine were primarily eliminated in the urine as conjugates. Unchanged active substance was not detected in the urine. Dapoxetine has a rapid elimination, as evidenced by a low concentration (less than 5% of peak) 24 hours after dosing. There was minimal accumulation of dapoxetine following daily dosing. The terminal half-life is approximately 19 hours following oral administration.

Special Populations

Race

Analyses of single dose clinical pharmacology studies using 60 mg dapoxetine indicated no statistically significant differences between Caucasians, Blacks, Hispanics and Asians. A clinical study conducted to compare the pharmacokinetics of dapoxetine in Japanese and Caucasian subjects showed 10% to 20% higher plasma levels (AUC and peak concentration) of dapoxetine in Japanese subjects due to lower body weight. The slightly higher exposure is not expected to have a meaningful clinical effect.

Elderly (age 65 years and over)

Analyses of a single dose clinical pharmacology study using 60 mg dapoxetine showed that healthy elderly subjects had a slight increase in AUC_{inf} , by approximately 12%, and a mean terminal half-life of approximately 26 hours. This slightly higher exposure and longer half-life is not expected to have a meaningful clinical effect.

Renal impairment

In a single dose clinical pharmacology study using 60 mg dapoxetine, no correlation was noted between creatinine clearance and dapoxetine C_{max} or AUC_{inf} in subjects with mild (creatinine clearance 50 to 80 mL/min), moderate (creatinine clearance 30 to <50 mL/min), and severe (creatinine clearance <30 mL/min) renal impairment. Dapoxetine pharmacokinetics have not been evaluated in patients requiring renal dialysis. Limited data (n=4) in subjects with severe renal impairment showed an approximate 100% increase in AUC_{inf} when compared to those healthy subjects with no renal impairment (see **PRECAUTIONS** and **DOSAGE AND ADMINSTRATIONS**).

Hepatic impairment

The pharmacokinetics of dapoxetine and desmethyldapoxetine are unchanged in patients with mild hepatic impairment. In patients with moderate hepatic impairment (ChildPugh Class B), unbound C_{max} of dapoxetine is increased by 55% and unbound AUC is increased by 120%. The unbound C_{max} and AUC of the active fraction were unchanged and doubled, respectively.

In severe hepatic impairment, the unbound C_{max} of dapoxetine was unchanged but the unbound AUC was increased more than 3-fold. The AUC of the active fraction was increased several-fold (see **CONTRAINDICATIONS** and **DOSAGE AND ADMINISTRATION**).

CYP2D6 Polymorphism

In a single dose clinical pharmacology study using 60 mg dapoxetine, plasma concentrations in poor metabolisers of CYP2D6 were higher than in extensive metabolisers (approximately 31% higher for C_{max} and 36% higher for AUC_{inf}) of dapoxetine and 98% higher for C_{max} and 161% higher for AUC_{inf} of desmethyldapoxetine). The active fraction of dapoxetine may be increased by approximately 46% at C_{max} and by approximately 90% for AUC. This increase may result in a higher incidence and severity of dose dependent adverse events (see **DOSAGE AND ADMINISTRATION**). The mean terminal half-life in poor metabolisers of CYP2D6 was approximately 22 hours, in comparison to a mean terminal half-life of approximately 19.5 hours, observed in extensive metabolisers of CYP2D6. The safety of dapoxetine in poor metabolisers of CYP2D6 is of particular concern with concomitant administration of other medicinal products that may inhibit the metabolism of dapoxetine such as moderate and potent CYP3A4 inhibitors (see **PRECAUTIONS** and **DOSAGE AND ADMINSTRATIONS**).

Plasma concentrations of dapoxetine and desmethyldapoxetine in CYP2D6 ultrarapid metabolisers are expected to be decreased.

CLINICAL TRIALS

The effectiveness of PRILIGY in the treatment of premature ejaculation (PE) was established in four double-blind, placebo-controlled clinical trials, in which a total of 1616 subjects were randomised to PRILIGY 30mg and 1612 to placebo. All subjects were 18 years of age or older; 99% were <64 years of age. All subjects were heterosexual males, in a stable relationship for at least 6 months, had PE defined by the DSM-IV-TR criteria and in two trials had at least moderate distress or interpersonal difficulty and had an intravaginal ejaculatory latency time (IELT; time from vaginal penetration to the moment of intravaginal ejaculation) of ≤ 2 minutes in a minimum of 75% of evaluable sexual intercourse events during the baseline period. Subjects with controlled hypertension (SBP<180 mmHg, DBP<100 mmHg) were included in Phase 3 studies. Subjects with other forms of sexual dysfunction, including erectile dysfunction and those using other forms of pharmacotherapy for the treatment of PE or antidepressants were excluded from all studies.

In all studies, subjects were instructed to administer PRILIGY 1-3 hours prior to anticipated sexual activity and not to take more than one dose per 24 hours. Three of the studies were 12 weeks in duration (C-2002-012, C-2002-013, R096769-PRE-3003), and one study was 24 weeks of treatment followed by a one week assessment of possible withdrawal effects (R096769-PRE-3001).

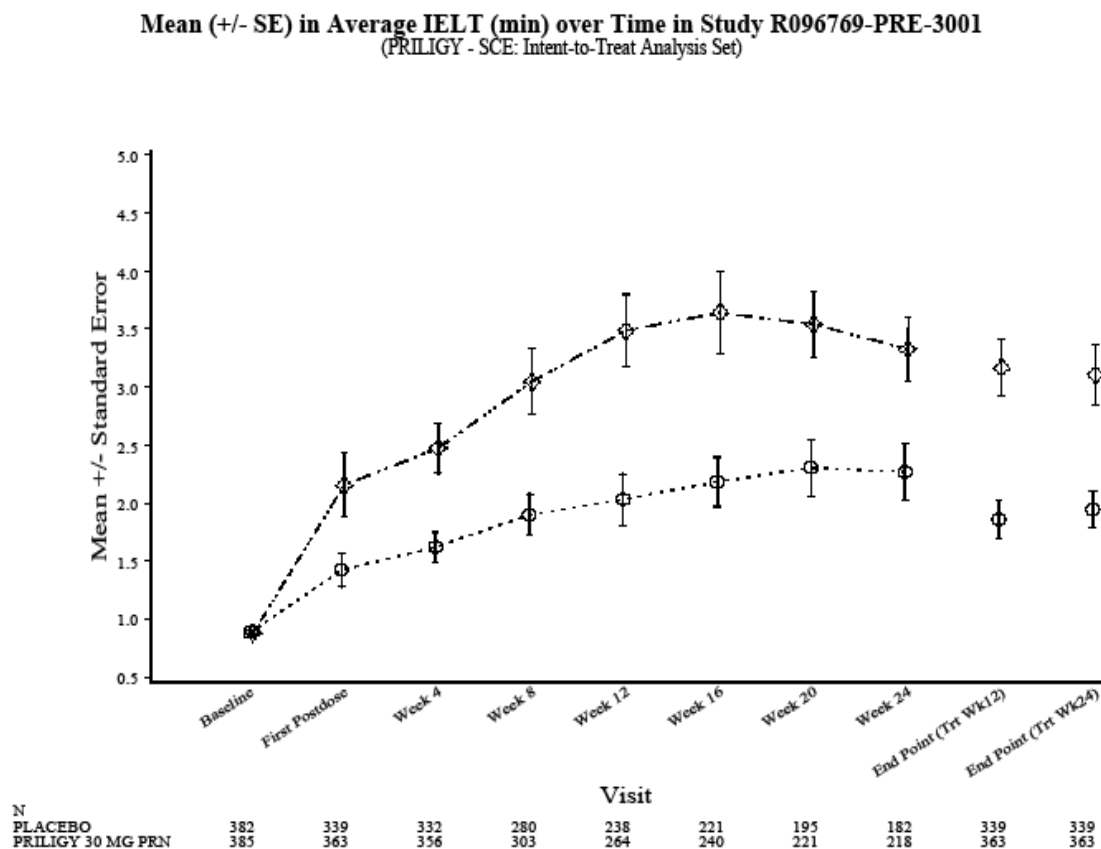
In the analysis of the pooled studies, mean average IELT at Week 12 (LPOCF) was significantly greater ($p<0.001$) in the PRILIGY 30mg (3.1 min) than in the placebo group (1.95 min) (Table 1). These results were similar to those seen in each Phase 3 study, where mean average IELT at Week 12 (LPOCF) was statistically greater for PRILIGY 30 mg compared to the placebo group. In the 12 week US studies that investigated PRILIGY 30mg (C-2002-012 and C-2002-013), 1.1% of subjects withdrew due to lack of efficacy, 4.8% due to personal reasons, 4.0% due to adverse events, 4.6% due to withdrawal of consent, 6.3% due to lost to follow up, 1.3% due to non-compliance or a protocol violation and 0.6% due to other reasons. In the 12 week Pan-Asian study R096769-PRE-3003 that investigated PRILIGY 30mg, 1.1% of subjects withdrew due to insufficient response, 9.9% due to personal reasons, 1.7% due to AEs, 0.8% due to lost to follow up, and 5.9% due to other reasons. In the 24 week EU study R096769-PRE-3001 that investigated PRILIGY 30mg, 6.4% of subjects withdrew due to insufficient response, 14.4% due to personal reasons, 3.9% due to AEs, 5.7% due to lost to follow up and 12.4% due to other reasons.

Table 1: Mean Average IELT[§] Results in Phase 3 Placebo-Controlled Studies

(Dapoxetine - SCE: ITT Analysis Set)			
---- At Study Endpoint+ ----			
	Baseline*	Placebo	Priligy 30 mg
Pooled Studies			
Mean Average IELT(SD), Minutes	0.94 (0.49)	1.95 (2.37)	3.1 (3.99)
Difference from baseline		1.01	2.16
Difference from placebo			1.15
C-2002-012			
Mean Average IELT (SD), Minutes	0.92 (0.49)	1.66 (2.09)	2.86 (3.59)
Difference from baseline		0.74	1.94
Difference from placebo			1.2
C-2002-013			
Mean Average IELT(SD), Minutes	0.90 (0.48)	1.84 (2.33)	2.70 (3.39)
Difference from baseline		0.94	1.8
Difference from placebo			0.86
R096769-PRE-3001			
Mean Average IELT(SD), Minutes	0.88 (0.5)	1.94 (2.89)	3.11 (4.88)
Difference from baseline		1.06	2.23
Difference from placebo			1.17
R096769-PRE-3003			
Mean Average IELT(SD), Minutes	1.06 (0.46)	2.42 (2.05)	3.85 (3.95)
Difference from baseline		1.36	2.79
Difference from placebo			1.43
+ Endpoint = Last observation carried forward (LPOCF) to week 12			
§ Calculated as the treatment group mean from individual subjects' average IELT (Studies C-2002-012, C-2002-013, R096769-PRE-3003) and Week 24 (Study R096769-PRE-3001)			
*Pooled placebo and Priligy 30 mg groups			

In a representative study (R096769-PRE-3001) with the longest treatment duration (24 weeks), 1162 subjects were randomized, 385 to placebo, 388 to PRILIGY 30 mg as needed, and 389 to PRILIGY 60 mg as needed. The mean average IELT at baseline and study endpoint for placebo and 30mg as needed treatment groups is shown in Figure 1. Increases in mean average IELT at the week 24 endpoint (LPOCF) were statistically significant ($p < 0.001$) in the PRILIGY group versus placebo. The magnitude of IELT prolongation was related to baseline IELT and was variable between individual subjects. The clinical relevance of PRILIGY treatment effects are described below in terms of patient reported response rates.

Figure 1: Study R096769-PRE-3001



Treatment Group: PLACEBO PRILIGY 30 MG PRN
 End Point (TRT WK12) = LPOCF to Week 12. End Point (TRT WK24) = LPOCF to Week 24.
 LPOCF is last post-baseline observation carried forward.

In addition to the primary endpoint of average IELT, meaningful treatment benefit to the patient in the above study was demonstrated using a definition of treatment response consisting of a composite of at least a 2-category increase in control over ejaculation (response options: very poor, poor, fair, good, and very good) plus at least a 1-category decrease in ejaculation-related distress (response options: not at all, a little bit, moderately, quite a bit, and extremely). A greater percentage of subjects responded in the PRILIGY group versus placebo beginning at Week 4 and up to and including Week 24 (this was statistically significant; $p=0.003$ for dapoxetine 30 mg versus placebo at Week 16, all other comparisons $p \leq 0.001$). Significant decrease in subject distress and significant improvement in subject satisfaction with sexual intercourse were also observed (response options: very poor, poor, fair, good, and very good). Improvements at weeks 12 and 24 (LPOCF) for the key secondary endpoints are presented in Table 2.

Table 2: Percentage of Subjects with Improvement in Key Secondary Endpoints (Study R096769-PRE-3001)

Key Secondary Endpoint (at LPOCF*)	Placebo %	PRILIGY 30 mg %
Treatment Response Composite (change ≥ 2 in control and ≤ -1 in distress)	(n=346)	(n=359)
Week 12	12.1	27.3*
Week 24	13.0	25.3*
Change ≤ -1 in Distress	(n=347)	(n=360)
Week 12	46.1	63.1*
Week 24	47.8	60.0*
Change ≥ 1 in Satisfaction	(n=347)	(n=359)
Week 12	31.7	51.3*
Week 24	35.7	48.5*

* p-value <0.001 for PRILIGY versus placebo; LPOCF is last post-baseline observation carried forward

Control rated as control over ejaculation: very poor, poor, fair, good, and very good

Satisfaction rated as satisfaction with sexual intercourse: very poor, poor, fair, good, and very good

Distress rated as distress related to timing of ejaculation: not at all, a little bit, moderately, quite a bit, and extremely

Other secondary patient reported outcome (PRO) endpoints were assessed in the clinical trials including clinical global impression of change in condition, CGIC, a commonly used measure in which patients assess the status of their condition. Patients were asked to compare their premature ejaculation from the start of the study, with response options ranging from much better to much worse. CGIC results by treatment group reported at the end of the above study are shown in Table 3.

Table 3: Results of Clinical Global Impression of Change in Condition at Study Endpoint (LPOCF*); Study R096769-PRE-3001

CGIC Response Outcome	Placebo n (%)	PRILIGY 30 mg n (%)
No Change or Worse**	236 (68.0%)	152 (42.3%)
Slightly Better	57 (16.4%)	97 (27.0%)+
Better	41 (11.8%)	74 (20.6%)
Much Better	13 (3.7%)	36 (10.0%)
Total	347 (100%)	359 (100%)

* LPOCF is last post-baseline observation carried forward

**No Change or Worse includes No Change, Slightly Worse, Worse or Much Worse

+At least Slightly Better CGIC response rate (includes Slightly Better, Better and Much Better): Placebo (32%) and Priligy 30 mg (57.7%)

Although PRILIGY 60 mg is not approved, this dose was used to test the withdrawal effects of chronic daily and as needed dosing of PRILIGY in the treatment of premature ejaculation in a placebo-controlled, double-blind, parallel-group study in which 1238 subjects were randomized. Subjects diagnosed with PE based on the DSM-IV-TR without an IELT restriction received placebo or 60 mg PRILIGY either once daily or as needed for 62 days followed by a withdrawal assessment phase of 7 days of additional PRILIGY treatment or placebo. Withdrawal effects after abrupt cessation of therapy were measured using the Discontinuation Emergent Signs and Symptoms (DESS), a clinician-rated instrument that queries for symptoms and signs associated with the discontinuation of serotonin reuptake inhibitor treatment. The DESS specifies a check list of 43 symptoms that are clinician rated as 1 of 4 categories (i.e., new symptom; old symptom, but worse; old symptom, but improved; and old symptom, but unchanged, or

symptom not present. Those symptoms rated by the clinician as “new” or “old, but worse” are counted as points indicative of a possible withdrawal effect. For each subject, discontinuation syndrome was defined as an increase in the weekly DESS score by at least 4 points from Day 63 to Day 70. In this study, there was no clear evidence of discontinuation (withdrawal) syndrome upon abrupt discontinuation of PRILIGY therapy. Consistent with the lack of discontinuation syndrome based on DESS, adverse event data showed little evidence of withdrawal symptoms. Similar results were seen in a second double-blind clinical trial with a 24-week treatment phase of 30 and 60 mg doses as needed followed by a 1-week withdrawal assessment period.

In the two multidose Phase 3 studies (C-2002-012 and C-2002-013) where the CYP2D6 metabolizer status was identified, a total of 120 poor metabolizers and 1598 extensive metabolizers were enrolled and treated with PRILIGY. No overall differences were seen in efficacy or safety between poor and extensive metabolisers.

INDICATIONS

PRILIGY is indicated for the treatment of premature ejaculation (PE) in men 18 to 64 years of age, who have all of the following:

- an intravaginal ejaculatory latency time (IELT) of less than two minutes; and
- persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the patient wishes; and
- marked personal distress or interpersonal difficulty as a consequence of PE; and
- poor control over ejaculation.

CONTRAINDICATIONS

PRILIGY is contraindicated in patients with known hypersensitivity to dapoxetine hydrochloride or to any of the excipients.

PRILIGY is contraindicated in patients with significant pathological cardiac conditions (such as heart failure (NYHA class II-IV), conduction abnormalities (second- or third-degree AV block or sick sinus syndrome) not treated with a permanent pacemaker, significant ischemic heart disease or significant valvular disease).

PRILIGY is contraindicated for concomitant treatment with monoamine oxidase inhibitors (MAOIs), or within 14 days of discontinuing treatment with an MAOI. Similarly, an MAOI should not be administered within 7 days after PRILIGY has been discontinued (see **PRECAUTIONS – Interactions with Other Medicines**).

PRILIGY is contraindicated for concomitant treatment with thioridazine, or within 14 days of discontinuing treatment with thioridazine. Similarly, thioridazine should not be administered within 7 days after PRILIGY has been discontinued (see **PRECAUTIONS – Interactions with Other Medicines**).

PRILIGY is contraindicated for concomitant treatment with serotonin reuptake inhibitors [selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs)] or other medicinal/herbal products with serotonergic effects [e.g., L-tryptophan, triptans, tramadol, linezolid, lithium, St. John's Wort (*Hypericum perforatum*)] or within 14 days of discontinuing treatment with these medicinal/herbal products. Similarly these medicinal/herbal products should not be administered within 7 days after PRILIGY has been discontinued (see **PRECAUTIONS – Interactions with Other Medicines**).

PRILIGY is contraindicated for concomitant treatment with potent CYP3A4 inhibitors such as ketoconazole, itraconazole, ritonavir, saquinavir, telithromycin, nefazodone, nelfinavir, atazanavir, etc. (see **PRECAUTIONS – Interactions with Other Medicines**).

PRILIGY is contraindicated in patients with moderate and severe hepatic impairment.

PRECAUTIONS

Patients must not take more than one tablet once every 24 hours due to increased risk of side effects (see Boxed Warning) and lack of additional benefit.

General

PRILIGY is only indicated in men with PE. Safety has not been established and there are no data on the ejaculation-delaying effects in men without PE.

Use with recreational drugs

Patients should be advised not to use PRILIGY in combination with recreational drugs. Recreational drugs with serotonergic activity such as ketamine, methylenedioxy-methamphetamine (MDMA) and lysergic acid diethylamide (LSD) may lead to potentially serious reactions if combined with PRILIGY. These reactions include, but are not limited to, arrhythmia, hyperthermia, and serotonin syndrome. Use of PRILIGY with recreational drugs with sedative properties such as narcotics and benzodiazepines may further increase somnolence and dizziness.

Ethanol

Combining alcohol with PRILIGY may increase alcohol-related neurocognitive effects and may also enhance neurocardiogenic adverse events such as syncope, thereby increasing the risk of accidental injury; therefore, patients should be advised to avoid alcohol while taking PRILIGY (see **PRECAUTIONS – Interactions with Other Medicines**).

Syncope

The number and percentage of subjects with syncope (characterized as loss of consciousness) was greater in PRILIGY-treated subjects than in those who were treated with placebo. A dose-response relationship for syncope is suggested based on subject incidence across all studies. In Phase 3 studies involving 6081 randomized subjects, the frequency of syncope characterised as a loss of consciousness was 0.06% for PRILIGY 30mg and 0.05% for placebo, compared with a higher rate of 0.23% for an unapproved dose (60mg) and 0.64% for all Phase 1 doses combined (30mg to 240mg) in Phase 1 non-PE subjects studies. In Phase 3 studies, three cases of syncope with bradycardia and sinus arrest (2 events, 5 seconds each; one event 28 seconds in duration) were observed during Holter monitor recording. Each subject spontaneously recovered normal sinus rhythm.

Possibly prodromal symptoms such as nausea, dizziness/lightheadedness, and diaphoresis were reported more frequently among patients treated with PRILIGY compared to placebo. In patients receiving 30 mg PRILIGY in Phase 3 clinical trials, nausea was reported in 11.0%, dizziness in 5.8% and hyperhidrosis/diaphoresis in 0.8%.

Syncope observed in the clinical trials were considered vasovagal in etiology and the majority occurred during the first 3 hours after dosing, after the first dose, or associated with study-related procedures in the clinic setting (such as blood draw and orthostatic maneuvers and blood pressure measurements). Possibly prodromal symptoms, such as nausea, dizziness, lightheadedness, palpitations, asthenia, confusion and diaphoresis generally occurred within the first 3 hours following dosing and often preceded the syncope. Patients need to be made aware that they could experience syncope at any time with or without prodromal symptoms during their treatment with PRILIGY. Prescribers should counsel patients about the importance of maintaining adequate hydration and about how to recognize prodromal signs and symptoms to decrease the likelihood of serious injury associated with falls due to loss of consciousness. If the patient experiences possibly prodromal symptoms, the patient should immediately lie down so his head is lower than the rest of his body or sit down with his head between his knees until the symptoms pass, and be cautioned to avoid situations where injury could result, including driving or operating hazardous machinery, should syncope or other CNS effects occur (see **PRECAUTIONS - Effects on Ability to Drive and Operate Machinery**.)

Combining alcohol with PRILIGY may enhance neurocardiogenic adverse events such as syncope, thereby increasing the risk of accidental injury; therefore, patients should be advised to avoid alcohol with taking PRILIGY.

Cardiovascular disease

Subjects with underlying cardiovascular disease were excluded from Phase 3 clinical trials. The risk of adverse cardiovascular outcomes from syncope (cardiac syncope and syncope from other causes) is increased in patients with underlying structural cardiovascular disease (e.g., documented outflow obstruction, valvular heart disease, carotid stenosis and coronary artery disease). There are insufficient data to determine whether this increased risk extends to vasovagal syncope in patients with underlying disease.

Cardiac Conduction

Alteration in cardiac conduction was observed only in preclinical isolated in vitro/ ex vivo models, and not in whole-animal testing. In clinical studies, supraventricular beats and arrhythmias were slightly higher on PRILIGY. A review of Holter data in over 3350 subjects in Phase 3 clinical trials demonstrated asymptomatic non-sustained ventricular tachycardia occurring in 0.2%, 0.3%, and 0.3% of placebo, PRILIGY 30 mg and PRILIGY 60 mg dose groups, respectively. In addition, no effect on QTc prolongation was detected in two Phase I thorough QT studies designed to investigate the effect of PRILIGY on cardiac repolarization.

Orthostatic hypotension

An orthostatic test should be performed before initiating therapy. In case of a history of documented or suspected orthostatic reaction, treatment with PRILIGY should be avoided.

Orthostatic hypotension has been reported in clinical trials. The prescriber should counsel the patient in advance that if he experiences possibly prodromal symptoms, such as lightheadedness soon after standing, he should immediately lie down so his head is lower than the rest of his body or sit down with his head between his knees until the symptoms pass. The prescriber should also inform the patient not to rise quickly after prolonged lying or sitting. In addition, PRILIGY should be prescribed with caution in patients taking medicinal products with vasodilatation properties (such as alpha adrenergic receptor antagonists, nitrates, PDE5 inhibitors) due to possible reduced orthostatic tolerance (see **PRECAUTIONS – Interactions with Other Medicines**).

Moderate CYP3A4 inhibitors

Caution is advised in all patients concomitantly treated with moderate CYP3A4 inhibitors. Unless the patient is known to be a CYP2D6 extensive metaboliser, caution is advised when used concomitantly with moderate CYP3A4 inhibitors (see **DOSAGE AND ADMINISTRATION** and **PRECAUTIONS – Interactions with Other Medicines**).

Potent CYP2D6 inhibitors

Caution is advised in patients taking potent CYP2D6 inhibitors. or in patients known to be of CYP2D6 poor metaboliser genotype, as this may increase exposure levels, which may result in a higher incidence and severity of dose dependent adverse events (see **DOSAGE AND ADMINISTRATION** and **PRECAUTIONS – Interactions with Other Medicines**).

Suicide/suicidal thoughts

SSRIs have been shown to increase the risk compared to placebo of suicidal thinking and suicidality in short-term studies in children and adolescents with Major Depressive Disorder and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24. In clinical trials with PRILIGY for the treatment of premature ejaculation, there was no clear indication of treatment-emergent suicidality.

Mania

PRILIGY should not be used in patients with a history of mania/hypomania or bipolar disorder and should be discontinued in any patient who develops symptoms of these disorders.

Seizure

Due to the potential of SSRIs to lower the seizure threshold, PRILIGY should be discontinued in any patient who develops seizures and avoided in patients with unstable epilepsy. Patients with controlled epilepsy should be carefully monitored.

Use in children and adolescents under age 18

PRILIGY should not be used in individuals below 18 years of age.

Co-morbid depression and psychiatric disorders

Men with underlying signs and symptoms of depression should be evaluated prior to treatment with PRILIGY to rule out undiagnosed depressive disorders. Concomitant treatment of PRILIGY with antidepressants, including SSRIs and SNRIs, is contraindicated (see **CONTRAINDICATIONS**). Discontinuation of treatment for ongoing depression or anxiety in order to initiate PRILIGY for the treatment of PE is not recommended. PRILIGY is not indicated for psychiatric disorders and should not be used in men with these disorders, such as schizophrenia, or in those suffering with co-morbid depression, as worsening of symptoms associated with depression cannot be excluded. This could be the result of underlying psychiatric disorder or might be a result of medicinal product therapy. Physicians should encourage patients to report any distressing thoughts or feelings at any time and if signs and symptoms of depression develop during treatment, PRILIGY should be discontinued.

Haemorrhage

There have been reports of bleeding abnormalities with SSRIs. Caution is advised in patients taking PRILIGY, particularly in concomitant use with medicinal products known to affect platelet function (e.g., atypical antipsychotics and phenothiazines, most tricyclic antidepressants [TCAs], acetylsalicylic acid, nonsteroidal anti-inflammatory drugs [NSAIDs], anti-platelet agents) or anticoagulants (e.g., warfarin), as well as in patients with a history of bleeding or coagulation disorders. (see **PRECAUTIONS – Interaction with Other Drugs**)

Renal Impairment

PRILIGY is not recommended for use in patients with severe renal impairment and caution is advised in patients with mild or moderate renal impairment (see **DOSAGE AND ADMINISTRATION** and **PHARMACOKINETICS**).

Withdrawal effects

Abrupt discontinuation of chronically administered SSRIs used to treat chronic depressive disorders has been reported to result in the following symptoms: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paraesthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania.

However, a double-blind clinical trial in subjects with PE designed to assess the withdrawal effects of 62 days of daily or as needed dosing with 60 mg PRILIGY showed no evidence of withdrawal syndrome and little evidence of withdrawal symptoms with only a slightly higher incidence of mild or moderate insomnia and dizziness reported in subjects switched to placebo after daily dosing (see **CLINICAL TRIALS**). Consistent results were seen in a second double-blind clinical trial with a 24-week treatment phase of 30 and 60 mg doses as needed followed by a 1-week withdrawal assessment period.

Mood related adverse events

In Phase 3 studies, PRILIGY 30 mg was associated with a higher incidence of mood related AEs, such as insomnia (2.2%), anxiety (1.1%) euphoric mood (0.2%), and depression (0.2%) compared to placebo (1.5%, 0.5%, 0%, 0.3%, respectively). Men with psychiatric disorders such as depression and anxiety were excluded from Phase 3 clinical studies. PRILIGY should not be used in men with concomitant psychiatric disorders, as it is unknown if the risk of these events and/or the underlying psychiatric condition could worsen (see **RECAUTIONS**).

Sexual Dysfunction

In Phase 3 studies, PRILIGY 30 mg was associated with a higher incidence of sexual AEs, such as erectile dysfunction (2.3%) and libido decreased (0.5%) compared to placebo (1.6% and 0.3%, respectively). Men with clinically significant erectile dysfunction and other sexual disorders were excluded from clinical studies. Caution should be used when prescribing PRILIGY to men with other forms of sexual dysfunction, as it is unknown if the sexual dysfunction could worsen.

Accidental injury

In Phase 3 studies, PRILIGY 30 mg was associated with a higher incidence of accidental injuries (2.7%) compared to placebo (1.8%). While some accidents were reported to be related to syncope occurrence, there was no clear correlation between accidental injury adverse events and events of dizziness or changes in alertness associated with PRILIGY administration. Patients should be cautioned to avoid situations where injury could result should syncope or symptoms such as dizziness occur (**see PRECAUTIONS, Effect on Ability to Drive or Operate Machinery and DOSAGE AND ADMINISTRATION**).

Effects on fertility

No effects on fertility were observed in male rats given dapoxetine HCl at up to 0.25% of the diet, corresponding to a dose of 158 mg/kg/day. Plasma concentrations of dapoxetine in the animals did not reach clinical levels. As such, the potential for effects on fertility in patients receiving PRILIGY is not known.

Fertility was unaffected in female rats given dapoxetine at up to 100 mg/kg/day by oral gavage, yielding exposure to dapoxetine (plasma AUC) marginally higher than that of men at the maximum recommended human dose of 60 mg/day.

Use in Pregnancy

Category C

PRILIGY is not indicated for use by women.

Dapoxetine was not teratogenic in rats at oral doses up to 100 mg/kg/day or in rabbits given up to 75 mg/kg/day during the period of organogenesis. Delayed ossification and an increased incidence of skeletal variations (extra ribs) were observed in fetuses at the highest doses tested, which were maternotoxic. Exposure to dapoxetine in rats (plasma AUC) was twice that of humans at the recommended clinical dose of 30 mg/day.

Dapoxetine and/or its metabolites cross the placenta in rats.

There are no adequate and well-controlled studies with dapoxetine in pregnant women. Neonates exposed to other SSRIs and SNRIs (serotonin and noradrenaline reuptake inhibitors) late in the third trimester have developed complications requiring prolonged hospitalisation, respiratory support and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypotonia, hypertonia, hyper-reflexia, tremor, jitteriness, irritability, lethargy, constant crying, somnolence and difficulty sleeping. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome.

There is no evidence to suggest that dapoxetine exposure has an effect on a partner's pregnancy based on limited observational data from the clinical trial database.

Use in Lactation

PRILIGY is not indicated for use by women.

It is not known if either dapoxetine or its metabolites are excreted in human breast milk.

Carcinogenicity

In studies with oral administration, dapoxetine was not carcinogenic to rats when administered daily for approximately two years at doses up to 225 mg/kg/day, yielding approximately three times the exposure to dapoxetine (plasma AUC) seen in human males given the recommended clinical dose of 30 mg. Dapoxetine also did not cause tumours in Tg.rasH2 mice when administered orally at the maximum possible doses of 100 mg/kg/day for 6 months and 200 mg/kg/day for 4 months. Exposure to dapoxetine in the mice at 100mg/kg/day after 6-months administration was equivalent to that seen in humans at the 30mg dose.

Daily topical dermal administration for 6 months to transgenic mice at 375, 750, or 1500 mg/kg/day produced some tumour promoter activity (papillomas at the application site) at 750 mg/kg/day or higher. Systemic exposure, to dapoxetine (plasma AUC) was approximately 2- to 3- fold that of males given the recommended clinical dose of 30 mg. The clinical relevance of this finding is unknown.

Genotoxicity

Dapoxetine was not mutagenic *in vitro* in the bacterial Ames assay or the forward mutation test in mouse lymphoma cells. Dapoxetine was not clastogenic in the *in vitro* chromosomal aberration test in Chinese hamster ovary cell or the *in vivo* mouse micronucleus assay. The major human metabolite, dapoxetine N-oxide, was negative in tests for bacterial mutagenicity and *in vitro* clastogenicity.

Interactions with Other Medicines

Potential for interaction with monoamine oxidase inhibitors

In patients receiving an SSRI in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued an SSRI and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Animal data on the effects of combined use of an SSRI and MAOIs suggest that these medicinal products may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, PRILIGY should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, an MAOI should not be administered within 7 days after PRILIGY has been discontinued (See **CONTRAINDICATIONS**).

Potential for interaction with thioridazine

Thioridazine administration alone produces prolongation of the QTc interval, which is associated with serious ventricular arrhythmias. Medicinal products such as PRILIGY that inhibit the CYP2D6 isoenzyme appear to inhibit the metabolism of thioridazine and the resulting elevated levels of thioridazine are expected to augment the prolongation of the QTc interval. PRILIGY should not be used in combination with thioridazine or within 14 days of discontinuing treatment with thioridazine. Similarly, thioridazine should not be administered within 14 days after PRILIGY has been discontinued (See **CONTRAINDICATIONS**).

Medicinal/herbal products with serotonergic effects

As with other SSRIs, co-administration with serotonergic medicinal/herbal products (including MAOIs, L-tryptophan, triptans, tramadol, linezolid, SSRIs, SNRIs, lithium and St. John's Wort (*Hypericum perforatum*) preparations) may lead to an incidence of serotonin associated effects. PRILIGY should not be used concomitantly with other SSRIs, MAOIs, other serotonergic medicinal/herbal products or within 14 days of discontinuing treatment with these medicinal/herbal products. Similarly, these medicinal/herbal products should not be administered within 7 days after Priligy has been discontinued. (See **CONTRAINDICATIONS**).

CNS active medicinal products

The use of PRILIGY in combination with CNS active medicinal products has not been systematically evaluated in patients with premature ejaculation. Consequently, caution is advised if the concomitant administration of PRILIGY and such medicinal products is required.

Effects of co-administered medicinal products on dapoxetine hydrochloride

In vitro studies in human liver, kidney, and intestinal microsomes indicate dapoxetine is metabolized primarily by CYP2D6, CYP3A4 and flavin monooxygenase 1 (FMO1). Therefore, inhibitors of these enzymes may reduce dapoxetine clearance.

CYP3A4 inhibitors - Potent CYP3A4 inhibitors

Administration of ketoconazole (200 mg twice daily for 7 days) increased the C_{max} and AUC_{inf} of dapoxetine (60 mg single dose) by 35% and 99%, respectively. Considering the contribution of both unbound dapoxetine and desmethyl dapoxetine, the C_{max} of the active fraction may be increased by approximately 25% and the AUC of the active fraction may be doubled if taken with potent CYP3A4 inhibitors.

The increases in the C_{max} and AUC of the active fraction may be markedly increased in a part of the population which lack a functional CYP2D6 enzyme, i.e., CYP2D6 poor metabolisers, or in combination with potent inhibitors of CYP2D6.

Therefore, concomitant use of PRILIGY and potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, ritonavir, saquinavir, telithromycin, nefazodone, nelfinavir and atazanavir, is contraindicated (see **CONTRAINDICATIONS**).

CYP3A4 inhibitors - Moderate CYP3A4 inhibitors

Concomitant treatment with moderate CYP3A4 inhibitors (e.g., erythromycin, clarithromycin, fluconazole, amprenavir, fosamprenavir, aprepitant, verapamil, diltiazem) may also give rise to significantly increased exposure of dapoxetine and desmethyl dapoxetine, especially in CYP2D6 poor metabolisers. The maximum dose of dapoxetine should be 30 mg if dapoxetine is combined with any of these drugs (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Potent CYP2D6 inhibitors

The C_{max} and AUC_{inf} of dapoxetine (60 mg single dose) increased by 50% and 88%, respectively, in the presence of fluoxetine (60 mg/day for 7 days). Considering the contribution of both unbound dapoxetine and desmethyl dapoxetine, the C_{max} of the active fraction may be increased by approximately 50% and the AUC of the active fraction may be doubled if taken with potent CYP2D6 inhibitors. These increases in the C_{max} and AUC of the active fraction are similar to those expected for CYP2D6 poor metabolisers and may result in a higher incidence and severity of dose dependent adverse events (see **PRECAUTIONS**).

PDE5 inhibitors

The pharmacokinetics of dapoxetine (60 mg) in combination with tadalafil (20 mg) and sildenafil (100 mg) were evaluated in a single dose crossover study (C-2003-027). Tadalafil did not affect the pharmacokinetics of dapoxetine. Sildenafil caused slight changes in dapoxetine pharmacokinetics (22% increase in AUC_{inf} and 4% increase in C_{max}), which are not expected to be clinically significant. However, PRILIGY should be prescribed with caution in patients who use PDE5 inhibitors due to possible reduced orthostatic tolerance (see **PRECAUTIONS**).

Effects of dapoxetine hydrochloride on co-administered medicinal products

Tamsulosin

Concomitant administration of single or multiple doses of 30 mg or 60 mg PRILIGY to patients receiving daily doses of tamsulosin did not result in changes in the pharmacokinetics of tamsulosin. The addition of PRILIGY to tamsulosin did not result in a change in the orthostatic profile and there were no differences in orthostatic effects between tamsulosin combined with either 30 or 60 mg PRILIGY and tamsulosin alone. However, PRILIGY should be prescribed with caution in patients who use alpha adrenergic receptor antagonists due to possible reduced orthostatic tolerance (see **PRECAUTIONS**).

Medicinal products metabolized by CYP2D6

Multiple doses of dapoxetine (60 mg/day for 6 days) followed by a single 50 mg dose of desipramine increased the mean C_{max} and AUC_{inf} of desipramine approximately 11% and 19%, respectively, compared to desipramine administered alone. Dapoxetine may give rise to a similar increase in the plasma concentrations of other drugs metabolized by CYP2D6. The clinical relevance is likely to be small.

Medicinal products metabolized by CYP3A

Multiple dosing of dapoxetine (60 mg/day for 6 days) decreased the AUC_{inf} of midazolam (8 mg single dose) by approximately 20% (range ~60 to 18%). The clinical relevance of the effect on midazolam is likely to be small in most patients. The increase in CYP3A activity may be of clinical relevance in some individuals concomitantly treated with a medicinal product mainly metabolized by CYP3A and with a narrow therapeutic window.

Medicinal products metabolized by CYP2C19

Multiple dosing of dapoxetine (60 mg/day for 6 days) did not affect the pharmacokinetics of a single 40 mg dose of omeprazole. Dapoxetine is unlikely to affect the pharmacokinetics of other CYP2C19 substrates.

Medicinal products metabolized by CYP2C9

Multiple dosing of dapoxetine (60 mg/day for 6 days) did not affect the pharmacokinetics or pharmacodynamics of a single 5 mg dose of glyburide. Dapoxetine is unlikely to affect the pharmacokinetics of other CYP2C9 substrates.

Medicinal products metabolized by CYP1A and 2B6

Repeated administration of dapoxetine induced CYP1A and 2B in laboratory animals. Dapoxetine may increase the clearance of substrates of CYP1A and 2B6.

PDE5 inhibitors

In a single-dose crossover study, dapoxetine (60 mg) did not affect the pharmacokinetics of tadalafil (20 mg) or sildenafil (100 mg).

Warfarin

There are no data evaluating the effect of chronic use of warfarin with PRILIGY; therefore, caution is advised when PRILIGY is used in patients taking warfarin chronically. (See **PRECAUTIONS**) In a pharmacokinetic study, dapoxetine (60 mg/day for 6 days) did not affect the pharmacokinetics or pharmacodynamics (PT or INR) of warfarin following a single 25mg dose.

Ethanol

Coadministration of a single dose of ethanol, 0.5 g/kg (approximately 2 drinks), did not affect the pharmacokinetics of dapoxetine (60 mg single dose) or the pharmacokinetics of ethanol, however, PRILIGY in combination with ethanol increased somnolence and significantly decreased self-rated alertness. Pharmacodynamic measures of cognitive impairment (Digit Vigilance Speed, Digit Symbol Substitution Test) did not show a significant separation from placebo with either ethanol or PRILIGY alone but did show a statistically significant effect when PRILIGY was coadministered with ethanol versus ethanol alone. Concomitant use of alcohol and PRILIGY could increase the chance or severity of adverse reactions such as dizziness, drowsiness, slow reflexes, or altered judgment. Combining alcohol with PRILIGY may increase these alcohol-related effects and may also enhance neurocardiogenic adverse events such as syncope, thereby increasing the risk of accidental injury; therefore, patients should be advised to avoid alcohol while taking PRILIGY (see **PRECAUTIONS**).

Effect on Ability to Drive or Operate Machinery

Dizziness, disturbance in attention, syncope, blurred vision and somnolence have been reported in subjects receiving dapoxetine in clinical trials. Therefore, patients should be warned to avoid situations where injury could result, including driving or operating hazardous machinery.

Combining alcohol with PRILIGY may increase alcohol-related neurocognitive effects and may also enhance neurocardiogenic adverse events such as syncope, thereby increasing the risk of accidental injury; therefore, patients should be advised to avoid alcohol while taking PRILIGY (see **PRECAUTIONS – Interactions with other Medicines**)

ADVERSE EFFECTS

The safety of PRILIGY was evaluated in 6081 subjects with premature ejaculation who were randomised in five Phase 3 double-blind, placebo-controlled clinical trials. Of these subjects, 1616 received PRILIGY 30 mg as needed and 1612 received placebo. A total of 241 subjects were exposed to PRILIGY 30mg for >121 days.

Syncope characterized as loss of consciousness has been reported in clinical trials and is considered medicinal product-related. The majority of cases occurred during the first 3 hours after dosing, after the first dose or associated with study-related procedures in the clinic setting (such as blood draw and orthostatic maneuvers and blood pressure measurements). Prodromal symptoms often preceded the syncope (See **PRECAUTIONS**). Orthostatic hypotension has been reported in clinical trials (See **PRECAUTIONS**).

The most frequently reported AEs in subjects receiving PRILIGY included nausea, diarrhoea, dizziness and headache (Table 4). These AE all occurred at higher frequency with doses of PRILIGY above 30 mg studied in phase 3 studies.

Table 4: Treatment-Emergent Adverse Events (≥1%) by System Organ Class and Preferred Term in Phase 3 Placebo-Controlled Studies

(Dapoxetine SCS: Intent-to-Treat Analysis Set)

	PLACEBO	DPX 30 MG PRN
System Organ Class	(N=1612)	(N=1616)
Preferred Term	n (%)	n (%)
Total no. subjects with adverse events	521 (32.3)	760 (47.0)
Gastrointestinal disorders	109 (6.8)	290 (17.9)
Nausea	35 (2.2)	178 (11.0)
Diarrhoea (includes defaecation urgency)	24 (1.5)	56 (3.5)
Dry mouth	6 (0.4)	20 (1.2)
Vomiting	6 (0.4)	16 (1.0)
Nervous system disorders	122 (7.6)	247 (15.3)
Dizziness (includes dizziness postural and dizziness exertional)	32 (2.0)	94 (5.8)
Headache	69 (4.3)	91 (5.6)
Somnolence (includes hypersomnia)	7 (0.4)	50 (3.1)
Infections and infestations	177 (11.0)	194 (12.0)
Nasopharyngitis	34 (2.1)	51 (3.2)
Influenza	25 (1.6)	34 (2.1)
Upper respiratory tract infection	48 (3.0)	33 (2.0)
Sinusitis	22 (1.4)	19 (1.2)
Psychiatric disorders	42 (2.6)	89 (5.5)
Insomnia (includes middle insomnia and initial insomnia)	17 (1.1)	36 (2.2)
Anxiety	5 (0.3)	17 (1.1)
General disorders and administration site conditions	35 (2.2)	79 (4.9)
Fatigue	14 (0.9)	32 (2.0)
Respiratory, thoracic and mediastinal disorders	59 (3.7)	70 (4.3)
Cough	16 (1.0)	13 (0.8)
Investigations	58 (3.6)	62 (3.8)
Blood creatine phosphokinase increased	23 (1.4)	15 (0.9)
Musculoskeletal and connective tissue disorders	59 (3.7)	60 (3.7)
Back pain	18 (1.1)	18 (1.1)
Reproductive system and breast disorders	39 (2.4)	60 (3.7)
Erectile dysfunction	23 (1.4)	37 (2.3)

Adverse event counts (%) are based on the number of subjects, not the number of events.

Studies included: C-2002-012, C-2002-013, R096769-PRE-3001 and R096769-PRE-3003.

The most common adverse drug reactions (≥5%) reported during clinical trials at a dose of 30mg PRILIGY were headache, dizziness and nausea. The most common events leading to discontinuation were nausea (0.9% of 30mg PRILIGY-treated subjects) and dizziness (0.7% of 30mg PRILIGY-treated subjects).

Adverse drug reactions reported by PRILIGY-treated subjects in these trials are shown in Table 5.

Table 5: Frequency of Adverse Drug Reactions

System Class	Organ	Adverse Drug Reactions			
		Very common ($> 1/10$)	Common ($\geq 1/100$ to $< 1/10$)	Uncommon ($\geq 1/1000$ to $< 1/100$)	Rare ($\geq 1/10000$ to $< 1/1000$)
Psychiatric disorders			Insomnia, Anxiety, Agitation, Restlessness, Libido decreased, Abnormal dreams	Depression, Depressed mood, Nervousness, Nightmare, Sleep disorder, Bruxism, Euphoric mood, Indifference, Apathy, Mood altered, Initial insomnia, Middle insomnia, Anorgasmia, Confusional state, Hypervigilance, Thinking abnormal, Disorientation, Loss of libido	
Nervous system disorders		Dizziness, Headache	Somnolence, Disturbance in attention, Tremor, Paraesthesia	Dysgeusia, Hypersomnia, Lethargy, Sedation, Depressed level of consciousness, Syncope, Syncope vasovagal, Dizziness postural, Akathisia	Dizziness exertional, Sudden onset of sleep ^a
Eye disorders			Vision blurred	Mydriasis, Visual disturbance	
Ear and labyrinth disorders			Tinnitus	Vertigo	
Cardiac disorders				Sinus arrest, Sinus bradycardia, Tachycardia	
Vascular disorders			Flushing	Hot flush, Hypotension, Systolic hypertension	
Respiratory, thoracic and mediastinal disorders			Sinus congestion, Yawning		
Gastrointestinal disorders		Nausea	Diarrhoea, Dry mouth, Vomiting, Constipation, Abdominal pain, Abdominal pain upper, Dyspepsia, Flatulence, Stomach discomfort, Abdominal distention	Abdominal discomfort, Epigastric discomfort	Defaecation urgency
Skin and subcutaneous tissue disorders			Hyperhidrosis	Pruritis, Cold sweat	
Reproductive system and breast disorders			Erectile dysfunction	Ejaculation failure, Paraesthesia of genital male, Male orgasmic disorder	
General disorders and administration site conditions			Fatigue, Irritability	Asthenia, Feeling hot, Feeling jittery, Feeling abnormal, Feeling drunk	
Investigations			Blood pressure increased	Heart rate increased, Blood pressure diastolic increased, Blood pressure orthostatic increased	

ADRs were determined from all clinical trial doses of dapoxetine, including those above 30 mg.

^a Reported as the verbatim term "falls asleep quickly at bedtime."

Adverse drug reactions reported in the long-term open-label extension trial were consistent with those reported in the double-blind studies and no additional adverse drug reactions were reported.

Postmarketing Data

No newly identified adverse drug reactions have been reported during postmarketing use of PRILIGY.

DOSAGE AND ADMINISTRATION

For oral use. Tablets should be swallowed whole. It is recommended that tablets be taken with at least one full glass of water. Patients should be cautioned to avoid situations where injury could result should syncope or its prodromal symptoms such as dizziness or lightheadedness occur (see **PRECAUTIONS**). PRILIGY has minor or moderate influence on the ability to drive and use machines. Dizziness, disturbance in attention, syncope, blurred vision and somnolence have been reported in subjects receiving PRILIGY in clinical trials. Therefore, patients should be warned to avoid situations where injury could result, including driving or operating hazardous machinery.

Adult men (18 to 64 years of age)

Patients must not take more than one tablet once every 24 hours due to increased risk of side effects (see Boxed Warning) and lack of additional benefit.

The recommended dose for all patients is 30 mg, taken as needed approximately 1 to 3 hours prior to sexual activity.

The maximum recommended dosing frequency is once every 24 hours. PRILIGY may be taken with or without food (see **PHARMACOKINETICS**).

The physician who elects to prescribe PRILIGY for the treatment of premature ejaculation should evaluate the risks and patient-reported benefits of the medicinal product after the first four weeks of treatment or after 6 doses, whichever occurred earlier to assess the patient risk-benefit balance and to determine whether continuing treatment with PRILIGY is appropriate.

Elderly (age 65 years and over)

Safety and efficacy of PRILIGY have not been established in patients age 65 years and over as limited data are available in this population (see **PHARMACOKINETICS**).

Children and adolescents

PRILIGY should not be used in individuals below 18 years of age.

Patients with renal impairment

No dose adjustment is required but caution is advised in patients with mild or moderate renal impairment. PRILIGY is not recommended for use in patients with severe renal impairment (see **PHARMACOKINETICS**).

Patients with hepatic impairment

No dose adjustment is required in patients with mild hepatic impairment. PRILIGY is contraindicated in patients with moderate and severe hepatic impairment (Child-Pugh Class B and C) (see **CONTRAINDICATIONS** and **PHARMACOKINETICS**).

Known CYP2D6 poor metabolisers or patients treated with potent CYP2D6 inhibitors

Caution is advised in patients known to be of CYP2D6 poor metaboliser genotype or in patients concomitantly treated with potent CYP2D6 inhibitors (see **PRECAUTIONS** and **PHARMACOKINETICS**).

Patients treated with moderate or potent inhibitors of CYP3A4

Concomitant use of potent CYP3A4 inhibitors is contraindicated. Caution is advised when used concomitantly with moderate CYP3A4 inhibitors (see **CONTRAINDICATIONS** and **PRECAUTIONS**).

OVERDOSAGE

There have been no reports of overdose during clinical trials.

There were no unexpected adverse events in a clinical pharmacology study of PRILIGY with daily doses up to 240 mg (two 120 mg doses given 3 hours apart). In general, symptoms of overdose with SSRIs include serotonin-mediated adverse reactions such as somnolence, gastrointestinal disturbances such as nausea and vomiting, tachycardia, tremor, agitation and dizziness.

In cases of overdose, standard supportive measures should be adopted as required. Due to high protein binding and large volume of distribution of dapoxetine hydrochloride, forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit. No specific antidotes for PRILIGY are known.

Contact the Poisons Information Centre (telephone 13 11 26) for advice on management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

PRILIGY Tablets are round, film-coated tablets and are available in packs of 3, 6 or 18 tablets. The 18 tablets pack size is not currently marketed.

30 mg: light grey tablets debossed with "30" inside a triangle on one side

PRILIGY tablets should be stored below 25°C.

NAME AND ADDRESS OF SPONSOR

JANSSEN-CILAG Pty Ltd
1-5 Khartoum Rd North Ryde NSW 2113 Australia
NZ Office: Auckland New Zealand

POISON SCHEDULE OF THE DRUG

Prescription Only Medicine

Date of TGA approval: 27 August 2010

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