Australian Government

Department of Health and Ageing

Therapeutic Goods Administration

Australian Public Assessment Report for Tapentadol

Proprietary Product Name: Palexia SR

Submission No: PM-2009-02489-3-1

Sponsor: CSL Ltd

February 2011

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	New Chemical Entity
Decision:	Approved
Date of Decision:	24 December 2010
Active ingredient(s):	Tapentadol (as hydrochloride)
Product Name(s):	Palexia SR (sustained release)
Sponsor's Name and Address:	CSL Ltd 45 Poplar Rd, Parkville, VIC 3052
Dose form(s):	Tablets
Strength(s):	50, 100, 150, 200 & 250 mg
Container(s):	PVC/PVDC – Al/PET/paper blister packs
Pack size(s):	7, 10, 14, 20, 28, 30, 40, 50, 56, 60, 90 & 100
Approved Therapeutic use:	For the management of moderate to severe chronic pain unresponsive to non-narcotic analgesia. There is currently no clinical trial data available regarding the safety and efficacy of Palexia SR in patients with pain due to malignancy.
Route(s) of administration:	Oral
Dosage:	Dosing to be individualised according to the severity of pain, previous treatment experience and the ability to monitor the patient. An initial dose of 50 mg bid for patients currently not taking opioid analgesics with dose titration every 3 days. Total daily doses greater than 500 mg have not been studied and are not recommended.
ARTG Number (s)	165332, 165346, 165347, 165356, 165357

Product Background

The two dose forms for tapentadol (the immediate release (IR) and sustained release (SR) formulations) were evaluated together though there were separate clinical trial programs for the immediate and sustained release dose forms.

Tapentadol is a centrally acting analgesic that exerts its pharmacological effects primarily by binding to mu-opioid receptors. Its binding affinity is approximately 18 times less than that of morphine. Tapentadol also inhibits noradrenaline reuptake and binds to 5-$HT_{2A,}$ β_1-adrenergic receptor, and the muscarinic receptor M_1.

The sponsor has proposed that tapentadol be scheduled as S8. A pharmacology study demonstrated that tapentadol demonstrated abuse potential comparable to that of hydromorphone. In the USA tapentadol is a federally controlled substance (C-II).

Regulatory Status

Palexia SR has a marketing authorisation in the European Union (since August 2010). The approved indication in the EU is as follows:
"Palexia SR is indicated for the management of severe chronic pain requiring centrally acting analgesic therapy."

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Product Information

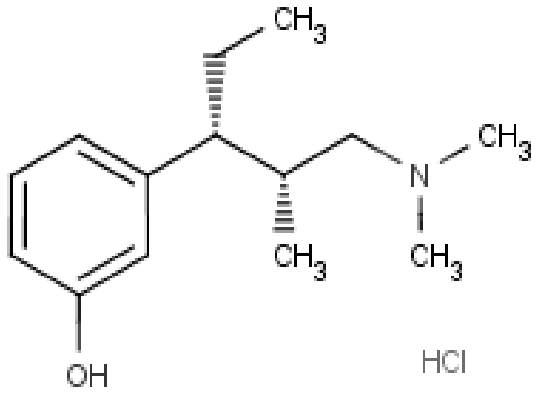
The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

Tapentadol is an opioid with centrally acting mu-agonist and noradrenaline uptake inhibitor properties. It shares a 3-(3-hydroxyphenyl)propylamino structural fragment with morphine and its analogues. It is isolated as the hydrochloride salt, the structure of which is shown below.

Figure 1. Structure



The drug substance has two chiral centres, and is manufactured as a single (*R,R*) stereoisomer. The drug substance is designated as BCS Class 1 (see below under *Bioavailability*).

The drug substance specifications include appropriate limits for enantiomeric purity and a limit for related substance.

Stability data have demonstrated that tapentadol hydrochloride is a stable substance. A retest period of 30 months with storage below 25°C has been approved.

Drug Product

The product is a sustained release, unscored, film-coated tablet, based on the matrix diffusion principle. Hypromellose is the gel-forming, release-controlling excipient; the film-coating does not contribute to the sustained release properties of the tablet. The cores of the five different strength tablets are not direct scales. They all contain high molecular weight hypromellose with adjustments to the quantity of silicified microcrystalline cellulose to maintain the same tablet weight for the 50, 100 & 150 mg tablets. The 200 & 250 mg tablets are targeted to another, higher weight, again by adjustment of the quantity of silicified microcrystalline cellulose. Silicified microcrystalline cellulose is a proprietary mixture. The 200 & 250 mg tablets are referred to as the SR2 formulation, while the three lower strengths are referred to as the SR2small formulation.

The finished product specifications are conventional. Individual degradation products are in accordance with International Conference on Harmonisation (ICH) guidelines.

A shelf life of 3 years with storage below 30°C has been approved for all strength tablets.

Bioavailability

A concurrent application to register tapentadol immediate release tablets has been submitted. The absolute bioavailability of the IR tablets was found to be only 32% under fasting conditions due to a

high first pass effect. Nevertheless, tapentadol hydrochloride is classified as BCS Class 1[1] (highly soluble and highly permeable).

A number of single dose studies and one steady state study have demonstrated that the various sustained release (SR) formulations used in clinical trials are bioequivalent to the SR tablet formulations proposed for registration.

A single dose study demonstrated that a high fat meal increased the maximum concentration of drug in serum (C_{max}) of the SR tablets by 18% but had no significant effect on area under the plasma concentration time curve (AUC). No dose-dumping was evident in individual subjects.

No studies have been performed to demonstrate bioequivalence of the five different strength SR tablets at equal dose. One single dose study showed a greater than proportional increase in C_{max}, and to a lesser extent AUC, with increasing dose. The dose-normalised C_{max} ratio for the 250 mg tablet compared to the 50 mg tablet is 1.74 (90% CI 1.64-1.85) and the corresponding AUC ratio is 1.18 (90% CI 1.14-1.22). These are unlikely to be clinically significant, particularly given that the dose-normalised C_{max} ratio for the 250 mg SR tablet relative to a 50 mg immediate release tablet is only 0.33 (90% CI 0.31-0.36). Clinical comment on this has been sought.

One single dose study (Study HP32) was aimed at developing an *in vitro-in vivo* correlation (IVIVC). By adjustment of the content of hypromellose, batches were produced with slow, medium, fast and extra fast dissolution rates. These batches were compared in cross-over fashion along with an oral solution of the drug. The two fast batches had similar serum concentration time profiles to the medium batch, while the slow batch had a very different *in vivo* profile. Originally, it appeared that the slow batch would pass the proposed tablet dissolution specification while the two fast batches would fail. The sponsor has now provided relevant dissolution data. Consideration of these results shows that:

- the dissolution method is discriminatory, showing a clear rank order correlation with C_{max};
- the slow batch fails the dissolution specification, while the fast batches are on the border of pass/fail.

Furthermore, dissolution data for 81 batches of Palexia SR tablets used in Phase III clinical trials show a high level of consistency with the proposed dissolution specification. The dissolution specification is now considered acceptable.

Quality Summary and Conclusions

This application was considered at the 134th meeting of the Pharmaceutical Subcommittee of the ACPM on 20 September 2010. All issues raised by the TGA following the initial evaluation of the application have been satisfactorily resolved, and there are now no objections to registration with respect to Chemistry, Manufacturing and Controls.

The subcommittee raised some additional, pharmacokinetic issues, which have been separately addressed by the company. The sponsor's responses have been referred to the Delegate for assessment (see below under *VI. Overall Conclusion and Risk/Benefit Assessment*).

[1] The Biopharmaceutics Classification System (BCS) is a guidance for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration. According to the BCS, drug substances are classified as follows: Class I: high permeability, high solubility; Class II: high permeability, low solubility; Class III: low permeability, high solubility; Class IV: low permeability, low solubility.

III. Nonclinical Findings

Introduction

The submitted nonclinical data were extensive and generally adequate. The relevant studies were generally Good Laboratory practice (GLP) compliant, apart from some safety pharmacology studies (discussed under the relevant subheading below). Tapentadol was administered as a liquid solution in nonclinical studies, rather than as the proposed clinical tablet forms. Relative exposure to tapentadol in most toxicity studies was quite low, as dosage levels were limited by adverse effects on the central nervous system (CNS). The nonclinical findings were generally consistent with effects on the μ-opioid pathway. Most pharmacological effects were observed at dose levels between that of morphine and tramadol, on a dose per body weight basis.

A large series of primary pharmacology studies (>25 studies) was submitted, providing extensive data regarding the relative efficacy of tapentadol in various models of pain, by different routes in multiple species. In addition, the toxicity of tapentadol was investigated in a substantial number of repeat dose toxicity studies (including >20 non-pivotal studies). The value of such a large number of studies and the relatively large group sizes in pharmacodynamic studies is questioned, given the very clear, quantifiable efficacy and safety profile of tapentadol and ensuing ethical concerns.

Pharmacology

Primary pharmacodynamics

Mechanism of action

Mechanistic studies primarily consisted of *in vitro* competitive receptor binding assays. Tapentadol bound to the following receptors *in vitro* with half maximal inhibitory concentration (IC_{50}) values <1 μM: μ-opioid receptor (μOR; IC_{50} values 0.2-0.23 μM), noradrenaline uptake transporter (IC_{50} values 0.62-0.64 μM), β_1-adrenergic receptor, 5-HT_{2A} receptor, 5-HT uptake transporter, σ_2 opioid receptor (IC_{50} value 0.60 μM).glutamate phenycyclidine (PCP) receptor. Of these, greatest binding affinity (K_i values) was for the μOR (K_i 0.096 μM for the rat receptor and 0.164 μM for the human receptor, compared to the clinical C_{max} at the MRHD[2] of 145 ng/mL[3] or 0.56 μM), followed by the σ_2 receptor (K_i 0.43 μM rat binding site) and noradrenaline uptake transporter (K_i 0.48 μM rat NA transporter. K_i values for the β_1-adrenergic receptor and 5-HT_{2A} receptor[4] were not reported.
Tapentadol bound to the μOR with circa 10-fold greater affinity than to other opioid receptors, although with 18-fold lower affinity than morphine and 7-fold lower affinity than morphine-6-O-glucuronide.
Other receptors demonstrating some binding inhibition by tapentadol (that is, K_i values <1 μM) included the κ- and δ-opioid receptors and M_1 muscarinic receptor. An extensive panel of receptors, ion channels, transporters and enzymes was shown to exhibit low or no tapentadol binding *in vitro*. The primary metabolite of tapentadol (tapentadol-glucuronide; ≤ 10 μM) demonstrated only slight binding to the μ-OR, noradrenaline uptake transporter, α1- and β_2-adrenergic receptors, dopamine D_{2S} receptor and 5-HT transporter *in vitro* (7-20%). Other tapentadol metabolites (for example, N-desmethyl metabolites) demonstrated binding affinity compared to tapentadol to μ-Orland noradrenaline and serotonin uptake transporters, however these metabolites are considered minor human metabolites and any potential receptor binding was not considered toxicologically significant.

Tapentadol inhibited binding of noradrenaline by the noradrenaline uptake transporter *in vitro*, with an IC_{50} value of 0.6 μM. In an *in vivo* study, tapentadol administration (4.64 and 10 mg/kg via the intraperitoneal (IP) route) induced a dose-related increase in extracellular levels of noradrenaline

[2] MRHD = maximum recommended human dose
[3] See **Relative exposure** below for a discussion of clinical C_{max}.
[4] 5-HT = serotonin

and 5-HT in the ventral hippocampus of the rat (increases to ≤ 550% and ≤ 225% of baseline levels, respectively). These increases were not observed with morphine (1-10 mg/kg IP), indicative of non-opioid receptor-mediated effects of tapentadol.

Limited additional data investigating the mechanism of action of tapentadol were submitted. Several *in vivo* efficacy studies examined the extent to which the anti-nociceptive effects of tapentadol could be blocked by a μOR antagonist (naloxone), an α_2-adrenergic receptor antagonist (yohimbine) or a non-selective 5-HT receptor antagonist (ritanserin). Naloxone completely inhibited the effects of tapentadol in a phenylquinone writhing test in mice, a paw incision model of post-operative pain in rats and following injection of yeast in a rat model of inflammatory pain. In contrast, naloxone only partially inhibited the effects of tapentadol in tail flick assay, following spinal nerve ligation and following formalin injection in rats. Similarly, yohimbine abrogated the effects of tapentadol in tail flick assays, models of mono-neuropathic pain and a formalin test in rats, but had no effect in a phenylquinone writhing test in mice and in a rat model of inflammatory pain. Ritanserin had no effect in a tail flick assay or a model of inflammatory pain in rats. Thus, the actions of tapentadol in both opioid receptor and noradrenaline uptake pathways elicit anti-nociceptive effects, depending on the particular animal model under study. Despite the increase in extracellular CNS serotonin levels in rats, no effect of ritanserin was seen under the conditions tested and the role of 5-HT receptor pathways was unclear. The sponsor did not investigate the potential contribution of other receptor pathways (for example, σ_2, or M_1 muscarinic receptors) to tapentadol-induced analgesia *in vivo*.

Efficacy

Tapentadol demonstrated dose-related efficacy (generally at all doses tested) in mouse, rat and dog models of acute pain, rat models of neuropathic pain and mouse and rat models of inflammatory pain. Several routes of administration were generally tested; the majority did not use the intended clinical (oral) route of administration. The sponsor added the comment that this was due to the low (lower than in humans) oral bioavailability in rodents and dogs. The following table (Table 1) summarises the minimal efficacious doses observed in different experimental models in different species; efficacy in most models was observed with tapentadol exposure (AUC-based) lower than that at the minimum recommended clinical dose (calculated by comparison with dose-normalised, AUC-based clinical exposure at the lowest usual recommended dose of 100 mg/day Palexia IR; refer to '**Relative exposure**' below). This demonstrates that the animal pain models selected were sensitive to the analgesic effects of tapentadol.

Table 1: Minimal efficacious doses in various animal pain models

Experimental model	Species	Route	MED (mg/kg)	Exposure margin (AUC)[a]
Acute pain				
Tail flick assay	Mouse	PO	21.5	0.3
		IV	1	0.2
	Rat	PO	68.1	0.2
		IV	0.464	0.08
		IT	14.7 µg	NA
	Dog	PO	No effect at 215	1.4
		IV	4.64	1.1
Phenylquinone writhing test	Mouse	PO	21.5	0.3
		IV	0.215-1	0.03-0.2
Colorectal distension (visceral pain)	Rat	IV	2.15	0.4
Paw incision (post-operative pain)		IP	0.681	0.03
Hot plate test: weak pain	Mouse	IV	2.15	0.3
		IP	4.64	0.2
Hot plate test: strong pain	Mouse	IP	10	0.4
Formalin test: acute (chemical) effects	Rat	IP	2.15	0.1
Neuropathic pain				
Cold allodynia: chronic constriction injury	Rat	IP	0.464	0.02
Tactile allodynia: chronic constriction injury		IP	0.316	0.01
Tactile allodynia: spinal nerve ligation		IV	0.1	0.02
Cold allodynia: cytostatic agent-induced polyneuropathy		IP	1	0.05
Paw pressure test: diabetic polyneuropathy		IP	3.16	0.1
		IV	0.326	0.05
Inflammatory pain				
Mustard oil-induced colitis: curative	Mouse	IV	10	2
Mustard oil-induced colitis: prophylactic			2.15	0.3
Paw pressure test: yeast injection	Rat	IV	1	0.2
		IP	4.64	0.2
		IT	10 µg	NA
Anti-nociceptive effects				
Formalin test: chronic effects	Rat	IP	2.15	0.1
Tooth pulp stimulation	Rabbit	IV	2.15	NA

[a]Extrapolated from pharmacokinetic and toxicokinetic data; calculated by comparison with dose-normalised, AUC-based clinical exposure at minimum recommended dose (417 ng.h/mL at 100 mg/day Palexia IR; refer to '**Relative exposure**' below)

IT = intrathecal; IV=intravenous; IP=intraperitoneal; MED = minimal efficacious dose; NA = no available pharmacokinetic data for this route

Efficacy was relatively lower in dogs compared to other species; it was unclear whether this was due to insensitivity of the pain models in this species, or whether it represented a general species-specific insensitivity to tapentadol. However, exaggerated pharmacological effects observed in toxicity studies are indicative of some response in this species. The efficacious IV dose range of tapentadol (that is, with 100% bioavailability) was generally between that of tramadol and morphine; efficacious tapentadol doses were generally 2-3x greater than morphine, on a mg dose per body weight basis.

Tapentadol-glucuronide showed no effect in tail-flick assays in mice and rats and in a phenylquinone writhing test in mice at respective exposures (AUC-based, extrapolated from pharmacokinetic data obtained following a single IV dose) 25, 4 and 11 times greater than the lowest usual recommended clinical dose. Thus, the glucuronide was considered to be an inactive metabolite of tapentadol. The effect of several other tapentadol metabolites in a phenylquinone writhing test was examined; significant effects were observed for the dihydroxy HCl, 3-OH,4-methoxy (racemic), 3-methoxy,4-OH HCl, N-desmethyl and N,N-Di-desmethyl metabolites. As these were minor metabolites in humans, these findings were not considered pharmacologically or toxicologically significant.

Secondary pharmacodynamics

A dose-related increase in emetic episodes was observed with tapentadol IP dosing (≥10 mg/kg) in ferrets, although the incidence and frequency was less than that of morphine (0.125 – 0.5 mg/kg subcutaneously (SC) and 0.4 mg/kg IP). Intravenous (IV) administration of tapentadol (10 - 21.5 mg/kg) resulted in reduced incidence and frequency of morphine-induced emesis in ferrets. Nausea and vomiting are noted as 'very common' adverse reactions in the Product Information.

Tapentadol demonstrated a dose-related antitussive effect following exposure to ammonia in rats with IV dosing (0.215 - 21.5 mg/kg), similar to that observed with codeine (≤ 21.5 mg/kg IV). A dose-related local anaesthetic effect, measured as an increase in the number of mechanical stimuli required to elicit a skin twitch response *in vivo*, was also observed following intradermal injection to guinea pig skin (0.05 – 0.5% solutions). Tapentadol inhibited guinea pig smooth muscle contraction *in vitro* (IC_{50} 1.49 µM). Effects of tapentadol treatment were abrogated by naloxone treatment, consistent with effects on the µOR.

Safety pharmacology

Numerous *in vivo* and *in vitro* studies investigated effects on the CNS (mice and rats), cardiovascular system (mice, rats, rabbits and dogs), renal and respiratory systems (rats), GI tract (mice) and cholinergic system (guinea pigs). The majority of studies were not GLP-compliant; the sponsor stated that this was because the studies were conducted prior to this requirement, but this did not appear to be the case for approximately half of the non-GLP studies. Nevertheless, the studies appeared to be adequately designed and documented.

CNS effects

In general, CNS effects following single IV or IP doses were consistent with effects on opioid pathways, for example, decreased exploration activity and motor coordination in mice and clinical signs (piloerection, pupil dilatation, loss of reflexes, reduced fear and grip strength, Straub response, *etc*.) in rats. Exposure in these studies was at least twice the estimated clinical C_{max} at the maximum recommended daily tapentadol dose, extrapolated from C_{1st} values following a single IV dose in pharmacokinetic studies[5]. Animal plasma exposure at the No Observed Adverse Effect Level (NOAEL) for CNS effects was similar to estimated maximum clinical C_{max} values.

[5] Refer to '**Relative exposure**' below for a discussion of exposure comparisons.

Convulsions were observed in rats at doses ≥ 18 mg/kg IV (circa 11x the clinical C_{max}) and an increased incidence of pentylenetetrazole (PTZ)-induced convulsions occurred at tapentadol doses ≥ 2 mg/kg IV. Pre-treatment with diazepam or phenobarbitone prevented tapentadol-induced convulsions and naloxone had a variable effect; no effect was observed in one study with 10 mg/kg IP naloxone, whereas a dose-related effect was observed in another study with 0.03 – 3 mg/kg IV or 10 mg/kg IP naloxone. The sponsor attributed the failure in the earlier study to the inconsistency of reversibility of opioid-induced convulsions by opioid antagonists. This was considered plausible, as other known opioid-related effects (for example the Straub response) were also unaffected by naloxone in that study. The effect of naloxone indicates that the convulsions are related to the opioidergic activity of tapentadol. Convulsions were also observed in multiple species in repeat dose toxicity studies, as discussed under the relevant subheading below.

Cardiovascular effects

In vitro studies indicated a potential for tapentadol-induced cardiac repolarisation disturbances, with concentration-related inhibition of hERG potassium (K^+) channel current amplitudes (IC_{50} 36.1 µM), effects on action potential duration in papillary muscle (increased in rabbits at ≥ 30 µM and decreased in guinea pigs at ≥ 10 µM) and decreased beating rate/heart rate in guinea pig cardiac tissue (≥ 3 µM). These concentrations are considerably greater than the clinical plasma C_{max} at the MRHD of 0.56 µM (145 ng/mL) or 0.77 µM (200 ng/mL)[6].

Heart rate and blood pressure were increased in conscious rats (for 60 min post-dose at ≥ 10 mg/kg IV) and dogs (≤ 15 min post-dose at ≥ 3 mg/kg IV; C_{1st} values were at least twice the estimated maximum clinical C_{max}) in a dose-related manner and tachycardia and atrioventricular block were observed at all doses in dogs. In contrast, blood pressure was decreased in anaesthetised rabbits (≥ 1 mg/kg IV) and dogs (≥ 0.5 mg/kg IV; C_{1st} values were 0.7 – 13x the estimated maximum clinical C_{max}), consistent with opioid-related cardiovascular depressant activity. There were no effects on QT interval[7] in anaesthetised dogs at extrapolated exposures at least twice the estimated maximum clinical C_{max}, although a dose-related (but not significant) prolongation of QT_c[8] was observed in conscious dogs at ≥ 3 mg/kg IV (3x the clinical C_{max}). Similarly, prolonged QT intervals (and generally QT_c when available) were frequently observed throughout treatment periods in repeat dose toxicity studies in dogs at PO doses ≥ 30 mg/kg/day (0.2x the clinical C_{max}). This was consistent with other opioid compounds and was considered to be potentially clinically relevant. Tapentadol-glucuronide, N-methyl tapentadol and tapentadol-sulfate demonstrated slight inhibition of hERG K^+ channel current amplitudes (respective IC_{50} values of >300 µM, 264 µM and >300 µM) *in vitro* and tapentadol-glucuronide showed no effect on action potentials in guinea pig papillary muscle at ≤ 300 µM).

Effect on renal function

A transient reduction in electrolyte excretion was observed following tapentadol administration (10 mg/kg IV) to rats. In contrast, increased urinary volume with accompanying decreases in osmolality and specific gravity was observed in repeat dose toxicity studies in rats. There were no treatment-related effects on urinary volume in dogs. This is unlikely to be of clinical concern, as the changes were minor and transient and did not occur across species.

[6] See '**Relative exposure**' below for a discussion of C_{max}.

[7] QT interval: a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death.

[8] QT_c: The QT interval is dependent on the heart rate (the faster the heart rate, the shorter the QT interval). To correct for changes in heart rate and thereby improve the detection of patients at increased risk of ventricular arrhythmia, a heart rate-corrected QT interval *QTc* is often calculated.

Respiratory effects

Tapentadol induced effects consistent with respiratory depression in conscious rats (for example, decreased respiratory rate, increased partial pressure of carbon dioxide (pCO2) and decreased partial pressure of oxygen (pO2)) at doses ≥ 4.64 mg/kg IV and 21.5 mg/kg IP, resulting in mortality with repeated doses at 15 mg/kg/day IV. Respiratory effects were observed following IV dosing at extrapolated C1st values ≥ 2 times the estimated maximum clinical Cmax and mortality occurred at 9x the estimated maximum clinical C_{max}. The effect on blood gases occurred at higher doses than with morphine in one study (twenty-five percent effective dose (ED_{25}) values of 10.4 mg/kg IV for tapentadol and 7.9 mg/kg IV for morphine). Tolerance to respiratory depression developed at a similar rate as morphine (after 22 days of repeated dosing once every 3-4 days). These findings were consistent with clinical signs observed in rats, rabbits and dogs in repeat dose toxicity studies, with laboured or irregular breathing, panting and reduced respiratory volume reported at doses ≥ 150 mg/kg/day PO (rats), 15 mg/kg/day IV (rabbits) and ≥ 80 mg/kg/day PO (dogs). C_{max} values at these doses were in the range 2-3 (rats) and 0.7-2 (dogs) times the estimated maximum clinical C_{max}.

Gastrointestinal effects

Tapentadol (2.15 – 68.1 mg/kg IP; equivalent to 0.01 – 0.4x the maximum recommended clinical exposure, based on mg/m^2) demonstrated inhibition of gastrointestinal (GI) transit (≤ 50%) and inhibition of prostaglandin-induced diarrhoea in mice (≤ 100%). The quantitative effect on GI tract activity was between that of morphine and tramadol.

Cholinergic effects

Tapentadol (0.1-2.15 µM) induced a concentration-dependent inhibition of acetylcholine-induced isotonic contractions of guinea pig ileum *in vitro*. The effect was quantitatively similar to that of atropine. No effect was observed for morphine (≤ 100 µM), indicative of a non-opioid effect of tapentadol.

Pharmacodynamic drug interactions

Tapentadol increased the duration of barbiturate-induced anaesthesia in mice in a dose-related manner (two hundered percent effective dose (ED_{200}) value of 71.2 mg/kg IP), although it was less potent than tramadol (ED_{200} value 43.4 mg/kg IP).

Combination treatment of tapentadol (4.64 – 31.6 mg/kg IV) with diazepam or tetrazepam attenuated the muscle-relaxing activity of the latter compounds in mice, measured as a reduction in the incidence of the effect, the duration of relaxation and the relaxation score. The sponsor did not consider this to represent a pharmacodynamic interaction, as the changes were not statistically significant. However, extrapolated AUC-based exposure margins were low (≤ 0.8), thus such interactions are potentially clinically relevant.

Pharmacokinetics

The pharmacokinetics of tapentadol following a single dose were investigated in mice (IV or PO dosing), rats (IV dosing) and dogs (PO dosing) and following repeated administration in mice (IP or SC dosing), rats (IV, IP, SC or PO dosing) and dogs (IV or PO dosing). Toxicokinetic data were obtained in most toxicity studies with tapentadol. Studies using the intended clinical (PO) route were investigated in mice, rats and dogs, as well as studies in the same species (and monkeys) with IV, SC and/or dietary administration. Validated methods were used in all studies. The studies were generally adequate.

Tapentadol was rapidly absorbed following PO administration in all nonclinical species, with C_{max} values reached within 1 h of dosing. This differed from the two formulations administered in clinical trials, with the time when the maximum plasma concentration was reached (t_{max}) estimated

at 1.5-2 h (tapentadol IR). Tapentadol was generally detected at all measured time points post-dose in rats (≤ 12 h) and dogs (≤ 24 h) and for 2-5 h post-dose in mice. Tapentadol was rapidly metabolised, based on tapentadol half-lives and t_{max} values for the primary metabolite (tapentadol-glucuronide) and exposure (AUC-based) to tapentadol-glucuronide was markedly greater (as much as 300x) than that of the parent compound in all species. AUC-based exposure was approximately dose-proportional in mice, but greater than dose-proportional in rats and dogs. Similar to humans, exposure to tapentadol and tapentadol-glucuronide appeared to be greater in female rats than males; there were no sex differences in mice and dogs. There was generally no evidence for accumulation with repeated dosing in animals, except in rats with twice-daily administration. The half-life of tapentadol was longer in mice and rats following PO dosing compared to IV dosing, which is suggestive of enterohepatic circulation. The bioavailability of tapentadol in mice following PO dosing was 40-47%.

The toxicokinetics of tapentadol were investigated following PO administration to juvenile rats between post-natal day (PND) 13-26 during a pre/post-natal development study. AUC- and C_{max}-based exposure to tapentadol and its glucuronide on PND13 was generally an order of magnitude greater than that of adult rats at comparable doses, possibly consistent with the younger age of the juvenile rats. Exposure margins (AUC and C_{max}) on PND26 were generally similar to that of adult rats at similar doses.

Distribution

Tapentadol was rapidly and widely distributed in rats following a single IV dose in a tissue distribution study. Radioactivity was detected in all tissues tested and all tissues except for white fat had radioactivity concentrations higher than blood at the C_{max}. Highest levels of radioactivity were detected in the kidneys, preputial gland, secretory glands (for example, lachrymal glands, salivary glands) and liver, with concentrations 5-10 times greater than blood. Radioactivity in target tissues (brain and spinal cord) was 2x and 1.4x greater than blood, respectively, indicative of good uptake by the CNS. Radioactivity was not detected, or was approaching the lower limit of quantification, in most tissues 72 h after the final dose. Tapentadol-glucuronide was detected at low levels (0.06 – 0.2x plasma levels) in extracellular fluid in the brain of rats following PO dosing, indicative of transfer of the metabolite across the blood-brain barrier and exposure in target tissues. Consistent with extensive tissue distribution, the volume of distribution following IV dosing was generally high (circa 4 L/kg in mice and 9-20 L/kg in rats).

Plasma/serum protein binding ranged from 11-20% in rabbits, mice, dogs, rats and humans (in ascending order) and results were similar over a tapentadol concentration range of 50 - 800 ng/mL. The ratio of tapentadol concentrations in blood versus serum or plasma was indicative of no accumulation of tapentadol in erythrocytes in dogs and some accumulation in human erythrocytes (23-53%). Tapentadol bound to melanin *in vitro* in a manner inversely proportional to concentration, with 48 – 27% binding in the above concentration range.

Metabolism

In vitro studies of tapentadol metabolism were conducted in liver microsomes from mice, rats, hamsters, guinea pigs, rabbits, mini-pigs, dogs, cynomolgus monkeys and humans and in hepatocytes from humans. When incubated under conditions for Phase II metabolism[9],

[9] *Phase II reactions* — usually known as conjugation reactions (for example, with glucuronic acid, sulfonates (commonly known as sulfation) , glutathione or amino acids) — are usually detoxication in nature and involve the interactions of the polar functional groups of Phase I metabolites. Sites on drugs where conjugation reactions occur include carboxyl (-COOH), hydroxyl (-OH), amino (NH_2) and sulfhydryl (-SH) groups. Products of conjugation reactions have increased molecular weight and are usually inactive unlike Phase I reactions which often produce active metabolites. Quantitatively, the smooth endoplasmic reticulum of the liver cell is the principal organ of drug metabolism, although every biological tissue has some ability to metabolize drugs.

glucuronidation of tapentadol was observed, although the rate of glucuronidation in human liver microsomes was ≥5x less than that of other species. Tapentadol glucuronidation was catalysed by several human isoforms *in vitro* and predominantly by uridine diphosphate-glucuronosyl transferases UGT1A6, UGT1A9 and UGT2B7. Under conditions favourable for activity by cytochrome P450 (CYP450) enzymes, metabolism of tapentadol produced a complex mix of oxidation, demethylation and cyclisation. As for glucuronidation pathways, the activity of CYP450 enzymes was lower (≥ 16-fold) in humans than other species. Human CYP450 enzymes involved in the formation of the major oxidative metabolites of tapentadol *in vitro* include CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2D6.

One *in vivo* study investigated the metabolism of tapentadol following repeated PO administration to mice, rats, dogs and humans. The overall pattern of metabolism was similar in all three species, with tapentadol-glucuronide being the primary metabolite in plasma/serum (accounting for 79-84% of total plasma/serum exposure (AUC)), followed by tapentadol catechol-glucuronide (4-10%) and N-desmethyl-tapentadol-glucuronide (4-9%). Tapentadol-sulphate was also detected in plasma from dogs (3%) and humans (4%), but not rats and tapentadol itself accounted for 3% of plasma exposure in humans and <1% in rats and dogs.

The potential for full chiral interconversion (switch of two chiral centers) of tapentadol *in vivo* was investigated in several species. Levels of the diastereomer (switch of one chiral center) in serum from rats, rabbits, dogs and humans following PO or SC dosing were 0.4-0.7% of tapentadol levels, compared to its specification limit (<1%) in the final product. Levels of the diastereomer in mouse serum were 1.1%. Extrapolated exposure levels (AUC) in animals at the doses administered were generally less than clinical exposure at the maximum recommended daily dose of tapentadol.

Excretion

The major route of elimination of tapentadol following PO dosing in mice, rats and dogs was in urine, accounting for 59-78% of the administered dose. Excretion was rapid in all species, with the majority excreted within 4-24 h. In rats, urinary excretion occurred to a greater extent in females (76%) than males (59%), with greater faecal excretion in male rats. A complex pattern of metabolites was detected in urine from mice, rats, dogs and humans, which was generally similar to the metabolite profile in plasma/serum. Tapentadol-glucuronide was the primary metabolite in urine from all species, accounting for 25-55% of the administered dose. Other major metabolites included tapentadol-catechol-glucuronide (2-39%), N-desmethyl-tapentadol-glucuronide (3-14%) and tapentadol itself (1-5%).

Pharmacokinetic drug interactions

Tapentadol was shown to be a slight inhibitor of CYP2D6 activity in human liver microsomes *in vitro*, with enzyme activity reduced by 19-61% in the concentration range 3.08-616 µM (compared to estimated clinical C_{max} of 0.8 µM at the MRHD). Induction of human CYP3A4 activity by tapentadol (≥ 0.7 µM) was observed in one *in vitro* study, although this finding was not observed in another *in vitro* study and following administration to rats (≤ 300 mg/kg PO). In the same *in vivo* study in rats, induction of CYP1A, CYP2B and slight induction of CYP2E activity was observed at doses ≥ 75 mg/kg PO (circa 0.1x AUC-based exposure at the MRHD); the results were generally dose-related and were more pronounced in males.

Tapentadol did not appear to be either an inhibitor or substrate of P-glycoprotein in human Caucasian colon adenocarcinoma cells (CACO-2) in vitro.

The potential for interactions with other medicines was investigated in an *in vitro* study. Glucuronidation of tapentadol was inhibited by several medicines, including diclofenac (≤ 90%), meclofenamate (≤ 90%), miconazole (≤ 70%), probenicid (≤ 67%) and naproxen (≤ 65%). Paracetamol enhanced tapentadol glucuronidation, although quantitative data were not provided. The sponsor did not consider the interaction with diclofenac to be clinically relevant, as inhibition

of tapentadol glucuronidation was predicted to be low (circa 6%) at clinical diclofenac concentrations). The most relevant interactions were considered to be with probenicid, meclofenamate and naproxen, with 45%, 36% and 27% inhibition of tapentadol glucuronidation predicted at clinical exposure levels, respectively.

Relative exposure

Exposure levels (plasma AUC-based) of tapentadol from the toxicity studies were compared with exposure data from human patients at the maximum recommended clinical dose. The maximum recommended starting daily dose of Palexia IR is 700 mg, which may be given as 100 mg every 4 h, with possibly an additional dose 1 h after the first dose. Thereafter, the maximum recommended maintenance daily dose is 100 mg every 4 h. Pharmacokinetic data were obtained in several clinical trials although data were not obtained following repeated administration of the maximum recommended clinical dose.

The sponsor provided mean clinical pharmacokinetic parameters for tapentadol calculated from data normalised to a 100 mg (tapentadol IR) from all relevant clinical studies. For calculation of AUC-based exposure margins, examination of data from individual trials indicated that the mean values were generally representative of clinical tapentadol exposure and were considered suitable for extrapolation to different dosage levels (taking linear pharmacokinetics into account)[10]. When extrapolated to the maximum recommended daily dose, a mean clinical AUC value of 2502 ng.h/mL (tapentadol IR) was obtained[11]. The extrapolated clinical AUC value obtained with this dosage form (2502 ng.h/mL) was therefore used for calculation of relative exposure (AUC) in nonclinical studies, as shown in Table 2 below.

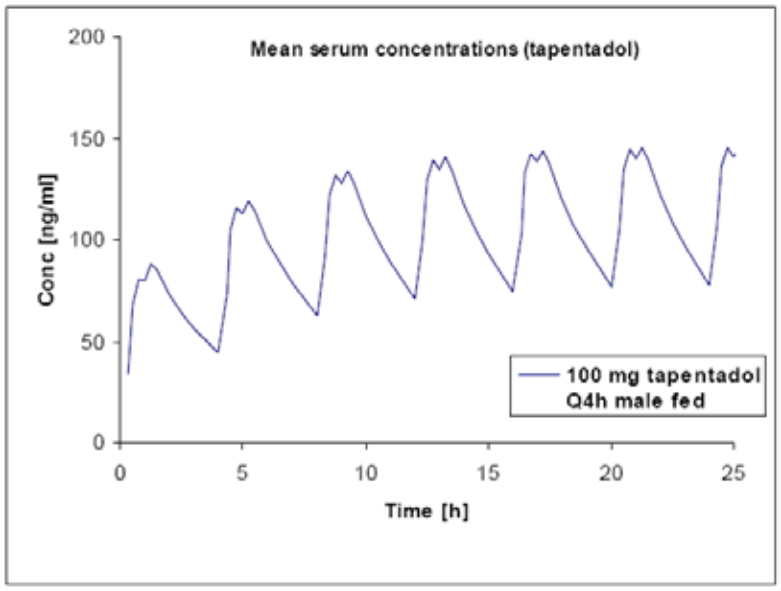
AUC-based exposure comparisons were made based on values calculated from time zero to infinity (0-∞) or from time zero to a pre-define time t (0-t), with a preference for the former, wherever possible; the values for t in each study are specified in Table 2. Some accumulation was noted with repeated dosing in humans (but not animals); accumulation factors were 1.4-1.7 in one study with Palexia IR. Exposure margins in nonclinical studies would be reduced by circa 30% if this was taken into account.

Some of the observed toxicities observed in nonclinical studies (for example, cardiovascular and CNS effects) are likely to be related to the peak plasma concentrations achieved in the animals, rather than the time-weighted exposure. Thus, risk assessment involves a comparison of these peak plasma levels with clinical plasma C_{max} values, particularly for safety pharmacology studies. The available clinical data indicate a mean plasma C_{max} value of 90.1 ng/mL after a single dose of tapentadol IR; clinical plasma C_{max} concentrations with repeated dosing of tapentadol IR at the maximum recommended daily dose are unknown but likely to be higher. In response to a question, the sponsor provided an estimate of the clinical plasma C_{max} of 145 ± 52 ng/mL under steady state conditions following the maximum recommended daily dose of tapentadol IR. This value was obtained by computer modelling; a diagram of a graphical representation of the simulation is shown in Figure 2 below (taken directly from the sponsor's response).

[10] When examining the consistency of exposure data, greater reliance was placed on data obtained in clinical trials using the clinical formulation (or more closely related formulations).

[11] IR: 417 x 6 = 2502 ng.h/mL. On the first day of dosing with IR, clinical exposure could be as much as 2919 ng.h/mL (417 x 7); however, for a comparison with repeated nonclinical dosing, the 6 doses/day clinical regimen is more appropriate.

Figure 2: Simulation of clinical serum concentrations following repeat dosing with tapentadol IR.



This graph indicates that the dosage regimen simulated was 100 mg tapentadol IR, every 4 h (that is, 600 mg/day) and not the maximum recommended starting dose of 700 mg/day (100 mg every 4 h, plus an extra 100 mg 1 h after the first dose). The sponsor provided relative exposure calculations by comparing plasma C_{max} values from nonclinical toxicity studies compared to the estimated clinical C_{max} of 145 ng/mL (from Figure 2 above); these are summarised in Table 3 below (column C_{max} A). There is no indication in the data of the steady state plasma C_{max} value at the maximum recommended starting dose of 700 mg/day tapentadol IR; it was estimated at circa 200 ng/mL, since each 100 mg dose in the graph above increases the peak concentration by circa 70 ng/mL. The sponsor stated that a C_{max} value of 197 ng/mL had been measured in a clinical trial (Study no. HP5503/25) with repeated dosing of 150 mg every 6 h (600 mg/day) and that this had shown no effect on the cardiovascular system. Thus, C_{max}- or C_{1st}-based exposure comparisons in nonclinical studies with a higher estimated clinical C_{max} of 200 ng/mL are also included in Table 3 below (column C_{max} B). Data from pharmacokinetic and safety pharmacology studies are also included in this table, to enable calculation of relevant exposure margins in safety pharmacology studies.

Doses highlighted in bold in both tables represent NOAELs for respective studies. AUC-based exposure margins were relatively low in most studies; the sponsor stated that the pharmacodynamic properties of tapentadol limited the dose in nonclinical studies. C_{max}-based exposure margins were generally adequate.

Table 2: Tapentadol exposure (AUC) calculations compared to. tapentadol IR in toxicity studies.

Study no.	Species	Treatment period	Dose (mg/kg/day)	Sex	AUC_{0-t} (ng.h/mL)	t (h)	Exposure multiples (AUC)
Repeat dose studies (PO administration)							
TP2470	Mouse	2 weeks	50, 100, 200	M/F	135, 257, 526	4[a]	0.05, 0.1, 0.2
TP2496		13 weeks	10, **30**, 100, 200	M/F	41, **178**, 548, 912	∞	0.02, **0.07**, 0.2, 0.4
TP2518		26 weeks[b]	**50**, 100, 200	M	**145**, 315, 763	V[c]	**0.06**, 0.1, 0.3
				F	**164**, 254, 633		**0.07**, 0.1, 0.3
TP2593	Rat	4 weeks	75, 150, 300	M	239, 718, 947	8[a]	0.1, 0.3, 0.4
				F	460, 1045, 2637		0.2, 0.4, 1.1
TP2645		13 weeks	**60**, 200, 400[d]	M	**1034**, 2254, 4828	24	**0.4**, 0.9, 1.9
				F	**979**, 4222, 11829		**0.4**, 1.7, 4.7
TP2397		26 weeks	**75**, 150, 300	M	**466**, 1115, 2165	∞	**0.2**, 0.4, 0.9
				F	**956**, 1505, 3114		**0.4**, 0.6, 1.2
TP2415	Dog	13 weeks	**10**, 35, 80	M/F	**18**, 106, 501	12[e]	**0.007**, 0.04, 0.2
TP2441		52 weeks	**10**, 30, 80	M	**23**, 142, 303	24	**0.009**, 0.06, 0.1
				F	**17**, 61, 407		**0.006**, 0.02, 0.2
Repeat dose studies (IV administration)							
TP2471	Rat	2 weeks	15, 30, 120	M/F	973, 2482, 10960	24	0.4, 1.0, 4.4
PH397/A	Monkey	SD	0.1, 0.32, 1, 3.2	M/F	191, 1212, 1380, 3568	∞	0.08, 0.5, 0.6, 1.4
TP2316		2 weeks	5[f]	M	1035	∞	0.4
Repeat dose studies (Dietary administration)							
TP2470	Mouse	2 weeks	50, 125, 250	M/F	75, 161, 210	24	0.03, 0.06, 0.08
TP2379	Mouse	13 weeks	50, 150, 250, 500, 1000	M	23, 78, 218, 417, 876	24	0.009, 0.03, 0.09, 0.2, 0.4
				F	33, 545[*], 144, 261, 387		0.01, 0.2[*], 0.06, 0.1, 0.2
TP2367	Rat	1 week	250, 1000	M	313, 1054	24	0.1, 0.4
				F	760, 2902		0.3, 1.2
TP2380		13 weeks	250, 500, 1000	M	470, 700, 1841	24	0.2, 0.3, 0.7
				F	1323, 2462, 1404		0.5, 1.0, 0.6
TP2418		26 weeks[b]	**10**, 50, 125, 250	M	**19**, 94, 274, 328	24	**0.007**, 0.04, 0.1, 0.1
				F	**17**, 156, 620, 1349		**0.006**, 0.06, 0.2, 0.5
Repeat dose studies (SC administration)							
TP2471	Rat	2 weeks	30, 45	M/F	1652, 4361	24	0.7, 1.7
TP2465	Rat	2 weeks	10, 30, 50[d]	F	838, 2288, 5130	∞	0.3, 0.9, 2.1
TP2464	Rabbit	2 weeks	10, 30, 50[d]	F	2712, 9512, 14046	∞	1.1, 3.8, 5.6
TP2559	Dog	13 weeks	8, 16, 32[d]	M/F	468, 528, 1956	∞	0.2, 0.4, 0.8
TP2455		13 weeks	40[d]	M	9270	∞	3.7
Studies in pregnant animals (PO administration)							
TP2834	Rat	GD6-17	**20**, **50**, 150, 300[d]	F	**155**, **760**, 3875, 5224	24	**0.06**, **0.3**, 1.5, 2.1
TP2772		GD6-17	50, 150, **300**[d]	F	542, 1668, **2546**	24	0.2, 0.7, **1.0**

Table continued on the next page.

Table 2. continued.

Studies in pregnant animals (SC administration)							
TP2510	Rat	GD6-17	**10**, 20, 40[d]	F	**814**, 1764, 3126	∞	**0.3**, 0.7, 1.3
TP2511	Rabbit	GD6-20	**4**, 10, 24[d]	F	**614**, 1920, 5742	∞	**0.2**, 0.8, 2.3
Studies in juvenile animals (PO administration)							
TP2772	Rat	PND13	**25**, 75, 150	M	**478**, 3266, 4760	4.5	**0.2**, 1.3, 1.9
				F	**628**, 6081, 6764		**0.3**, 2.4, 2.7
Pharmacokinetics in humans							
NA	Human	NA	700 mg/day	M/F	2502[g]	∞	NA

[a]$AUC_{0\text{-}24\ h}$ values could not be extrapolated; not all exposure to analyte occurred within the measured time period (that is, actual exposure was greater than documented). [b]The study duration was 104 weeks (carcinogenicity study), but toxicokinetic data were only available after ≤26 weeks. [c]AUC values for tapentadol were 0-5, 8 or 24 h, depending on dose level & time point; tapentadol levels were usually very low or not detectable by 5 h post-dose. [d]Twice daily dosing; AUC values are for 24 h exposure.

[e]AUC values were estimated to be approximately similar to 0-24 h values, based on concentration profiles.

[f]Monkeys were administered 15 mg/day; dose was adjusted for 3 kg body weight. [g]Clinical exposure in cross-study comparison, normalised to 100 mg and multiplied by 6 to obtain exposure at maximum recommended daily dose (see text).

[*]Considered an outlier based on high values in one mouse. NA = not applicable; SD = single dose; V = variable; NOAELs are highlighted in bold

Table 3: Tapentadol exposure (C_{max}) calculations compared to. tapentadol IR in toxicity studies.

Study no.	Species	Treatment period	Dose (mg/kg/day)	Sex	C_{max} (ng/mL)	Exposure multiples (C_{max} A)	Exposure multiples (C_{max} B)
Repeat dose studies (PO administration)							
TP2470	Mouse	2 weeks	50, 100, 200	M/F	143, 292, 350	1.0, 2.0, 2.4	0.7, 1.5, 1.8
TP2496		13 weeks	10, **30**, 100, 200	M/F	33, **85**, 349, 1056	0.2, **0.6**, 2.4, 7.3	0.2, **0.4**, 1.7, 5.3
TP2518		26 weeks[a]	**50**, 100, 200	M	**114**, 467, 828	**0.8,** 3.2, 5.7	**0.6**, 2.3, 4.1
				F	**205**, 238, 610	**1.4,** 1.6, 4.2	**1.0**, 1.2, 3.1
TP2593	Rat	4 weeks	75, 150, 300	M	64, 312, 531	0.4, 2.2, 3.7	0.3, 1.6, 2.7
				F	308, 597, 2476	2.1, 4.1, 17	1.5, 3.0, 12
TP2645		13 weeks	**60**, 200, 400[b]	M	**414**, 758, 1244	**2.9**, 5.2, 8.6	**2.1**, 3.8, 6.2
				F	**425**, 1409, 3733	**2.9**, 9.7, 26	**2.1**, 7.0, 19
TP2397		26 weeks	**75**, 150, 300	M	**252**, 507, 1451	**1.7**, 3.5, 10	**1.3**, 2.5, 7.3
				F	**520**, 451, 912	**3.6**, 3.1, 6.3	**2.6**, 2.3, 4.6
TP2415	Dog	13 weeks	**10**, 35, 80	M/F	**4.3**, 39, 327	**0.03**, 0.3, 2.3	**0.02**, 0.2, 1.6
TP2441		52 weeks	**10**, 30, 80	M	**6.8**, 49, 145	**0.05**, 0.3, 1.0	**0.03**, 0.2, 0.7
				F	**6.3**, 32, 221	**0.04**, 0.2, 1.5	**0.03**, 0.2, 1.1
Repeat dose studies (IV administration)							
TP2471	Rat	2 weeks	15, 30, 120	M/F	44, 108, 473	0.3, 0.7, 3.3	0.2, 0.5, 2.4
PH397/A	Monkey	SD	0.1, 0.32, 1, 3.2	M/F	142, 1047, 1518, 3589	1.0, 7.2, 10, 25	0.7, 5.2, 7.6, 18
TP2316		2 weeks	5[c]	M	852	5.9	4.3
Repeat dose studies (Dietary administration)							
TP2470	Mouse	2 weeks	50, 125, 250	M/F	8.8, 19, 32	0.06, 0.1, 0.2	0.04, 0.1, 0.2
Repeat dose studies (SC administration)							
TP2471	Rat	2 weeks	30, 45	M/F	70, 182	0.5, 1.3	0.4, 0.9
TP2465		2 weeks	10, 30, 50[b]	F	352, 907, 2441	2.4, 6.3, 17	1.8, 4.5, 12
TP2464	Rabbit	2 weeks	10, 30, 50[b]	F	593, 2099, 2845	4.1, 14, 20	3.0, 10, 14
TP2559	Dog	13 weeks	8, 16, 32[b]	M/F	130, 337, 623	0.9, 2.3, 4.3	0.7, 1.7, 3.1
TP2455		13 weeks	40[b]	M	1965	14	9.8
Studies in pregnant animals (PO administration)							
TP2834	Rat	GD6-17	**20**, **50**, 150, 300[b]	F	**48**, **355**, 1186, 1441	**0.3**, **2.4**, 8.2, 10	**0.2**, **1.8**, 5.9, 7.2
TP2772		GD6-17	50, 150, **300**[b]	F	254, 601, **810**	1.8, 4.1, **5.6**	1.3, 3.0, **4.1**
Studies in pregnant animals (SC administration)							
TP2510	Rat	GD6-17	**10**, 20, 40[b]	F	**298**, 764, 1169	**2.1**, 5.3, 8.1	**1.5**, 3.8, 5.8
TP2511	Rabbit	GD6-20	**4**, 10, 24[b]	F	**149**, 582, 1513	**1.0**, 4.0, 10	**0.7**, 2.9, 7.6
Studies in juvenile animals (PO administration)							
TP2772	Rat	PND13	**25**, 75, 150	M	**129**, 1055, 2459	**0.9**, 7.3, 17	**0.6**, 5.3, 12
				F	**159**, 4070, 2347	**1.1**, 28, 16	**0.8**, 20, 12
Single dose pharmacokinetic studies (IV administration)							
PK653	Rat	SD	3.5, 7, 14	M/F	344, 854, 1692	2.4, 5.9, 12	1.7, 4.3, 8.5

Table continued on the next page.

Table 3. continued.

Safety pharmacology studies (IV administration)							
SP103/A	Dog	SD	0.5, 1.5, 4.5	M/F	135, 257, 526	0.9, 3.3, 10	0.7, 2.4, 7.2
SP35/A		SD	3, 6, 9	M	665, 1105, 2531	4.6, 7.6, 17	3.3, 5.5, 13
Pharmacokinetics in humans							
NA	Human	NA	700 mg/day	M/F	145 (A) or 200 (B)[d]	NA	NA

[a]The study duration was 104 weeks (carcinogenicity study), but toxicokinetic data were only available after ≤26 weeks

[b]Twice daily dosing. [c]Monkeys were administered 15 mg/day; dose was adjusted for 3 kg body weight. [d]Estimated C_{max} at the maximum recommended clinical dose of 100 mg every 4 h (A) or with an additional 100 mg 1 h after the first dose (B). NA = not applicable; SD = single dose; NOAELs are highlighted in bold

Toxicology

General toxicity

The acute toxicity of tapentadol was investigated following a single IV or PO dose to mice and rats. Long-term repeat dose studies by the PO route were conducted in mice (13 weeks), rats (26 weeks) and dogs (52 weeks). More than 20 other repeat dose studies of shorter duration by various routes (PO, dietary, IV, SC) were also conducted in mice, rats and dogs, with limited analyses in rabbits and monkeys. The studies were generally adequate, although different dosage levels were tested at different time points in the 6-month study in rats and no control groups were included in the acute toxicity study. NOAELs were established in long term studies, although exposure margins (AUC) were generally low. Histopathology analysis was frequently not conducted in non-pivotal repeat dose studies.

Dosage levels were limited due to excessive toxicity at higher doses; dose-limiting toxicities were congestive/haemorrhagic changes and convulsions in mice, rats and dogs. Toxicity findings were generally dose-related, with incidence and severity increasing with dose. The primary toxicity observed in mice and rats was liver toxicity, as discussed further below. Other toxicities were generally consistent with the primary pharmacology of tapentadol and included CNS effects as discussed below. QT interval prolongation was observed in dogs; refer to '**Safety pharmacology**' above for details. Increased white blood cell (WBC) counts, primarily due to increased lymphocytes, was consistently observed in rats at PO doses≥150 mg/kg/day. One study indicated that the relative proportion of lymphocyte subtypes remained consistent with control groups. Consistent with opioid administration, respiratory effects were observed in rats, rabbits and dogs; refer to '**Safety pharmacology**' above for details. Reduced body weight gain was observed in rats and dogs, generally consistent with reduced food intake.

Hepatic toxicity

Treatment related effects on the liver were frequently observed following repeated dosing in mice and rats., At doses ≥ 100 mg/kg/day PO (circa 0.1x clinical exposure, based on AUC) in mice these were characterised by liver enlargement, accentuated lobular pattern, congestion/haemorrhage and hepatocyte vacuolation.. Typical changes in rats included enlarged liver and centrilobular hypertrophy at ≥ 150 mg/kg/day PO or ≥ 30 mg/kg twice a day (bid) PO and an increased incidence of fatty change at ≥ 75 mg/kg/day PO (exposures ≥ 0.3x clinical exposure). Increased serum hepatic enzymes (ALP, LDH, AST and ALT[12]) were frequently observed in both species at high doses. The sponsor attributed these findings to adaptive changes as a result of hepatic enzyme induction and provided a detailed discussion of this issue, particularly pertaining to the high variability and

[12]ALP= alkaline phosphatase, LDH= lactate dehydrogenase, AST=aspartate aminotransferase; ALT=alanine aminotransferase;

reversibility of any liver findings. This was considered plausible. No evidence of liver toxicity was observed in dogs. The relevance to humans appears to be low.

CNS effects

Severe convulsions, often leading to euthanasia were observed in mice, rats and dogs by various routes (respective AUC-based exposure margins following PO dosing were 0.5, 2.2-5.4 and 0.1-0.2). Convulsive effects were considered to be typical for opioids[13]. Other clinical signs consistent with effects on the CNS were observed in rats and dogs at exposures lower than human exposure at the maximum recommended clinical dose; these findings were considered to be exaggerated primary pharmacology. In rats, clinical signs included excited and abnormal behaviour (for example, bedding in mouth) and sedation in rats and exophthalmos, subdued behaviour, recumbency, hunched posture at high doses. Findings in dogs included hypoactivity, salivation, vomiting, recumbency, whimpering, tremor and fearful behaviour.

Toxicity of tapentadol-glucuronide

Intracerebroventricular (ICV) administration of high doses of several tapentadol metabolites (tapentadol-glucuronide, N-desmethyl-tapentadol-glucuronide and tapentadol catechol-glucuronide; ≥ 3.16 μg/animal) in primary pharmacodynamic studies induced severe convulsions in mice. Tapentadol-glucuronide is known to distribute to the brain following PO dosing in rats (refer to '***Distribution***' below), although at levels appreciably lower than plasma levels. The relationship between the brain concentrations achieved via ICV administration and those in the brain of patients on therapeutic doses is unknown. The risk of convulsions due to tapentadol-glucuronide exposure is considered to be low and unlikely to be of greater concern than the risk of convulsions from tapentadol itself. No data were available regarding the potential for CNS distribution for other relevant metabolites, although the same risk profile is expected to apply.

Genotoxicity

The genotoxicity of tapentadol was investigated *in vitro* with a bacterial reverse mutation assay and mammalian chromosomal aberration assays and *in vivo* with one chromosomal aberration assay and an unscheduled DNA synthesis assay in rats. The studies were GLP compliant, the concentrations used were adequate and the assays were validated with appropriate controls.

Negative results were observed in all studies, except for one mammalian chromosomal aberration assay. In this assay, an increased number of cells with chromosomal aberrations, primarily chromosome breaks or fragments and chromatid exchanges, were observed at tapentadol concentrations associated with cytotoxicity. The second chromosome aberration assay did not replicate the experimental conditions associated with positive findings. Toxicokinetic data were not obtained in the *in vivo* assays, although distribution to bone marrow was observed following administration of 10 mg/kg IV to rats in a pharmacokinetic study. Exposure at the maximum dose in the chromosomal aberration assay (40 mg/kg IV) was equivalent to 1.4x clinical exposure, based on extrapolated AUC and at the maximum dose in the unscheduled DNA synthesis assay (350 mg/kg PO) exposure was 1.5x MRHD.

The battery of genetic toxicology assays used to investigate tapentadol was consistent with the relevant EU ICH[14] Guideline[15]s and the weight of evidence from these assays suggested that tapentadol presented no significant genotoxic potential at the proposed clinical dose range.

[13] Frenk H (1983) Pro- and anticonvulsant actions of morphine and the endogenous opioids: involvement and interactions of multiple opiate and non-opiate systems. *Brain Res Rev* **6**, 197-210.
[14] International Conference on Harmonisation
[15] ICH Topic S2B Genotoxicity: A standard battery of genotoxicity testing of pharmaceuticals. http://www.tga.gov.au/docs/pdf/euguide/ich/017495en.pdf

Carcinogenicity

Two-year carcinogenicity studies were conducted by PO administration of tapentadol to mice and dietary administration to rats. The studies were GLP compliant and generally adequate. Toxicokinetic data were obtained only up to Week 26 in both studies, but extrapolation up to two years should be valid, given the lack of accumulation of tapentadol in these species. Actual dietary intake approximated the proposed doses in rats. AUC-based exposure margins were low in both species (less than human exposure at the maximum recommended daily clinical dose), although they were similar to exposure levels attained in repeat dose toxicity studies, during which pharmacological and toxicological effects were observed.

It is questionable whether the dosage levels in the mouse study were adequate, as there was limited evidence of toxicity (including negligible effects on body weight gain) and AUC-based exposure margins were low (≤ 0.3). There was no clear treatment-related effect on mortality; although a dose-related increase in mortality with undetermined cause was reported (≥ 100 mg/kg/day), it was difficult to determine whether this represented a true treatment-related effect due to the method of tabulation of mortality data and as there were limited data regarding in-life clinical signs. High mortality in this study and the pivotal 13-week repeat dose study (due to convulsions) at 300 mg/kg/day PO identified this as exceeding the maximum tolerated dosage (MTD) level by this route. The highest dosage level tested in PO studies in mice was 200 mg/kg/day. Exposure margins (AUC) of 0.4 were not exceeded in any study in mice; thus, it was unknown whether dosing at a higher level (between 200 and 300 mg/kg/day PO) may have been informative, but it seems feasible that a dosage level >200 mg/kg/day may have been tolerated, although the resultant exposure margin may not have escalated much further. The dosage levels in the study in rats were considered adequate, as body weight gain at the HD was reduced by sufficient magnitude and the toxicity profile was consistent with repeat dose toxicity studies.

Tapentadol was generally well-tolerated with long-term dosing in both species. A significant trend towards a dose-response relationship for hepatocellular tumours (adenoma and carcinoma) was observed in mice, when the highest dose group was excluded (due to a shortened treatment period). There were no accompanying pre-neoplastic lesions in mice and the total incidence was low. A high, dose-related incidence of hepatocellular hypertrophy was observed in rats at dietary doses ≥ 125 mg/kg/day, but there were no associated hepatocellular adenomas or carcinomas. Liver findings in both species occurred at AUC-based exposures circa 0.1x the MRHD. These findings may be consistent with adaptive changes to the liver reported in repeat dose toxicity studies. The potential clinical relevance of these liver findings is unknown.

Based on assumed treatment-related mortality (mice) and recorded effect on body weight gain (rats), dosing levels were probably approaching/at the MTD in these species; however, the low systemic exposure margins attained (due to toxicity) have limited the adequacy of the testing for carcinogenic potential.

A statistically significant trend towards increased incidence of thyroid follicular cell hypertrophy and hyperplasia was observed in treated female rats. These findings were attributed by the sponsor to enhanced liver enzyme activity as a consequence of centrilobular hepatocellular hypertrophy although an increased incidence of follicular cell hypertrophy was observed in the absence of hepatocellular hypertrophy at 50 mg/kg/day. Although a statistical trend was identified, the incidence of these findings was comparable to control groups, was similar in males and females and was consistent with known effects of CNS-acting drugs on thyroid function in rats[16]. Thus, the proliferative effects on the thyroid were not considered to be clinically relevant.

[16] Capen, CC (1999) Thyroid and parathyroid toxicology. In *Endocrine and hormonal toxicology*. Harvey PW, Rush K, Cockburn A (eds). John Wiley & Sons, New York.

Reproductive toxicity

The submitted studies included a fertility and early embryonic development study in rats, embryofetal development studies in rats and rabbits and pre/post-natal development studies in rats. The studies were GLP-compliant and generally adequate.

Placental transfer of tapentadol was confirmed in a pre-postnatal study in rats, with relatively high levels of tapentadol and its glucuronide (≥ 23% of maternal plasma levels of tapentadol and ≥ 8% of maternal tapentadol-glucuronide levels) detected in F_1 fetuses on gestation day (GD) 20. Low levels of tapentadol and tapentadol-glucuronide were also detected in milk from lactating rats on PND7.

In a rat fertility study, there were no apparent effects in males at doses ≤ 12 mg/kg/day IV (estimated AUC exposure 0.3-fold the clinical exposure[17]), although histopathology analyses were not conducted. In females, a dose-related reduction in the numbers of corpora lutea, implantations and live fetuses were observed, although these findings were associated with maternal toxicity and were within historical control ranges. Pre- and post-implantation losses were increased. These findings are most likely attributable to maternal toxicity (clinical signs and usually reduced body weight gain observed at doses ≥ 6 mg/kg/day). In rabbits, tapentadol administration at maternotoxic doses during organogenesis (15 mg/kg/day IV and ≥ 5 mg/kg bid SC) was associated with increased post-implantation loss, late resorptions and dead fetuses.

An increased incidence of incomplete fetal ossification at various sites was observed following SC dosing during organogenesis (5-20 mg/kg BID; AUC exposure 0.2-0.6x the MRHD) in rats. Although the incidence was generally dose-related and statistically significant at the highest dose, the toxicological significance of the finding was unclear as most values were within historical control ranges and no variations or malformations were reported in another rat embryofetal development study with IV dosing eliciting maternal toxicity (≤ 15 mg/kg/day). Fetal cerebral ventricular dilation was observed at SC doses ≥ 10 mg/kg BID. A possible treatment-related effect of tapentadol cannot be excluded for this finding, due to the observed dose-response and CNS activity of tapentadol; this finding occurred at maternotoxic doses.

Multiple dose-related fetal malformations (ablepharia, cleft palate, fused or misaligned sternebrae, spina bifida, amelia/phocomelia and gastroschisis or thoracogastroschisis) were observed in a rabbit embryofetal development study with SC dosing. The findings were generally associated with maternal toxicity (≥ 5 mg/kg BID), specifically their compromised nutritional status and exposures (AUC) were generally 0.8 – 2.3x exposure at the MRHD (0.2 at the NOEL). With IV administration to rabbits up to 9 mg/kg/day, post-implantation losses, late resorptions and dead fetuses were increased but no malformations reported (although maternotoxicity was also less severe); unfortunately, toxicokinetics was not included in the study design as only serum concentrations were measured. Serum concentrations in rabbits at the highest IV dose were similar to those at the highest dose in the rabbit study with SC dosing. Thus, exposure at the highest dose by both routes was apparently comparable. This apparent inconsistency between SC and IV results in rabbits is puzzling and could have been investigated further. The toxicological significance of these findings is uncertain.

Tapentadol administration (≥ 25 mg/kg bid PO; AUC-based exposure 0.2x the MRHD) during lactation was associated with increased pup mortality, particularly between PND1-4, in rats. Pup mortality occurred at doses lower than maternotoxic doses. Several treated females experienced difficulties delivering (and were euthanised); the relationship to treatment was unclear given the low incidence and lack of dose-response.

[17] Extrapolated from Study TP2471.

Pregnancy classification

The sponsor proposes a Pregnancy Category C for tapentadol. This was considered acceptable, as the majority of fetal/pup findings reported in reproductive toxicity studies were associated with maternal toxicity and compromised nutritional status and the malformations in rabbits were not seen consistently in all studies. The majority of other registered opioid analgesics are Pregnancy Category C.

Use in children

Tapentadol is contra-indicated for use in children.

Limited toxicity data were obtained following PO dosing of juvenile rats in a pre/post-natal development study. The findings were generally similar to those seen with adult rats, namely mortality (one death was associated with convulsions), clinical signs consistent with opioid administration (sedation, tremors, hypoactivity, hypersensitivity to noise) and reduced body weight gain at doses ≥ 75 mg/kg/day (circa twice the AUC-based clinical exposure at the MRHD). Exposure at the NOAEL was 0.2-0.3x the clinical AUC.

Local tolerance

The absence of local tolerance studies was acceptable for an orally administered drug.

Dependence

Several studies investigated the dependence and tolerance potential of tapentadol in mice, rats and monkeys. The studies were generally adequate and validated with appropriate positive and negative controls.

A dose-related increased incidence of naloxone-precipitated (1 and 1.5, but not 2 h post-dose) withdrawal jumping was observed in mice at doses ≥ 10 mg/kg IP (estimated exposure <0.1x AUC-based exposure at the MRHD). Likewise, behavioural changes (teeth chattering, sniffing, licking, grooming, hyperactivity and Straub tail) were observed following naloxone induced- or spontaneous withdrawal in rats, at tapentadol doses ≥ 4.64 mg/kg/day SC (estimated exposure 0.1x AUC-based exposure at the MRHD). The behavioural effects of tapentadol withdrawal were generally less pronounced than that of morphine or tramadol. Thus, consistent with its μOR agonist activity, tapentadol was considered to confer potential for dependence in mice and rats.

Positive reinforcing and rewarding effects were observed in rats (increased time spent in a tapentadol-associated environment) and monkeys (increased self-administration) at exposures markedly lower (<0.1x, based on AUC) than that at the MRHD. The effects in rats were prevented by co-administration of naloxone. In a drug discrimination study in rats, tapentadol demonstrated morphine-like discriminative stimulus effects and no response to D-amphetamine (suggestive of no psychostimulant-like behavioural effects). The reinforcing and rewarding effects of tapentadol were comparable with morphine and tramadol.

Tolerance to the analgesic effect of tapentadol was observed in rats following repeated administration in tail flick assays and in chronic constriction injury models of peripheral mono-neuropathy. This effect was observed as early as three days of treatment, with full tolerance development after several weeks, at estimated exposures less than the MRHD. Development of tolerance to tapentadol was delayed compared to that of morphine or tramadol, generally by circa 10 days. Cross-tolerance to morphine was observed with tapentadol: tapentadol-tolerant rats were also tolerant to morphine, however morphine-tolerant rats remained sensitive to tapentadol.

Factors to consider in a benefit risk assessment

Tapentadol is a new chemical entity for the treatment of moderate to severe pain. A wide variety of different patient groups could be envisaged to receive tapentadol treatment, including both short-

term and chronic treatment. Thus, the risk-benefit analysis of tapentadol may vary, depending on the specific patient group, the etiology/pathology of the pain/pain syndrome being treated and intended duration of treatment. Tapentadol-induced analgesia is mediated primarily through μOR activation and also via inhibition of noradrenaline re-uptake pathways; possible functional contribution(s) through other receptor pathways was not fully explored. Antinociception was clearly and quantitatively demonstrated in several nonclinical species, with an efficacy profile generally between that of morphine and tramadol. The nonclinical activity profile is supportive of the proposed clinical indication.

The toxicity profile of tapentadol is not dissimilar from other analgesics, particularly tramadol. The primary toxicities observed were CNS effects, including convulsions and hepatotoxicity in rodents (including proliferative/neoplastic changes), possibly consistent with adaptive changes. A multi-species effect on the cardiovascular system was observed, including QT interval prolongation in conscious dogs. Effects on female fertility, embryofetal development/teratogenicity and postnatal survival were observed in test species, mostly associated with maternotoxicity. Consistent with other opioids, tapentadol exhibited dependence potential, withdrawal effects and tolerance development in animals. Achieved animal/human exposure margins in the nonclinical studies were quite low due to dose-limiting toxicity, particularly CNS, thereby limiting the ability of the nonclinical studies to assess the safety of tapentadol despite the nonclinical toxicity profile *per se* not necessarily representing a greater concern than that of other μ-opioid agonists.

There are a number of concerns with the use of tapentadol, which should be considered in a risk-benefit analysis for the proposed indication:

- As relative exposure in nonclinical studies was generally quite low, the safety assessment of tapentadol will rely primarily on clinical data.
- The adequacy of testing for carcinogenic potential was constrained by dose-limiting toxicity in the rodent species at exposures below clinical exposure.
- Tapentadol should not be used during pregnancy, unless the possible benefits of tapentadol treatment outweigh the risks to the fetus or infant. Tapentadol should not be used during lactation.

The above toxicity concerns have been identified and described in the safety specification in the Risk Management Plan.

A risk-benefit assessment therefore needs to consider: (i) the adequacy of evidence for clinical safety, (ii) the relative safety and efficacy of tapentadol compared to other registered analgesics and (iii) the potential toxicities versus the clinical need, severity of the proposed indications and duration of treatment.

Nonclinical Summary and Conclusions

- The submitted nonclinical data were extensive and generally adequate. The relevant studies were mainly GLP-compliant, apart from some safety pharmacology studies. Relative animal/human exposure to tapentadol in most toxicity studies was quite low, due to dose-limiting toxicity. Most pharmacological effects occurred at dose levels between that of morphine and tramadol, on a dose per body weight basis.

- Tapentadol exerts its pharmacological effects primarily through activation of the μ-opioid receptor (μOR), which was demonstrated *in vitro* (K_i 0.096-0.164 μM, compared to C_{max} of 145 ng/mL or 0.56 μM at the maximum recommended clinical dose) and *in vivo*, based on antagonism of its pharmacological effects by naloxone in mice and rats. Tapentadol binding affinity to the μOR was circa 10x greater than to other ORs, 18x less than morphine and 7x less

than morphine-6-O-glucuronide. High affinity binding to several other receptors was observed, including σ_2 receptor (K_i 0.43 μM), noradrenaline uptake transporter (K_i 0.48 μM), β_1-adrenergic receptor, 5-HT_{2A} receptor (IC_{50} values <1 μM), κ- and δ-ORs and M_1 muscarinic receptor (K_i values <1 μM).

- The pharmacological effects of tapentadol are partially attributable to inhibition of noradrenaline re-uptake in the CNS. The functional role of 5-HT receptor pathways was unclear from the nonclinical data. The potential contribution of other candidate receptor pathways to tapentadol-induced analgesia was not investigated.

- Tapentadol induced dose-related analgesia in several mouse, rat, rabbit and dog models of acute, neuropathic and inflammatory pain, generally at extrapolated exposures (AUC) lower than that at the minimum recommended clinical dose. The efficacious dose range of tapentadol was generally between that of tramadol and morphine; efficacious tapentadol doses were generally 2-3x greater than morphine, on a dose (mg) per body weight basis.

- In ferrets, tapentadol (IV) reduced the incidence and frequency of morphine-induced emesis, but induced an emetic effect with IP dosing. Tapentadol exhibited antitussive properties in rats and a local anaesthetic effect on guinea pig skin.

- Tapentadol inhibited smooth muscle contraction *in vitro*. Consistent with this, inhibition of GI transit and prostaglandin-induced diarrhoea was observed in mice (exposure margins 0.01-0.5). Additionally, combination treatment with diazepam or tetrazepam attenuated their muscle-relaxing activity at clinically relevant doses in mice.

- Safety pharmacology studies identified a multi-species effect on the cardiovascular system. Decreased blood pressure was observed in anaesthetised rabbits and dogs (IV dosing), consistent with opioid-related cardiovascular depressant activity. In contrast, increased heart rate and blood pressure occurred in conscious rats and dogs, in addition to tachycardia and atrioventricular block in dogs following IV administration. This was associated with QT interval prolongation in dogs at exposures similar to or lower (0.2-3x) than clinical exposure. Respiratory depression (bradypnea, changes in blood gas levels, irregular breathing, reduced respiratory volume) were observed in safety pharmacology and toxicity studies in rats, rabbits and dogs, at 0.7-3x maximum clinical exposure (C_{max}).

- The pharmacokinetics of tapentadol were generally similar in mice, rats, dogs and humans, although oral absorption profiles differed in animals and humans, primarily due to the different dosage forms involved (administration of an oral solution to animals compared to immediate- or slow-release tablets to humans). There was generally no accumulation in animals with repeated dosing, although exposure was greater in female rats and humans than males but similar in both sexes in mice and dogs. Tapentadol was rapidly and widely distributed following IV administration to rats, almost all tissues had radioactivity levels higher than blood (brain 2x, spinal cord 1.4x). Highest levels were detected in the kidneys, preputial gland, secretory glands and liver (5-10x blood). Plasma protein binding was low (11-20%) in rabbits, mice, dogs, rats and humans.

- Tapentadol is rapidly metabolised in all species to form a complex mix of glucuronidation and oxidation products. Exposure to the pharmacologically inactive primary metabolite of tapentadol (tapentadol-glucuronide; circa 80% of total plasma/serum exposure) was up to 300x parent compound. Tapentadol glucuronidation was catalysed primarily by human UGT1A6, UGT1A9 and UGT2B7 *in vitro* and human CYP450 enzymes involved in tapentadol metabolism *in vitro* include CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2D6. Tapentadol

and its metabolites were rapidly excreted in all species, primarily in urine (59-78% of dose). Tapentadol glucuronidation was inhibited *in vitro* by probenicid, meclofenamate and naproxen (45%, 36% and 27% inhibition at clinical exposures, respectively). Tapentadol inhibited human CYP2D6 activity *in vitro* by 19-61% at high concentrations (3.1-616 µM, compared to clinical C_{max} of 0.56 µM) and induced CYP1A, CYP2B and CYP2E in rats at PO exposures one-tenth the maximum anticipated clinical exposure.

- Toxicity studies consisted of single dose IV and PO (mice, rats), long-term PO repeat dose (mice, 13 weeks; rats, 26 weeks; dogs, 52 weeks) and >20 other repeat dose studies of shorter duration (PO, dietary, IV, SC) in these species. Excessive toxicity (congestive changes and convulsions/CNS effects in mice, rats and dogs) constrained dose levels and exposure margins were low (generally <1). Severe convulsions, considered an opioid effect, were observed by various routes (exposure margins: mice 0.5, rats 2.2-5.4, dogs 0.1-0.2); other CNS effects represented exaggerated pharmacology. The primary finding in rodents was hepatic effects, consistent with adaptive changes following hepatic enzyme induction (enlarged liver, accentuated lobular pattern, hepatocyte vacuolation, centrilobular hypertrophy), at exposures≥ 0.1-0.3x the maximum clinical exposure.

- An adequate battery of genotoxicity studies comprised an *in vitro* bacterial reverse mutation assay, *in vitro* mammalian chromosome aberration assays and an *in vivo* mammalian chromosome aberration assay and unscheduled DNA synthesis assay. Tapentadol gave a positive result in 1 of 2 *in vitro* chromosome aberration assays at cytotoxic concentrations, but the weight of evidence suggested that tapentadol presented no significant genotoxic potential at the proposed clinical dose range.

- Two-year carcinogenicity studies were conducted in mice (PO) and rats (dietary). A trend towards hepatocellular adenoma and carcinoma was observed in mice and dose-related hepatocellular hypertrophy was observed in rats (exposure margins of circa 0.1 in both species). These lesions were possibly related to adaptive changes seen in toxicity studies.

- In a rat fertility study, there were reductions in the number of corpora lutea, implantations and live fetuses at tapentadol doses associated with maternal toxicity. Tapentadol administration to pregnant rats and rabbits was also associated with increased pre- and post-implantation loss, increased resorptions and reductions in the number of implantations at maternotoxic doses.

- Placental transfer of tapentadol was confirmed in rats. Administration during organogenesis elicited delays in skeletal maturation (incomplete ossification) and cerebral ventricular dilation in rats at SC doses ≥ 10 mg/kg/day (exposure 0.2-0.6x maximum clinical exposure), but limited effects followed IV treatment (≤ 15 mg/kg/day). In rabbits, reduced fetal viability, skeletal delays and other variations were observed with SC dosing (≥ clinical exposure), along with multiple malformations including gastroschisis/ thoracogastroschisis, amelia/phocomelia and cleft palate (≥ 10 mg/kg/day) and ablepharia, encephalopathy and spina bifida (24 mg/kg/day). Rabbits treated IV (9 mg/kg/day) showed fewer effects and no malformations. Embryofetal toxicity, including malformations, may be secondary to compromised maternal nutrition.

- Low levels of tapentadol and tapentadol-glucuronide were detected in milk from lactating rats following PO dosing. Tapentadol administration (PO) during lactation resulted in increased pup mortality between PND1-4 in rats at doses lower than maternotoxic doses (exposure margins of 0.3).

- Tapentadol demonstrated potential for dependence in rodents, at very low exposure margins (≤0.1). Behavioural signs of tapentadol withdrawal were generally less pronounced than those

of morphine or tramadol. Positive reinforcing effects were observed in rats and monkeys (exposure margins <0.1) and were generally comparable with morphine and tramadol. Tolerance to tapentadol analgesia commenced in rats within days, with full development after 3 weeks (slower than morphine or tramadol tolerance). Tapentadol-tolerant rats were also tolerant to morphine, however morphine-tolerant rats remained sensitive to tapentadol.

Recommendations

Tapentadol-induced analgesia is mediated primarily through μOR activation and also via inhibition of noradrenaline re-uptake pathways. Antinociception in several nonclinical models was clearly demonstrated, with an efficacy profile between that of morphine and tramadol. The nonclinical activity profile is supportive of the proposed clinical indication.

The primary toxicities observed were CNS effects, including convulsions and hepatic effects in rodents (including proliferative/neoplastic changes), possibly consistent with adaptive changes. A multi-species effect on the cardiovascular system was observed, including QT interval prolongation in conscious dogs. Effects on female fertility, embryofetal development/ teratogenicity and postnatal survival were observed, mostly associated with maternotoxicity. Consistent with other opioids, tapentadol exhibited dependence potential, withdrawal effects and tolerance development in animals. The risk of reproductive toxicity is not addressable by clinical data and appropriate statements in the Product Information are recommended. Tapentadol dose levels were limited in all nonclinical species due to excessive toxicity(particularly CNS) and resulting animal/human systemic exposure margins were quite low, thereby limiting the ability of the nonclinical studies to assess the safety of tapentadol.

The above toxicity concerns have been identified and described in the safety specification in the Risk Management Plan.

Provided the clinical data adequately address the relevant concerns above, there are no nonclinical objections to the registration of tapentadol.

IV. Clinical Findings

Introduction

Clinical Development Programme

This submission included full reports from 27 completed clinical studies of tapentadol SR (17 Phase I and 10 Phase II/III studies). Reports of serious adverse events and pregnancies were provided for ongoing studies with tapentadol SR (four Phase I studies and four Phase III studies) occurring after 31 October 2008 with a cut-off date again of 28 February 2009. The four ongoing Phase III studies are two studies in cancer pain (PAI-3013/KF15 and PAI-3014/KF16), an open-label extension study (PAI-3010/KF18), and a study in which tapentadol SR is given after a comparison of tapentadol IR and oxycodone IR (PAI- 3020/KF41).

The Phase I studies of tapentadol SR included in this submission supplement the Phase I studies performed with tapentadol IR that assessed biopharmaceutical, pharmacokinetic, pharmacodynamic, safety and tolerability information, influences of intrinsic and extrinsic factors, and abuse potential.

Efficacy and safety studies

Overview of pivotal studies

The efficacy and tolerability of tapentadol SR were investigated in four Phase II double-blind, placebo and active-controlled studies. These were conducted to provide guidance for the development of the clinical Phase III trials.

In Phase III, two placebo- and active-controlled (oxycodone controlled-release (CR) formulation) studies were conducted to assess the efficacy of tapentadol SR in the relief of moderate to severe pain in subjects with chronic pain due to osteoarthritis of the knee (PAI-3008/KF11 and PAI-3009/KF12). One placebo and active- controlled (oxycodone CR) study was conducted to assess the efficacy of tapentadol SR in the relief of moderate to severe pain in subjects with chronic low back pain (PAI-3011/KF23). Studies KF5503/11, KF5503/12 and KF5503/23 were nominated as the pivotal studies. They are summarised in Table 4 below)

There was a further placebo-controlled efficacy study in subjects with painful diabetic peripheral neuropathy (PAI-3015/KF36). A randomized one year safety study (PAI-3007/KF24) with two treatment groups (tapentadol SR and oxycodone CR) was performed which supplied comparative long-term safety in addition to data on maintenance of efficacy.

Furthermore, a study was performed in subjects with low back pain to establish the dose equivalence and direct conversion between tapentadol IR and tapentadol SR (PAI-3019/KF39).

In addition, two studies in cancer pain were ongoing at the time of this submission; one open-label extension study, and a comparative study of gastrointestinal tolerability.

Table 4: Pivotal Phase III studies supporting the efficacy of tapentadol SR

Clinical Trial Number (No. of patients, safety analysis sets)	Pain Model	Active Comparator
KF5503/11 (n=1030)	Treatment of Moderate to Severe Chronic Pain Due to Osteoarthritis of the Knee	Oxycodone CR
KF5503/12 (n=990)	Treatment of Moderate to Severe Chronic Pain Due to Osteoarthritis of the Knee	Oxycodone CR
KF5503/23 (n=981)	Treatment of Moderate to Severe Chronic Low Back Pain	Oxycodone CR

Proposed Australian Indication

The request for “pain unresponsive to non narcotic analgesia” for the Australian PI is consistent with the patients included in the pivotal Phase III trials, who, if they were on non-opioid treatment, were only eligible if they were dissatisfied with treatment because of analgesic efficacy.

In the pivotal Phase III trials the efficacy and safety of tapentadol SR was demonstrated across moderate to severe pain intensities. Patients included in the trials had a baseline score of ≥5 on an 11-point numerical rating scale (NRS). At the start of the titration period, 10 – 20% patients were classified as moderate and 80 – 90% were classified as severe (defined as ≥6 on 11-point NRS).

GCP aspects

All clinical studies were performed according to Good Clinical Practice (GCP) guidelines

Pharmacokinetics

Introduction

The pharmacokinetics and pharmacodynamics of tapentadol SR were characterised in 13 clinical pharmacology studies and in subjects with moderate to severe chronic pain in two Phase II studies and in five Phase III studies.

Several prolonged-release formulations were developed and investigated. The formulation designated as SR1 was the first formulation of tapentadol SR developed for the treatment of chronic pain. This formulation, however, did not suffice for a full clinical development. Therefore, a second prolonged-release formulation was developed and designated as SR2. This tablet has been used in all Phase III studies. For the three lower dose strengths of tapentadol SR, 50 mg, 100 mg, and 150 mg, a smaller tablet formulation, designated SR2small, was developed. This is the to-be-marketed

formulation for these dose strengths, and offers a more convenient and easy to swallow tablet than tapentadol SR2 at the same dose strengths.

Four bioequivalence studies, performed in healthy subjects, were conducted to support the bridging between tapentadol SR2 and tapentadol SR2small.

A single-dose escalation study using the tapentadol SR1 formulation (at doses of 25, 50, 100 and 200 mg) was performed in Japanese healthy subjects (HP47).

The effects of tapentadol SR1 on electrocardiogram (ECG) parameters were studied in a thorough QT/QTc[18] (HP10) study at multiple doses of 86 mg and 172 mg. The results of this study are regarded as supportive to another thorough QT study using multiple doses of 100 mg and 150 mg tapentadol IR (PAI-1018/HP25) because the total daily doses and the peak serum tapentadol concentrations were higher in PAI-1018/HP25 than in HP10.

No additional documentation was submitted assessing the influence of age, race/ethnicity, hepatic impairment and renal impairment on the pharmacokinetics of tapentadol. This was addressed within the tapentadol IR submission.

Phase I studies assessing the potential effect of concomitant medication on the pharmacokinetics of tapentadol were also described in the tapentadol film-coated tablets submission (Palexia IR) and were not repeated in the current tapentadol SR submission.

Food effect studies assessing the effect of food on the pharmacokinetics of tapentadol when administered as a prolonged-release formulation were conducted for tapentadol SR.

Comparison and analyses of results across trials

For cross-study comparison, single dose data of tapentadol SR2 up to 250 mg under fasted conditions were analysed from the following studies with a cut-off date of 31 Oct 2008: PAI-1004/HP18, PAI-1021/HP27, PAI-1020/HP28, PAI-1025/HP29, PAI-1012/HP32, HP33, PAI-1023/HP36, and PAI-1022/HP41. All these studies were biopharmaceutical studies. Pharmacokinetic data from subjects who vomited within the first 6 hr after drug intake were not included in the analysis set.

A study (PAI-1021/HP27) dedicated to the evaluation of the dose proportionality of tapentadol exposure following increasing doses (50 mg to 250 mg) of tapentadol SR2. The pharmacokinetics of tapentadol increased dose proportionally after a single oral administration of tapentadol SR2 50, 100, 200, and 250 mg for AUC parameters. The C_{max} for the tapentadol SR2 formulation increased with dose, but did not fulfil the criteria for dose proportionality. However, graphical exploration of the data suggested approximate linearity between C_{max} and dose in the dose-range between 50 mg and 250 mg. For the cross-study comparison, dose-normalisation to 200 mg of tapentadol (selected as being in the upper range of the clinically effective dose) and subsequent data pooling across doses has, therefore, only been carried out for the AUC and oral clearance (CL/F). No dose normalisation was applied to C_{max} and data pooling for C_{max} and t_{max} was performed for each dose separately.

[18] The requirements for a 'Thorough QT/QTc Study' are described at page 6 of CHMP/ICH/2/04. Note for Guidance on Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. http://www.tga.gov.au/docs/pdf/euguide/ich/000204entga.pdf

QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death. The QT interval is dependent on the heart rate (the faster the heart rate, the shorter the QT interval). To correct for changes in heart rate and thereby improve the detection of patients at increased risk of ventricular arrhythmia, a heart rate-corrected QT interval *QTc* is often calculated.

A summary of cross-study pharmacokinetic parameters for tapentadol after administration of tapentadol SR2 doses from 50 mg to 250 mg is given in Table 5 (AUC, half-life ($t_{1/2}$) and CL/F) and Table 6 (C_{max} and t_{max}). For the area under the plasma concentration time curve from time zero to infinity ($AUC_{inf)}$ for a tapentadol dose normalised to 200 mg, the inter-subject co-variance (CV) was estimated at 27.4% which is slightly lower than the cross-study CV observed for AUC_{inf} for tapentadol IR (34%). The cross-study mean for AUC_{inf} observed for the tapentadol SR2 formulation dose normalised to 200 mg is 805 ng.h/mL. After dose normalisation to 100 mg, the resulting AUC_{inf} (403 ng.h/mL) corresponds very closely with the cross-study mean of 417 ng.h/mL (dose normalized to 100 mg) for the tapentadol IR formulation. This demonstrates the similar dose-normalised exposure achieved with the tapentadol IR and tapentadol SR formulations.

Across all doses of tapentadol SR2, the mean ± standard deviation (SD) terminal phase half-life after administration was 5.9 ± 2.0 h. The median time to reach maximum serum tapentadol concentration ranged between 3 hr to 6 hr for doses of 50-250 mg. The mean cross-study oral clearance (CL/F) was 4449 ± 1199 mL/min (n = 292), with an inter-subject coefficient of variance (CV) of 27.0%.

The estimate for the inter-subject CV for C_{max} ranged from 23.8% to 32.7% for the dose range of 50-250 mg. This range is slightly lower than the cross study CV for C_{max} (39%) observed for the tapentadol IR formulation. The median time to reach maximum serum concentration (t_{max}) ranged from 3.00 and 6.00 hr. The individual ranges of t_{max} were very similar across all doses.

Table 5: Cross-Study Mean Pharmacokinetic Parameters (AUC_{last*}, AUC_{inf}, $t_{1/2}$, CL/F) for Tapentadol After a Single Dose of Tapentadol SR2 in the Fasted State, Dose Normalised to 200 mg

Parameter	Units	N	Mean ± SD	%CV
AUC_{last}	ng.h/mL	294	789 ± 219	27.8
AUC_{inf}	ng.h/mL	292	805 ± 220	27.4
$t_{1/2}$	h	292	5.9 ± 2.0	33.7
CL/F	mL/min	292	4449 ± 1199	27.0

Dataset for cross-study comparison

N = number of observations; CV = coefficient of variation; SD = standard deviation; PR2 = prolonged release formulation 2

*area under the plasma concentration time curve from time zero to the last quantifiable concentration

Table 6: Cross Study Pharmacokinetic Parameters (t_{max}, C_{max}) for Tapentadol After a Single Dose of Tapentadol SR2 in the Fasted State

Parameter	Units	N		Value	%CV
Tapentadol PR2 50 mg					
t_{max}	h	59	Median (range)	3.00 (0.50 - 12.00)	
C_{max}	ng/mL	59	Mean ± SD	10.2 ± 2.42	23.8
Tapentadol PR2 100 mg					
t_{max}	h	59	Median (range)	3.00 (1.00 - 12.00)	
C_{max}	ng/mL	59	Mean ± SD	26.9 ± 8.01	29.8
Tapentadol PR2 150 mg					
t_{max}	h	24	Median (range)	6.00 (1.00 - 12.00)	
C_{max}	ng/mL	24	Mean ± SD	36.7 ± 11.7	31.8
Tapentadol PR2 200 mg					
t_{max}	h	59	Median (range)	4.00 (1.00 - 9.00)	
C_{max}	ng/mL	59	Mean ± SD	61.3 ± 17.9	29.2
Tapentadol PR2 250 mg					
t_{max}	h	93	Median (range)	5.00 (1.00 - 12.02)	
C_{max}	ng/mL	93	Mean ± SD	81.1 ± 26.5	32.7

Dataset for cross-study comparison

N = number of observations; CV = coefficient of variation; SD = standard deviation; PR2 = prolonged release formulation 2

Effect of Food

The effect of food on the bioavailability of tapentadol SR2 was assessed in two Phase I studies. In the key food-effect study (PAI-1020/HP28) that evaluated the effect of a high-fat, high-calorie breakfast on the single dose bioavailability of tapentadol at the highest to-be-marketed dose strength of 250 mg, there was no significant effect on the AUC parameters (8% higher in fed state) of tapentadol. A small increase, estimated from the analysis of variance (ANOVA), of about 18% in C_{max} was observed. However, since this increase was still well within the inter-subject variability for C_{max} of tapentadol observed in this study (30-33%), the increase in C_{max} was not expected to have an impact on safety or efficacy. Similar results were obtained in an earlier, supportive study (PAI-1003/HP17) using the higher dose of 300 mg tapentadol SR2. In this study, the mean C_{max} in the fed state was 28% higher than in the fasted state, but again there was no significant change in AUC between the fasted and fed states.

Data from the key food-effect study (PAI-1020/HP28) was compared to the pooled pharmacokinetic data obtained in the fasted condition. Since the key food effect study was conducted at the highest recommended dose of 250 mg, the AUCs of the pooled pharmacokinetic data were also normalised to a 250 mg dose. No dose normalisation was applied for C_{max} and hence the comparison of C_{max} is more limited. The comparison showed that under fasted or fed conditions, the C_{max} (mean ± SD) of tapentadol was 81.1 ± 26.5 ng/mL (n = 93) and 93.7 ± 28.1 ng/mL (n = 32), respectively. The area under the plasma concentration time curve from time zero to the last measurable time point area under the plasma concentration time curve from time zero to the last quantifiable concentration (AUC_{last}) (mean ± SD) under fasted and fed conditions were 986 ± 274 ng.h/mL (n = 294) and 1164 ± 338 ng.h/mL (n = 32), respectively. The AUC_{inf} (mean ± SD) under fasted and fed conditions were 1006 ± 275 ng.h/mL (n = 292) and 1168 ± 337 ng.h/mL (n = 32), respectively. The ratios for fed to fasting conditions of C_{max} (1.16), AUC_{last} (1.18) and AUC_{inf} (1.16) were similar to those observed in the key food interaction study.

Pharmacokinetics of Tapentadol Following Multiple-Dose Administration

Two Phase I multiple-dose studies using tapentadol SR formulations were performed in healthy subjects: a multiple-dose bioequivalence study (HP54) and a study to evaluate ECG parameters after tapentadol SR1 (HP10). The calculated accumulation ratio (ratio of C_{max} at steady state $C_{max,ss}$ [multiple-dose] to C_{max} [single-dose], as shown in Table 7) was between 1.5 and 1.6 in HP10, the calculated accumulation ratio (ratio of $C_{4h,ss}$ [multiple-dose] to C_{4h} [single-dose], Table 7) was between 1.51 and 1.65 in HP54. As C_{max} was not calculated on Day 1 in HP54 due to the single sample, the serum level at 4 h (C_{4h}) has been used. The accumulation ratios for tapentadol are close to the theoretically expected value of approximately 1.3 (calculated using the formula: $R = 1/(1-2\text{-}\varepsilon)$ where $\varepsilon = \tau/t_{1/2}$) suggesting that the accumulation was generally in line with the $t_{1/2}$ of tapentadol and the dosing interval.

Table 7: Pharmacokinetic Parameters for Tapentadol at Steady state Following Dosing Every 12 Hours In Healthy Subjects (HP10, HP54)

		Pharmacokinetic parameters				
Study Formulation	**Dose**	**$C_{max,ss}$ or $C_{4h,ss}$ [a] ng/mL**	**C_{max} or C_{4h} [a] ng/mL**	**AUC_{tau} ng·h/mL**	**$t_{1/2}$ h**	**Accumulation ratio [b]**
HP5503/10						
Tapentadol PR1 (n = 35)	86 mg	47.0 ± 14.7 [31.2]	31.1 ± 7.62 [24.5]	377 ± 95.1 [25.2]	5.7 ± 1.0 [17.0]	1.56
Tapentadol PR1 (n = 35)	172 mg	92.1 ± 24.3 [26.4]	60.4 ± 14.6 [24.2]	779 ± 213 [27.4]	5.3 ± 0.8 [15.4]	1.53
HP5503/54						
Tapentadol PR2 (n = 22)	150 mg	66.1 ± 17.3 [26.1]	40.0 ± 10.3 [25.8]	655 ± 159 [24.3]	5.1 ± 1.0 [19.8]	1.65
Tapentadol PR2small (n = 22)	150 mg	64.0 ± 16.1 [25.2]	42.3 ± 10.6 [25.0]	625 ± 162 [26.00]	5.0 ± 1.0 [20.9]	1.51

Data expressed as mean ± SD [%coefficient of variation]

a) $C_{max,ss}$ and C_{max} refer to HP10 and $C_{4h,ss}$ and C_{4h} refer to HP54

b) Calculated from ratio of $C_{max,ss}/C_{4h,ss}$ and of C_{max}/C_{4h}

n = number of subjects; %CV = coefficient of variation in percent; SD = standard deviation.

The pharmacokinetic parameters of tapentadol obtained after administration of the tapentadol SR tablet in the Phase I studies HP10 and HP54 are listed in Table 8 for a direct comparison to the single dose data. The concentration-related parameter (area under the plasma concentration time curve over a dosing interval or AUC_{tau}) was dose-normalised to a 200 mg dose for comparison to the pooled pharmacokinetic data obtained in a fasted condition. The data shown from studies HP10 and HP54 refer to steady state values. The similarity between AUC_{tau} and $t_{1/2}$ observed at steady state in these two studies and AUC_{inf} and $t_{1/2}$ obtained from the pooled pharmacokinetic data from the single-dose studies provides supportive evidence that there is no relevant change in tapentadol pharmacokinetics with time.

Table 8: Dose-Normalised (to 200 mg) Pharmacokinetic Parameters of Tapentadol after Administration of Tapentadol SR Tablets in the Fasted State to Healthy Subjects

	Formulation	Study	Dose	n	Dose normalized AUC_{inf}, ng.h/mL	$t_{1/2}$, h
Single dose; Dataset for cross-study comparison				292	805 ± 220 [27.4]	5.9 ± 2.0 [33.7]
				n	**DN- AUC_{tau}, ng.h/mL**	**$t_{1/2}$, h**
Multiple dose (steady state)	Tapentadol PR1	HP10	86 mg	35	877 ± 221 [25.2]	5.7 ± 1.0 [17.0]
	Tapentadol PR2	HP54	150 mg	22	873 ± 212 [24.3]	5.1 ± 1.0 [19.8]
	Tapentadol PR2small	HP54	150 mg	22	833 ± 216 [26.0]	5.0 ± 1.0 [20.9]
	Tapentadol PR1	HP10	172 mg	35	906 ± 248 [27.4]	5.3 ± 0.8 [15.4]

Data expressed as mean ± SD [% CV]

%CV = coefficient of variation in percent; h = hour; n = number of subjects; SD = standard deviation

The median time to reach maximum serum concentrations in steady state ranged from 2 hr to 4 hr for the tapentadol SR1 86 mg, tapentadol SR1 172 mg, tapentadol SR2 250 mg, and tapentadol SR2small 250 mg formulations in HP10 and HP54.These results are a little shorter than the median time to reach maximum serum concentrations of the pooled pharmacokinetic data after single dosing (median t_{max} ranged from 3-6 hr after single oral administration of tapentadol SR2 50 mg to 250 mg tablets. The individual tmax at steady-state ($t_{max,ss}$) values in the multiple dose data from HP10 and HP54 (1.0-7.0 hr) are also completely within the range of individual values observed in the pooled single dose pharmacokinetic data (0.5-12.02 hr).

In the thorough QT study (HP10), steady state was investigated by analysis of the ratios of the pre-dose concentrations of two consecutive dosing times. The results indicated that steady state had been achieved after the third dose (on Day 2).

This time for the attainment of steady state corresponds to the results of HP54. Statistical analysis of the trough concentrations indicated that steady state had been achieved after the third dose on Day 2.

Exposure of Tapentadol after Administration of the Tablet Formulations

Pharmacokinetic data collected in healthy subjects during Phase I studies using the prolonged-release formulations were compared to data obtained from subjects participating in Phase III studies. There are two single-dose studies and two multiple-dose studies in healthy subjects included in this comparison:

• Dose-proportionality after single-dose using tapentadol SR2 (PAI-1021/HP27).

• Pivotal single-dose food effect using tapentadol SR2 (PAI-1020/HP28).

• Multiple-dose thorough QT trial (HP10) with tapentadol SR1 tablets.

• Multiple-dose bioequivalence (HP54) using tapentadol SR2 and tapentadol SR2 small formulations.

These studies were selected because PAI-1021/HP27 and PAI-1020/HP28 are pivotal Phase I studies, and HP10 and HP54 are Phase I multiple dose studies.

Serum concentrations measured in the following four Phase III studies (all using the tapentadol SR2 formulation) were used for comparative purposes:

• Multiple-dose serum concentrations in subjects with pain due to osteoarthritis of the knee: PAI-3008/KF/11 using tapentadol SR2.

• Multiple-dose serum concentrations in subjects with pain due to osteoarthritis of the knee: PAI3009/KF12 using tapentadol SR2.

• Multiple-dose serum concentrations in subjects with low back pain: PAI-3011/KF23 using tapentadol SR2.

• Multiple-dose serum concentrations in subjects with painful diabetic peripheral neuropathy: PAI-3015/KF36 using tapentadol SR2.

These four Phase III studies are the key efficacy studies with a similar design in terms of sparse sampling.

The pharmacokinetic parameters of tapentadol obtained after administration of the tapentadol SR tablet in the Phase I studies PAI-1021/HP27, PAI-1020/HP28, HP10, and HP54 are listed in Table 9. The concentration-related parameters have (where appropriate) been dose-normalised to a 200 mg dose (selected as being in the upper range of the clinically effective dose) to facilitate comparison.

Table 9: Dose-Normalised (to 200 mg) Pharmacokinetic Parameters of Tapentadol After Administration of Tapentadol SR Tablets to Healthy Male and Female Subjects (PAI-1021/HP27, PAI-1020/HP28, HP10, and HP54)

				Dose normalized		
Trial	Dose (PR form)	n	t_{max} h	C_{max} [a] ng/mL	AUC [b] ng.h/mL	$t_{1/2}$ h
Multiple dose (steady state)						
HP10	86 mg bid (PR1)	35	4.00 (2.00–5.00)	109 ± 34.1 [31.2%]	877 ± 221 [25.2%]	5.7 ± 1.0
	172 mg bid (PR1)	35	4.00 (2.00–7.00)	107 ± 28.3 [26.4%]	906 ± 248 [27.4%]	5.3 ± 0.8
HP54	150 mg bid (PR2small)	22	2.00 (1.50–5.02)	104 ± 28.4 [27.4%]	833 ± 216 [26.0%]	5.0 ± 1.0
	150 mg bid (PR2)	22	2.00 (1.00–5.00)	106 ± 24.0 [22.7%]	873 ± 212 [24.3%]	5.1 ± 1.0
Single dose						
PAI-1021/HP27	200 mg (PR2)	36	5.00 (1.00–9.00)	62.5 ± 17.9 [28.7%]	825 ± 191 [23.2%]	5.2 ± 0.9
PAI-1020/HP28	250 mg (PR2)	28	6.00 (2.00–9.00)	62.9 ± 20.8 [33.0%]	846 ± 231 [27.3%]	5.1 ± 1.1

Data expressed as mean ± SD [%CV], except for t_{max}: median (range)

%CV = coefficient of variation in percent; DN = dose-normalized to 200 mg; h = hour; n = number of subjects; SD = standard deviation; PR = prolonged-release (formulation 1 or 2)

a) Although C_{max} should not strictly be dose-normalised (C_{max} is dose linear rather than dose proportional) this has been carried out here to better enable a direct comparison with serum concentrations in subjects with pain.

b) AUC_{tau} for HP10 and HP54, AUC_{inf} for PAI-1021/HP27 and PAI-1020/HP28

The pharmacokinetic results were very consistent across the two single-dose studies (PAI-1021/HP27 and PAI-1020/HP28). The data from HP10 and HP54 refer to steady state values in each case. The similarity between AUC_{tau} observed at steady state in these two studies and AUC_{inf} in the single-dose studies supports the fact that tapentadol pharmacokinetics are not subject to relevant changes with time. These cross-study data are also derived from 3 tapentadol SR formulations (PR1, PR2, and PR2small), again showing the similarity of tapentadol pharmacokinetics between these three formulations.

Descriptive statistics of exposure after administration of the tapentadol SR tablet in the Phase III studies is provided in Table 10. Once again, the concentrations have been dose normalised to a dose of 200 mg to facilitate comparison to the data generated in healthy subjects. Each study used the same dosing regimens: 100 mg, 150 mg, 200 mg or 250 mg twice daily administrations of tapentadol SR2 tablets. For the start of maintenance and after 4 weeks of treatment, a similar range of median times post dose (approximately 2-6 hr) was adopted in the double-blind active and placebo controlled studies (PAI-3008/KF11, PAI-3009/KF12, and PAI-3011/KF23).

Thus, although concentrations do not refer to the maximum serum concentration, they span the time interval around the expected time to peak for tapentadol (3-6 hr).

Table 10: Dose-Normalised (to 200 mg) Serum Tapentadol Concentrations After Administration of Tapentadol SR to Male and Female Subjects with Severe Pain (PAI-3008/KF11, PAI-3009/KF12, PAI-3011/KF23, PAI-3015/KF36)

	Start maintenance		4 weeks maintenance	
	n	Mean ± SD	n	Mean ± SD
KF5503/11				
100 mg	49	78.6 ± 49.0	49	79.4 ± 64.0
150 mg	72	81.2 ± 58.7	43	78.0 ± 43.9
200 mg	67	69.0 ± 48.2	46	74.3 ± 44.5
250 mg	54	63.4 ± 44.8	58	63.6 ± 52.6
KF5503/12				
100 mg	102	81.4 ± 45.2	82	69.2 ± 45.8
150 mg	62	72.7 ± 36.4	46	73.6 ± 48.9
200 mg	53	63.5 ± 38.9	44	71.9 ± 49.4
250 mg	22	84.8 ± 42.0	32	81.5 ± 53.4
KF5503/23				
100 mg	40	70.6 ± 50.4	37	87.2 ± 64.0
150 mg	52	59.9 ± 58.3	36	53.5 ± 57.3
200 mg	61	70.6 ± 46.9	33	87.3 ± 66.6
250 mg	61	66.6 ± 40.1	81	59.4 ± 47.4
KF5503/36			8 weeks maintenance	
100 mg	52	91.0 ± 64.0	20	68.4 ± 58.4
150 mg	59	77.3 ± 49.9	20	69.1 ± 44.8
200 mg	52	83.6 ± 69.3	19	71.8 ± 53.8
250 mg	184	61.5 ± 44.4	64	74.9 ± 53.6

h = hour(s); n = number of subjects; SD = standard deviation

The mean (dose-normalised) concentrations observed in subjects with pain are lower than the C_{max} data reported for healthy subjects using extensive rather than sparse blood sampling. The dose-normalised exposures were relatively consistent between the studies for each of the four dose levels. The data show that the serum concentrations for each treatment regimen were relatively stable over a maintenance period of 4 or 8 weeks.

Comment: Overall, the data presented in this section indicate that the tapentadol SR tablet formulations perform consistently and predictably between studies and dose levels, both in healthy subjects and in subjects with chronic pain.

Evaluator's overall conclusions on pharmacokinetics

• Under fasted conditions, the absolute oral bioavailability of tapentadol SR is approximately 32% due to a high first pass metabolism.

• Following a single oral dose of tapentadol SR, the median time to reach maximum serum tapentadol concentrations was between 3-6 hr for doses of 50 mg to 250 mg. Mean C_{max} varied from 10.1 to 81.1 ng/mL in the dose range of 50 to 250 mg, and inter-subject variability varied from 23.8 to 32.7%.

• A dose proportional increase in the AUC of tapentadol was observed over the therapeutic dose range of 50 to 250 mg tapentadol SR tablets. C_{max} increased with dose, but did not fulfil the criteria for dose proportionality. Graphical exploration of the data however, suggested approximate linearity between C_{max} and dose in the dose range of 50 mg to 250 mg tapentadol.

• The C_{max} increased by 18% and the AUC of tapentadol by 8% when a single dose of tapentadol SR 250 mg was administered after a high-fat, high-calorie breakfast. The effect of concomitant food intake on the pharmacokinetics of tapentadol is considered to be of no clinical significance.

• The exposure (AUC_{tau}) of tapentadol following multiple doses of tapentadol SR is similar to the exposure (AUC_{inf}) following single dose administration of tapentadol SR indicating that the pharmacokinetics of tapentadol are predictable, and with no evidence for relevant deviations from time-independent pharmacokinetics.

• Steady state serum tapentadol concentrations are attained after the third dose (on Day 2). Following dosing every 12 hr, the accumulation ratio for tapentadol based on $C_{max,ss}$ was about 1.5 suggesting that the accumulation is in line with the $t_{1/2}$ of tapentadol and the dosing interval.

• The terminal phase half-life (after oral administration) is on average 5.9 ± 2.0 hr and CL/F is on average 4449 ± 1199 mL/min across all doses of tapentadol SR.

• The dose-normalised (to 100 mg) AUC_{inf} (403 ng.h/mL) and the inter subject coefficient of variation (CV; 27.4%) across all doses of tapentadol SR (50 to 250 mg) correspond very closely with the cross-study mean for the dose-normalised (to 100 mg) AUC_{inf} (417 ng.h/mL) and the inter subject CV (34%) for the tapentadol IR formulation.

• The pharmacokinetics of tapentadol following single and multiple doses of tapentadol SR indicate that the tapentadol SR tablet formulations perform consistently and predictably between studies and dose levels, both in healthy subjects and in subjects with chronic pain.

• In subjects with chronic pain (Phase II/ III studies), the mean serum tapentadol concentrations following multiple doses of tapentadol SR remained relatively stable at all dose levels for a maintenance dose period of at least 4 weeks.

Drug Interactions

No significant new drug interaction data were provided in relation to the tapentadol SR formulation.

Pharmacodynamics

No significant new pharmacodynamic data were provided in relation to the tapentadol SR formulation.

Efficacy

The following efficacy data were submitted for evaluation to support registration of tapentadol SR/PR: four Phase II studies, four Phase III efficacy studies, one long term safety study, and one study comparing the immediate-release and prolonged-release formulation in the development program of tapentadol SR involving subjects with moderate to severe low back pain, painful osteoarthritis of the hip or knee, and painful diabetic peripheral neuropathy (the study in this indication is considered to be supportive). All four Phase III efficacy studies were adequate and well-controlled, using double-blind designs and controls (strong analgesics or placebo, or both).

The first set of two Phase II studies conducted with tapentadol SR were performed with low doses (tapentadol SR up to 86 mg twice daily) in fixed dose designs. The second set of two Phase II studies used a fixed dose titration design with an initial two weeks of forced titration followed by two weeks on a stable dose. The Phase III development program for tapentadol SR was based on a combination of efficacy studies with controlled dose adjustment (PAI-3008/KF11, PAI-3009/KF12, and PAI-3011/KF23) and a study with a fixed dose maintenance design (PAI-3015/KF36), all using twice daily dosing. The pain conditions (listed above) were chosen because they usually present with moderate to severe pain which is often treated with opioids.

Phase II and Phase III studies evaluating the efficacy of tapentadol SR are summarised in Table 11.

Table 11: Overview of Study Designs of Phase II/ III Tapentadol SR Chronic Pain Studies

	Pain Condition [a]	Design [b]	Treatment dosing and duration	Active Comparator
Phase 2 Studies				
KF5503/09	OA	DB/PC	4 weeks fixed dose	Oxycodone CR
KF5503/10	LBP	DB/PC	4 weeks fixed dose	Tramadol SR
PAI-2001/KF19	OA	DB/PC	2 weeks forced dose titration 2 weeks fixed dose maintenance	Oxycodone CR
PAI-2002/KF20	LBP	DB/PC	2 weeks forced dose titration 2 weeks fixed dose maintenance	Tramadol SR
Phase 3 Studies				
PAI-3008/KF11	OA	DB/PC	3 weeks flexible dose titration 12 weeks controlled dose adjustment maintenance	Oxycodone CR
PAI-3009/KF12	OA	DB/PC	3 weeks flexible dose titration 12 weeks controlled dose adjustment maintenance	Oxycodone CR
PAI-3011/KF23	LBP	DB/PC	3 weeks flexible dose titration 12 weeks controlled dose adjustment maintenance	Oxycodone CR
PAI-3015/KF36 [a]	DPN	RW/DB/PC	3 weeks open-label flexible dose titration (tapentadol PR) 12 weeks fixed dose maintenance	None
PAI-3019/KF39 [b]	LBP	DB/CO (IR/PR)	3 weeks flexible dose titration (tapentadol IR) 2 weeks fixed dose maintenance per period	None
PAI-3007/KF24 [c]	OA, LBP	OL	1 week flexible dose titration 1 year controlled dose adjustment maintenance	Oxycodone CR

a) Enrichment procedures (ie, responder criteria after the Titration Period) to continue long-term treatment on a fixed dose only in subjects who benefited from the treatment.

b) Tapentadol IR/PR 2-way cross-over conversion study.

c) Study designed primarily as long-term safety study with limited efficacy evaluations.

OA = osteoarthritis, LBP = low back pain, DPN = diabetic peripheral neuropathy, DB = double-blind, PC = placebo controlled, RW = randomized withdrawal, OL = open-label, CO = cross-over, IR = immediate release; PR = prolonged release; CR = controlled release; SR = sustained release

The initial evidence for efficacy of tapentadol was obtained using an oral tapentadol IR formulation as well as from IV administration in the initial Phase II studies of acute pain conditions. Following the development of a tapentadol SR formulation, two placebo-and active-controlled Phase II studies employing doses of tapentadol SR up to 86 mg twice daily in subjects with chronic pain were performed. One study was performed in subjects with chronic pain due to osteoarthritis (KF09), and one study in subjects with chronic low back pain (KF10). These were followed by two additional Phase II studies using doses of tapentadol SR up to 200 mg twice daily in a forced titration, fixed dose design, again with one study in subjects with chronic osteoarthritis pain (PAI- 2001/KF19), and in one study in chronic low back pain (PAI-2002/KF20).

There were six Phase III studies performed using doses of tapentadol SR up to 250 mg twice daily. Four studies assessed tapentadol SR analgesic efficacy, one study evaluated the equivalence of tapentadol IR and tapentadol SR, and one study evaluated the long-term safety of tapentadol SR. Three of the Phase III efficacy studies used a controlled dose adjustment design and included placebo and the active comparator, oxycodone CR. Two of these studies were performed in patients with chronic osteoarthritis pain (PAI-3008/KF11 and PAI-3009/KF12) and one study was performed in patients with chronic low back pain (PAI-3011/KF23). A period of flexible titration was followed by a 12-week maintenance period with controlled dose adjustment.

An additional efficacy study used a placebo-controlled, randomised withdrawal design and was performed in painful diabetic peripheral neuropathy (PAI-3015/KF36). Following three weeks of open-label titration with tapentadol SR, subjects entered a double blind 12-week fixed dose maintenance period. This study was nominated to be supportive.

Study PAI-3019/KF39 was performed to assess the relative analgesic efficacy of tapentadol IR and tapentadol SR using a cross-over design after three weeks of titration to optimal dose with tapentadol IR.

Study PAI-3007/KF24 assessed the long term safety of tapentadol SR over one year, using oxycodone CR as a control. Information on efficacy over an extended period of treatment for up to one year was also obtained.

Study designs

The Phase II studies and the Phase III studies PAI-3008/KF11, PAI-3009/KF12 and PAI-3011/KF23 were parallel group, randomised, double-blind, placebo- and active-controlled studies. Subjects were randomised at the beginning of the treatment period. Phase II studies used fixed doses or forced titration; no individual dose adjustments were allowed. To more closely reflect clinical practice, the Phase III studies mentioned above had a controlled dose adjustment design consisting of a 3-week titration period followed by a 12-week maintenance period during which subjects could adjust their dose within pre-defined parameters.

Study PAI-3015/KF36 included an enrichment design with an initial titration period using tapentadol SR followed by a randomised withdrawal maintenance period. At the end of the titration period, a responder criterion (a minimum improvement of 1 on the 11-point NRS at the end of the open-label titration) was used to select subjects to continue long-term treatment who benefited from the treatment. This enrichment procedure results in a more homogeneous study population of initial treatment responders and minimises long-term exposure of subjects to a treatment to which they may not be responsive (Rowbotham 2005). This design is also consistent with medical practice in which treatment is only continued on a stable dose regimen when an initial treatment effect has been established. An enriched design was used in at least two previous placebo-controlled studies in the treatment of neuropathic pain (Byas-Smith 1995, Lynch 2003) and a 3-week period is considered sufficient to establish an initial treatment effect for the purpose of enriched enrolment in painful diabetic peripheral neuropathy (Byas-Smith 1995).

Study PAI-3007/KF24 was a long-term (up to one year) open-label safety study in which subjects were randomised to receive tapentadol SR or oxycodone CR in a ratio of 4:1. An open-label design is commonly used for safety studies. The duration of the study was chosen to comply with guidelines (CPMP/ICH/375/95)[19].

A cross-over design (tapentadol SR and tapentadol IR; 2 by 2-week periods) was used for study PAI-3019/KF39 following an initial 3-week titration period with tapentadol IR. This design allowed an estimation of the relative analgesic efficacy of tapentadol IR and tapentadol SR and reduced variability between treatments.

In the Phase III studies patients with moderate pain and sever pain were enrolled. In the three controlled dose adjustment efficacy studies (PAI-3008/KF11, PAI-3009/KF12, and PAI-3011/KF23), subjects were required to have taken analgesic medication for at least three months and be dissatisfied with their treatment. If they were taking opioids, the dissatisfaction could be either due to efficacy or tolerability, for non-opioids the reason had to be lack of efficacy. Subjects had to answer the following questions:

• Is the subject dissatisfied with his/her current analgesic treatment?

− Due to inadequate analgesia.

[19]ICH Topic E 1. Population Exposure: The Extent of Population Exposure to Assess Clinical Safety. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002747.pdf

− Due to poor tolerability.

Selection Criteria for Subject Populations

A summary of the most relevant study selection criteria for Phase II studies is given in Table 12 and for Phase III studies in Table 13.

Table 12: Summary of Subject Selection Criteria of Phase II Studies

	KF09	KF10	PAI-2001/KF19	PAI-2002/KF20
Cause of pain	Osteoarthritis of hip or knee	Low back pain	Osteoarthritis of knee	Low back pain
Age range (years)	40 – 75	18 – 75	≥40	≥18
Sex	Male and female	Male and female	Male and female	Male and female
Baseline pain:				
11-point NRS	≥4 with a ≥1 increase after washout	≥4 with a ≥1 increase after washout		
100 mm VAS			At screening: ≥50 (not on opioids) ≤50 (on opioids) Flare at end of washout: ≥50 and ≥18 increase	At screening: ≥50 (not on opioids) ≤50 (on opioids)

NRS = Numerical rating scale; VAS = visual analog scale

Table 13: Summary of Subject Selection Criteria of Phase III Studies

	PAI-3008/KF11	PAI-3009/KF12	PAI-3011/KF23	PAI-3007/KF24	PAI-3019/KF39	PAI-3015/KF36
Pain condition	Osteoarthritis of the knee	Osteoarthritis of the knee	Low back pain	Osteoarthritis of hip or knee, or low back pain	Low back pain	Diabetic peripheral neuropathy
Age range (years)	≥40	≥40	≥18	≥18	≥18	≥18
Sex	Male and female	Male and female	Male and female	Male and female	Male and female	Male and female
Baseline pain (11-point NRS) [b]	≥5	≥5	≥5	≥4	≥5	≥5 [a]

a) To be randomized into the double-blind Maintenance Period, subjects had to have at least a 1-point reduction in the average pain intensity score on an 11-point NRS from the beginning (baseline) to the end of the open-label Titration Period.

b) The baseline pain was always measured after washout and before the start of Titration Period.

NRS = Numerical rating scale

Study drug dosing - Phase III efficacy studies

The dose range of tapentadol SR selected for use in the Phase III studies was 100 to 250 mg given twice daily, with a starting dose of 50 mg twice daily for the titration periods. Results of Phase II studies indicated that the lowest effective dose of tapentadol SR was 100 mg twice daily. Subjects treated with tapentadol SR 25-50-100 mg twice daily showed a numerically greater decrease in pain intensity than placebo but the difference was not statistically significant (PAI-2001/KF19 and PAI-2002/KF20). However, the pain scores were in the same range as with oxycodone CR 20 mg twice daily (-42.9 [tapentadol PR] versus -41.8) or tramadol SR 200 mg twice daily (-20.3 [tapentadol PR] versus -21.2).

To explore doses above tapentadol SR 200 mg twice daily, the highest dose used in Phase II studies, tapentadol SR 250 mg twice daily was included in the Phase III studies. Data from the clinical development of tapentadol, suggested an equianalgesic dose ratio for oxycodone IR to tapentadol IR of approximately 1:5. Oxycodone CR was chosen as the comparator for studies in osteoarthritis, low back pain and diabetic peripheral neuropathy, with a dose range of 20 mg to 50 mg twice daily as this is the range that is widely used in clinical practice. The dosage range and the dose steps

correspond well to the therapeutic range indicated for the testing of tapentadol SR in Phase III (100 to 250 mg twice daily).

Dosing Interval and Duration

Pharmacokinetic data support the use of tapentadol SR twice daily. Maximum tapentadol concentrations occur within 3 to 6 hr after the intake of tapentadol SR with a terminal $t_{1/2}$ of 4.3 hr. The use of long-acting opioids or prolonged-release preparations may reduce the risk of intermittent withdrawal symptoms associated with pain peaks compared to the use of short-acting preparations. Therefore, a twice daily (morning and evening) dosing scheme was employed for the Phase II and Phase III studies of tapentadol SR.

The Phase III studies fulfilled the requirements of the nociceptive pain guideline (CPMP/EWP/612/00[20]) to study subjects for a sufficient period of time. Subjects with moderate to severe pain in the tapentadol SR Phase III placebo-controlled efficacy studies were evaluated for 15 weeks, with the first three weeks allowing titration to an optimal dose in terms of efficacy and tolerability.

The design of the Phase III studies in subjects with osteoarthritis and low back pain (PAI-3008/KF11, PAI-3009/KF12, and PAI-3011/KF23) included an initial flexible three week titration period to the optimal dose followed by controlled dose adjustment during a 12 week maintenance period. The study in subjects with painful diabetic peripheral neuropathy (PAI-3015/KF36) used a 3-week open-label flexible titration period followed by a 12-week double-blind fixed dose maintenance period. During titration, the starting dose for tapentadol SR was 50 mg and for oxycodone CR was 10 mg, both given twice daily for 3 days. The dose was then increased to 100 mg tapentadol SR twice daily and 20 mg oxycodone CR twice daily. Subjects were to receive this dose for the next 4 days. These were the minimum doses allowed for the remainder of the studies.

Thereafter, in the PAI-3008/KF11, PAI-3009/KF12 and PAI-3011/KF23 studies, increases in the dose at 3-day intervals were allowed in increments of 50 mg tapentadol SR twice daily, 10 mg oxycodone CR twice daily or placebo to achieve a stable optimal dose in terms of a balance between individual pain relief and tolerability. Dose decreases were allowed at any time using the same dose steps, down to the minimum dose. This variation in daily dosing is referred to as controlled dose adjustment.

The reasons for the use of flexible titration and controlled dose adjustment are similar as the individual's response to opioid therapy varies, requiring individual dose adjustments to achieve optimal efficacy and to minimise adverse effects (AEs), mainly gastrointestinal- or central nervous system-related symptoms which often limit the use of opioids at dose levels relieving pain in clinical practice. Flexible titration, with continuous controlled dose adjustment during ongoing therapy as needed, also reflects the consensus statement of the American Academy of Pain Medicine and American Pain Society that the "treatment plan should be tailored to both the individual and the presenting problem" (American Pain Society 1997). Flexible titration is also in line with recommendations for the use of opioids in chronic non-cancer pain (Kalso 2003).

Active Controls

The active control in the Phase II studies of low back pain was tramadol SR (100 mg twice daily in KF10 and 100-150-200 mg twice daily in PAI-2002/KF20). Tramadol has been proven to be effective and well-tolerated in chronic low back pain at doses of 200 to 400 mg daily as an immediate release formulation (Schnitzer 2000) and as a slow release formulation (Sorge 1997).

[20] Note for guidance on clinical investigation of medicinal products for treatment of nociceptive pain. http://www.tga.gov.au/docs/pdf/euguide/ewp/061200final.pdfhttp://www.tga.gov.au/docs/pdf/euguide/ewp/061200final.pdf

The active control was oxycodone CR in the Phase II studies of osteoarthritis at a dose of 20 mg twice daily, and in the Phase III studies PAI-3008/KF11, PAI-3009/KF12, and PAI-3011/KF23 using a dose range of 20 to 50 mg twice daily. Oxycodone CR was chosen as the active control in Phase III studies because it is a commonly used opioid analgesic prescribed for chronic-pain syndromes in clinical practice. The dose range of oxycodone CR used in the Phase III studies was similar to the dose ranges shown to be effective in comparable double blind studies of oxycodone

In the PAI-3008/KF11, PAI-3009/KF12 and PAI-3011/KF23 studies, oxycodone CR was used to confirm model validity in case of non-significant results on the primary endpoint with tapentadol SR (assay sensitivity). The results were not used for direct comparison with tapentadol SR within each study, although it was used to assess the clinical relevance of the effects seen and the overall benefit-risk profile of tapentadol SR.

A pre-specified meta-analysis, comparing tapentadol SR and oxycodone CR, was performed using pooled data of the PAI-3008/KF11, PAI-3009/KF12, and PAI-3011/KF23 studies to test for the non-inferiority of the efficacy of tapentadol SR to oxycodone .This comparison is important for clinicians who are familiar with the dosing of the widely marketed product oxycodone CR.

Rescue and Additional Analgesic Medication

Paracetamol was allowed at different total daily doses in the tapentadol SR Phase II studies.

In the Phase III studies of osteoarthritis (PAI-3008/KF11and PAI-3009/KF12) and low back pain (PAI-3011/KF23), paracetamol up to 1000 mg per day was allowed during the titration period. However, it was not allowed during the last three days of the titration period or at all during the maintenance period with the exception of up to 1000 mg per day for no more than 3 consecutive days for reasons other than the study-related pain.

In the Phase III studies of osteoarthritis (PAI-3008/KF11 and PAI-3009/KF12) and low back pain (PAI-3011/KF23), rescue medication was restricted to the titration period.

In the diabetic peripheral neuropathy study (PAI-3015/KF36), supplemental paracetamol was allowed during the open-label titration. Tapentadol SR 25 mg was allowed twice daily for the first four days of the maintenance period and once daily for the rest of the maintenance period.

In PAI-3019/KF39 (comparing tapentadol IR and tapentadol SR) in chronic low back pain, paracetamol up to 2000 mg per day was allowed at any time. Paracetamol, at 1000 mg daily, was allowed as additional analgesic medication for a maximum of seven consecutive days and no more than fourteen days out of thirty days during the one-year safety study, PAI-3007/KF24.

Efficacy Evaluations

Table 14 summarises the principal efficacy evaluations in Phase II and Phase III studies.

Table 14: Efficacy Parameters Evaluated in Phase II and Phase III Tapentadol SR Chronic Pain Studies

Study	Pain intensity	PGIC	WOMAC	BPI	SF-36	EQ-5D	Use of Rescue medication
KF09	NRS		X		X		X
KF10	NRS			X	X		X
PAI-2001/KF19	VAS/NRS	X	X		X	X	X
PAI-2002/KF20	VAS/NRS	X			X	X	X
PAI-3008/KF11	NRS	X	X		X	X	
PAI-3009/KF12	NRS	X	X		X	X	
PAI-3011/KF23	NRS	X		X	X	X	
PAI-3015/KF36	NRS	X		X	X	X	X
PAI-3019/KF39	NRS						X
PAI-3007/KF24	NRS	X			X	X	

NRS = Numerical Rating Scale; VAS = Visual Analog Scale; PGIC = patient global impression of change; WOMAC = Western Ontario McMaster Questionnaire; BPI = Brief Pain Inventory; SF-36 = Short Form 36; EQ-5D = EuroQol-5 dimension

Statistical methodology

Primary Endpoint and Statistical Hypothesis for the Primary Objective

The change from baseline of the average pain intensity over the 12-week maintenance period using an LOCF[21] imputation strategy was accepted by EMEA at a Scientific Advice meeting in 2006[22]. Evaluation of the primary endpoint at Week 12 of the maintenance period was recommended by the FDA[23].

For PAI-3015/KF36, the primary endpoint was the change from baseline (start of double-blind) in average pain intensity over the last week of the double-blind maintenance period at Week 12. The primary null hypothesis tested for the studies was that the tapentadol SR group was not different from the placebo group in the primary efficacy endpoint. The alternative hypothesis was that the tapentadol SR group was different from the placebo group in the primary efficacy endpoint.

The primary statistical objective for PAI-3019/KF39 was to assess whether the two double-blind treatment formulations, tapentadol IR and tapentadol SR, were clinically equivalent with regard to efficacy. This was assessed according to whether a 95% confidence interval (CI) for the difference in mean average pain intensity score after two weeks of double-blind treatment (tapentadol SR to

[21] LOCF: The most important problem during the performance of the clinical trial is the occurrence of the dropout. For instance, when the patients drop out before a response can be obtained they cannot be included in the analysis, even not in an ITT analysis. When the patients are examined on a regular basis, a series of the measurements is obtained. In that case, the measurements obtained before the patient dropped out can be used to establish the unknown measurement at the end of the study. The Last-Observation-Carried-Forward (LOCF) method allows for the analysis of the data. But, the recent research shows that this method gives a biased estimate of the treatment effect and underestimates the variability of the estimated result. Let's assume that there are 8 weekly assessments after the baseline observation. If a patient drops out of the study after the third week, then this value is "carried forward" and assumed to be his or her score for the 5 missing data points. The assumption is that the patients improve gradually from the start of the study until the end, so that carrying forward an intermediate value is a conservative estimate of how well the person would have done had he or she remained in the study. The advantages to this approach are that it minimises the number of the subjects who are eliminated from the analysis, and it allows the analysis to examine the trends over time, rather than focusing simply on the endpoint.

[22] EMEA/CHMP/SAWP/363827/2006

[23] IND 61,345; August 24, 2006 EOP2 minutes

tapentadol IR) was included within a range (-2 to 2) derived from the literature (Grossett 2005) and pre-specified in the protocol.

As the primary objective of PAI-3007/KF24 was safety, no primary efficacy endpoint was defined for this study.

For the PAI-3008/KF11, PAI-3009/KF12, and PAI-3011/KF23 studies and the pooled efficacy analysis, the primary endpoint analyses were based on an analysis of co-variance (ANCOVA) model. The model included treatment and pooled analysis centre as factors and baseline pain intensity score as a covariate. Treatment effect of tapentadol SR versus placebo was estimated based on least-square (LS) means of the difference. The p-value for the treatment difference along with the two-sided 95% CI were presented. The primary efficacy analysis was performed using the intent-to-treat (ITT)[24] Analysis Set and the LOCF imputation method for missing values.

In PAI-3015/KF36, the primary efficacy variable was analysed using an ANCOVA model. The model included treatment, country, subject's tapentadol SR dose category at the end of open-label titration period, and subject's prior opioid use status as factors and with baseline average pain intensity score at randomisation (at start of double-blind maintenance period) as a covariate. Treatment effects were estimated based on the difference in LS means of the changes from baseline. The 95% confidence interval and p-value were presented for tapentadol SR compared with placebo.

For PAI-3019/KF39, pain intensity scores including 95% CIs were summarised. The mean of the average pain intensity scores was analysed with a 2-period cross-over analysis of variance model including treatment, period and subject (fitted as a fixed effect) in the per protocol (PP[25]) analysis set. The equivalence of tapentadol SR and tapentadol IR was assessed by referring the 95% confidence interval to the pre-specified equivalence margin (-2, 2) which is equivalent to a Schuirmann's two 1-sided t-tests approach.

Imputation Methods and Sensitivity Analyses of the Primary Variable

For the PAI-3008/KF11, PAI-3009/KF12, PAI-3011/KF23, and PAI-3015/KF36 studies and the pooled efficacy analysis, all intermittent missing measurements were imputed by linear interpolation, including consecutive missing pain assessments, as long as they were followed by a subsequent pain assessment. Pain assessments not performed due to treatment discontinuation were imputed at the subject level using the LOCF as the primary imputation method. Various imputation strategies were employed to investigate the influence of discontinuation on the primary efficacy outcomes and hence the robustness of the estimated treatment effects (strategies in compliance with the Note for Guidance on Statistical Principles for Clinical Studies [CPMP/ICH/363/96[26]]).

[24] ITT: The randomized clinical trials analyzed by the intention-to-treat (ITT) approach provide the unbiased comparisons among the treatment groups. Since it came up in the 1960s, the principle of the ITT has become widely accepted for the analysis of the controlled clinical trials. In the ITT population, none of the patients is excluded and the patients are analyzed according to the randomization scheme.

[25] PP: The analysis can only be restricted to the participants who fulfill the protocol in the terms of the eligibility, interventions, and outcome assessment. This analysis is known as an "on-treatment" or "per protocol" analysis. Also, the per-protocol restricts the comparison of the treatments to the ideal patients, that is, those who adhered perfectly to the clinical trial instructions as stipulated in the protocol. This population is classically called the per-protocol population and the analysis is called the per-protocol-analysis. A per-protocol analysis envisages determining the biological effect of the new drug. However, by restricting the analysis to a selected patient population, it does not show the practical value of the new drug.

[26] ICH Topic E 9. Statistical Principles for Clinical Trials. Note for guidance on statistical principles for clinical trials. http://www.tga.gov.au/docs/pdf/euguide/ich/036396en.pdf

Secondary endpoints

Distribution of Responder Rates using Pain Intensity

Responder rates for a given percent improvement value were defined as the proportion of subjects equal to and above that given value (in percentiles). A graphical representation of the distribution of responder rates was presented for each treatment group. The distribution of responder rates was estimated by the Kaplan-Meier estimate and compared among the treatment groups using a log-rank test. In addition, responder rates for achieving at least 30% and 50% improvement were compared using the Cochran-Mantel-Haenszel test, presenting the p-value for the pairwise differences in responder rates between the treatment arms. The analysis was performed using the ITT Analysis Set.

Time to Treatment Discontinuation due to Lack of Efficacy

The time to treatment discontinuation due to lack of efficacy was calculated in days as the duration from Study Day 1 to treatment discontinuation. Subjects who completed the active treatment period of the study were censored at the last observation time-point. Subjects who discontinued from the active treatment period for reasons other than lack of efficacy were censored at the time of discontinuation. The distribution of the time to treatment discontinuation due to lack of efficacy was estimated by the Kaplan-Meier estimate and compared among the treatment groups using the log-rank test for the ITT Analysis Set.

Dose-response studies

KF09

Study KF09 was a randomised, multicentre, double-blind, double-dummy, placebo and active controlled, parallel group, multiple-dose, Phase II study in subjects with osteoarthritis of the hip or knee. After washout, a pain score of at least 4 points on an 11-point NRS scale with an increase in pain intensity of at least 1 point was required for randomisation. After screening and washout, subjects were randomised to receive tapentadol SR (21.5 mg, 43 mg, and 86 mg; twice daily), oxycodone CR (20 mg twice daily) or placebo for 4 weeks. The primary endpoint was the change from baseline in "overall pain intensity since last visit" at the final visit.

A total of 384 subjects were randomized. Subjects were 40 years to 75 years of age (mean, 59.2 years). The majority of subjects were female (67.5%) and white (88.2%).

Results

Primary endpoint

There was a decrease in pain intensity (11-point NRS) from baseline at each of the weekly visits in all groups. At the final visit (Week 4), the mean changes from baseline were not significantly different between the treatment groups ($p = 0.0679$).

Secondary efficacy parameters

There was no significant difference across groups for WOMAC[27] and Short Form (SF)-36[28] scores, or for any other secondary endpoint.

[27] Western Ontario and McMaster University (WOMAC) questionnaire.

[28] The SF-36 is a multi-purpose, short-form health survey with only 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. It measures eight domains of health: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. It yields scale scores for each of these eight health domains, and two summary measures of physical and mental health. It is a generic measure, as opposed to one that targets a specific age,

KF10

Study KF10 was a randomised, multicentre, double-blind, placebo and active controlled, parallel-group, multiple-dose, Phase II study in subjects with low back pain. After washout, a pain score of at least 4 points on an 11-point NRS scale with an increase in pain intensity of at least 1 point was required for randomisation. After screening and washout, subjects were randomised to receive tapentadol SR (21.5 mg, 43 mg, and 86 mg; twice daily), tramadol SR (100 mg twice daily) or placebo for 4 weeks. The primary endpoint was the change from baseline in "overall pain intensity since last visit" at the final visit. A total of 448 subjects were randomised. Subjects were 18 years to 75 years of age (mean age, 56.4 years). The majority of subjects were female (59.7%) and white (97.3%).

Results

Primary Endpoint

At the final visit (Week 4), the mean change from baseline pain intensity (11-point numerical rating scale (NRS[29])) was not significantly different between the treatment groups (p = 0.7437).

Secondary Efficacy Parameters

There was no significant difference across groups for Brief Pain Inventory (BPI)[30] and SF-36, or for any other secondary endpoint.

PAI-2001/KF19

Study PAI-2001/KF19 was a randomised, multicentre, double-blind, placebo- and active-controlled, parallel-group, Phase II study in subjects with osteoarthritis of the knee. After screening and washout, subjects were randomised to receive tapentadol SR (25-50- 100 mg or 100-150-200 mg twice daily), oxycodone CR (10-10-20 mg twice daily), or placebo. The first dose in the sequence was given for 3 days, the second for the next 11 days, and the third dose was given for the final 2 weeks of the study. Subjects had to have pain intensity of ≥ 50 mm on a 100-mm visual analogue scale (VAS)[31], or if they had received regular treatment with opioids, a pain score ≤ 50 mm at the screening visit. In addition, subjects had to meet criteria for a flare state at the end of the washout period: an average pain intensity of ≥ 50 mm on a 100-mm VAS during the preceding 24 hr and an increase of ≥ 18 mm on the 100-mm VAS relative to the score at the start of the washout. The primary efficacy endpoint was the change over the preceding 24 hr in average pain intensity compared to baseline evaluated at the end of Week 4 on a 100-mm VAS using LOCF.

A total of 670 subjects were randomised. The majority of subjects were female (62%), white (83%), and younger than 65 years of age (78%). In addition, most subjects did not have opioid treatment prior to the study (82%).

Results

Primary Endpoint

Subjects in the tapentadol SR 100-150-200 mg group had a significantly greater reduction in average pain intensity than those in the placebo group (p = 0.021). Subjects in the tapentadol SR 25-

disease, or treatment group. The SF-36 is available for two recall periods: standard (4-week recall) and acute (1-week recall).

[29] Numerical rating scale where 0=no pain and 10=worst possible pain.

[30] The BPI is a tool for assessing clinical pain. The BPI allows patients to rate the severity of their pain and the degree to which their pain interferes with common dimensions of feeling and function.

[31] VAS is a simple assessment tool consisting of a 10 cm line with 0 on one end, representing no pain, and 10 on the other, representing the worst pain ever experienced, which a patient marks to indicate the severity of his or her pain.

50-100 mg and oxycodone 10-10-20 mg groups showed a numerically greater decrease compared to placebo indicating improvement, but the difference did not reach statistical significance. The LS mean difference (standard error) from placebo was -5.9 mm (3.34) for tapentadol SR 25-50-100 mg and - 8.4 mm (3.30) for tapentadol SR 100-150-200mg on a 100 mm VAS. For subjects on tapentadol SR 100-150-200 mg twice daily, at the end of the 150 mg dose step the LS mean difference (standard error) from placebo was -9.7 (3.09) on a 100 mm VAS (p = 0.002), indicating that tapentadol SR 150 mg twice daily was effective.

Secondary Efficacy Parameters

A responder analysis showed a tendency for a greater response (at least a 30% decrease in average pain intensity) in subjects on tapentadol SR 100-150-200 mg (p = 0.051) tapentadol SR 25-50-100 mg (p = 0.108), and oxycodone CR 10-10-20 mg (p = 0.059) than in subjects on placebo. Tapentadol SR (100-150-200 mg) showed a statistically significant difference from placebo at the last visit in terms of Patient's Global Impression of Change (PGIC) (p = 0.003) and WOMAC global scores (p = 0.022).

Similar PGIC results were observed in the oxycodone CR and the tapentadol SR (25-50-100 mg) groups. Results of the SF-36 and European Quality of Life-5 Dimensions (EQ-5D[32]) indicated greater improvement in health status with tapentadol SR (100-150- 200 mg) than with placebo.

PAI-2002/KF20

Study PAI-2002/KF20 was a randomised, multicentre, double-blind, placebo- and active-controlled, parallel-arm, Phase II study in subjects with moderate to severe chronic low back pain. After screening, subjects were randomised to receive tapentadol SR (25-50- 100 mg or 100-150-200 mg twice daily), tramadol SR (100-150-200 mg twice daily), or placebo following a single blind placebo run-in of 3 to 7 days. The first dose in the sequence was given for 3 days, the second for the next 11 days and the third dose was given for the final 2 weeks of the study. Subjects had to have pain intensity of ≥ 50 mm on a 100-mm VAS, or if they had received regular treatment with opioids, a pain score ≤ 50 mm at the screening visit. The primary efficacy endpoint was the change over the preceding 24 hr in average pain intensity compared to baseline evaluated at the end of Week 4 on a 100-mm VAS using LOCF.

A total of 698 subjects were randomised. The majority of subjects were female (65%), white (99%), and younger than 65 years of age (82%). In addition, most subjects had no prior opioid treatment (82%). At screening, the majority of subjects (85%) had a pain intensity of at least 50 mm on the VAS.

Results

Primary endpoint

The change from baseline in the average pain intensity in the tapentadol SR treatment groups did not reach statistical significance compared to the placebo group (tapentadol SR 25-50-100 mg: p = 0.495; tapentadol SR 100-150-200 mg: p = 0.312). There was also no statistically significant difference between the tramadol SR and the placebo group either (p = 0.213).

Secondary Efficacy Parameters

There was no difference between the groups in the percentage of subjects who demonstrated at least a 30% improvement in “average pain intensity” or in PGIC scores. Apart from a statistically significant difference between tapentadol SR 100-150-200 mg and placebo groups (p = 0.007) at the

[32] EQ-5D™ is a standardised instrument for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status.

end of titration on the SF-36 domain of “bodily pain”, there were no differences between the treatment groups and placebo on SF-36. The active treatment groups were better than placebo on the EQ-5D health status index (tapentadol SR 25-50-100 mg, p = 0.007; tapentadol SR 100-150-200 mg, p = 0.010; and tramadol SR 100-150-200 mg, p = 0.034).

Comment: Overall, tapentadol SR was not shown to be superior to placebo or active comparators in the Phase II studies. The results do not support that tapentadol is effective for treatment of moderate to severe pain.

Phase III - Main (pivotal) studies

The pivotal Phase III efficacy studies for assessment of tapentadol SR in the treatment of moderate to severe pain are PAI-3008/KF11, PAI-3009/KF12 and PAI-3011/KF23. For studies PAI-3008/KF11, PAI-3009/KF12 and PAI-3011/KF23, after screening, washout, and randomisation, subjects received study drug titrated to an optimal dose over 3 weeks, followed by a 12-week maintenance period with controlled dose adjustment of twice daily placebo, tapentadol SR 100 to 250 mg, and oxycodone CR 20 to 50 mg.

PAI-3008/KF11

Study design

This was a randomised, multicentre, double-blind, parallel-group study, comparing the efficacy and safety of controlled dose-adjustment regimen of tapentadol SR to placebo in subjects with moderate to severe chronic pain due to osteoarthritis (OA) of the knee. Approximately 942 subjects (314 per treatment group) were planned and randomised in a 1:1:1 ratio to tapentadol SR, oxycodone CR or placebo. The study consisted of five periods:

• Screening period (Visit V1).

• Washout period (Visit V2 [optional, visit or phone contact]).

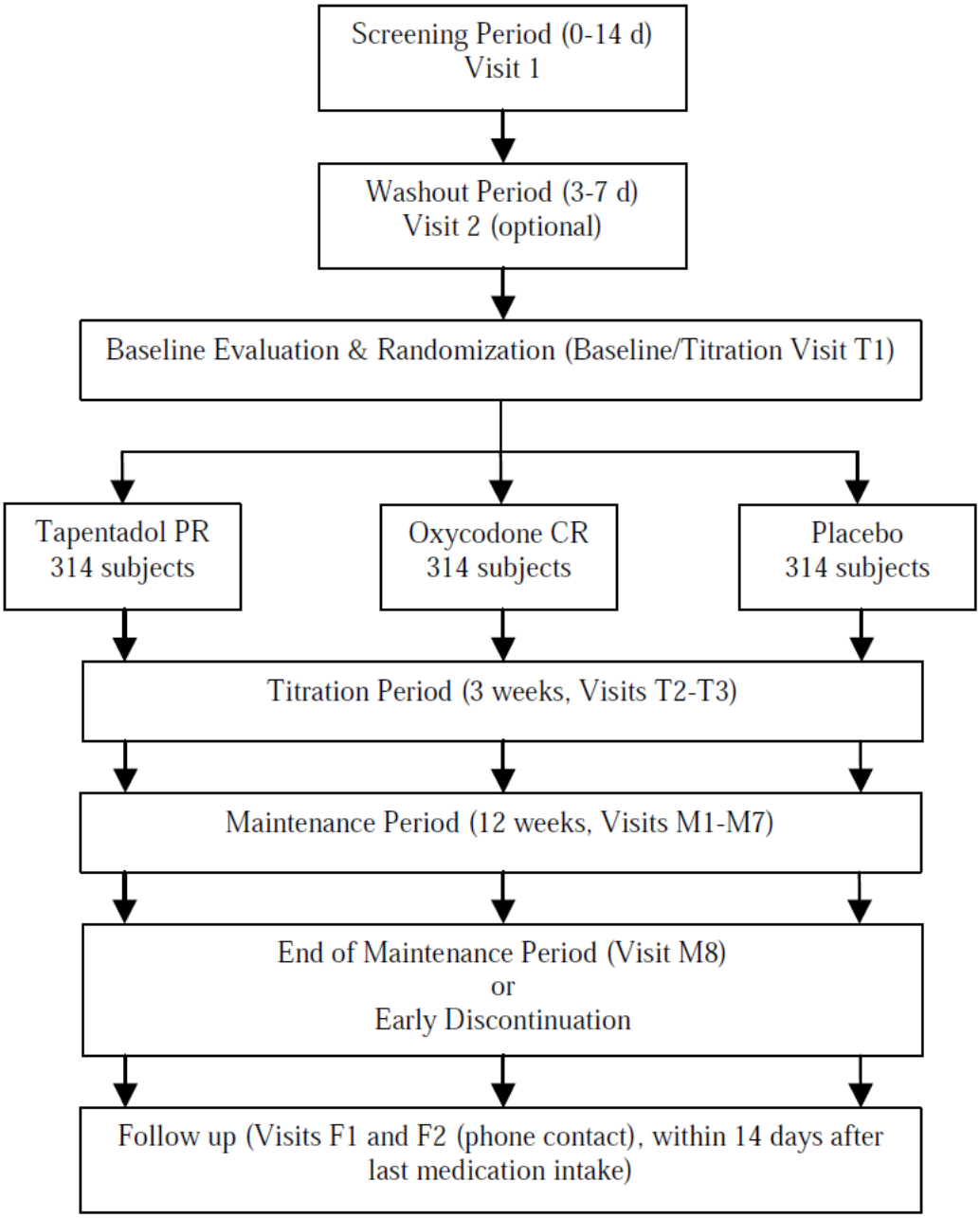
• Titration period (Visits T1 to T3).

• Maintenance period (Visits M1 to M8).

• Follow-up period (Visits F1 and F2 [phone contact]).

The overall study design is showed in Figure 3.

Figure 3: Study Design (Study R331333-PAI-3008; KF5503/11)



The primary objective of the study was to evaluate the efficacy and safety of orally administered tapentadol SR at doses of 100 to 250 mg twice a day in subjects with moderate to severe chronic pain from OA of the knee.

For the FDA, the primary efficacy endpoint was defined as the change from baseline of the average pain intensity over the last week of the maintenance period at Week 12 of the daily pain intensity on an 11-point numerical rating scale (NRS). For non-US regulatory authorities, the primary efficacy endpoint was defined as the change from baseline of the average pain intensity over the 12-week maintenance period of the daily pain intensity on an 11-point NRS. The primary endpoint for one region was considered as secondary endpoint in the other.

Demographic and baseline characteristics

The demographic characteristics were similar between treatment groups in study PAI-3008/KF11. Some 83.4% of patients were categorised as having severe pain at the start of the titration period.

The prior use of opioids was 32.4%. Table 15 below summarises dissatisfaction with previous analgesic treatment in the three controlled dose adjustment efficacy studies.

Subject Disposition and Study Completion/Withdrawal

The study was conducted from 07 February 2007 to 04 June 2008. A total of 1,578 subjects were screened; 1030 were randomised at 112 sites in Australia (4 sites), Canada (15 sites), New Zealand (6 sites); and the United States of America (87 sites). For the double-blind period, the 1030 subjects were randomised to the three treatment groups in a 1:1:1 ratio (339 subjects in the placebo, 346 in the tapentadol SR, and 345 in the oxycodone CR groups. A summary of subject disposition is provided in Figure 4 below.

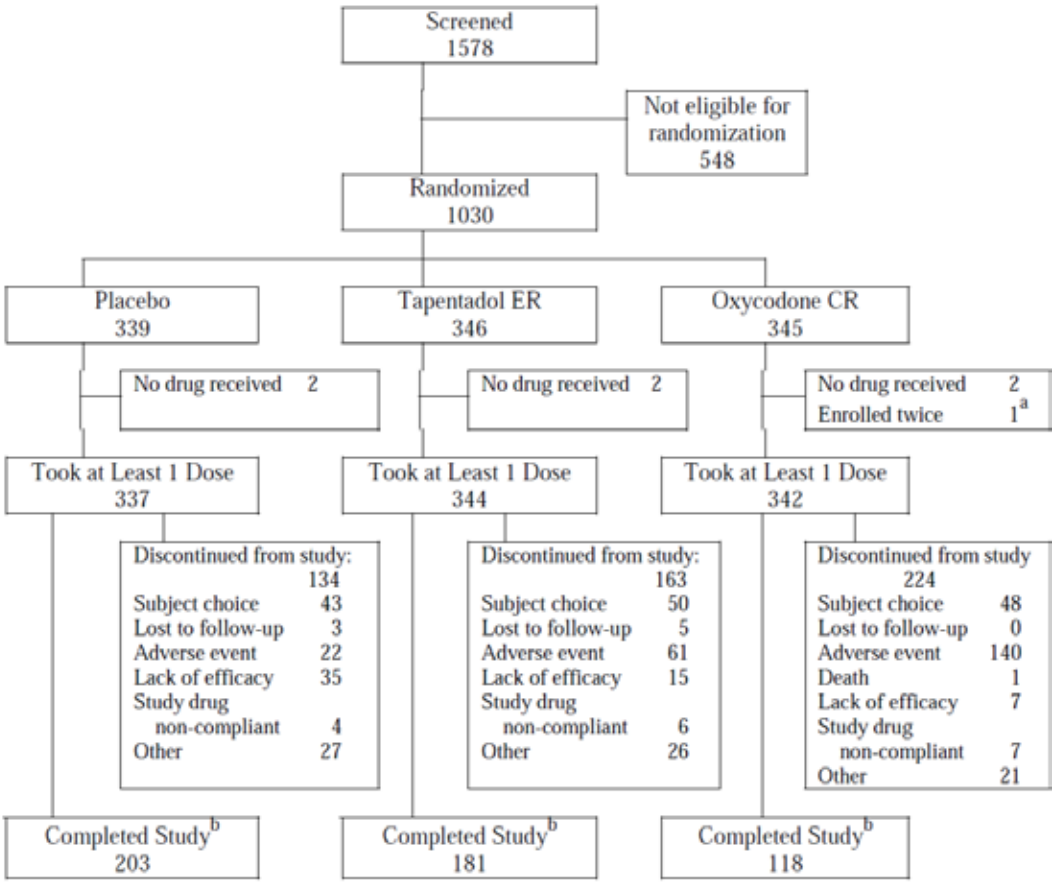
Treatment completion was defined as completion of the titration and maintenance periods (15 weeks) including Visit M8. Fewer subjects in the oxycodone CR group (35.4%) completed the 15-week treatment period (Visits T1 through M8) than subjects in the placebo (61.4%) and tapentadol SR (57.3%) groups. Across all treatment groups, discontinuations were higher during the titration period than during the maintenance period.

The percentage of subjects in the oxycodone CR group (49.4%) who discontinued during the titration period was twice the percentage of subjects who discontinued from either the tapentadol SR (23.3%) or placebo (24.6%) groups.

Table 15: Dissatisfaction with Previous Analgesic Treatment in 3 Controlled Dose Adjustment Efficacy Studies

Study		Placebo	Tapentadol PR	Oxycodone CR
PAI-3008/KF11	Prior opioid use	114/337 (33.8%)	109/344 (31.7%)	108/342 (31.6%)
	Prior analgesics	334/337 (99.1%)	344/344 (100%)	338/342 (98.8%)
	Dissatisfied			
	Inadequate analgesia	330/334 (98.8%)	340/344 (98.8%)	334/338 (98.8%)
	Poor tolerability	4/334 (1.2%)	4/344 (1.2%)	4/338 (1.2%)
PAI-3009/KF12	Prior opioid use	56/337 (16.6%)	52/319 (16.3%)	47/331 (14.2%)
	Prior analgesics	336/337 (99.7%)	319/319 (100%)	331/331 (100%)
	Dissatisfied			
	Inadequate analgesia	332/336 (98.8%)	317/319 (99.4%)	330/331 (99.7%)
	Poor tolerability	4/336 (1.2%)	2/319 (0.6%)	1/331 (0.3%)
PAI-3011/KF23	Prior opioid use	172/319 (53.9%)	178/318 (56.0%)	165/328 (50.3%)
	Prior analgesics	318/319 (99.7%)	318/318 (100%)	328/328 (100%)
	Dissatisfied			
	Inadequate analgesia	312/318 (98.1%)	310/318 (97.5%)	325/327 (99.4%)
	Poor tolerability	6/318 (1.9%)	8/318 (2.5%)	2/327 (0.6%)

Figure 4: Subject Disposition (Study R331333-PAI-3011/KF5503/23)



[a] Subject 805259 at Site 001302 was randomized twice. The subject did not receive treatment for the first randomization and for the purpose of analysis only the second randomization was included

[b] Includes all subjects who were enrolled in the open-label extension (PAI-3010/KF18) or who completed all follow-up visits in the current study.

Extent of Exposure

The extent of exposure in studies PAI-3008/KF11, PAI- 3009/KF12 and PAI-3011/KF23 is summarised in Table 16 (tapentadol PR) and Table 17 (oxycodone CR).

Table 16: Exposure to Tapentadol SR

	PAI-3008/KF11	PAI-3009/KF12	PAI-3011/KF23	Pooled efficacy analysis
Titration				
Average mean total daily dose	244.6 mg	221.4 mg	250.9 mg	239.1 mg
Median modal total daily dose	300.0 mg	200.0 mg	300 mg	300.0 mg
Maintenance				
Average mean total daily dose	357.9 mg	315.2 mg	381.8 mg	351.4 mg
Median modal total daily dose	400.0 mg	300.0 mg	400.0 mg	400.0 mg
Distribution of modal total daily dose during Maintenance (n [%])				
N	264	242	235	738
<100	0	1 (0.4)	2 (0.9)	3 (0.4)
≥100 - <200mg	2 (0.8)	0	1 (0.4)	3 (0.4)
≥200 - <300mg	66 (25.0)	94 (38.8)	46 (19.6)	206 (27.9)
≥300 - <400mg	49 (18.6)	49 (20.2)	38 (16.2)	135 (18.3)
≥400 - <500mg	62 (23.5)	57 (23.6)	41 (17.4)	160 (21.7)
≥500mg	85 (32.2)	41 (16.9)	107 (45.5)	231 (31.3)
Percentage of time on modal dose during Maintenance (median, days)	95.30	98.75	94.10	96.4%

PR = prolonged release; N, n = number of subjects

Table 17: Exposure to Oxycodone CR

	PAI-3008/KF11	PAI-3009/KF12	PAI-3011/KF23	Pooled efficacy analysis
Titration				
Average mean total daily dose	40.9 mg	37.2 mg	44.6 mg	40.9
Median modal total daily dose	40.0 mg	40.0 mg	40 mg	40.0
Maintenance				
Average mean total daily dose	70.7 mg	54.1 mg	71.4 mg	65.4 mg
Median modal total daily dose	80.0 mg	40.0 mg	80.0 mg	60.0 mg
Distribution of modal total daily dose during Maintenance (n [%])				
N	173	183	199	553
<20mg	0	1 (0.5)	0	1 (0.2)
≥20 - <40mg	0	1 (0.5)	1 (0.5)	2 (0.4)
≥40 - <60mg	41 (23.7)	101 (55.2)	43 (21.6)	185 (33.5)
≥60 - <80mg	35 (20.2)	37 (20.2)	46 (23.1)	118 (21.3)
≥80 - <100mg	47 (27.2)	31 (16.9)	53 (26.6)	130 (23.5)
≥100mg	50 (28.9)	12 (6.6)	56 (28.1)	117 (21.2)
Percentage of time on modal dose during Maintenance (median, days)	94.00	97.70	93.30	94.2%

CR = controlled release; N, n = number of subjects

Results

Primary endpoint

For the primary efficacy analysis, tapentadol SR showed a statistically significant reduction in average pain intensity compared to placebo at both Week 12 of the maintenance period and the overall maintenance period using LOCF (both p-values <0.001, an LS mean difference of -0.7 for Week 12 of the maintenance period and the overall maintenance period) (see Table 18). The comparison between oxycodone CR and placebo demonstrated a statistically significant reduction in average pain intensity for the overall maintenance period (p = 0.049). At Week 12 of the maintenance period oxycodone CR demonstrated a numerically greater reduction in average pain intensity compared to placebo but this reduction was not statistically significant (p = 0.069).

Table 18: Change From Baseline in Average Pain Intensity Scores Based on NRS (LOCF) (Study R331333-PAI-3008; KF5503/11: Intent-to-Treat Analysis Set)

	Placebo	Tapentadol ER	Oxycodone CR
Baseline			
N	336	344	342
Mean (SD)	7.2 (1.29)	7.4 (1.35)	7.2 (1.29)
Median (Range)	7.2 (4 to 10)	7.3 (3 to 10)	7.2 (4 to 10)
Week 12 of Maintenance			
N	337	344	342
Mean (SD)	5.0 (2.61)	4.4 (2.48)	4.7 (2.35)
Median (Range)	5.0 (0 to 10)	4.0 (0 to 10)	5.0 (0 to 10)
Change from Baseline to Week 12 of Maintenance			
N	336	344	342
Mean (SD)	-2.2 (2.54)	-3.0 (2.39)	-2.6 (2.38)
Median (Range)	-1.9 (-10 to 5)	-2.8 (-10 to 3)	-2.3 (-10 to 3)
LS Mean Change	-2.3	-2.9	-2.6
LS Mean Difference versus Placebo (SE)		-0.7 (0.18)	-0.3 (0.18)
95% CI (versus Placebo)[a]		(-1.04, -0.33)	(-0.68, 0.02)
P-value (versus Placebo)		<0.001	0.069
Overall Maintenance			
N	337	344	342
Mean (SD)	5.1 (2.48)	4.4 (2.40)	4.7 (2.26)
Median (Range)	5.0 (0 to 10)	4.0 (0 to 10)	5.0 (0 to 10)
Change from Baseline to Overall Maintenance			
N	336	344	342
Mean (SD)	-2.2 (2.37)	-2.9 (2.29)	-2.5 (2.27)
Median (Range)	-1.9 (-10 to 3)	-3.0 (-10 to 3)	-2.3 (-10 to 3)
LS Mean Change	-2.2	-2.9	-2.6
LS Mean Difference versus Placebo (SE)		-0.7 (0.17)	-0.3 (0.17)
95% CI (versus Placebo)[a]		(-1.00, –0.33)	(-0.67, -0.00)
P-value (versus Placebo)		<0.001	0.049

[a] Test for no difference between treatment from ANCOVA model with factor(s) treatment, pooled center and baseline pain intensity as covariate (type III SS) unadjusted p-value.

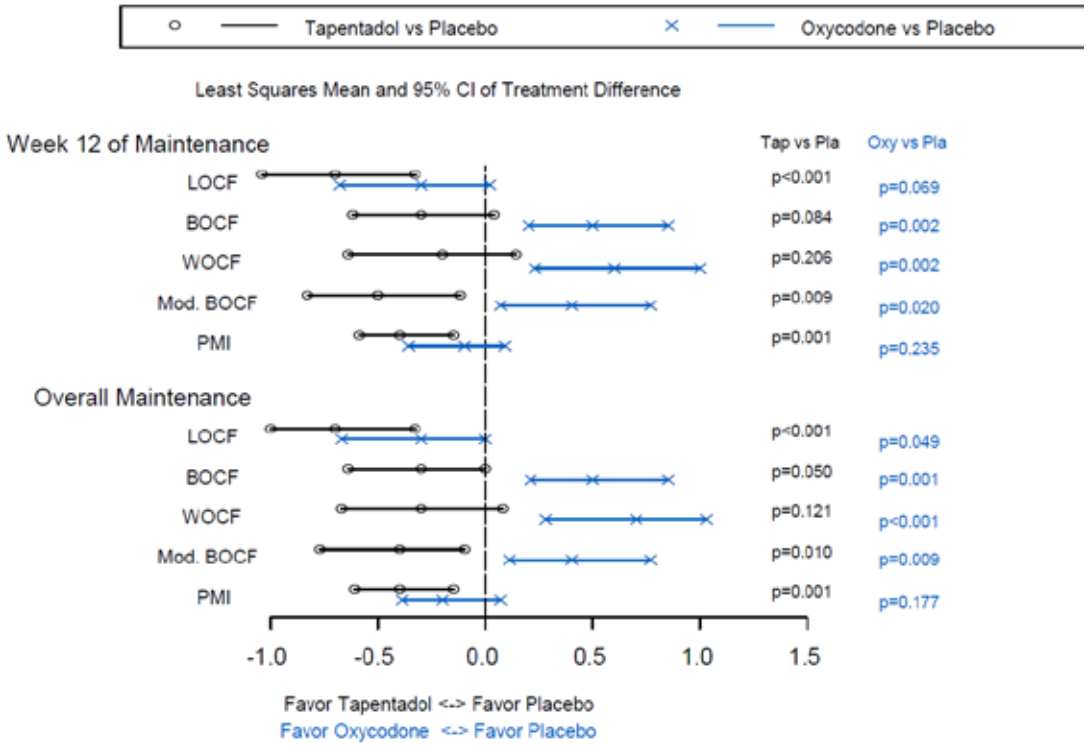
LOCF = last observation carried forward

Average pain scores are the averages of all scores recorded during the baseline period or during each time period (Week 12 of maintenance or overall maintenance).

Tapentadol ER = Tapentadol PR

Tapentadol SR showed a significant difference in pain intensity change from baseline compared with placebo during the overall maintenance period (p <0.001) and during the last week of the maintenance period (p <0.001) using LOCF and also modified Baseline Observation Carried Forward (BOCF) and the placebo mean imputation (PMI) imputations (see Figure 5).

Figure 5: Pairwise Comparisons of Change in Average Pain Intensity for Tapentadol SR versus Placebo, and Oxycodone CR versus Placebo, for Different Imputation Methods in Subjects With Osteoarthritis (PAI-3008/KF11: Intent to Treat Analysis Set)



LOCF = last observation carried forward; BOCF = baseline observation carried forward; WOCF = worst observation carried forward; PMI = placebo mean imputation; Mod BOCF = modified BOCF; CI = confidence interval; Tap = tapentadol; Pla = placebo; Oxy = oxycodone.

For LOCF, the LS mean difference versus placebo (standard error) was -0.7 (0.17) for tapentadol SR and -0.3 (0.17) for oxycodone CR, respectively, for the change from baseline to the overall maintenance period, and -0.7 (0.18) and -0.3 (0.18) for the change from baseline to Week 12 of the maintenance period. Statistical significance was not reached for the primary endpoints when applying the most conservative imputation methods, BOCF and worst observation carried forward (WOCF). For the comparison of tapentadol SR and placebo, BOCF over the overall maintenance period also failed to reach statistical significance (p = 0.050). Oxycodone CR was significantly more effective than placebo in the reduction of pain intensity for the overall maintenance period (confirming assay sensitivity), but not the last week of maintenance period using the LOCF imputation method. For the more conservative imputation methods (modified BOCF, BOCF and WOCF), pain intensity outcomes were significantly worse for oxycodone CR than for placebo. In particular, the oxycodone CR results were influenced by the high discontinuation rate of subjects in this group. An analysis using observed cases for tapentadol SR and oxycodone CR subjects who completed treatment in all three treatment groups confirmed the results of the primary analysis using LOCF.

Secondary efficacy parameters

Overall, the difference in distributions of responder rates was not statistically significant between tapentadol SR and placebo. The distribution of responder rates at Week 12 showed that a statistically significantly higher percentage of subjects showed a greater improvement in response in the placebo group than in the oxycodone group (p = 0.002). The proportion of subjects in the tapentadol SR group with at least 50% improvement in pain intensity at Week 12 of the maintenance period was statistically significantly greater (32.0%) than in the placebo group (24.3%; p = 0.027) (see Table 19). There were no statistically significant differences between tapentadol SR (43.0%) and placebo (35.9%) in the proportion of subjects showing at least 30% improvement in pain intensity at Week 12 of the maintenance period (p = 0.058).

Table 19: Responder Rates Based on 30% and 50% Improvement in Average Pain Intensity (Based on NRS) (PAI-3008/KF/11, Intent-to-Treat Analysis Set)

	Placebo	Tapentadol PR		Oxycodone CR	
Response	Subjects (%)	Subjects (%)	p-value [a]	Subjects (%)	p-value [a]
30%	35.9	43.0	0.058	24.9	0.002
50%	24.3	32.0	0.027	17.3	0.023 [c]

a) P-value versus placebo. Pairwise comparison: Generalized Cochran-Mantel-Haenszel test for general association.

b) Indicates superiority of placebo over oxycodone CR.

When comparing oxycodone CR to placebo, there was a statistically significantly greater proportion of subjects in the placebo group with at least 30% improvement and 50% improvement (p = 0.002 and p = 0.023, respectively). Tapentadol SR and oxycodone CR were statistically significantly better than placebo in terms of time to discontinuation due to lack of efficacy (p <0.001) as well as PGIC at endpoint (p <0.018) (see Table 20 below).

For WOMAC subscale scores, tapentadol SR was statistically significantly better than placebo for pain, physical function (with the exception of maintenance Week 6) and global score throughout the maintenance period. Tapentadol SR also showed a numerical improvement over placebo with respect to stiffness although the difference was not statistically significant at all time-points. The difference to placebo in global score was statistically significant at Week 12 of the maintenance period (in subjects who completed treatment) for both oxycodone CR and (p = 0.038) and tapentadol SR (p = 0.005). Tapentadol SR was more effective (p <0.001) than oxycodone CR in improving health status (EQ- 5D). At endpoint, significant improvement in the physical component summary of the SF-36 health survey was also seen in subjects receiving tapentadol SR compared to placebo. Subjects in the oxycodone CR group showed significant deterioration on the SF-36 mental component summary compared to placebo. Improvement from baseline in the quality of sleep (Item 4) was observed in all treatment groups at endpoint, and neither tapentadol SR nor oxycodone CR was significantly different from placebo.

Table 20: Patient Global Impression of Change at Endpoint (PAI-3008/KF/11, Intent-to-Treat Analysis Set, LOCF)

	Placebo			TapentadolPR			OxycodoneCR		
	N	%	Cum.%	N	%	Cum.%	N	%	Cum.%
VeryMuchImproved	23	8.4	8.4	52	20.2	20.2	27	13.5	13.5
Much Improved	74	27.1	35.5	99	38.4	58.5	67	33.5	47.0
Minimally Improved	64	23.4	59.0	54	20.9	79.5	53	26.5	73.5
No Change	66	24.2	83.2	33	12.8	92.2	19	9.5	83.0
Minimally Worse	30	11.0	94.1	8	3.1	95.3	20	10.0	93.0
Much Worse	11	4.0	98.2	10	3.9	99.2	13	6.5	99.5
Very Much Worse	5	1.8	100.0	2	0.8	100.0	1	0.5	100.0
Total	273			258			200		
Overall P-value [a]			<0.001						
P-value(minus Placebo) [b]						<0.001			0.018

a) Generalized Cochran-Mantel-Haenszel test for row mean scores differ.

b) Pairwise comparison: Generalized Cochran-Mantel-Haenszel test for row mean scores differ.

N = number of subjects; Cum. = cumulative.

Exploratory Efficacy Analyses

Average Pain Intensity Score by Subgroups

Average Pain Intensity Score by Baseline Pain Category

Most subjects (83.4%) had baseline pain intensity scores categorised as severe. Tapentadol SR showed statistically significant reductions in average pain intensity scores compared with placebo at Week 12 of the maintenance period for subjects with baseline pain intensity scores categorised as severe (p=0.002) over the entire maintenance period (p <0.001) (see Table 21). For subjects with baseline pain intensity scores categorised as moderate, comparison of the average pain intensity scores for tapentadol SR and placebo was not statistically significant in either the last week of the maintenance period (p=0.181) or the overall maintenance period (p=0.463). The LS mean differences from placebo were the same between subjects with moderate and severe baseline pain for the change at Week 12 of maintenance (-0.6) but lower for subjects with moderate baseline pain than severe baseline pain for the overall maintenance period (-0.3 versus -0.6, respectively). For the oxycodone group, the difference in pain intensity scores from placebo was not statistically significant in either the severe or moderate categories.

Table 21: Change From Baseline in Average Pain Intensity Scores Based on NRS by Baseline Pain Intensity Category (LOCF) (Study R331333-PAI-3008; KF5503/11: Intent-to-Treat Analysis Set)

	Placebo		Tapentadol ER		Oxycodone CR	
	Mod	Sev	Mod	Sev	Mod	Sev
Week 12 of Maintenance						
N	61	275	49	293	58	284
LS Mean Change	-1.4	-2.4	-2.1	-3.0	-1.9	-2.7
LS Mean Difference versus Placebo (SE)			-0.6(0.48)	-0.6 (0.20)	-0.5 (0.42)	-0.3 (0.20)
95% CI (versus Placebo)[a]			(-1.60, 0.31)	(-1.04, –0.24)	(-1.32, 0.34)	(-0.74, 0.05)
P-value (versus Placebo)			0.181	0.002	0.244	0.089
Overall Maintenance						
N	61	275	49	293	58	284
LS Mean Change	-1.6	-2.4	-1.9	-3.0	-2.0	-2.7
LS Mean Difference versus Placebo (SE)			-0.3 (0.45)	-0.6 (0.19)	-0.4 (0.39)	-0.4 (0.19)
95% CI (versus Placebo)[a]			(-1.23, 0.56)	(-1.02, -0.26)	(-1.21, 0.34)	-0.75, 0.01)
P-value (versus Placebo)			0.463	<0.001	0.270	0.057

[a] Test for no difference between treatment from ANCOVA model with factor(s) treatment, pooled center and baseline pain intensity as covariate (type III SS) unadjusted p-value.
LOCF = last observation carried forward; mod = moderate; sev = severe
Average pain scores are the averages of all scores recorded during the baseline period or during each week.
Baseline pain intensity categories: moderate is defined as ≥4 to <6; severe is defined as ≥6.
Week 12 of maintenance = last week of maintenance
Tapentadol ER = Tapentadol PR

Average Pain Intensity Score by Prior Opioid Use

The mean changes in average pain scores from baseline to Week 12 of the maintenance period and the overall maintenance period showed a slightly greater difference between tapentadol and placebo for subjects who took prior opioid medications (difference of -0.9 at Week 12 of the maintenance period and -0.8 for the overall maintenance period) than for subjects who did not take prior opioids (-0.7 for both endpoints). Similar results were observed when comparing the oxycodone CR and placebo groups. Mean changes in average pain scores from baseline to Week 12 of the maintenance period and overall maintenance period showed a slightly greater difference between oxycodone CR and placebo for subjects who took prior opioid medications (difference of –0.6 for Week 12 of maintenance period and –0.5 for the overall maintenance period) than for subjects who did not take prior opioids (-0.3 for both endpoints). In both active treatment groups, the mean total daily dose was higher in subjects who took prior opioids than those who did not and corresponds to the greater improvement in average pain scores from baseline observed in these subjects.

Sex, age, race

There were no significant differences between the tapentadol SR and placebo groups for the subgroups of sex, age group, or race in the efficacy variables.

Evaluator's comment: This double-blind, placebo- and comparator-controlled, study utilising a controlled dose-adjustment regimen was conducted to assess the efficacy and safety of orally administered tapentadol SR at doses of 100 mg to250 mg twice a day in subjects with moderate to severe chronic pain from OA of the knee. The demographic characteristics of subjects enrolled are representative of the clinical population of patients with OA. Approximately 2/3 of the subjects (67.6%) in this study were opioid-naïve (defined as not having used an opioid medication in the 3 months prior to start of the study), consistent with the nature of the disease and available treatment options.

A greater percentage of subjects in the tapentadol SR and placebo groups completed the double-blind period than subjects in the oxycodone CR group. Approximately 2/3 of the oxycodone CR subjects discontinued the study.

In terms of the primary efficacy endpoint the study demonstrated superiority of tapentadol SR over placebo in change from baseline of the average pain intensity at Week 12 of the maintenance period (for the US regulatory authority) or over the 12-week maintenance period (for non-US regulatory authorities), using LOCF imputation. Tapentadol also showed statistically significant differences compared to placebo on PMI and modified BOCF imputations for both Week 12 of the maintenance period and the overall maintenance period, and demonstrated a trend towards significance by using BOCF imputation for the overall maintenance period (p=0.0502). Statistical significance was not reached for the BOCF imputation at Week 12 of the maintenance period, or for WOCF for either period.

In relation to responder rates, the difference in distributions of responder rates was not statistically significant between tapentadol SR and placebo. In addition, for subjects with baseline pain intensity scores categorised as moderate, comparison of the average pain intensity scores for tapentadol SR and placebo was not statistically significant in either the last week of the maintenance period (p=0.181) or the overall maintenance period (p=0.463).

Oxycodone was statistically significantly better than placebo on the primary efficacy endpoint for the overall maintenance period using LOCF and PMI imputation, demonstrating assay sensitivity. However it was not statistically significantly superior at Week 12. The more conservative imputation methods (modified BOCF, BOCF, and WOCF) resulted in pain intensity outcomes that were statistically significantly worse than placebo. These findings are a reflection of the large number of oxycodone CR-treated subjects who discontinued the study. The fact that the oxycodone comparator showed poor efficacy in the study raises concerns about the validity of the study.

The high prevalence of opioid-naïve subjects in this study contributed to the ability of subjects to remain in the study even without active treatment (placebo arm, 65.0% opioid-naïve and 54.4% opioid-experienced subjects completed treatment). In the tapentadol treatment group, the ability of opioid-naïve and opioid-experienced subjects to remain in the study was comparable (58.3% opioid-naïve and 55.0% opioid-experienced subjects completed treatment), while in the oxycodone CR treatment group, opioid-naïve subjects were even more prone to discontinue the treatment early and drop out of the study, as compared to opioid-experienced subjects (31.2% opioid-naïve and 44.4% opioid-experienced subjects completed treatment).

The secondary efficacy measure, responder analysis, indicated that the proportion of subjects with 50% improvement in the tapentadol SR group was statistically significantly greater (p=0.027) than the response in the placebo group. The percent of tapentadol SR subjects with 30% improvement in tapentadol SR was not statistically significant (p=0.058). Oxycodone CR treatment was statistically significantly worse for all measures of responders, and this once again raises concerns about interpretation and validity of the results.

Importantly, for subjects with baseline pain intensity scores categorised as moderate, comparison of the average pain intensity scores for tapentadol SR and placebo was not statistically significant in either the last week of the maintenance period (p=0.181) or the overall maintenance period (p=0.463).

Overall the clinical evaluator considers that this study does not provide convincing evidence of efficacy of tapentadol PR. It is of concern that oxycodone was shown to have such poor efficacy in this study. This raises major concerns about the validity of the study results. In addition, results for responder rates and exploratory efficacy analyses did not consistently support efficacy of tapentadol. It is notable when examining the efficacy results when analysed for baseline pain severity, the difference between tapentadol SR and placebo did not reach statistical significance. These results do not support use of tapentadol SR for treatment of severe chronic pain and for moderate pain.

PAI-3009/KF12

Study design

Study PAI-3009/KF12 was a randomised multicentre, double-blind, placebo- and active-controlled, parallel-arm, Phase III study in subjects with moderate to severe chronic pain due to osteoarthritis of the knee. The study design was identical to that of the PAI- 3008/KF11 study.

Demographic and baseline characteristics

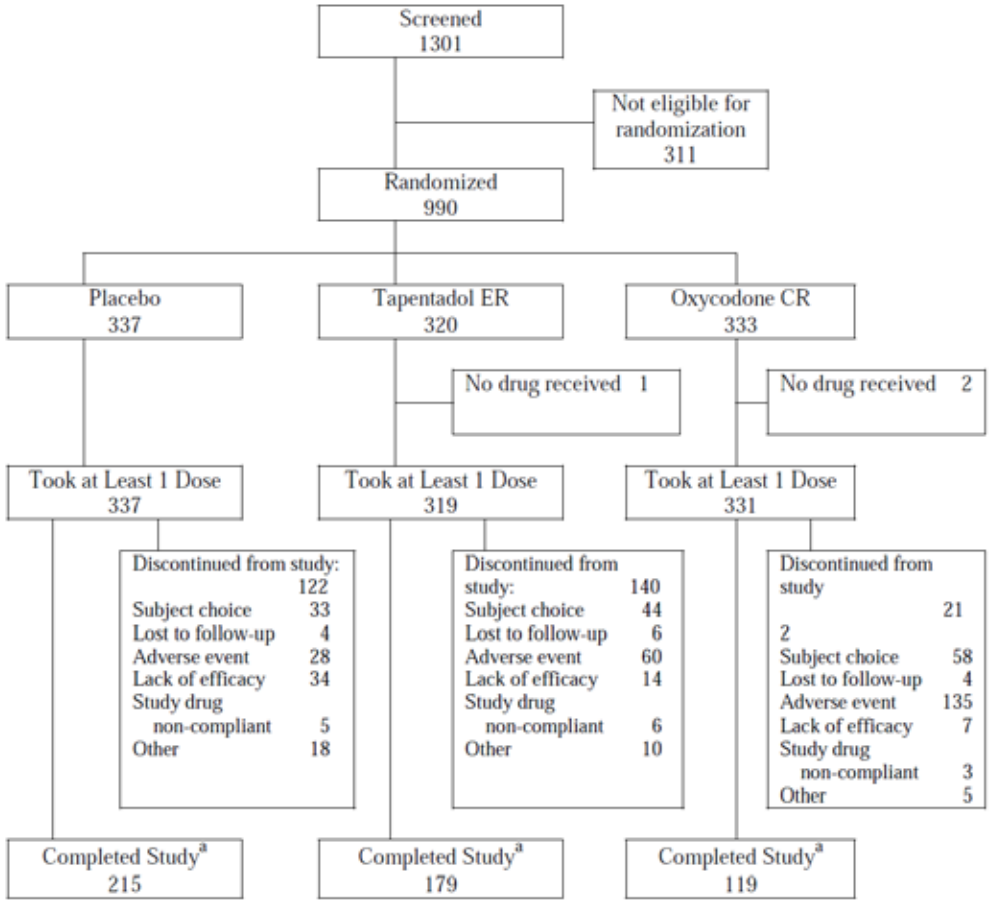
There were 990 subjects randomised. The mean age was 62.1 (range 40 to 87) years and the majority of subjects were female (71.6%), white (99.3%) and younger than 65 years of age (60.7%). All participants were recruited in the European Union. Fewer subjects in the oxycodone CR group (36.6%) than in the placebo (65.6%) and tapentadol SR (58.3%) groups completed the 15-week treatment period. This was primarily due to adverse events. In the active treatment groups, discontinuations were higher during the titration period than during the maintenance period. In addition, most subjects had not taken opioids during the three months prior to the screening visit (84.3%) and were categorised as having severe baseline pain intensity (NRS ≥6, 88.9%).

Subject disposition and study completion/withdrawal information

The study was conducted from 04 June 2007 to 18 July 2008. A total of 1301 subjects were screened; 990 were randomised at 79 sites in Austria (4 sites), Croatia (3 sites), Germany (12 sites), Hungary (8 sites), Latvia (3 sites), Poland (6 sites), Portugal (5 sites), Romania (9 sites), Slovakia (4 sites), Spain (11 sites), the Netherlands (4 sites) and the United Kingdom (10 sites). For the double-blind period, the 990 subjects were randomised to the three treatment groups in a 1:1:1 ratio (337 subjects in the placebo, 320 in the tapentadol SR and 333 in the oxycodone CR groups).

Figure 6 below summarises the disposition of patients in the study. In the placebo group, the percentage of subjects who discontinued was identical in the titration and maintenance periods. In the tapentadol SR and oxycodone CR groups, discontinuation rates were higher during the titration period than during the maintenance period. The percentage of subjects in the oxycodone CR group (44.7%) who discontinued during the titration period was approximately twice the percentage of subjects who discontinued from the tapentadol SR group (24.1%) and more than twice the percentage of subjects who discontinued from the placebo group (17.2%). The percentage of subjects who discontinued due to adverse events during the titration period was more than twice as high in the oxycodone CR group (31.1%) as in the tapentadol SR group (11.9%). The percentage of subjects who discontinued during the maintenance period was similar across the treatment groups, although the percentage who discontinued due to adverse events was higher in the oxycodone CR group (11.5%) than in the tapentadol SR (6.9%) and placebo (3.6%) groups.

Figure 6: Subject Disposition (Study R331333-PAI-3009; KF5503/12)



[a] Includes all subjects who completed both double-blind treatment and all follow-up visits.

Results

Primary endpoint

For all three treatment groups, there was a reduction in average pain intensity both at Week 12 of the maintenance period and for the overall maintenance period, however the results were not statistically significant (see Table 22). On comparing tapentadol SR with placebo using LOCF, the difference in reduction was not statistically significant at Week 12 of the maintenance period (LS mean difference of -0.3 [p=0.152]) or for the overall maintenance period (LS mean difference of -0.2 [p=0.135]). Oxycodone CR showed numerically smaller reductions in average pain intensity compared with placebo, but the difference was also not statistically significant at Week 12 (LS mean difference of 0.2 [p=0.279]) or for the overall maintenance period (LS mean difference of 0.1 [p=0.421]).

Table 22: Change From Baseline in Average Pain Intensity Scores Based on NRS (LOCF) (Study R331333-PAI-3009; KF5503/12: Intent-to-Treat Analysis Set)

	Placebo	Tapentadol ER	Oxycodone CR
Baseline			
N	336	319	331
Mean (SD)	7.3 (1.12)	7.3 (1.09)	7.3 (1.10)
Median (Range)	7.3 (5 to 10)	7.3 (5 to 10)	7.3 (5 to 10)
Week 12 of Maintenance			
N	337	319	331
Mean (SD)	4.8 (2.47)	4.5 (2.48)	5.0 (2.44)
Median (Range)	5.0 (0 to 10)	4.1 (0 to 10)	5.0 (0 to 10)
Change from Baseline to Week 12 of Maintenance			
N	336	319	331
Mean (SD)	-2.5 (2.30)	-2.7 (2.40)	-2.3 (2.36)
Median (Range)	-2.2 (-9 to 3)	-2.7 (-9 to 3)	-2.0 (-9 to 5)
LS Mean Change	-2.4	-2.6	-2.2
LS Mean Difference versus Placebo (SE)		-0.3 (0.18)	0.2 (0.18)
95% CI (versus Placebo)[a]		(-0.61, 0.09)	(-0.16, 0.54)
p value (versus Placebo)		0.152	0.279
Overall Maintenance			
N	337	319	331
Mean (SD)	5.0 (2.24)	4.7 (2.28)	5.1 (2.29)
Median (Range)	5.0 (0 to 10)	4.9 (0 to 10)	5.0 (0 to 10)
Change from Baseline to Overall Maintenance			
N	336	319	331
Mean (SD)	-2.2 (2.06)	-2.5 (2.18)	-2.1 (2.17)
Median (Range)	-2.0 (-8 to 3)	-2.3 (-9 to 3)	-1.8 (-8 to 5)
LS Mean Change	-2.2	-2.4	-2.1
LS Mean Difference versus Placebo (SE)		-0.2 (0.16)	0.1 (0.16)
95% CI (versus Placebo)[a]		(-0.55, 0.07)	(-0.18, 0.44)
p value (versus Placebo)		0.135	0.421

[a] Test for no difference between treatment from ANCOVA model with factor(s) treatment, pooled center and baseline pain intensity as covariate (type III SS) unadjusted p value.
LOCF = last observation carried forward
Average pain scores are the averages of all scores recorded during the baseline period or during each week.
Tapentadol ER = Tapentadol PR

There were no statistically significant differences between tapentadol and placebo in the primary efficacy endpoints using any of the imputation methods. There was a statistically significantly greater reduction in the average pain intensity in the placebo group compared to the oxycodone CR group, when BOCF, WOCF and the modified BOCF methods were applied to each endpoint.

Secondary efficacy parameters

Overall, the difference in distributions of responder rates was not statistically significant between tapentadol SR and placebo. The distribution of responder rates at Week 12 showed that a statistically significantly higher percentage of subjects experienced a greater improvement in response in the placebo group than in the oxycodone group (p = 0.017) (see Table 23). There was a

higher proportion of subjects with at least 30% improvement in the placebo group (p <0.001) when comparing oxycodone CR to placebo.

Table 23: Responder Rates Based on 30% and 50% Improvement in Average Pain Intensity (Based on NRS) (Intent-to-Treat Analysis Set)

	Placebo	Tapentadol PR		Oxycodone CR	
Response	Subjects (%)	Subjects (%)	p-value [a]	Subjects (%)	p-value [a]
30%	40.9	41.1	0.976	26.0	<0.001 [b]
50%	27.0	31.0	0.256	22.1	0.138

a) P-value versus placebo. Pairwise comparison: Generalized Cochran-Mantel-Haenszel test for general association.

b) Indicates superiority of placebo over oxycodone CR.

The tapentadol SR and oxycodone CR groups showed statistically significant superiority over placebo in the time to treatment discontinuation due to lack of efficacy (p ≤0.027). There was a statistically significant difference when comparing the distribution of PGIC categories at endpoint for tapentadol SR to placebo (p = 0.015) but not when comparing oxycodone CR to placebo (p = 0.204) (see Table 24). There was no difference between tapentadol SR and placebo for WOMAC global scores or the WOMAC subscales at Week 12 of the maintenance period, EQ-5D health status index at endpoint or SF-36 at endpoint except for the comparison of tapentadol SR and placebo on the mental health subscale where placebo was statistically superior. The difference between the oxycodone CR and placebo groups in the EQ-5D health status index was statistically significant in favour of placebo as was the mental component summary of the SF-36. Deterioration from baseline in the quality of sleep (Item 4) was observed in all treatment groups at endpoint, and neither tapentadol SR nor oxycodone CR was significantly different from placebo.

Table 24: Patient Global Impression of Change at Endpoint (PAI-3008/KF/12, Intent-to-Treat Analysis Set, LOCF)

	Placebo			TapentadolPR			OxycodoneCR		
	N	%	Cum.%	N	%	Cum.%	N	%	Cum.%
VeryMuchImproved	33	11.2	11.2	40	16.1	16.1	25	11.8	11.8
Much Improved	94	32.0	43.2	99	39.9	56.0	65	30.7	42.5
Minimally Improved	76	25.9	69.0	61	24.6	80.6	51	24.1	66.5
No Change	59	20.1	89.1	22	8.9	89.5	30	14.2	80.7
Minimally Worse	15	5.1	94.2	9	3.6	93.1	19	9.0	89.6
Much Worse	14	4.8	99.0	14	5.6	98.8	19	9.0	98.6
Very Much Worse	3	1.0	100.0	3	1.2	100.0	3	1.4	100.0
Total	294			248			212		
Overall P-value [a]			0.002						
P-value(minus Placebo) [b]						0.015			0.204

a) Generalized Cochran-Mantel-Haenszel test for row mean scores differ.

b) Pairwise comparison: Generalized Cochran-Mantel-Haenszel test for row mean scores differ.

N = number of subjects; Cum. = cumulative.

Exploratory Efficacy Analyses

Average Pain Intensity Score by Baseline Pain Category

Most subjects (88.9%) had baseline pain intensity scores categorised as severe. For those subjects, the change in pain intensity scores from baseline to Week 12 or for the overall maintenance period did not differ significantly for the comparison of tapentadol SR and placebo or the comparison of oxycodone CR and placebo (see Table 25). Likewise, for subjects with moderate baseline pain intensity, the differences from placebo were not statistically significant for either active-treatment group.

Table 25: Change From Baseline in Average Pain Intensity Scores Based on NRS by Baseline Pain Intensity Category (LOCF) (Study R331333-PAI-3009; KF5503/12: Intent-to-Treat Analysis Set)

	Placebo		Tapentadol ER		Oxycodone CR	
	Mod	Sev	Mod	Sev	Mod	Sev
Week 12 of Maintenance						
N	42	294	35	284	32	299
LS Mean Change	-1.6	-2.5	-2.3	-2.7	-1.1	-2.3
LS Mean Difference versus Placebo (SE)			-0.7 (0.52)	-0.2 (0.19)	0.4 (0.56)	0.1 (0.19)
95% CI (versus Placebo)[a]			(-1.75, 0.35)	(-0.61, 0.14)	(-0.66, 1.56)	(-0.25, 0.49)
p value (versus Placebo)			0.186	0.225	0.424	0.522
Overall Maintenance						
N	42	294	35	284	32	299
LS Mean Change	-1.4	-2.3	-2.1	-2.5	-1.1	-2.2
LS Mean Difference versus Placebo (SE)			-0.7 (0.46)	-0.2 (0.17)	0.3 (0.48)	0.1 (0.17)
95% CI (versus Placebo)[a]			(-1.63, 0.20)	(-0.57, 0.11)	(-0.68, 1.25)	(-0.28, 0.39)
p value (versus Placebo)			0.124	0.184	0.557	0.741

[a] Test for no difference between treatment from ANCOVA model with factor(s) treatment, pooled center and baseline pain intensity as covariate (type III SS) unadjusted p value.
LOCF = last observation carried forward; mod = moderate; sev = severe
Average pain scores are the averages of all scores recorded during the baseline period or during each week.
Baseline pain intensity categories: moderate is defined as <6; severe is defined as ≥6.
Tapentadol ER = Tapentadol PR

Average Pain Intensity Score by Prior Opioid Use

The mean changes in average pain scores from baseline to Week 12 of the maintenance period and for the overall maintenance period showed a greater improvement in pain intensity for the tapentadol SR group than the placebo group in subjects who did not take prior opioids (LS mean difference of -0.4 for both endpoints using LOCF). For subjects who took prior opioids, there was a greater improvement in the placebo group than the tapentadol SR group (LS mean difference of 0.8 for both endpoints). The converse was observed for the oxycodone CR group: decreases in average pain scores were larger in the placebo group than in the oxycodone CR group for subjects who did not take prior opioids (LS mean differences of 0.3 at Week 12 and 0.2 for overall maintenance period) whereas decreases were similar in the two groups for subjects who did take prior opioids (LS mean difference of -0.0 for both endpoints). In both active-treatment groups, the mean total daily dose was higher in subjects who took prior opioids than those who did not.

Comment: This study did not achieve its primary efficacy endpoint to demonstrate superiority of tapentadol SR over placebo in the change from baseline of the average pain intensity at Week 12 of the maintenance period (for the FDA) or over the 12-week maintenance period (for non-U.S. regulatory authorities), using LOCF imputation. Statistical significance was also not reached for the primary endpoint when applying more conservative imputation methods, that is,, BOCF, WOCF, modified BOCF, and PMI.

The study did not demonstrate assay sensitivity, as the active comparator oxycodone CR did not demonstrate superiority over placebo for the primary efficacy endpoint. There were no consistent, statistically significant differences between active treatment and placebo for the secondary efficacy measures or the exploratory analyses.

Statistically significant improvements in pain intensity were not demonstrated in this study when tapentadol SR 100 to 250 mg twice a day was administered in a controlled dose-adjustment design for up to 15 weeks to subjects with moderate to severe chronic OA of the knee.

Overall, the results from the study do not support efficacy of tapentadol SR in the treatment of moderate or severe pain.

PAI-3011/KF23

Study design

Study PAI-3011/KF23 was a randomised, multi-centre, double-blind, placebo- and active-controlled, parallel-arm, Phase III study in subjects with moderate to severe chronic low back pain. The study design was identical to that of the PAI-3008/KF11 study.

Demographic and baseline characteristics

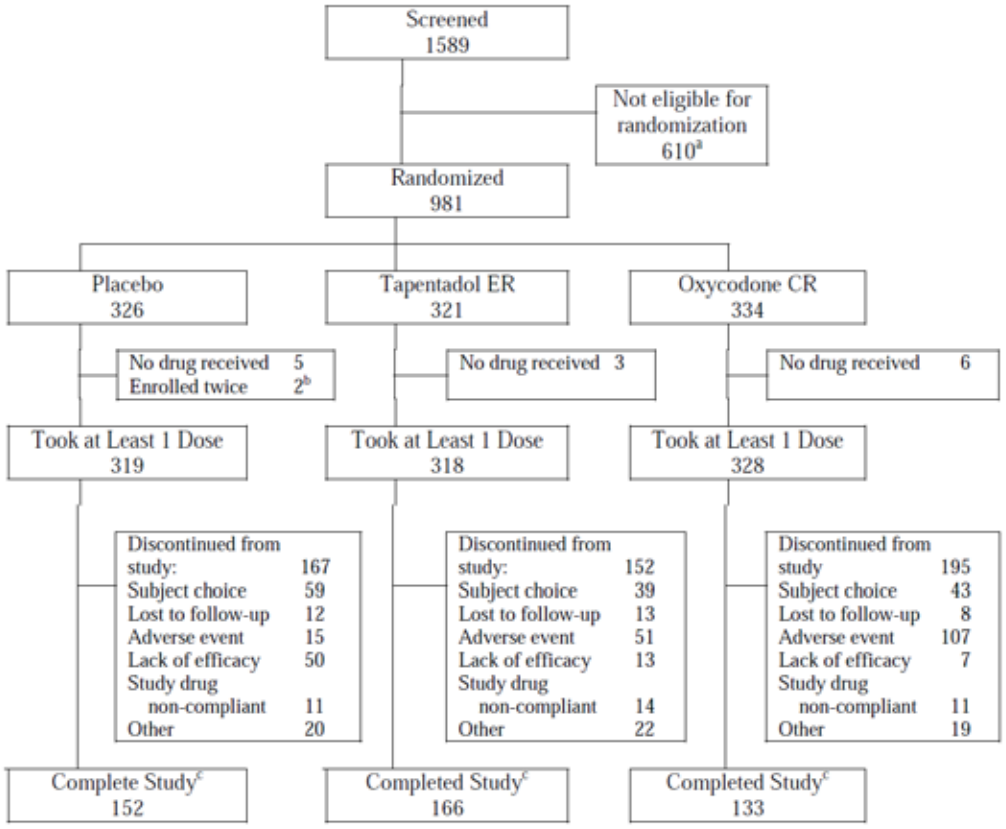
There were 981 subjects randomised. The mean age was 49.9 (range 18 to 89) years and the majority of subjects were female (57.9%), white (73.3%), younger than 65 years of age (84.6%), and recruited in the US (83.2%). The percentage of subjects completing study treatment was greater in the tapentadol SR group (54.1%) and placebo group (50.5%), than in the oxycodone CR group (43.3%).

Across all treatment groups, discontinuations were higher during the titration period than during the maintenance period. In addition, most subjects took opioids during the 3 months prior to the screening visit (53.4%) and were categorized as having severe baseline pain intensity (NRS ≥6, 88.5%).

Subject disposition and study completion/withdrawal information

The study was conducted from 21 February 2007 to 12 March 2008. A total of 1,589 subjects were screened; 981 subjects were randomised at 103 sites in Australia (3 sites), Canada (15 sites), and the United States of America (85 sites). The 981 subjects were randomised to the 3 treatment groups in a 1:1:1 ratio (326 subjects in the placebo; 321 in the tapentadol SR and 334 in the oxycodone CR groups). A greater percentage of subjects in the tapentadol SR group (52.2%) than in the placebo (47.6%) and the oxycodone CR groups (40.5%) completed the study. The most common reasons for study discontinuation in the active-treatment groups were adverse events followed by subject choice (subject withdrew consent) (see Figure 7). Subjects completing treatment included all subjects who completed the double-blind treatment period (Visits T1 through M8). Overall, a greater number of subjects discontinued from the study (53.3%) than discontinued from treatment (50.8%). This difference is attributed to the number of subjects who discontinued from the study due to subject choice (14.6%), which included subjects who did not return for the follow-up visit after the end of treatment.

Figure 7: Subject Disposition (Study R331333-PAI-3011/KF5503/23)



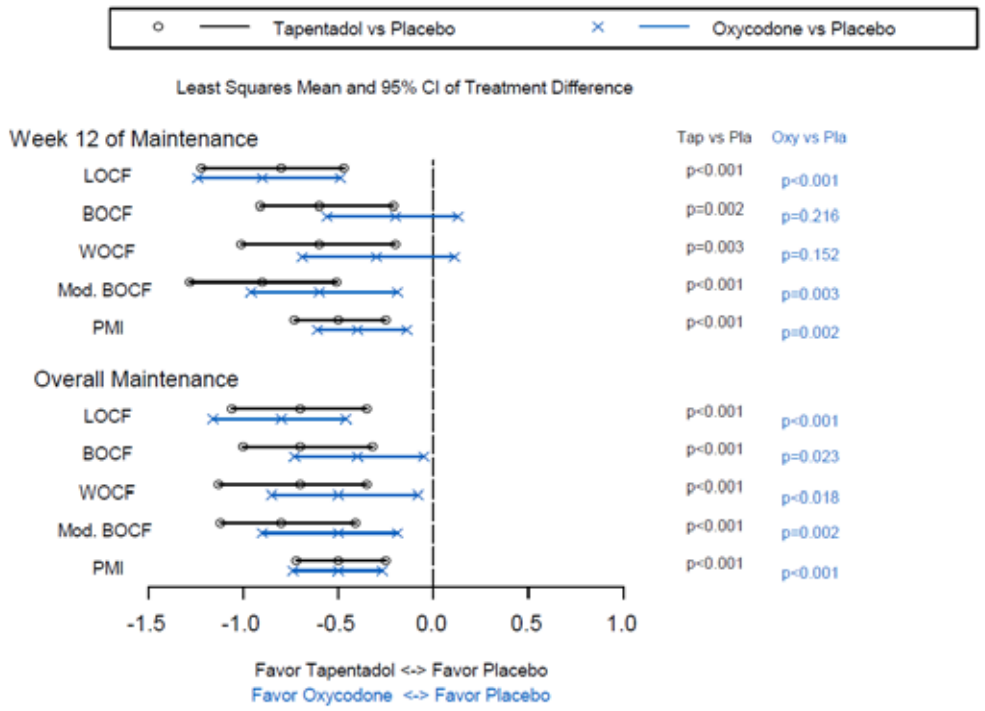
[a] Subject 114595 at Site 011310 and Subject 114931 at Site 011302 were randomized in error, but did not take study drug.
[b] Subject 114509 at Site 001460 was randomized again in the study as Subject 115511 at Site 001414, and Subject 114819 at Site 001533 was randomized again as Subject 115718 at Site 001460.
[c] Includes all subjects who were enrolled in the open-label extension (PAI-3010/KF18) or who completed all follow-up visits in the current study.

Results

Primary endpoint

In comparison with placebo, tapentadol SR showed a significantly greater change from baseline pain intensity during the overall maintenance period ($p < 0.001$) and during the last week of the maintenance period ($p < 0.001$) using LOCF, and also WOCF, BOCF, modified BOCF, and PMI imputations ($p \leq 0.003$) (see Figure 8). For LOCF, the LS mean difference versus placebo (standard error) was -0.7 (0.18) for tapentadol SR and -0.8 (0.18) for oxycodone CR, respectively, for the change from baseline to the overall maintenance period, and -0.8 (0.19) and -0.9 (0.19) for the change from baseline to Week 12 of the maintenance period. Oxycodone CR was significantly more effective than placebo in the reduction of pain intensity for the overall maintenance period and the last week of maintenance period (confirming assay sensitivity), by all imputations except BOCF and WOCF at the last week of the maintenance period.

Figure 8: Pairwise Comparisons of Change in Average Pain Intensity for Tapentadol SR versus Placebo, and Oxycodone CR versus Placebo, for Different Imputation Methods in Subjects With Low Back Pain (PAI-3011/KF23: Intent to Treat Analysis Set)



LOCF = last observation carried forward; BOCF = baseline observation carried forward; WOCF = worst observation carried forward; PMI = placebo mean imputation; Mod BOCF = modified BOCF; CI = confidence interval; Tap = tapentadol; Pla = placebo; Oxy = oxycodone.

Secondary efficacy parameters

The difference in the distribution of responder rates compared to placebo was statistically significant (p = 0.004) in favour of tapentadol SR. The proportions of subjects with at least a 30% improvement and at least a 50% improvement in pain intensity scores at Week 12 of the maintenance period were statistically significantly greater in the tapentadol SR group (39.7% and 27%, respectively) than in the placebo group (27.1% and 18.9%; p <0.001 and p = 0.016, respectively) (see Table 26). The proportions of subjects with at least a 30% improvement and at least a 50% improvement for oxycodone CR compared with the placebo group were not statistically significantly different (p-values of 0.365 and 0.174, respectively).

Table 26: Responder rates based on 30% and 50% improvement using average pain intensity scores at Week 12 of the maintenance period (based on NRS) (PAI-3011/KF23: Intent-to-Treat Analysis Set)

Response	Placebo	Tapentadol PR		Oxycodone CR	
	Subjects (%)	Subjects (%)	p-value [a]	Subjects (%)	p-value [a]
30%	27.1	39.7	<0.001	30.4	0.365
50%	18.9	27.0	0.016	23.3	0.174

a) P-value versus placebo. Pairwise comparison: Generalized Cochran-Mantel-Haenszel test for general association.

Tapentadol SR and oxycodone CR were statistically significantly superior to placebo in terms of time to treatment discontinuation due to lack of efficacy (p <0.001) as well as for the distribution of PGIC scores at endpoint (p <0.001) (see Table 27).

Table 27: Patient Global Impression of Change at Endpoint (PAI-3008/KF/23, Intent-to-Treat Analysis Set, LOCF)

	Placebo			TapentadolPR			OxycodoneCR		
	N	%	Cum.%	N	%	Cum.%	N	%	Cum.%
VeryMuchImproved	24	9.8	9.8	43	18.2	18.2	47	22.4	22.4
Much Improved	56	22.9	32.7	88	37.3	55.5	79	37.6	60.0
Minimally Improved	53	21.6	54.3	64	27.1	82.6	55	26.2	86.2
No Change	66	26.9	81.2	26	11.0	93.6	13	6.2	92.4
Minimally Worse	24	9.8	91.0	9	3.8	97.5	8	3.8	96.2
Much Worse	15	6.1	97.1	4	1.7	99.2	5	2.4	98.6
Very Much Worse	7	2.9	100.0	2	0.8	100.0	3	1.4	100.0
Total	245			236			210		
Overall P-value [a]			<0.001						
P-value(minus Placebo) [b]						<0.001			<0.001

a) Generalized Cochran-Mantel-Haenszel test for row mean scores differ.

b) Pairwise comparison: Generalized Cochran-Mantel-Haenszel test for row mean scores differ.

N = number of subjects; Cum. = cumulative.

For the BPI at endpoint, both active-treatment groups showed statistically significant reductions ($p \leq 0.002$ for all comparisons except pain interference score for oxycodone CR with $p = 0.023$) in pain interference score, pain subscale scores and the total score compared with placebo. Both tapentadol SR and oxycodone CR significantly improved health status (EQ-5D). Tapentadol SR and oxycodone CR were significantly better than placebo on the physical component summary score of the SF-36, suggesting both treatments improved physical health status. There was a statistically significant improvement from baseline in the quality of sleep (Item 4) in the tapentadol SR group compared with the placebo group ($p = 0.003$) at endpoint. Results for the comparison of oxycodone CR and placebo were not significant.

Exploratory Efficacy Analyses

Average Pain Intensity Score by Baseline Pain Category

Most subjects (88.5%) had baseline pain intensity scores categorised as severe (at least 6). Tapentadol SR showed statistically significant reductions in average pain intensity scores compared with placebo at Week 12 of the maintenance period and over the entire maintenance period for subjects with baseline pain intensity scores categorised as severe (p-values <0.001) and for subjects with baseline pain intensity scores categorised as moderate (p-values ≤0.028) (see Table 28).Subjects entering the trial with moderate pain improved more, on average, than subjects entering the trial with severe pain. The sponsor added the comment that the decrease from baseline was higher in subjects with severe baseline pain than in subjects with moderate baseline pain in all treatment groups and that it is the fact that the difference between severe and moderate pain was greatest for the placebo group which resulted in a greater difference (compared to placebo) for moderate than severe baseline pain. For the oxycodone CR group, the reductions in pain intensity scores from placebo were also statistically significantly different in the severe or moderate categories (p-values ≤0.039).

Table 28: Change From Baseline in Average Pain Intensity Scores Based on NRS by Baseline Pain Intensity Category (LOCF) (Study R331333-PAI-3011; KF5503/23: Intent-to-Treat Analysis Set)

	Placebo		Tapentadol ER		Oxycodone CR	
	Mod	Sev	Mod	Sev	Mod	Sev
Last Week of Maintenance						
N	40	276	35	277	33	290
LS Mean Change	-0.6	-2.2	-2.4	-3.1	-2.0	-3.0
LS Mean Difference versus Placebo (SE)			-1.8 (0.67)	-0.8 (0.21)	-1.5 (0.58)	-0.8 (0.21)
95% CI (versus Placebo)[a]			(-3.15, –0.48)	(-1.23, –0.41)	(-2.63, –0.29)	(-1.21, –0.40)
P-value (versus Placebo)			0.009	<0.001	0.015	<0.001
Overall Maintenance						
N	40	276	35	277	33	290
LS Mean Change	-0.9	-2.3	-2.3	-3.0	-2.0	-3.0
LS Mean Difference versus Placebo (SE)			-1.4 (0.63)	-0.7 (0.20)	-1.2 (0.55)	-0.8 (0.19)
95% CI (versus Placebo)[a]			(-2.70, –0.16)	(-1.08, -0.31)	(-2.28, -0.06)	(-1.16, -0.40)
P-value (versus Placebo)			0.028	<0.001	0.039	<0.001

[a] Test for no difference between treatment from ANCOVA model with factor(s) treatment, pooled center and baseline pain intensity as covariate (type III SS) unadjusted p-value.
LOCF = last observation carried forward; mod = moderate; sev = severe
Average pain scores are the averages of all scores recorded during the baseline period or during each week.
Baseline pain intensity categories: moderate is defined as <6; severe is defined as ≥6.
Last Week = Week 12
Tapentadol ER = Tapentadol PR

Average Pain Intensity Score by Prior Opioid Use

Tapentadol SR showed statistically significant reductions in average pain intensity scores compared with placebo at Week 12 of the maintenance period and over the entire maintenance period for subjects with prior opioid use (LOCF; p-values ≤0.015) and for subjects with no prior opioid use (p-values ≤0.001). Similar results were observed in the oxycodone CR group.

For the tapentadol SR and placebo comparison, the mean changes in average pain scores from baseline to Week 12 of the maintenance period and the overall maintenance period were greater for subjects who did not take prior opioid medications (difference from placebo in the mean change from baseline of -1.1 at Week 12 of the maintenance period and –1.0 for the overall maintenance period) than for subjects who took prior opioids (-0.7 at Week 12 and -0.6 for the overall maintenance period).

Similar results were not observed in the oxycodone CR group. Mean changes in average pain scores from baseline to Week 12 of the maintenance period and to the overall maintenance period were greater for subjects who took prior opioid medications (difference from placebo in the mean change from baseline of –1.0 for both endpoints) than for subjects who did not take prior opioids (-0.8 at Week 12 of the maintenance period and -0.7 for the overall maintenance period).

Sex, Age, race

There were no differences between the tapentadol SR and placebo groups for the subgroups of sex, age group, or race in the primary efficacy variable.

Comment: Study KF5503/23 did demonstrate efficacy of tapentadol SR across some of the primary and secondary variables. The study achieved its primary efficacy endpoint of change from baseline of the average pain intensity at Week 12 or over the 12 week maintenance period using LOCF imputation. The efficacy results were confirmed by achieving statistically significant differences for the primary comparison of tapentadol SR group vs. the placebo group in all of the more conservative imputation methods (BOCF, WOCF, modified BOCF, and PMI).

Oxycodone CR was statistically significantly better than placebo on the primary efficacy endpoint for the overall maintenance period and over the 12 week maintenance period in all imputations, except at Week 12 of the maintenance period when the BOCF and WOCF imputation methods were applied. These findings may be a reflection of the large number of oxycodone CR-treated subjects who discontinued the study (56.7% of all subjects in the oxycodone CR group).

The secondary efficacy measure, responder analysis, indicated that the proportions of subjects with 30% and 50% improvement (with prematurely discontinued subjects considered not improved) in the tapentadol SR group were statistically significantly greater than the response in the placebo group. The comparisons of oxycodone CR and placebo were not statistically significant. Once again, the fact that the comparator performed poorly in this parameter raises concerns about the validity of the overall results.

In both active-treatment groups, subjects with moderate baseline pain improved more, on average, than subjects with severe baseline pain. In the tapentadol SR group, subjects with no prior opioid use had greater improvements from baseline in pain scores than subjects with prior opioid use. Similar results were not observed for the oxycodone CR group. In the oxycodone CR group, subjects with prior opioid use had greater improvements from baseline in pain scores than subjects with no prior opioid use.

Overall, in this study efficacy results for tapentadol SR 100 mg to 250 mg twice a day were more robust than oxycodone CR. This may have been influenced by the improved tolerability and reduced rate of discontinuation of subjects in the tapentadol SR group compared to oxycodone CR.

When examining the efficacy results when analysed for baseline pain severity, the difference between tapentadol SR and placebo did reach statistical significance, however only 11.5% of the patients had moderate pain, therefore the number of patients analysed for this factor is small. The efficacy results overall are not persuasive for treatment of moderate pain.

Supportive studies

PAI-3015/KF36

Study design

Study PAI-3015/KF36 was a randomised, multicentre, double-blind, placebo-controlled Phase III study using a withdrawal design in subjects with painful diabetic peripheral neuropathy. After washout and a pain evaluation period, the subjects received open-label tapentadol SR titrated to an optimal dose of between 100 mg and 250 mg twice daily over 3 weeks, followed by a 12 week double-blind maintenance period at the start of which they were randomised to continue on their optimal dose or placebo. Subjects were required to have an average pain intensity score at the beginning of the open-label phase of more than 5 on an NRS. In order to be randomised, subjects had to have at least a 1 point improvement in pain intensity on the NRS at the end of the open-label titration period. The primary efficacy endpoint was the change from baseline at randomisation in average pain intensity over the last week of the double-blind maintenance period at Week 12, as determined by twice-daily measurements on an 11-point NRS. Safety assessments were based on the incidence of treatment-emergent adverse events and on laboratory evaluations, vital signs, physical examinations, patient assessment of constipation symptoms, 12-lead ECG, and clinical and subjective opioid withdrawal scale measurements.

Demographics and baseline characteristics

A total of 591 subjects were enrolled in the open-label titration and 395 subjects were randomised into the double-blind maintenance period. The demographic characteristic of the subjects at the start of the open-label titration and at the start of the double-blind maintenance period were similar. Demographic and baseline characteristics were also similar between the tapentadol SR and placebo

treatment groups. At the start of the double-blind maintenance period, the mean age was 60.2 (range 29 to 87) years and the majority of subjects were male (60.4%), white (69.9%) and younger than 65 years of age (65.8%). Approximately one third of subjects (33.7% at the start of the open-label titration and 34.4% at the start of the double-blind maintenance period) were "opioid experienced" (that is, before screening they had received an opioid analgesic for at least three weeks continuously or intermittently, regardless of the response to the opioid analgesic).

The percentage of subjects classified as having severe pain (≥6 on an 11-point NRS) was 79.4% at the start of the open-label titration, however only 11.8% at the start of the double-blind maintenance period. At the start of the double-blind maintenance period, the majority of subjects (55.5%) had baseline pain intensity scores categorised as mild.

Extent of exposure

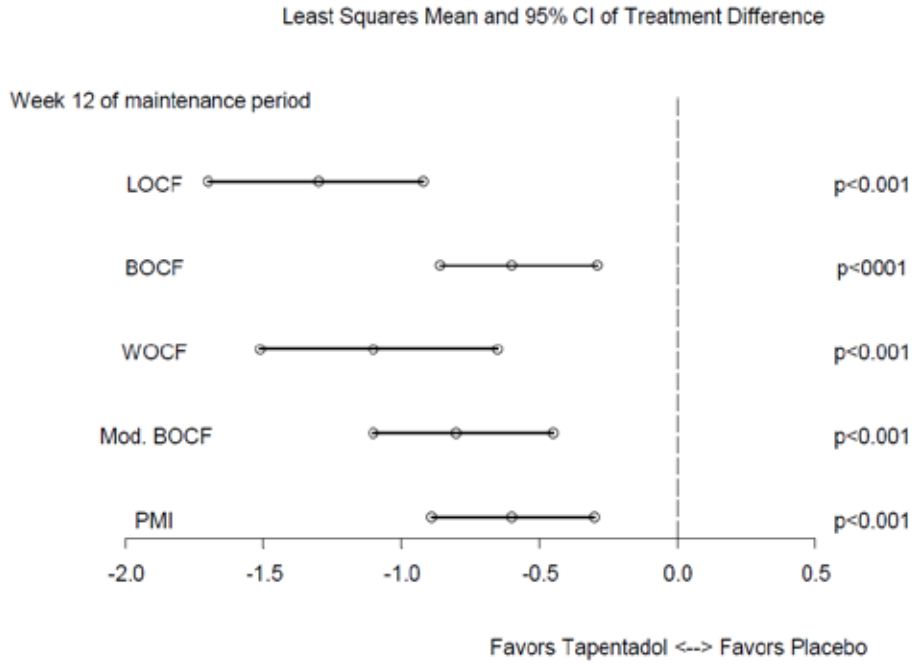
In PAI-3015/KF36, the median treatment duration during the 3-week open-label titration period was 21 days (3 weeks), with most subjects (82.7%) exposed to tapentadol SR for at least 15 days. The average mean total daily dose of tapentadol SR (including supplemental medication of tapentadol SR) during maintenance was 421.60 mg. During the open-label titration period, approximately one-half of subjects (ITT Analysis Set) were titrated to an optimal dose of 250 mg tapentadol SR twice daily. Of the subjects randomised to tapentadol SR, 15.3% were on 100 mg twice daily, 17.3% were on 150 mg twice daily, 13.3% were on 200 mg twice daily and 54.1% were on 250 mg twice daily. During the double-blind maintenance period, the median duration of treatment was 84 days (12 weeks) in both treatment groups, with approximately 70% of subjects in each group exposed to study drug for more than 70 days (10 weeks).

Results

Primary endpoint

During the double-blind maintenance period, subjects randomised to tapentadol SR maintained a stable average pain intensity, whereas the average pain intensity in the placebo subjects increased. The difference between the treatment groups was statistically significant using LOCF ($p < 0.001$), BOCF, WOCF, modified (mod.) BOCF and PMI (see Figure 9). For the primary efficacy analysis, tapentadol SR showed a statistically significant difference in average pain intensity compared to placebo at Week 12 of the double-blind maintenance period ($p<0.001$, LS mean difference compared to placebo: -1.3).

Figure 9: Comparison of Change in Average Pain Intensity Between Tapentadol SR and Placebo for Different Imputation Methods in Subjects With Painful Diabetic Peripheral Neuropathy (PAI-3015/KF36: Intent to Treat Analysis Set)



LOCF = last observation carried forward; BOCF = baseline observation carried forward; WOCF = worst observation carried forward; PMI = placebo mean imputation; Mod BOCF = modified BOCF; CI = confidence interval.

Secondary efficacy parameters

In PAI-3015/KF36, responder rates were based on changes in pain intensity from start of the open-label titration period during which all subjects (including later placebo subjects) were treated with tapentadol SR. Nevertheless, differences in 30% and 50% responder rates between tapentadol SR and placebo groups were similar in this study and in studies PAI-3008/KF11 and PAI-3011/KF23. The difference in the distribution of responder rates compared to placebo was statistically significant ($p = 0.0317$) and in favour of tapentadol SR. The proportion of subjects who showed at least 30% improvement in pain intensity at Week 12 of the double-blind treatment period was 42.2% in placebo and 53.6% in tapentadol SR. The proportion of subjects who showed at least 50% improvement in pain intensity at Week 12 of the double-blind treatment period was 27.6% in placebo and 37.8% in tapentadol SR. The difference in proportion of subjects showing at least 30% improvement and at least 50% improvement was statistically significant when comparing tapentadol SR to placebo ($p = 0.017$ and $p = 0.028$, respectively).

Tapentadol SR was statistically significantly superior to placebo in terms of time to treatment discontinuation due to lack of efficacy ($p < 0.001$) as well as for the distribution of PGIC scores at endpoint ($p < 0.001$). On the BPI at endpoint, tapentadol SR showed statistically significant reductions from the start of the open-label titration period ($p \leq 0.001$) in pain interference score, pain subscale score and the total score compared with placebo. Assessments that evaluated health status (EQ-5D and SF- 36) showed positive effects of tapentadol SR compared with placebo that were consistent with the outcome of the efficacy assessments. There were no statistically significant differences between the tapentadol SR and placebo groups in the distribution of the overall sleep quality ratings at endpoint.

Average Pain Intensity by Subgroups

Average Pain Intensity by Pain Category at the Start of Double-Blind Treatment

The mean pain intensity score based on the 11-point NRS at the start of the open-label titration period was 7.3. By the end of the open-label titration period (that is, at the start of the double-blind maintenance period) the mean pain intensity score was 3.5 with 11.8% of subjects categorised as "severe" (pain intensity score at the start of the double-blind maintenance period ≥6). At the start of the double-blind maintenance period, the majority of subjects (55.5%) had baseline pain intensity scores categorised as mild.

In the tapentadol SR group, mean pain intensity scores decreased for subjects with moderate or severe pain at the start of the double-blind (DB) period and increased slightly for subjects with mild pain at the start of the DB. In the placebo group, subjects with mild baseline (start DB period) pain showed greater increases in average pain scores at Week 12 of the double-blind maintenance period than subjects with moderate or severe baseline (start double-blind) pain. The difference between the tapentadol SR and placebo groups was greater for subjects with mild baseline pain (difference of –1.6) than for subjects with moderate or severe baseline pain (differences of –0.9 for moderate baseline pain and-0.6 for severe baseline pain); however, more subjects in both groups had mild baseline pain (103 subjects in the tapentadol SR group and 113 in the placebo group) than moderate (65 and 50 subjects, respectively) or severe baseline pain (22 and 24 subjects, respectively).

Average Pain Intensity by Prior Opioid Use

The mean reduction in average pain scores from the start of the open-label titration period to Week 3 of the open-label titration period were slightly less for opioid-naïve subjects (-3.1) than for opioid-experienced subjects (-3.4). Sixty-five percent of subjects in the ITT analysis set were opioid naïve. There were no differences in the mean changes in average pain scores from the start of the double-blind maintenance period to Week 12 of the double-blind maintenance period for opioid-naïve subjects and opioid-experienced subjects in either treatment group. There was no difference between opioid-naïve subjects and opioid-experienced subjects for the difference to placebo in change from baseline pain intensity (difference of -1.4 between tapentadol and placebo for both opioid-naïve and for opioid-experienced subjects).

Comment: This study is not pivotal in terms of efficacy and is considered a supportive study. There was no active control, and the majority of patients entering the double blind period did not have moderate or severe pain, which is the indication being sought by the sponsor.

In this study, in order to be randomised, subjects had to have at least a 1 point improvement in pain intensity on the NRS at the end of the open-label Titration Period. According to relevant EMEA guidelines (CPMP/EWP/612/00[33]) previous exposure of the trial population to analgesics may be relevant to the interpretation of results. In this study patients who did not respond in the open-label period were excluded, and this may have resulted in selection of subjects more likely to respond.

PAI-3007/KF24

Study design

Study PAI-3007/KF24 assessed the long term safety of tapentadol SR over one year, using oxycodone CR as a control. Information on efficacy over an extended period of treatment for up to one year was obtained. Study PAI-3007/KF24 was a randomised, open-label, active controlled, parallel arm, Phase III long term safety study in subjects with moderate to severe chronic pain due to osteoarthritis of the hip or knee, or low back pain. After screening and randomisation, subjects

[33] Note for Guidance on Clinical Investigation of Medicinal Products for Treatment of Nociceptive Pain. http://www.tga.gov.au/docs/pdf/euguide/ewp/061200final.pdf

were titrated to an optimal dose of tapentadol SR (100 to 250 mg twice daily) or oxycodone CR (20 to 50 mg twice daily) followed by controlled dose adjustment (the total duration was 52 weeks). A baseline score of at least 4 on an 11 point NRS, calculated as the average pain intensity during the last three days prior to randomisation after washout, was required.

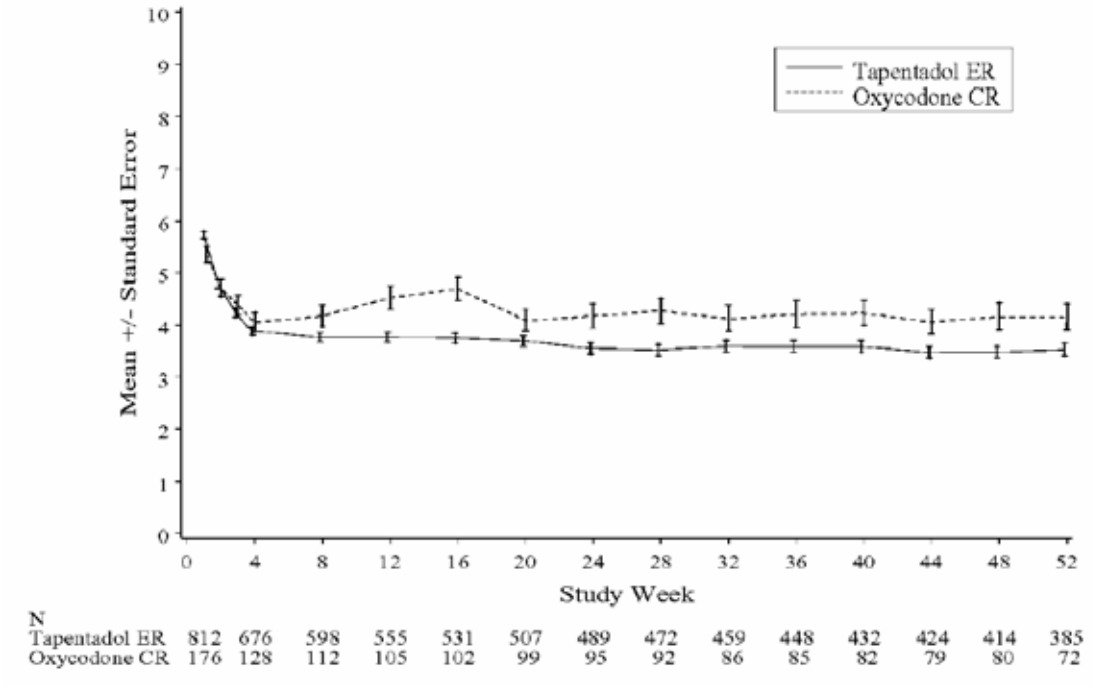
Demographics

A total of 1121 subjects were randomised to receive tapentadol SR (896 subjects) or oxycodone CR (225 subjects). The mean age was 57.0 (range 20 to 90) years and the majority of subjects were female (57.3%), white (89.1%), and younger than 65 years of age (72.1%). Approximately 90% of subjects had severe pain (11 point NRS ≥6) at baseline. In addition, approximately one-half of the subjects took opioids during the three months prior to the screening visit. Fewer subjects in the oxycodone CR group (35.0%) completed the 52-week treatment period than subjects in the tapentadol SR group (46.2%). The most common reason for treatment discontinuation for both treatment groups was the occurrence of an adverse event (22.7% in the tapentadol SR group and 36.8% in the oxycodone CR group).

Results

Pain intensity scores decreased over time, with mean scores at endpoint of 4.37 and 4.52 for the tapentadol SR and oxycodone CR groups, respectively. Mean baseline pain intensity scores were 7.58 for the tapentadol SR group and 7.61 for the oxycodone CR group. Through the first four weeks after first dose, the mean pain intensity scores were similar in both treatment groups. From that point onward, mean pain intensity scores were numerically and consistently lower in the tapentadol SR group than in the oxycodone CR group (see Figure 10). The time course of average pain intensity scores suggested a more stable pain reduction with tapentadol SR than oxycodone CR.

Figure 10: Time Course of Average Pain Intensity Score During Treatment (PAI-3007/KF24; Intent to Treat Analysis Set)



Tapentadol ER = tapentadol PR; N = number of subjects

Secondary efficacy parameters

For PGIC, a greater percentage of subjects on tapentadol SR (48.1%) reported "very much improved", or "much improved" than on oxycodone CR (41.2%). The most frequently reported change for both groups was "much improved". Improvement in sleep quality was observed in both treatment groups at endpoint, with 54.6%subjects in the tapentadol SR group and 47.7% subjects in the oxycodone CR group rating the overall quality of sleep as good or excellent.

PAI-3019/KF39

Study design

Study PAI-3019/KF39 was performed to assess the relative analgesic efficacy of tapentadol IR and tapentadol SR using a cross-over design after three weeks of titration to optimal dose with tapentadol IR. Study PAI-3019/KF39 was a randomised, double-blind, multicentre, two-period, cross-over study to establish the dose equivalence and direct conversion between tapentadol IR and tapentadol SR in subjects with moderate to severe low back pain. Subjects were titrated to an optimal dose of tapentadol IR (50 mg, 75 mg or 100 mg every 4 or 6 hr, with a maximum total daily dose of 500 mg) for 21 days. This was followed by two double-blind fixed dose (using the optimal total daily dose given either as tapentadol IR or tapentadol SR) treatment cross-over periods, each of 14 days duration. The primary efficacy endpoint, assessed using a non-inferiority test, was the mean average pain intensity score during the last 3 days of each double-blind treatment period, using twice daily 11-point NRS pain intensity evaluations.

Demographics

A total of 116 subjects were enrolled in the open-label titration period; 88 subjects were randomised and 87 subjects were included in the double-blind Safety Analysis Set. The main reasons for withdrawal from open-label treatment were: adverse event (16 subjects), noncompliance with study medication (6 subjects), subject choice (4 subjects), lost to follow-up (2 subjects) and lack of efficacy (1 subject). The median age was 53.6 years (range 21-88) and the majority of subjects were women (56%), white (77.6%), and under 65 years of age (74.1%) for the subjects in the open-label Safety Analysis Set. The mean pre-treatment pain intensity, based on the 11-point NRS, at the start of the open-label titration was 7.3, with 85.3% of subjects having pain categorised as severe (≥6 on an 11 point NRS). Opioid analgesics were taken by 46.6% of subjects within the 3 months prior to screening.

Results

The total mean pain intensity score decreased from a pre-treatment value of 7.3 to a mean score of 4.2 after 3 weeks of open-label treatment (before the start of the double-blind cross-over). The estimated mean average pain intensity score over the last 3 days of treatment from the primary analysis was 4.0 for tapentadol SR and 3.9 for tapentadol IR. The estimated difference in mean primary endpoint values (mean average pain intensity score over the last 3 days of treatment: tapentadol SR to tapentadol IR) was 0.1 with a 95% CI of (-0.09, 0.28). The 95% CI from the primary analysis is contained well within the margin of (-2, 2) pre-specified in the protocol.

In addition to the protocol-defined equivalence margin, the results from the primary analysis were compared with those of PAI-3011/KF23, which obtained a model-based estimate of the difference in means (tapentadol SR to Placebo) of –0.8 with 95% CI (-1.22, -0.47), using a similar NRS-based average pain intensity score endpoint, in a similar population of subjects with chronic low back pain but over a longer duration of treatment exposure. If a mean difference of 0.8 is assumed to be clinically relevant, then a stricter criterion of equivalence must be applied in this study than the (-2, 2) stated in the protocol. The sponsor commented that it could be argued that, if this study had used a much stricter equivalence margin of (-0.28, 0.28), representing 50% retention of the tapentadol SR

effect as estimated by an 86% CI from PAI-3011/KF23, equivalence could be concluded using a standard of evidence which exceeds that in the work of Rothmann 2003.

Comment: This study demonstrated that tapentadol IR can be directly converted into an approximately equivalent total daily dose of tapentadol PR, and vice-versa, with equivalent efficacy.

It is of concern however, that the equivalence margin in the study was + or – 2 on the 11 point pain scale. The clinical evaluator considered the margin too wide. In study PAI-3015/KF36 for example, ***a change of 1 point was considered to be a significant change, and this may have been a more appropriate margin for this study.***

Pooled analysis of efficacy

Pooled analysis of efficacy

The sponsor presented a pooled analysis of efficacy. Data from studies PAI-3008/KF11, PAI-3009/KF12 and PAI-3011/KF23 were pooled thereby giving a global assessment of efficacy across studies of identical design in different pain conditions. This enables more detailed evaluation of subgroups and secondary efficacy endpoints as sample size calculations in the individual studies referred to the primary endpoints only and the studies were not powered for secondary endpoint or subgroup analyses.

Primary Efficacy Analysis

For all three treatment groups, there was a reduction in average pain intensity both for the overall maintenance period and at Week 12 of the maintenance period. The reductions were numerically larger in the tapentadol SR group than in the other treatment groups. When comparing tapentadol SR with placebo using LOCF, the difference in reduction was statistically significant for the overall maintenance period (LS mean difference of -0.5) and at Week 12 of the maintenance period (LS mean difference of -0.6) (see Tables 29 and 30). Oxycodone CR showed numerically smaller reductions in average pain intensity than tapentadol SR, but they were still statistically significant compared to placebo for the overall maintenance period (LS mean difference of -0.3) and at Week 12 of the maintenance period (LS mean difference of -0.3). The results with oxycodone CR were affected by the high treatment discontinuation rate, particularly in the titration period.

Table 29: Pairwise Comparison of the Change From Baseline in Average Pain Intensity Scores (Based on NRS) to Overall Maintenance (Pooled Tapentadol SR Formulation Phase III Studies Integrated Summary of Efficacy: Intent to Treat Analysis Set)

		Placebo	Tapentadol PR	Oxycodone CR
LOCF	N	988	975	996
	LS Mean	-2.2	-2.7	-2.5
	LS Mean Difference versus Placebo (SE)		-0.5 (0.10)	-0.3 (0.10)
	95% CI (versus Placebo) [a]		(-0.73;-0.34)	(-0.52;-0.14)
	P-value (versus Placebo)		<0.001	<0.001
	LS Mean Difference tapentadol PR versus oxycodone CR (SE)		0.2 (0.10)	
	95% CI [a]		(0.01;0.40)	
	P-value		0.037	
BOCF	N	988	975	996
	LS Mean	-1.8	-2.1	-1.5
	LS Mean Difference versus Placebo (SE)		-0.3 (0.09)	0.2 (0.09)
	95% CI (versus Placebo) [a]		(-0.51;-0.14)	(0.07;0.43)
	P-value (versus Placebo)		<0.001	0.008 [b]
	LS Mean Difference tapentadol PR versus oxycodone CR (SE)		0.6 (0.09)	
	95% CI [a]		(0.39;0.76)	
	P-value		<0.001	
WOCF	N	988	975	996
	LS Mean	-1.4	-1.7	-1.1
	LS Mean Difference versus Placebo (SE)		-0.3 (11)	0.3 (11)
	95% CI (versus Placebo) [a]		(-0.55;-0.13)	(0.11;0.54)
	P-value (versus Placebo)		0.002	0.003 [b]
	LS Mean Difference tapentadol PR versus oxycodone CR (SE)		0.7 (11)	
	95% CI [a]		(0.45;0.88)	
	P-value		<0.001	
Mod BOCF	N	988	975	996
	LS Mean	-1.8	-2.3	-1.7
	LS Mean Difference versus Placebo (SE)		-0.4 (0.10)	0.1 (0.10)
	95% CI (versus Placebo) [a]		(-0.63;-0.24)	(-0.05;0.34)
	P-value (versus Placebo)		<0.001	0.141
	LS Mean Difference tapentadol PR versus oxycodone CR (SE)		0.6 (0.10)	
	95% CI [a]		(0.39;0.77)	
	P-value		<0.001	

Table 29 (cont):

		Placebo	Tapentadol PR	Oxycodone CR
PMI	N	988	975	996
	LS Mean	-2.9	-3.3	-3.2
	LS Mean Difference versus Placebo (SE)		-0.4 (0.07)	-0.3 (0.07)
	95% CI (versus Placebo) [a]		(-0.48;-0.22)	(-0.40;-0.14)
	P-value (versus Placebo)		<0.001	<0.001
	LS Mean Difference tapentadol PR versus oxycodone CR (SE)		0.1 (0.07)	
	95% CI [a]		(-0.05;0.21)	
	P-value		0.249	
Observed (treatment completed)	N	588	550	381
	LS Mean	-3.0	-3.5	-3.6
	LS Mean Difference versus Placebo (SE)		-0.5 (0.12)	-0.6 (0.13)
	95% CI (versus Placebo) [a]		(-0.77;-0.31)	(-0.83;-0.31)
	P-value (versus Placebo)		<0.001	<0.001
	LS Mean Difference tapentadol PR versus oxycodone CR (SE)		-0.0 (0.13)	
	95% CI [a]		(-0.29;0.23)	
	P-value		0.815	

Studies included are PAI-3008/KF11, PAI-3009/KF12 and PAI-3011/KF23; dose range for tapentadol PR: 100 mg to 250 mg twice daily; dose range for oxycodone CR: 20 mg to 50 mg twice daily.

a) Test for no difference between treatments from ANCOVA model with factor(s) treatment, pooled center and baseline pain intensity as covariate (type 3 SS) unadjusted p-value.

b) Oxycodone CR significantly worse than placebo

LOCF = last observation carried forward; BOCF = baseline observation carried forward; WOCF = worst observation carried forward; PMI = placebo mean imputation; Mod BOCF = modified BOCF; CI = confidence interval; LS = least square; SE = standard error; ANCOVA = Analysis of covariance; NRS = Numeric rating scale; PR = prolonged release; CR = controlled release.

Table 30: Pairwise Comparison of the Change From Baseline in Average Pain Intensity Scores (Based on NRS) to Week 12 of Maintenance (Pooled Tapentadol SR Formulation Phase III Studies Integrated Summary of Efficacy: Intent to Treat Analysis Set)

		Placebo	Tapentadol PR	Oxycodone CR
LOCF	N	988	975	996
	LS Mean	-2.2	-2.8	-2.6
	LS Mean Difference versus Placebo (SE)		-0.6 (0.11)	-0.3 (0.11)
	95% CI (versus Placebo) [a]		(-0.80;-0.39)	(-0.53;-0.12)
	P-value (versus Placebo)		<0.001	0.002
	LS Mean Difference tapentadol PR versus oxycodone CR (SE)		0.3 (0.11)	
	95% CI [a]		(0.06;0.48)	
	P-value		0.011	
BOCF	N	988	975	996
	LS Mean	-1.6	-1.9	-1.3
	LS Mean Difference versus Placebo (SE)		-0.3 (0.10)	0.3 (0.10)
	95% CI (versus Placebo) [a]		(-0.47;-0.09)	(0.11;0.50)
	P-value (versus Placebo)		0.004	0.002 [b]
	LS Mean Difference tapentadol PR versus oxycodone CR (SE)		0.6 (0.10)	
	95% CI [a]		(0.39;0.78)	
	P-value		<0.001	
WOCF	N	988	975	996
	LS Mean	-1.1	-1.4	-0.8
	LS Mean Difference versus Placebo (SE)		-0.3 (0.11)	0.4 (0.11)
	95% CI (versus Placebo) [a]		(-0.50;-0.06)	(0.14;0.59)
	P-value (versus Placebo)		0.015	0.001 [b]
	LS Mean Difference tapentadol PR versus oxycodone CR (SE)		0.6 (0.11)	
	95% CI [a]		(0.42;0.87)	
	P-value		<0.001	
Mod BOCF	N	988	975	996
	LS Mean	-1.8	-2.3	-1.6
	LS Mean Difference versus Placebo (SE)		-0.5 (0.11)	0.1 (0.11)
	95% CI (versus Placebo) [a]		(-0.72;-0.30)	(-0.06;0.35)
	P-value (versus Placebo)		<0.001	0.176
	LS Mean Difference tapentadol PR versus oxycodone CR (SE)		0.7 (0.11)	
	95% CI [a]		(0.44;0.86)	
	P-value		<0.001	

Table 30 (cont):

		Placebo	Tapentadol PR	Oxycodone CR
PMI	N	988	975	996
	LS Mean	-3.0	-3.4	-3.3
	LS Mean Difference versus Placebo (SE)		-0.4 (0.07)	-0.2 (0.07)
	95% CI (versus Placebo) [a]		(-0.49;-0.23)	(-0.37;-0.10)
	P-value (versus Placebo)		<0.001	<0.001
	LS Mean Difference tapentadol PR versus oxycodone CR (SE)		0.1 (0.07)	
	95% CI [a]		(-0.01;0.26)	
	P-value		0.065	
Observed (treatment completed)	N	572	536	372
	LS Mean	-3.1	-3.7	-3.7
	LS Mean Difference versus Placebo (SE)		-0.6 (0.13)	-0.6 (0.15)
	95% CI (versus Placebo) [a]		(-0.90;-0.37)	(-0.89;-0.30)
	P-value (versus Placebo)		<0.001	<0.001

Studies included are PAI-3008/KF11, PAI-3009/KF12 and PAI-3011/KF23; dose range for tapentadol PR: 100 mg to 250 mg twice daily; dose range for oxycodone CR: 20 mg to 50 mg twice daily.

a) Test for no difference between treatments from ANCOVA model with factor(s) treatment, pooled center and baseline pain intensity as covariate (type 3 SS) unadjusted p-value.

b) Oxycodone CR significantly worse than placebo.

LOCF = last observation carried forward; BOCF = baseline observation carried forward; WOCF = worst observation carried forward; PMI = placebo mean imputation; Mod BOCF = modified BOCF; N = number of subjects; CI = confidence interval; LS = least square; SE = standard error; ANCOVA = Analysis of covariance; NRS = Numeric rating scale; PR = prolonged release; CR = controlled release.

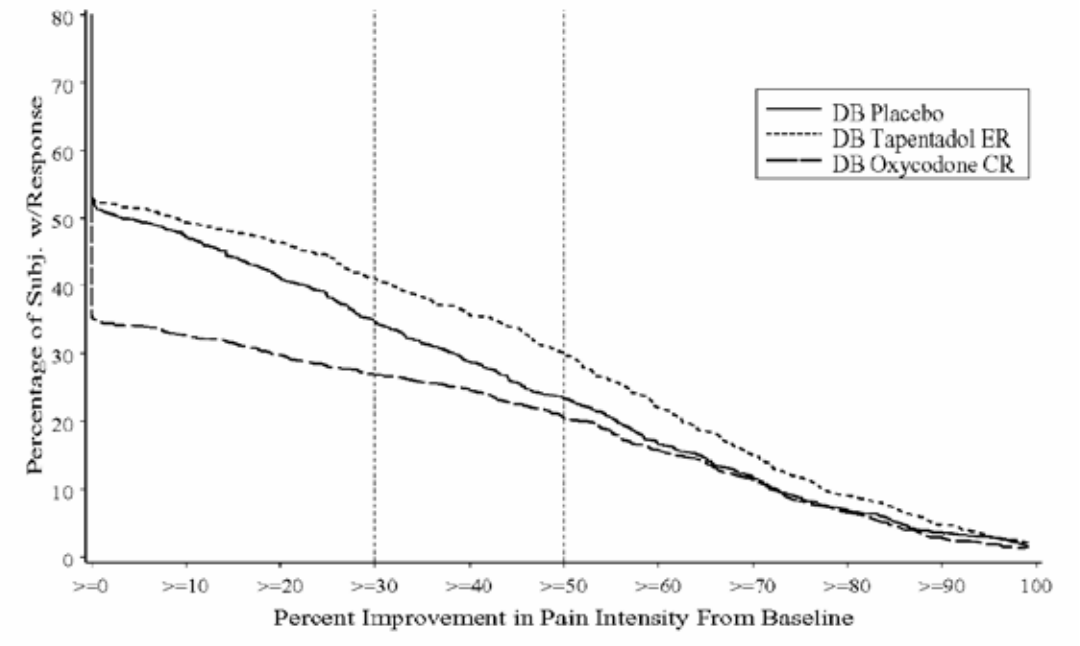
In a post hoc analysis, the two studies in osteoarthritis (PAI-3008/KF11 and PAI-3009/KF12) were pooled for an analysis of the primary endpoint. As expected, the difference to placebo for change from baseline in average pain intensity over the maintenance period was less than in the pooled analysis of all three studies. The least square mean difference (standard error (SE)) versus placebo (LOCF) for tapentadol SR and for oxycodone CR were -0.5 (0.12), p <0.001 and -0.1 (0.12), p = 0.251, respectively.

Secondary Efficacy Analyses

Responder Analysis – Average Pain Intensity Score at Week 12 of the Maintenance Period

All degrees of response were considered for the distribution of responder rates. The distribution of subjects meeting a given degree of improvement was analysed with a log-rank test. The difference in the distribution of responder rates was statistically significant between tapentadol SR and placebo (p = 0.006), with more tapentadol SR than placebo responders, and between oxycodone CR and placebo (p = 0.023), with fewer oxycodone CR than placebo responders (see Figure 11) and was statistically significant for tapentadol SR over oxycodone CR (p <0.001).

Figure 11: Distribution of Responder Rates Based on Percent Change from Baseline in Pain Intensity at Week 12 of the maintenance period (Pooled Tapentadol SR Phase III Studies, Integrated Summary of Efficacy, Intent to Treat Analysis Set)



Studies included are PAI-3008/KF11, PAI-3009/KF12 and PAI-3011/KF23

DB = double-blind; Subj = subjects; w\ = with; ER = tapentadol PR; PR = prolonged release; CR = controlled release

More subjects had a 30% or 50% improvement in average pain intensity in the tapentadol SR than in the placebo group (p >0.001). Fewer subjects in the oxycodone CR group than in the placebo group had a 30% or 50% improvement, and this difference was statistically significant for 30% improvement (p <0.001) (see Table 31). The low responder rates seen with oxycodone CR were in agreement with the BOCF and WOCF methods for the primary endpoint, as the responder rate analysis counts subjects who discontinue as non-responders and the conservative imputation methods use the baseline or worst pain score, thus having a similar effect on the analyses.

Table 31: Responder Rates Based on 30% and 50% Improvement in Average Pain Intensity (11-point NRS) (Pooled Tapentadol SR Phase III Studies, Integrated Summary of Efficacy: Intent to Treat Analysis Set)

	Placebo N = 991	Tapentadol PR N = 978	Oxycodone CR N = 999
Pain Intensity ≥30% Improved			
N (%)	345 (34.8)	404 (41.3)	270 (27.0)
Overall P-value [a]	<0.001		
P-value (minus placebo) [b]		0.003	<0.001 [c]
P-value (minus tapentadol PR) [b]			<0.001
Pain Intensity ≥50% Improved			
N (%)	233 (23.5)	294 (30.1)	208 (20.8)
Overall P-value [a]	<0.001		
P-value (versus placebo) [b]		<0.001	0.153
P-value (versus tapentadol PR) [b]			<0.001

Studies included are PAI-3008/KF11, PAI-3009/KF12 and PAI-3011/KF23; dose range for tapentadol PR: 100 mg to 250 mg twice daily; dose range for oxycodone CR: 20 mg to 50 mg twice daily

a) Generalized Cochran-Mantel-Haenszel test for general association controlling for study.

b) Pairwise comparison: Generalized Cochran-Mantel-Haenszel test for general association controlling for study.

c) Oxycodone CR signifantly worse than placebo.

N = number of subjects; NRS = numerical rating scale; PR = prolonged release; CR = controlled release

Patient's Global Impression of Change

At the endpoint, 56.7% of subjects in the tapentadol SR group, 49.8% of subjects in the oxycodone CR group and 37.5% of subjects in the placebo group reported "very much improved" or "much improved" in the overall status. There was a significant difference in the distribution of PGIC scores favouring tapentadol SR and oxycodone CR over placebo (p-values <0.001), and favouring tapentadol SR over oxycodone CR (p = 0.001).

Subgroup analyses

Average Pain Intensity Score (NRS, LOCF) by Baseline Pain Category

In the pooled efficacy analysis, most subjects (86.9%) had baseline pain intensity scores categorised as severe. Subjects on tapentadol SR had significantly greater reduction in average pain intensity (for both the change from baseline to the overall maintenance period and at Week 12 of the maintenance period primary endpoints) than those on placebo in both the severe (p <0.001) and moderate (p = 0.011) pain subsets. The overall improvement in pain scores (LS mean) was numerically greater in subjects with severe baseline pain than in those with moderate baseline pain for all three treatment groups (see Table 32). However, due to the placebo group showing the largest difference in pain reduction between the two subgroups, the LS mean differences versus placebo were greater in the moderate baseline pain group than in the severe baseline pain group for tapentadol SR and oxycodone CR.

Table 32: Pairwise Comparison of the Change From Baseline in Average Pain Intensity Scores (11-point NRS) by Baseline Pain Intensity Category (Pooled Tapentadol SR Phase III Studies, Integrated Summary of Efficacy: Intent to Treat Analysis Set)

Baseline pain category		Placebo	Tapentadol PR	Oxycodone CR
Overall Maintenance Period				
Moderate	N	143	119	123
	LS Mean	-1.4	-2.1	-1.8
	LS Mean Difference versus placebo (SE)		-0.7 (0.29)	-0.5 (0.27)
	95% CI (versus Placebo) [a]		(-1.31;-0.17)	(-0.99;0.06)
	P-value		0.011	0.085
	LS Mean Difference tapentadol PR versus oxycodone CR (SE)		0.3 (0.29)	
	95% CI [a]		(-0.30;0.85)	
	P-value		0.345	
Severe	N	845	854	873
	LS Mean	-2.3	-2.8	-2.7
	LS Mean Difference versus placebo (SE)		-0.5 (0.11)	-0.4 (0.11)
	95% CI (versus placebo) [a]		(-0.73;-0.31)	(-0.57;-0.15)
	P-value		<0.001	<0.001
	LS Mean Difference tapentadol PR versus oxycodone CR (SE)		0.2 (0.11)	
	95% CI [a]		(-0.05;0.37)	
	P-value		0.134	
Last Week of Maintenance				
Moderate	N	143	119	123
	LS Mean	-1.2	-2.2	-1.8
	LS Mean Difference versus placebo (SE)		-1.0 (0.31)	-0.5 (0.29)
	95% CI (versus placebo) [a]		(-1.60;-0.38)	(-1.11;0.03)
	P-value		0.002	0.066
	LS Mean Difference tapentadol PR versus oxycodone CR (SE)		0.5 (0.32)	
	95% CI [a]		(-0.17;1.08)	
	P-value		0.153	
Severe	N	845	854	873
	LS Mean	-2.4	-2.9	-2.7
	LS Mean Difference versus placebo (SE)		-0.6 (0.12)	-0.3 (0.12)
	95% CI (versus Placebo) [a]		(-0.79;-0.33)	(-0.56;-0.11)
	P-value		<0.001	0.004
	LS Mean Difference tapentadol PR versus oxycodone CR (SE)		0.2 (0.12)	
	95% CI [a]		(-0.00;0.45)	
	P-value		0.054	

Studies included are PAI-3008/KF11, PAI-3009/KF12 and PAI-3011/KF23; baseline pain intensity categories: moderate is defined as ≥4 and <6; severe is defined as ≥6; dose range for tapentadol PR: 100 mg to 250 mg twice daily; dose range for oxycodone CR: 20 mg to 50 mg twice daily.

a) Test for no difference between treatments from ANCOVA model with factor(s) treatment, pooled center and baseline pain intensity as covariate (type 3 SS) unadjusted p-value.

LOCF = last observation carried forward; LS = least square; SE = standard error; CI = confidence interval; NRS = numerical rating scale; ANCOVA = Analysis of covariance; N = number of subjects; PR = prolonged release; CR = controlled release.

In PAI-3015/KF36, the baseline pain intensity was measured at the end of the open-label titration period, after 3 weeks of treatment with tapentadol SR, and not at the beginning of the titration period as in PAI-3008/KF11, PAI- 3009/KF12 and PAI-3011/KF23. Only subjects who responded to tapentadol SR were randomised to placebo or tapentadol SR. This would have an impact on interpretation of results because it results in selective enrolment of subjects likely to respond.

After the tapentadol SR titration period, more subjects in both groups had mild baseline pain (103 subjects in the tapentadol SR group and 113 subjects in the placebo group) than moderate pain (65 subjects and 50 subjects, respectively) or severe baseline pain (22 subjects and 24 subjects, respectively). The difference in pain intensity between the tapentadol SR and placebo groups at Week 12 of the maintenance period was greater for subjects with mild baseline pain measured at the end of the open-label titration period (difference of –1.6) than for subjects with moderate or severe baseline pain (differences of –0.9 for moderate baseline pain and –0.6 for severe baseline pain). This might be due to a presumably greater initial improvement during the titration period in subjects with mild base pain and a subsequent greater aggravation in pain after withdrawal of active treatment.

Average Pain Intensity Score (NRS; LOCF) by Prior Opioid Use

The percentage of subjects previously treated with opioids differed largely between the studies (15.7% in PAI-3009/KF12, 32.4% in PAI-3008/KF11, and 53.4% in PAI-3011/KF23). Most prior opioids used were tramadol containing products in PAI-3009/KF12, and hydrocodone combination products in PAI-3008/KF11 and PAI-3011/KF23. However, there was a wide variability in the products used, their doses and the dosing regimens. Therefore, the effect of prior opioids on efficacy was only analysed by use and non-use.

There was no consistent pattern with regards to differences in effect size between subjects previously treated and not treated with opioids across the individual studies PAI-3008/KF11, PAI-3009/KF12, and PAI-3011/KF23. The larger sample size of the pooled efficacy analysis allows smaller effects, if present, to be detected. In the pooled efficacy analysis the raw mean changes in average pain scores from baseline to the overall maintenance period and to Week 12 of the maintenance period showed a slightly greater improvement in pain intensity for the tapentadol SR group compared to the placebo group in subjects who did not take prior opioids (difference in raw mean change from baseline to placebo of -0.6 for the overall maintenance period and -0.7 at Week 12) than for subjects who took prior opioids (-0.5 and -0.6, respectively). This small difference in response between subjects previously treated with opioids and those not previously treated with opioids is not considered to be of practical relevance for the clinical use of tapentadol SR.

In PAI-3015/KF36, there was no relevant difference in treatment effect between opioid-naïve and opioid-experienced subjects in each treatment group.

Average Pain Intensity Score (NRS; LOCF) by Sex, Age Group, and Race

The differences from placebo in raw mean changes from baseline were similar for male and female subjects treated with tapentadol SR, but were lower for female subjects (difference in raw mean change from baseline -0.2 for the overall maintenance period and of -0.3 at Week 12 of Maintenance) treated with oxycodone CR than for male subjects (-0.5 and -0.5, respectively). In PAI-3015/KF36, tapentadol SR showed greater improvement over placebo in pain intensity scores for females than males.

The differences from placebo for both tapentadol SR and oxycodone CR in raw mean changes from baseline were similar for subjects aged above 65 years (-0.6 for the overall maintenance period and -0.7 at Week 12 of Maintenance for tapentadol SR; -0.2 and -0.3, respectively, for oxycodone CR) than those aged below 65 years of age (-0.6 and -0.6; -0.4 and -0.3). In PAI-3015/KF36, differences between tapentadol SR and placebo were similar between subjects less than 65 years old and subjects 65 years or older.

There were no clinically relevant differences in treatment effect when results were analysed by race.

Meta-analysis comparison of tapentadol SR to oxycodone CR

The sponsor presented a meta-analysis comparing tapentadol SR to Oxycodone CR. The main efficacy and safety objectives of the supplemental differentiation meta-analysis were to establish a superior safety profile of tapentadol SR versus oxycodone CR with regards to constipation, and to establish the non-inferior efficacy of tapentadol SR versus oxycodone CR. The analyses included the PAI-3008/KF11, PAI-3009/KF12 and PAI-3011/KF23 studies. The statistical analysis plan for the meta-analysis was finalised prior to completion of the first Phase III clinical study in the tapentadol SR development program.

Event rates for gastrointestinal events, nausea, constipation, vomiting, nausea and/or vomiting were statistically significantly higher in the oxycodone CR group than in the tapentadol SR group ($p < 0.001$). A life-table analysis of the time to the first of these individual events confirmed the findings from the incidence analysis, as the time to event for nausea, constipation, vomiting, nausea and/or vomiting were all statistically significantly longer ($p < 0.001$) for tapentadol SR than for oxycodone CR. The analysis supported that the gastrointestinal tolerability profile of tapentadol SR is superior to that of oxycodone CR and the first objective was therefore satisfied.

Non-inferiority of tapentadol SR to oxycodone CR in terms of efficacy

Analysis demonstrated that tapentadol SR is non-inferior to oxycodone CR for both definitions of the primary endpoint (50% retention of oxycodone CR effect; $p < 0.001$) (see Table 33).

Table 33: Meta-analysis Comparison of Tapentadol SR versus Oxycodone CR for 3 Phase III Studies (Intent to Treat Analysis Set)

Endpoint	Estimate	Standard Error	Df	T Value	P-value [a]
Average Pain Score – Observed Cases					
Overall Maintenance Period	-0.2695	0.0946	2079	-2.8480	0.004
Last Week of Maintenance Period	-0.3556	0.1206	1490	-2.9489	0.003
Average Pain Score - LOCF					
Overall Maintenance Period	-0.3883	0.0873	2953	-4.4491	<0.001
Last Week of Maintenance Period	-0.4482	0.0936	2953	-4.7881	<0.001
Average Pain Score - BOCF					
Overall Maintenance Period	-0.4615	0.0835	2953	-5.5247	<0.001
Last Week of Maintenance Period	-0.4477	0.0869	2953	-5.1541	<0.001
Average Pain Score - WOCF					
Overall Maintenance Period	-0.5173	0.0966	2953	-5.3529	<0.001
Last Week of Maintenance Period	-0.4792	0.1016	2953	-4.7172	<0.001
Average Pain Score - Mod. BOCF					
Overall Maintenance Period	-0.5214	0.0869	2953	-5.9966	<0.001
Last Week of Maintenance Period	-0.5950	0.0946	2953	-6.2890	<0.001
Average Pain Score - PMI					
Overall Maintenance Period	-0.2269	0.0598	2953	-3.7918	<0.001
Last Week of Maintenance Period	-0.2530	0.0595	2953	-4.2533	<0.001

Studies included are PAI-3008/KF11, PAI-3009/KF12, and PAI-3011/KF23; dose range for tapentadol PR: 100 mg to 250 mg twice daily; dose range for oxycodone CR: 20 mg to 50 mg twice daily.

a) Test for no difference between treatments from ANCOVA model with factor(s) treatment, study and baseline pain intensity as covariate (type 3 SS) Contrast with Hauschke50 : Test for 50% retention of oxycodone to placebo effect.

LOCF = last observation carried forward; BOCF = baseline observation carried forward; WOCF = worst observation carried forward; PMI = placebo mean imputation; Mod BOCF = Modified baseline observation carried forward – an imputation based on patient global impression of change; DF = degrees of freedom; ANCOVA = Analysis of covariance; PR = prolonged release; CR = controlled release.

A prespecified condition for the non-inferiority analysis was that the treatment by study interaction was not significant at the p = 0.10 level. If there was a treatment by study interaction, then the treatment effects could be dissimilar across studies. For the LOCF analysis (ANCOVA), the interaction of treatment with study was significant for both endpoints (overall maintenance period: p = 0.005, Week 12 of maintenance period: p = 0.004). As the interaction effect was due to the difference in the results of the PAI- 3009/KF12 versus those of the PAI-3008/KF11 and PAI-3011/KF23 studies as prespecified, an analysis was performed with a reduced pooling of the latter 2 studies. In the reduced pooling set there was no study by treatment interaction for the primary LOCF analyses. The superiority of oxycodone CR to placebo was demonstrated in the reduced pooling set (see Table 34) for both endpoints using LOCF (p <0.001). Non-inferiority of tapentadol SR to oxycodone CR was demonstrated for all endpoints and imputations.

Table 34: Meta-analysis Comparison of Tapentadol SR versus Oxycodone CR for 2 Phase III Studies (Intent to Treat Analysis Set)

Endpoint	Estimate	Standard Error	Df	T Value	P-value [a]
Average Pain Score – Observed Cases					
Overall Maintenance Period	-0.3540	0.1185	1359	-2.9866	0.003
Last Week of Maintenance Period	-0.5194	0.1498	968	-3.4672	<0.001
Average Pain Score - LOCF					
Overall Maintenance Period	-0.4150	0.1090	1968	-3.8092	<0.001
Last Week of Maintenance Period	-0.4811	0.1155	1968	-4.1662	<0.001
Average Pain Score - BOCF					
Overall Maintenance Period	-0.5417	0.1047	1968	-5.1733	<0.001
Last Week of Maintenance Period	-0.5185	0.1071	1968	-4.8410	<0.001
Average Pain Score - WOCF					
Overall Maintenance Period	-0.5754	0.1211	1968	-4.7532	<0.001
Last Week of Maintenance Period	-0.5244	0.1254	1968	-4.1817	<0.001
Pain Score - Mod. BOCF					
Overall Maintenance Period	-0.5857	0.1090	1968	-5.3736	<0.001
Last Week of Maintenance Period	-0.6575	0.1168	1968	-5.6295	<0.001
Average Pain Score - PMI					
Overall Maintenance Period	-0.2827	0.0738	1968	-3.8308	<0.001
Last Week of Maintenance Period	-0.3170	0.0725	1968	-4.3732	<0.001

Studies included are PAI-3008/KF11 and PAI-3011/KF23; dose range for tapentadol PR: 100 mg to 250 mg twice daily; dose range for oxycodone CR: 20 mg to 50 mg twice daily.

a) Test for no difference between treatments from ANCOVA model with factor(s) treatment, study and baseline pain intensity as covariate (type 3 SS) contrast with Hauschke50: Test for 50% retention of oxycodone to placebo effect

LOCF = last observation carried forward; BOCF = baseline observation carried forward; WOCF = worst observation carried forward; PMI = placebo mean imputation; Mod BOCF = Modified baseline observation carried forward – an imputation based on patient global impression of change; DF = degrees of freedom; ANCOVA = Analysis of covariance; PR = prolonged release; CR = controlled release.

Analysis of clinical information relevant to dosing recommendations

Pooled data from studies PAI-3008/KF11, PAI-3009/KF12, and PAI-3011/KF23 were used. The efficacy results were similar across the entire dose range of 100 to 250 mg twice daily (see Table 35 below).

Table 35: Mean Raw Changes from Baseline Pain (11-Point NRS) at Week 12 of Maintenance in Observed Cases per Dose Category (Pooled Tapentadol SR Phase III Studies, Intent to Treat Analysis Set; Integrated Summary of Efficacy)

Dose category Twice daily dosing Tapentadol PR/ Oxycodone CR	Tapentadol PR			Oxycodone CR		
	N	Mean baseline pain	Mean raw change from baseline at Week 12 of maintenance	N	Mean baseline pain	Mean raw change from baseline at Week 12 of maintenance
100 to <150 mg/ 20 to <30 mg	146	7.1	-4.0	119	7.2	-4.0
150 to <200 mg/ 30 to <40 mg	99	7.1	-3.8	84	7.4	-3.9
200 to <250 mg/ 40 to <50 mg	113	7.3	-3.7	80	7.4	-3.8
≥250 mg/ ≥50 mg	186	7.7	-3.4	92	7.7	-3.2

Studies included are PAI-3008/KF11, PAI-3009/KF12 and PAI-3011/KF23

N = number of subjects; NRS = numerical rating scale; PR = prolonged release; CR = controlled release

Persistence of efficacy and/or tolerance effects

There was no evidence for tolerance to tapentadol SR, either over 3 months (Studies PAI-3008/KF11, PAI-3009/KF12, PAI-3011/KF23 and PAI-3015/KF36) or over one year (Study PAI-3007/KF24).

The long-term safety and maintenance of pain relief beyond 12 weeks and lasting at least up to one year study were examined in study PAI-3007/KF24. An analysis of average mean total daily dose and mean pain score in subjects who completed one year of treatment (N = 412 for tapentadol SR and N = 78 for oxycodone CR) did not indicate development of tolerance to either tapentadol SR or oxycodone CR. The average mean total daily dose in both treatment groups increased for approximately 4 weeks but was then maintained until the end of the study, at approximately 375 mg for tapentadol SR and 70 mg for oxycodone CR. This was associated with a relatively stable pain intensity score.

Product information (PI) with respect to efficacy

The clinical evaluator concluded that the data submitted for evaluation did not adequately support approval of tapentadol SR for treatment of moderate to severe pain.

Clinical Evaluator's overall conclusions on clinical efficacy

Pivotal efficacy data that assessed tapentadol SR (100 mg to 250 mg twice daily) for the treatment of moderate to severe chronic pain were provided in three representative pain conditions (chronic painful osteoarthritis, chronic low back pain and painful diabetic peripheral neuropathy). The majority of subjects (≥80%) had severe pain at baseline, therefore the body of data in patients with moderate pain is not substantial.

In ***Study PAI-3008/KF/11,*** in terms of the primary efficacy endpoint, the study demonstrated superiority of tapentadol SR over placebo in change from baseline of the average pain intensity at Week 12 of the maintenance period or over the 12-week maintenance period using LOCF imputation. Tapentadol also showed statistically significant differences compared to placebo on PMI and modified BOCF imputations for both Week 12 of the maintenance period and the overall maintenance period, and demonstrated a trend towards statistical significance by using BOCF imputation for the overall maintenance period (p=0.0502). Statistical significance was not reached for the BOCF imputation at Week 12 of the maintenance period, or for WOCF for either period.

In relation to responder rates, the difference in distributions of responder rates was not statistically significant between the tapentadol SR and placebo groups. In addition, for subjects with baseline pain intensity scores categorised as moderate, comparison of the average pain intensity scores for

tapentadol SR and placebo was not statistically significant in either the last week of the maintenance period (p=0.181) or the overall maintenance period (p=0.463).

Oxycodone was statistically significantly better than placebo on the primary efficacy endpoint for the overall maintenance period using LOCF and PMI imputation, demonstrating assay sensitivity. However it was not statistically significantly superior at Week 12. The more conservative imputation methods (modified BOCF, BOCF and WOCF) resulted in pain intensity outcomes that were statistically significantly worse than placebo. These findings are a reflection of the large number of oxycodone CR-treated subjects who discontinued the study. The fact that the oxycodone comparator showed poor efficacy in the study raises concerns about the validity of the study.

The secondary efficacy measure, responder analysis, indicated that the proportion of subjects with 50% improvement in the tapentadol SR group was statistically significantly greater (p=0.027) than the response in the placebo group. The percent of tapentadol SR subjects with 30% improvement in tapentadol SR was not statistically significant (p=0.058). Oxycodone CR treatment was statistically significantly worse for all measures of responders and this once again raises concerns about interpretation and validity of the results**.**

Importantly, for subjects with baseline pain intensity scores categorised as moderate, comparison of the average pain intensity scores for tapentadol SR and placebo was not statistically significant in either the last week of the maintenance period (p=0.181) or the overall maintenance period (p=0.463).

Overall the clinical evaluator considered that this study did not provide convincing evidence of efficacy of tapentadol SR. It is of major concern that oxycodone was shown to have such poor efficacy in this study. This raises concerns about the validity of the study results. In addition, results for responder rates and exploratory efficacy analyses did not consistently support efficacy of tapentadol SR. It is notable when examining the efficacy results when analysed for baseline pain severity, the difference between tapentadol SR and placebo did not reach statistical significance. These results do not support use of tapentadol SR for treatment of severe chronic pain and for moderate pain.

Study PAI-3009/KF12 did not achieve its primary efficacy endpoint to demonstrate superiority of tapentadol SR over placebo in the change from baseline of the average pain intensity at Week 12 of the maintenance period or over the 12-week maintenance period using LOCF imputation. Statistical significance was also not reached for the primary endpoint when applying more conservative imputation methods, that is, BOCF, WOCF, modified BOCF and PMI.

The study did not demonstrate assay sensitivity, as the active comparator oxycodone CR did not demonstrate superiority over placebo for the primary efficacy endpoint. There were no consistent, statistically significant differences between active treatment and placebo for the secondary efficacy measures or the exploratory analyses. Overall, the results from the study do not support efficacy of tapentadol SR in the treatment of moderate or severe pain**.**

Study KF5503/23 did demonstrate efficacy of tapentadol SR across some of the primary and secondary variables. The study achieved its primary efficacy endpoint of change from baseline of the average pain intensity at Week 12 or over the 12-week maintenance period using LOCF imputation. The efficacy results were confirmed by achieving statistically significant differences for the primary comparison of tapentadol SR group versus the placebo group in all of the more conservative imputation methods (BOCF, WOCF, modified BOCF and PMI).

Oxycodone CR was statistically significantly better than placebo on the primary efficacy endpoint for the overall maintenance period and over the 12-week maintenance period in all imputations, except at Week 12 of the maintenance period when the BOCF and WOCF imputation methods were applied.

The secondary efficacy measure, responder analysis, indicated that the proportions of subjects with 30% and 50% improvement (with prematurely discontinued subjects considered not improved) in the tapentadol SR group were statistically significantly greater than the response in the placebo group. The comparisons of oxycodone CR and placebo were not statistically significant. Once again, the fact that the comparator performed poorly in this measure raises concerns about the validity of the overall results.

In both active-treatment groups, subjects with moderate baseline pain improved more, on average, than subjects with severe baseline pain. In the tapentadol SR group, subjects with no prior opioid use had greater improvements from baseline in pain scores than subjects with prior opioid use. Similar results were not observed for the oxycodone CR group. In the oxycodone CR group, subjects with prior opioid use had greater improvements from baseline in pain scores than subjects with no prior opioid use.

When examining the efficacy results analysed for baseline pain severity, the difference between tapentadol SR and placebo did reach statistical significance. However, only 11.5% of the patients had moderate pain, therefore the number of patients analysed for this factor is small. The efficacy results overall are not persuasive for treatment of moderate pain.

Overall the clinical evaluator considered that the efficacy data submitted for evaluation did not adequately support efficacy of tapentadol SR in the treatment of moderate or severe pain.

Safety

Tapentadol PR

Introduction

Safety data from four completed Phase II double-blind studies, five completed Phase III double-blind studies and one completed Phase III open-label study performed with the tapentadol SR formulation were submitted. The safety data from the Phase II/ III Multiple-dose Double-blind Safety Analysis Set and from the long-term, open-label, Phase III tapentadol SR safety study (PAI-3007/KF24) will be discussed in this report.

Patient exposure

Phase II/ III Multiple-dose Double-blind Safety Analysis Set

In the Pooled All Phase II/ III Tapentadol SR Studies grouping, 1,284 subjects took tapentadol SR for more than 12 weeks, 494 of these subjects took tapentadol SR for more than 24 weeks, and 243 of these subjects took tapentadol SR for more than 52 weeks (see Table 36). The mean treatment duration (defined as the number of days on study drug) and the mean total duration (defined as the number of days on study drug including intermediate days with no drug intake) were similar in the "all" tapentadol SR group (86.2 days and 86.6 days, respectively). As the treatment duration and total duration are nearly the same, the discussion in the following section focuses on total duration. Subjects in the "all" tapentadol SR group remained on treatment longer than subjects in the "all" oxycodone CR group (mean total duration: 86.6 days and 65.0 days, respectively).

Table 36: Extent of Exposure – Duration of Treatment (All Studies) (Tapentadol PR Formulation Phase II/ III Studies Integrated Summary of Safety: Safety Analysis Set)

Summarized Period: Treatment	Placebo (N = 1497)	Placebo (Post Tap PR) (N = 193)	All Tap PR (N = 3610 [a])	All Oxy CR (N = 1472)	All Tra PR (N = 249)
Total Duration, Days					
n	1497	193	3610	1472	249
Category, n (%)					
>0 to ≤ 4 Weeks	519 (34.7)	38 (19.7)	1465 (40.6)	674 (45.8)	180 (72.3)
>4 to ≤ 8 Weeks	333 (22.2)	14 (7.3)	768 (21.3)	236 (16.0)	69 (27.7)
>8 to ≤ 12 Weeks	35 (2.3)	66 (34.2)	93 (2.6)	51 (3.5)	0
>12 to ≤ 16 Weeks	560 (37.4)	75 (38.9)	688 (19.1)	375 (25.5)	0
>16 to ≤ 20 Weeks	50 (3.3)	0	81 (2.2)	37 (2.5)	0
>20 to ≤ 24 Weeks	0	0	21 (0.6)	5 (0.3)	0
>24 to ≤ 28 Weeks	0	0	13 (0.4)	2 (0.1)	0
>28 to ≤ 32 Weeks	0	0	14 (0.4)	4 (0.3)	0
>32 to ≤ 36 Weeks	0	0	12 (0.3)	3 (0.2)	0
>36 to ≤ 40 Weeks	0	0	15 (0.4)	2 (0.1)	0
>40 to ≤ 44 Weeks	0	0	10 (0.3)	2 (0.1)	0
>44 to ≤ 48 Weeks	0	0	9 (0.2)	1 (0.1)	0
>48 to ≤ 52 Weeks	0	0	178 (4.9)	29 (2.0)	0
>52 Weeks	0	0	243 (6.7)	51 (3.5)	0
Mean (SD)	58.3 (41.69)	66.9 (30.08)	86.6 (111.15)	65.0 (85.28)	22.6 (9.99)
Median	31.0	84.0	29.0	29.0	28.0
Range	(1;129)	(1;105)	(1;388)	(1;385)	(1;39)

Includes studies: KF5503/09, KF5503/10, PAI-2001/KF19, PAI-2002/KF20, PAI-3008/KF11, PAI-3009/KF12, PAI-3011/KF23, PAI-3015/KF36, and PAI-3007/KF24

For PAI-3015/KF36, table summarizes exposure to study drug, excluding supplemental doses of tapentadol PR. Exposure to study drug (including supplemental tapentadol PR) is summarized in study-level output (Mod5.3.5.1\KF5503/36\Sec4.7.3).

a In PAI-2002/KF20, 3 subjects took tapentadol PR, but no details on the exact dose are available. These subjects were excluded from the exposure analysis (Subject 302604; Subject 302612, and Subject 302619).

N = total number of subjects; n = number of subjects per category; Oxy = Oxycodone, PR = prolonged release; SD = standard deviation, Tap = Tapentadol, Tra = Tramadol

Exposure to tapentadol SR was very similar when comparing treatment duration (days on drug only) and total duration (days on and off drug, including days with no drug intake), indicating a good compliance with study drug administration. In the "all" tapentadol SR group, the average of the mean total daily dose (TDD) (the mean of the individual mean TDDs for all subjects) was 260.8 mg and the median mean TDD (the median of the individual mean TDDs for all subjects) was 260.5 mg based on the number of days on study drug. Based on the number of days on and off study drug the average of the mean TDD was 259.0 mg and the median mean TDD was 257.3 mg.

Long-Term Open-Label Phase III Tapentadol SR Safety Study (PAI-3007/KF24)

In the 52-week, open-label tapentadol SR study (PAI-3007/KF24), the dose of study drug was to be titrated to the subject's individually determined optimal dose during a 1-week titration period. Thereafter, the dose was to remain constant. However, controlled dose adjustments were permitted. Overall, during the 52-week treatment period, the average of the mean treatment duration was 210.9 days in the tapentadol SR group; 487 subjects took tapentadol SR for at least 6 months and 227 of these subjects took tapentadol SR for 52 weeks, thus fulfilling the requirements of ICH E1 (CPMP/ICH/137/9 1995[34]). Subjects in the tapentadol SR group remained on treatment longer than

[34] Note for guidance on structure and content of clinical study reports. http://www.tga.gov.au/docs/pdf/euguide/ich/013795en.pdf

subjects in the oxycodone CR group (median of 268.0 days and 59.0 days, respectively). Table 37 summarises duration of exposure for PAI-3007/KF24.

Table 37: Duration of Exposure to Study Medication (Study PAI-3007; KF24: Safety Analysis Set)

	Tapentadol PR	Oxycodone CR
Treatment duration, days		
N	894	224
Category, n (%)		
>0 - <3 months	337 (38)	119 (53)
≥3 - <6 months	70 (8)	13 (6)
≥6 - <9 months	42 (5)	9 (4)
≥9 - <12 months	218 (24)	39 (17)
≥1 year	227 (25)	44 (20)
Mean (SD)	210.9 (157.43)	160.6 (163.09)
Median	268.0	59.0
Range	(1;385)	(1;384)

CR = controlled release, N = total number of subjects, n = number of subjects per category, PR = prolonged release; SD = standard deviation

In the tapentadol SR group, the average of the mean TDD was 326.7 mg and the median modal TDD was 400.0 mg. The median modal total daily tapentadol SR dose achieved in the long-term study (400.0 mg) was the same as that achieved during the double-blind maintenance period in the Double-Blind Controlled Dose Adjustment Phase III Tapentadol SR Studies grouping (400.0 mg). In the oxycodone CR group, the average of the mean TDD was 51.5 mg and the median modal TDD was 40.0 mg.

The mean modal and average mean TDD were stable throughout the duration of the 52 week study (see Table 38). In this long-term study, the stability of the TDDs coupled with the stability of the analgesic scores throughout the study supports that there was no acquired tolerance to the tested dose ranges in the 52 week duration of the study for tapentadol SR and oxycodone CR in this population.

Table 38: Extent of Exposure to Study Medication Over Time (Study PAI-3007/KF/24: Safety Analysis Set)

	Tapentadol PR (N = 894)	Oxycodone CR (N = 224)
Week Period: Week 1-4		
Mean dose (days on/off drug)		
n	894	224
Mean (SD)	259.2 (73.98)	42.3 (16.96)
Mode dose (days on/off drug)		
n	878	212
Mean (SD)	297.89 (106.828)	47.92 (22.675)
Week Period: Week 9-12		
Mean dose (days on/off drug)		
n	602	114
Mean (SD)	374.9 (111.30)	67.7 (24.73)
Mode dose (days on/off drug)		
n	592	113
Mean (SD)	379.14 (110.642)	68.32 (24.308)
Week Period: Week 21-24		
Mean dose (days on/off drug)		
n	515	99
Mean (SD)	388.4 (112.08)	72.7 (25.22)
Mode dose (days on/off drug)		
n	509	97
Mean (SD)	391.36 (111.733)	73.40 (24.786)
Week Period: Week 33-36		
Mean dose (days on/off drug)		
n	467	88
Mean (SD)	394.9 (111.33)	74.5 (25.01)
Mode dose (days on/off drug)		
n	466	88
Mean (SD)	396.14 (111.230)	74.77 (25.279)
Week Period: Week 49-52		
Mean dose (days on/off drug)		
n	421	80
Mean (SD)	392.5 (113.33)	74.2 (26.65)
Mode dose (days on/off drug)		
n	421	80
Mean (SD)	395.96 (114.675)	74.25 (25.890)

CR = controlled release, N = total number of subjects, n = number of subjects per category, PR = prolonged release; SD = standard deviation;

Adverse events

Pooled All Phase II/ III Tapentadol SR Studies

A summary of the incidence of treatment-emergent adverse events (TEAEs) in at least 5% of subjects in any treatment group in the Pooled All Phase II/ III Tapentadol SR Studies grouping is provided in Table 39.

Table 39: Incidence of TEAEs by System Organ Class (SOC) and Preferred Term (PT) in at Least 5% of Subjects in Any Pooled Treatment Group (All Studies) (Tapentadol SR Formulation Phase II/ III Studies Integrated Summary of Safety: Safety Analysis Set)

System Organ Class Preferred Term	Placebo (N = 1498) n (%)	Placebo (Post Tap PR) (N = 193) n (%)	All Tap PR (N = 3613) n (%)	All Oxy CR (N = 1472) n (%)	All Tra PR (N = 249) n (%)
Total no. subjects with TEAEs	**817 (54.5)**	**100 (51.8)**	**2589 (71.7)**	**1271 (86.3)**	**163 (65.5)**
Gastrointestinal disorders	**370 (24.7)**	**27 (14.0)**	**1464 (40.5)**	**952 (64.7)**	**93 (37.3)**
Nausea	128 (8.5)	12 (6.2)	704 (19.5)	531 (36.1)	55 (22.1)
Constipation	85 (5.7)	2 (1.0)	493 (13.6)	464 (31.5)	29 (11.6)
Vomiting	44 (2.9)	2 (1.0)	269 (7.4)	292 (19.8)	34 (13.7)
Dry mouth	26 (1.7)	1 (0.5)	217 (6.0)	66 (4.5)	5 (2.0)
Diarrhoea	78 (5.2)	8 (4.1)	199 (5.5)	78 (5.3)	8 (3.2)
Nervous system disorders	**288 (19.2)**	**27 (14.0)**	**1308 (36.2)**	**662 (45.0)**	**65 (26.1)**
Dizziness	77 (5.1)	3 (1.6)	495 (13.7)	291 (19.8)	25 (10.0)
Headache	170 (11.3)	10 (5.2)	427 (11.8)	174 (11.8)	23 (9.2)
Somnolence	44 (2.9)	0	408 (11.3)	240 (16.3)	20 (8.0)
General disorders and administration site conditions	**138 (9.2)**	**19 (9.8)**	**583 (16.1)**	**290 (19.7)**	**46 (18.5)**
Fatigue	48 (3.2)	2 (1.0)	253 (7.0)	139 (9.4)	14 (5.6)
Skin and subcutaneous tissue disorders	**80 (5.3)**	**15 (7.8)**	**481 (13.3)**	**332 (22.6)**	**40 (16.1)**
Pruritus	20 (1.3)	0	176 (4.9)	183 (12.4)	10 (4.0)
Hyperhidrosis	16 (1.1)	6 (3.1)	160 (4.4)	75 (5.1)	27 (10.8)
Musculoskeletal and connective tissue disorders	**167 (11.1)**	**34 (17.6)**	**395 (10.9)**	**132 (9.0)**	**17 (6.8)**
Myalgia	9 (0.6)	14 (7.3)	42 (1.2)	10 (0.7)	1 (0.4)
Bone pain	2 (0.1)	10 (5.2)	16 (0.4)	1 (0.1)	2 (0.8)
Ear and labyrinth disorders	**23 (1.5)**	**2 (1.0)**	**109 (3.0)**	**49 (3.3)**	**19 (7.6)**
Vertigo	12 (0.8)	1 (0.5)	68 (1.9)	31 (2.1)	18 (7.2)

Adverse events were coded using MedDRA version 11

Placebo (Post Tap PR) indicates data relating to subjects in PAI-3015/KF36 who received placebo after dosing with tapentadol PR.

Note: Percentages calculated using the number of subjects in each treatment group as a denominator.

CR = controlled release, N = total number of subjects; n = number of subjects per category, Oxy = Oxycodone, PR = prolonged-release, Tap = Tapentadol, Tra = Tramadol.

In the Pooled All Phase II/ III Tapentadol SR Studies grouping, the overall percentage of subjects with at least one TEAE in the "all" tapentadol SR group (71.7%) was higher than the placebo (54.5%) and placebo-post tapentadol SR (51.8%) groups, but lower than the "all" oxycodone CR group (86.3%). The treatment group labelled placebo-post tapentadol SR identifies subjects in Study PAI-3015/KF36 who received placebo in the double-blind phase after dosing with tapentadol SR in the open-label phase of this trial. Data of these subjects obtained during tapentadol treatment are included in the “all” tapentadol SR group. The most commonly reported TEAEs in the "all" tapentadol SR group were those affecting the gastrointestinal disorders SOC and nervous system disorders SOC. The percentage of subjects with TEAEs affecting either the gastrointestinal disorders SOC or the nervous system disorders SOC was higher in the “all” tapentadol SR group than in the placebo group and lower than in the “all” oxycodone CR group. The most commonly

reported TEAEs (incidence ≥10%) in the “all” tapentadol SR group were nausea, dizziness, constipation, headache, and somnolence.

In the Pooled All Phase II/ III Tapentadol SR Studies grouping, the overall percentage of subjects with TEAEs considered to be related to study drug (TEAEs reported as certain, possible, probable/likely related to study drug by the investigator) in the "all" tapentadol SR group (55.1%) was higher than the placebo (30.6%), and placebo-post tapentadol SR (24.4%) groups, but lower than the "all" oxycodone CR group (76.3%). In the active treatment groups, TEAEs affecting the gastrointestinal disorders SOC and nervous system disorders SOC were considered related to study drug at the highest frequency (34.5% and 29.3%, respectively, in the "all" tapentadol SR group; and 59.9% and 39.9%, respectively, in the "all" oxycodone CR group).

The majority of subjects in all treatment groups in the Pooled All Phase II/ III Tapentadol SR Studies grouping experienced TEAEs that were mild to moderate as worst TEAE intensity. In the SOCs considered most relevant (SOC of selected TEAEs), that is, gastrointestinal, nervous system, and skin and subcutaneous disorders, less subjects reported severe adverse events in the “all” tapentadol SR group than in the “all” oxycodone CR group. In the "all" tapentadol SR group, the most frequently reported severe TEAEs were vomiting (39/269 subjects), headache (41/427 subjects) and nausea (61/704 subjects). In the "all" oxycodone CR group, the most frequently reported severe TEAEs were constipation (42/464 subjects), somnolence (24/240 subjects) and vomiting (37/292 subjects). No differences in the safety profile were observed in age or gender subgroups.

Adverse Events with Prolonged Treatment

Study PAI-3007/KF24 investigated subjects for up to one year using an open-label design and a 4:1 randomisation to either tapentadol SR (dose range 100 mg to 250 mg) or oxycodone CR (dose range 20 mg to 50 mg) administered by controlled adjustment of dose. Overall, tapentadol SR was well tolerated across the studied dose range. The overall incidence of TEAEs was lower in the tapentadol SR group (85.7%) than in the oxycodone CR group (90.6%). The most frequent treatment emergent adverse events were constipation (22.6% versus 38.6%), nausea (18.1% versus 33.2%), dizziness (14.8% versus 19.3%), somnolence (14.9% versus 11.2%), headache (13.3% versus 7.6%), vomiting (7.0% versus 13.5%), fatigue (9.7 versus 10.3%), pruritus (5.4% versus 10.3%), and insomnia (6.7% versus 4.0%).

The incidences for the common TEAEs were well in line with the ones observed in studies of 15 weeks duration, and the lower frequency, especially for gastrointestinal events, compared to oxycodone CR was seen.

Meta-analysis Comparison of Tapentadol SR to Oxycodone CR

The sponsor presented a meta-analysis comparing tapentadol SR to Oxycodone CR. The main safety objectives of the supplemental differentiation meta-analysis were to establish a superior safety profile of tapentadol SR versus oxycodone CR with regard to constipation. The analyses included the PAI-3008/KF11, PAI-3009/KF12, and PAI-3011/KF23 studies.

A gastrointestinal TEAE occurred in 42.8% of tapentadol SR subjects and in 65.6% of oxycodone CR subjects ($p<0.001$). The incidence of nausea, constipation, vomiting, nausea and/or vomiting were statistically significantly higher in the oxycodone CR group ($p<0.001$).

Serious adverse events and deaths

In the completed Phase II/ III studies and PAI-3007/KF24 there were no deaths among subjects who received tapentadol SR.

Phase II/ III Tapentadol SR Completed Studies

In the Pooled All Phase II/ III Tapentadol SR Studies grouping, the percentage of subject with serious adverse events from the time of the first dose to within 30 days after last dose of study drug was low in all treatment groups: "all" tapentadol SR (2.5%; 89/3613), placebo (1.0%; 15/1498), placebo (post-tapentadol SR) (1.6%; 3/193) and "all" oxycodone CR (3.2%; 47/1472) groups. No single serious adverse event (PT) occurred at a frequency greater than 0.1% in the "all" tapentadol SR, placebo or "all" oxycodone CR groups. The most commonly reported serious adverse events in the "all" tapentadol SR and "all" oxycodone CR groups were those affecting the cardiac disorders SOC (0.4% and 0.5%, respectively), gastrointestinal disorders SOC (0.3% and 0.6%, respectively) and infections and infestations SOC (0.5% and 0.3%, respectively).

Laboratory findings, vital signs, physical findings, ECGs

Pooled All Phase II/ III Tapentadol PR

There were no clinically relevant changes from baseline to endpoint in mean values for laboratory parameters for any treatment group in the Pooled All Phase II/ III Tapentadol SR Studies grouping. The percentage of subjects with an abnormal laboratory result at any time during treatment and with a normal baseline value was low (<1% in most laboratory texts) and similar between the placebo and "all" tapentadol SR treatment groups.

The percentage of subjects with liver injury or liver abnormalities at any time during the post-baseline treatment period was 18% throughout all treatment groups, considering subjects with normal or abnormal values at baseline. In subjects with normal values at baseline, the percentage of subjects with liver injury or liver abnormalities was similar for the placebo, “all” tapentadol SR and “all” oxycodone CR treatment groups (8%, 9%, and 9%, respectively). Most of these cases constituted unspecific liver abnormalities, and <1% were cases of liver injury (5 subjects in the “all” tapentadol group, 2 subjects in the “all” oxycodone CR group, and 3 subjects in the placebo group).

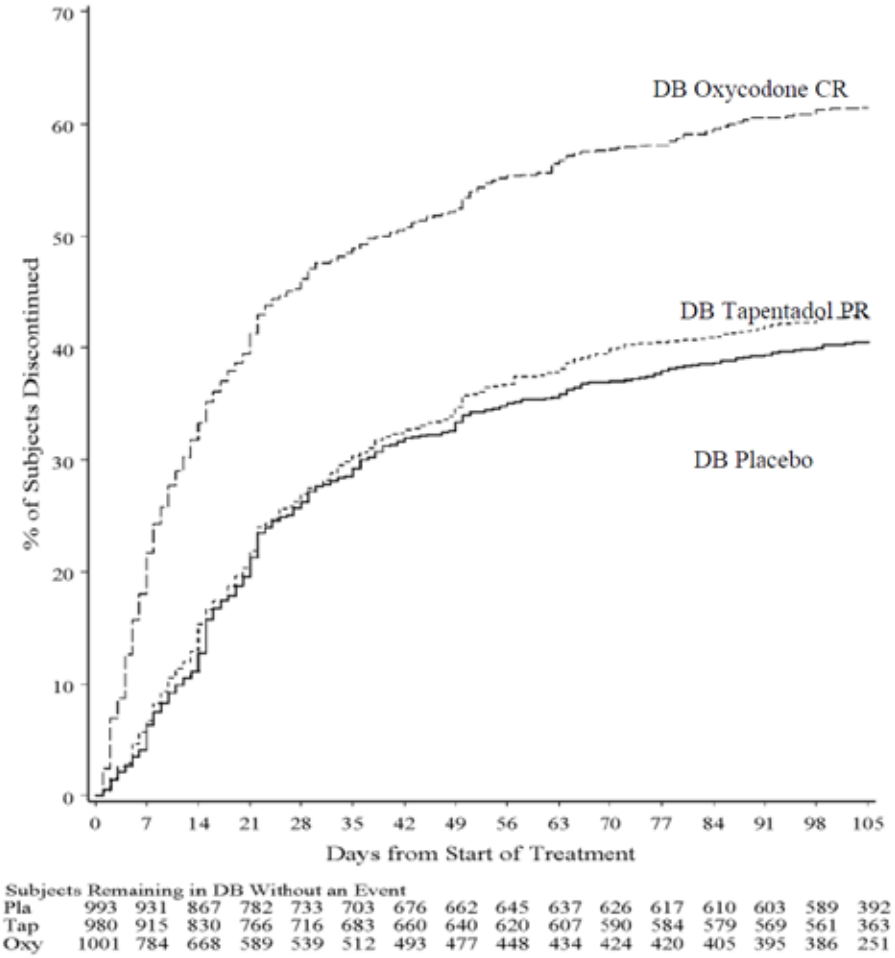
There were no clinically relevant changes from baseline in mean values for pulse rate, systolic or diastolic blood pressure, respiratory rate or ECGs for any of the treatment groups at endpoint in the Pooled All Phase II/ III Tapentadol SR Studies grouping.

Discontinuation due to adverse events

In the pooled Phase II/ III multiple dose studies, 18.1% of subjects on tapentadol SR, 37.4% of subjects on oxycodone CR and 6.3% of subjects on placebo discontinued due to TEAEs. In the tapentadol SR and oxycodone CR groups, discontinuation was primarily because of gastrointestinal events (7.9% versus 23.7%), nervous system disorders (7.1% versus 16%), skin disorders (1.6% versus 6.0%), and general disorders (2.6% versus 5.6%). Multiple reasons for discontinuation were possible.

Discontinuations were analysed for the double-blind period of the Phase III OA/lower back pain studies (KF5503/11, KF5503/12 and KF5503/23). In these double-blind, placebo-controlled Phase III efficacy studies with controlled dose adjustment, the time to discontinuation due to TEAEs was longest in the placebo group, and shortest in the oxycodone CR (see Figure 12). The time to discontinuation in the tapentadol SR group was slightly shorter than in the placebo group. Most discontinuations due to treatment emergent adverse events occurred in the titration period.

Figure 12: Kaplan-Meier Plot of Time to Discontinuation due an Adverse Event (Pooled Tapentadol SR Phase III Studies, Safety Analysis Set)



No. Subjects Remaining in DB Without an Event

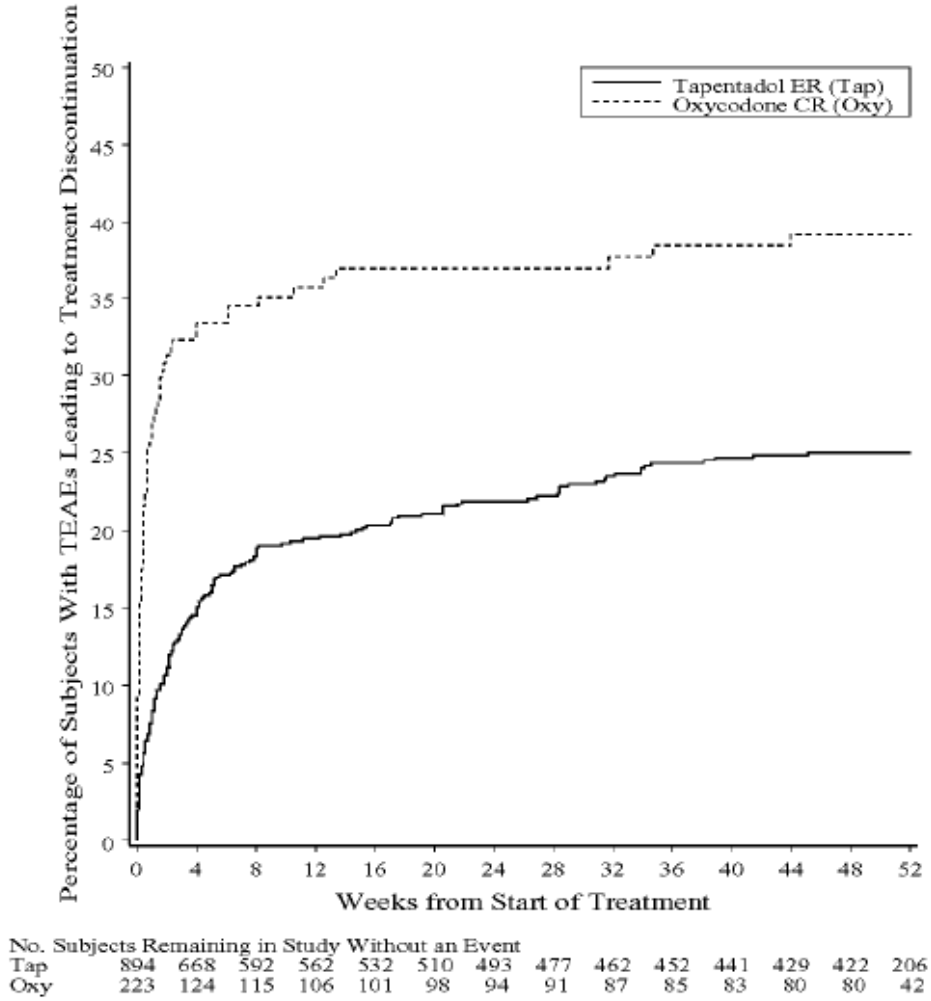
DB Pla	993	931	867	782	733	703	676	662	645	637	626	617	610	603	589	392
DB Tap	980	915	830	766	716	683	660	640	620	607	590	584	579	569	561	363
DB Oxy	1001	784	668	589	539	512	493	477	448	434	424	420	405	395	386	251

DB = double-blind; Oxy = oxycodone, Pla = placebo; Tap = tapentadol; No. = number
Studies included: PAI-3008/KF11, PAI-3009/KF12, PAI-3011/KF23

In KF5503/24 a higher percentage of subjects with TEAEs leading to discontinuation was observed in the oxycodone CR group (82 subjects, 36.8%) than in the tapentadol SR group (198 subjects, 22.1%). The most common TEAEs that led to treatment discontinuation were nausea, vomiting, constipation, dizziness, fatigue, and somnolence, all of which were reported in a higher percentage of subjects in the oxycodone CR group.

Figure 13 illustrates the time to treatment discontinuation due to TEAEs. The median time to treatment discontinuation due to TEAEs could not be calculated for either treatment group because less than 50% of subjects discontinued treatment due to TEAEs. Overall, there was a statistically significant difference between groups ($p<0.001$) in the time to treatment discontinuation due to TEAEs.

Figure 13: Time to Onset of TEAEs Leading to Discontinuation (Study R331333-PAI-3007/KF5503/24: Safety Analysis Set)



Tapentadol ER= Tapentadol PR=Tapentadol SR

Other safety aspects

The incidence of adverse drug reactions related to the concept of respiratory depression (aggregate preferred term of "respiratory depression") for tapentadol SR was only reported in 2 of 3613 subjects (0.1%). Both subjects were in the long term safety trial (PAI- 3007\KF24).

In the pooled Phase II/ III multiple dose studies there were 635 subjects in the tapentadol SR group that were assessed between Day 2 and Day 4 after discontinuing study medication; 11.8% of subjects had a Clinical Opiate Withdrawal Scale score category of mild withdrawal and 2.0% with a score category of moderate withdrawal. Similar frequencies were seen for the 244 subjects assessed in the oxycodone CR group (mild: 13.5%, moderate: 1.6%). Assessments on Day 5 or later were available for 1145 subjects treated with tapentadol SR (mild: 5.1%, moderate: 0.3%) and for 447 subjects having received oxycodone CR (mild: 10.7%; moderate: 2.0%).

Subjects were also assessed using the Subjective Opiate Withdrawal Scale (SOWS) in the Phase III controlled dose adjustment studies (PAI-3008/KF11, PAI-3011/KF23) performed in the US and in subjects recruited in the US for study PAI-3007/KF24. For subjects who had assessment between two and four days after the last study drug intake, the mean total SOWS score ranged from 4.9 to 5.0 for placebo, 7.5 to 9.1 for tapentadol SR and 9.6 to 10.8 for oxycodone CR. For subjects who had assessments 5 days or more after discontinuation from the study drug, the mean total SOWS was 5.9 for placebo, 6.7 for tapentadol SR and 8.5 for oxycodone CR. These results are consistent

with the data from the Clinical Opiate Withdrawal Scale and suggest that subjects stopping tapentadol SR abruptly are at low risk of having a clinically relevant withdrawal syndrome.

The use of a total daily dose of tapentadol SR above 500 mg was not formally studied. Management of an overdose should include standard measures for overdose with substances having mu-opioid receptor agonist activity, and symptomatic treatment.

Post marketing experience

No post-marketing data were submitted for evaluation

Evaluator's overall conclusions on clinical safety

The TEAEs observed with tapentadol SR treatment in the investigated dose range are qualitatively similar to those of a centrally acting analgesic. The most common (>10%) treatment emergent adverse events were those listed in the SOCs gastrointestinal and nervous system disorders, and included nausea, dizziness, constipation, headache and somnolence. The incidence of gastrointestinal TEAEs was lower for tapentadol SR than for oxycodone CR. In the long-term safety study, the incidence of constipation for subjects on tapentadol SR was markedly lower than for oxycodone CR. Most treatment emergent adverse events reported with tapentadol SR were of mild or moderate intensity. Fewer subjects reported severe adverse events in the tapentadol SR group than in the oxycodone CR group for the SOCs (gastrointestinal, nervous system disorders, and skin and subcutaneous tissue disorders) relevant to a mu-opioid receptor agonist.

The safety following exposure of up to one year was not qualitatively different to that with shorter exposure. The exposure to tapentadol SR calculated for treatment duration (days on drug) and total duration (days on and off drug, including days with no drug intake) was very similar, suggesting good compliance with study drug administration.

In the pooled Phase II/ III multiple dose studies, 18% of subjects on tapentadol SR discontinued due to TEAEs, primarily because of gastrointestinal events, general disorders, nervous system disorders and skin disorders. This was markedly lower than with oxycodone CR (37%) and the difference was particularly notable in the titration period. This was primarily due to the difference in discontinuation rates because of gastrointestinal and central nervous system TEAEs.

Tapentadol shows a low potential for respiratory depression with a low frequency and limited clinical relevance. Drug withdrawal as an adverse event was reported with a relative frequency below 1% (uncommon). However, physicians should be vigilant for symptoms of withdrawal and treat patients accordingly should they occur.

The overall safety profile of tapentadol SR is as expected for a drug with mu-opioid receptor agonist activity. Tapentadol SR showed an improved overall tolerability compared to oxycodone CR, reflected by a decreased frequency and lower intensity of TEAEs and a lower rate of treatment discontinuations due to adverse events. This improvement was most apparent for nausea, vomiting, constipation, somnolence, dizziness and pruritus. The improved tolerability profile may translate to patients taking tapentadol SR having better long term compliance.

Clinical Summary and Conclusions

Efficacy

Pivotal efficacy data that assessed tapentadol SR (100 mg to 250 mg twice daily) for the treatment of moderate to severe chronic pain were provided from three studies.

In study PAI-3008/KF/11, in terms of the primary efficacy endpoint, the study demonstrated superiority of tapentadol SR over placebo in change from baseline of the average pain intensity at Week 12 of the maintenance period or over the 12 week maintenance period using LOCF imputation. In relation to responder rates, the difference in distributions of responder rates was not statistically significant between tapentadol SR and placebo. In addition, for subjects with baseline

pain intensity scores categorised as moderate, comparison of the average pain intensity scores for tapentadol SR and placebo was not statistically significant in either the last week of the maintenance period (p=0.181) or the overall maintenance period (p=0.463). These results do not provide robust support of efficacy of tapentadol SR.

Oxycodone was statistically significantly better than placebo on the primary efficacy endpoint for the overall maintenance period using LOCF and PMI imputation, demonstrating assay sensitivity. However, it was not statistically significantly superior at Week 12. The more conservative imputation methods (modified BOCF, BOCF and WOCF) resulted in pain intensity outcomes that were statistically significantly worse than placebo. The fact that the oxycodone comparator showed poor efficacy in the study raises concerns about the validity of the study.

The secondary efficacy measure, responder analysis, indicated that the proportion of subjects with 50% improvement in the tapentadol SR group was statistically significantly greater (p=0.027) than the response in the placebo group. The percent of tapentadol SR subjects with 30% improvement in tapentadol SR was not statistically significant (p=0.058). Oxycodone CR treatment was statistically significantly worse for all measures of responders, and this once again raises concerns about interpretation and validity of the results**.**

Importantly, for subjects with baseline pain intensity scores categorised as moderate, comparison of the average pain intensity scores for tapentadol SR and placebo was not statistically significant in either the last week of the maintenance period (p=0.181) or the overall maintenance period (p=0.463).

Overall the clinical evaluator considered that this study did not provide convincing evidence of efficacy of tapentadol SR. It is of major concern that oxycodone was shown to have such poor efficacy in this study and this raises concerns about the validity of the study results.

Study PAI-3009/KF12 did not achieve its primary efficacy endpoint to demonstrate superiority of tapentadol SR over placebo in the change from baseline of the average pain intensity at Week 12 of the maintenance period or over the 12 week maintenance period using LOCF imputation.

The study did not demonstrate assay sensitivity, as the active comparator oxycodone CR did not demonstrate superiority over placebo for the primary efficacy endpoint. There were no consistent, statistically significant differences between active treatment and placebo for the secondary efficacy measures or the exploratory analyses. Overall, the results from the study do not support efficacy of tapentadol SR in the treatment of moderate or severe pain**.**

Study KF5503/23 did demonstrate efficacy of tapentadol SR across some of the primary and secondary variables. The study achieved its primary efficacy endpoint of change from baseline of the average pain intensity at Week 12 or over the 12 week maintenance period using LOCF imputation. The efficacy results were confirmed by achieving statistically significant differences for the primary comparison of tapentadol SR group versus the placebo group in all of the more conservative imputation methods (BOCF, WOCF, modified BOCF and PMI).

Oxycodone CR was statistically significantly better than placebo on the primary efficacy endpoint for the overall maintenance period and over the 12 week maintenance period in all imputations, except at Week 12 of the maintenance period when the BOCF and WOCF imputation methods were applied.

The secondary efficacy measure, responder analysis, indicated that the proportions of subjects with 30% and 50% improvement (with prematurely discontinued subjects considered not improved) in the tapentadol SR group were statistically significantly greater than the response in the placebo group. The comparisons of oxycodone CR and placebo were not statistically significant. Once again, the fact that the comparator performed poorly in this parameter raises concerns about the validity of the overall results.

When examining the efficacy results analysed for baseline pain severity, the difference between tapentadol SR and placebo did reach statistical significance. However, only 11.5% of the patients had moderate pain, therefore the number of patients analysed for this factor is small. The efficacy results overall are not persuasive for treatment of moderate pain.

Overall the clinical evaluator considered that the efficacy data submitted for evaluation do not adequately support efficacy of tapentadol SR in the treatment of moderate or severe pain.

Safety

The safety data from the clinical studies with tapentadol SR was consistent with the overall safety profile expected for a drug with mu-opioid receptor agonist activity.

Tapentadol SR showed an improved overall tolerability compared to oxycodone CR, reflected by a decreased frequency and lower intensity of TEAEs and a lower rate of treatment discontinuations due to adverse events. This improvement was most apparent for nausea, vomiting, constipation, somnolence, dizziness, and pruritus.

Discontinuations due to TEAEs (or adverse drug reactions) were mainly due to gastrointestinal and central nervous system adverse events. Importantly, the incidence of discontinuation seen with tapentadol SR was markedly lower than with oxycodone CR. The improved tolerability profile suggests that patients taking tapentadol SR will have better long term compliance.

Benefit risk assessment

It was the Clinical Evaluator's opinion that tapentadol SR does not have a favourable benefit to risk ratio for the management of moderate or severe chronic pain. The studies have not adequately established efficacy compared to placebo in the conditions studied.

Conditions for registration

Overall the clinical evaluator considered that the data did not adequately support efficacy of tapentadol SR in the treatment of moderate or severe pain. The clinical evaluator recommended that the application to register tapentadol SR (Palexia SR) ***should be rejected.***

V. Pharmacovigilance Findings

Risk Management Plan

Information is provided on the following safety concerns:

- Important identified risks: potential for abuse and convulsion.
- Important potential risks: overdose, off-label use in paediatric patients, potential for medication errors, accidental exposure and diversion.
- Important missing information: use in paediatrics.

For each of these, routine pharmacovigilance (PhV) and risk minimisation activities are proposed.

A summary of the Risk Managment Plan is presented in Table 40 below.

Table 40: Summary of the Risk Management Plan

Safety concern	**Proposed pharmacovigilance activities (routine and additional)**	**Proposed risk minimisation activities (routine and additional)**
Potential for abuse Overdose Diversion	Routine Pharmacovigilance Practices are considered to be sufficient.	Appropriate labelling and the use of legal status of the drug. No further risk-minimisation activities, other than labelling has been conducted to date. No further risk minimisation activities are identified as necessary or requested to date.
Convulsion	Routine Pharmacovigilance Practices are considered to be sufficient.	Appropriate labelling. No further risk-minimisation activities, other than labelling has been conducted to date. No further risk-minimisation activities are identified as necessary or requested to date.
Potential for medication errors Accidental exposure	Routine Pharmacovigilance Practices are considered to be sufficient.	Appropriate labelling. No further risk-minimisation activities, other than labelling has been conducted to date. No further risk minimisation activities are identified as necessary or requested to date.
Use in paediatrics Off label use in paediatric patients	Routine Pharmacovigilance Practices are considered to be sufficient.	Appropriate labelling. No further risk-minimisation activities, other than labelling has been conducted to date. No further risk minimisation activities are identified as necessary or requested to date. A development program to address the paediatric population is defined in the agreed PIP.

Upon evaluation of the RMP by the Office of Product Review (OPR), it was considered that the information provided in this RMP was generally acceptable. However, a number of issues were identified. It was considered that information on evaluation of the need for additional risk minimisation activities and justification of the lack of these should have been provided. The sponsor has provided a comprehensive response.

The final OPR recommendations are that:

- More detailed information on use in pregnancy and results from toxicological studies on fertility and development are included in the Australian PI.
- There is reference to the possibility of serotonin syndrome with concomitant use of serotonergic drugs and tapendatol in the Australian PI.
- If approved for marketing in Australia, an agreed RMP for tapendatol should be provided to the TGA prior to its entry onto the ARTG and that this should adhere to the EU RMP template with particular attention to the following:
  - Evaluation of the need for additional risk minimisation activities and justification of the lack of these;
  - Presentation of details of important identified and potential risks in accordance with 1.5.2 of the template and the risk minimisation plan as per section 4 of the template; and
  - Provision of adequate information in the template Annexes.

The amendments requested by OPR were addressed in a subsequently submitted RMP.

VI. Overall Conclusion and Risk/Benefit Assessment

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

Quality

There are no objections in respect of Chemistry, Manufacturing and Controls to registration of tapentadol SR tablets, however the retest period applied to the API should be restricted to 30 months rather than the 36 months proposed by the company.

There were concerns raised by the Pharmaceutical subcommittee (PSC) regarding the pharmacokinetics of this formulation. With this dose form C_{max}, and to a lesser extent AUC, increase more than dose proportionally with increasing SR tablet strength. The mean dose-normalised AUC_{inf} increased across the dose strengths 50, 100, 200 and 250 mg; the dose-normalised AUC_{inf} ratio for the 250 mg tablet compared to the 50 mg tablet was 1.18 (90% CI 1.14-1.22). The sponsor contends that although this difference is statistically significant, it is unlikely to be clinically significant.

With respect to C_{max}, the sponsor concedes that there is departure from dose proportionality. The dose-normalised C_{max} ratio for the 250 mg tablet compared to the 50 mg tablet is 1.74 (90% CI 1.63-1.89). However, this is also unlikely to be clinically significant given that the dose-normalised C_{max} ratio for the 250 mg SR tablet relative to a 50 mg immediate release tablet is only 0.33 (90% CI 0.31-0.36).

Nonclinical

A revised report was issued following the sponsor's response to the initial evaluation. The nonclinical evaluator stated that, provided clinical data adequately address the nonclinical concerns discussed below, there are no nonclinical objections to registration.

The nonclinical evaluator noted that the primary toxicities observed with tapentadol were CNS effects, including convulsions and hepatic effects in rodents (including proliferative/neoplastic changes), possibly consistent with adaptive changes. A multi-species effect on the cardiovascular system was observed including QT interval prolongation in conscious dogs. Effects on female fertility, embryofetal development/ teratogenicity and postnatal survival were observed, mostly associated with maternotoxicity. Consistent with other opioids, tapentadol exhibited dependence potential, withdrawal effects and tolerance development in animals. Tapentadol dose levels were limited in all nonclinical species due to excessive toxicity, particularly to the CNS. Resulting animal/ human systemic exposure margins were therefore quite low, limiting the ability of the nonclinical studies to assess the safety of tapentadol.

The above toxicity concerns are now identified and described in the safety specification in the Risk Management Plan.

Tapentadol was shown to be a slight inhibitor of CYP2D6 activity in human liver microsomes *in vitro* with enzyme activity reduced by 19-61% in the concentration range 3.08 – 616 µM (compared to the estimated clinical C_{max} of 0.8 µM at the maximum recommended human dose (MRHD)). Tapentadol did not appear to be an inhibitor or a substrate for P-glycoprotein in CACO-2 human colon carcinoma cells *in vitro.* Glucuronidation of tapentadol was inhibited by diclofenac (≤ 90%), meclofenamate (≤ 90%), miconazole (≤ 70%), probenicid (≤ 67%), and naproxen (≤ 65%). The sponsor did not consider the interaction with diclofenac to be clinically relevant, as inhibition of tapentadol glucuronidation was predicted to be low (circa 6%) at clinical diclofenac concentrations. The most relevant interactions were considered to be with probenicid, meclofenamate and naproxen with 45%, 36% and 27% inhibition of tapentadol glucuronidation predicted at clinical exposure levels respectively.

Toxicity studies consisted of single dose IV and oral (mice, rats), long-term oral repeat dose (mice, 13 weeks; rats, 26 weeks; dogs, 52 weeks) and more than 20 other repeat dose studies of shorter duration in these species. Excessive toxicity (congestive changes and convulsions/CNS effects in mice, rats and dogs) constrained dose levels and exposure margins were generally <1. Severe convulsions, considered an opioid effect, were observed by various routes with exposure margins:

mice 0.5, rats 2.2 – 5.4; dogs 0.1 – 0.2. The primary toxicity in rodents was hepatotoxicity, consistent with adaptive changes following hepatic enzyme induction (enlarged liver, accentuated lobular pattern, hepatocyte vacuolation, centrilobular hypertrophy) at exposure more than 0.1 to 0.3 times the maximum clinical exposure.

Placental transfer of tapentadol was confirmed in rats. Low levels of tapentadol and tapentadol-glucuronide were detected in milk from lactating rats following oral dosing. Tapentadol administration during lactation resulted in increased pup mortality between PND1-4 in rats at doses lower than maternotoxic doses (exposure margins of 0.3).

Clinical

Pharmacokinetics

Several prolonged-release formulations were developed and investigated. The SR2 formulation of the 200 mg and 250 mg tablets that is proposed for marketing was used in the Phase III studies. For the three lower dose strengths of tapentadol SR (50 mg, 100 mg, and 150 mg,) a smaller tablet formulation, designated SR2small, was developed. This is the to-be-marketed formulation for these dose strengths, and offers a more convenient and easy to swallow tablet than tapentadol SR2 at the same dose strengths. The SR2small is bioequivalent to the SR2 tablet of the same strength.

Absolute bioavailability is similar to that of the IR formulation at ~32%. T_{max} is 3 – 6 hours in the dose range 50 – 250 mg. AUC was dose proportional within the 50 – 250 mg dose range. C_{max} increases were not dose proportional, with mean C_{max} from the 50 mg, 100 mg and 200 mg tablets 10.1 ng/mL, 25.5 ng/ mL and 62.5 ng/mL respectively. As with the IR form, food increased AUC and C_{max} but not to a clinically significant extent (the mean increases in AUC and C_{max} were 8% and 18%, respectively). On multiple dosing the accumulation ratio was ~1.6. Steady state concentrations were obtained after the third dose following dosing every 12 hours. Mean (SD) $t_{½}$ was 5.9 (2) hours. The inter subject CV for AUC was 27.4%.

Pharmacodynamics

PD studies used the IR formulation. In a pain model using carbon dioxide (CO_2)-laser-somato-sensory evoked potentials on ultraviolet (UV) B-irradiated skin a dose-response relationship for analgesic effect was seen with single doses of 50 mg, 75 mg, and 100 mg of tapentadol IR.

Tapentadol had no relevant effect on electrocardiogram (ECG) parameters (QT interval, heart rate, PR interval, QRS duration, T-wave or U-wave morphology). Multiple doses of tapentadol IR were associated with a dose-related reduction in serum testosterone but most of the testosterone values remained within the normal range. Tapentadol IR showed a similar drug-liking to that of estimated equi-analgesic doses of hydromorphone IR in a study in opioid experienced, non-dependent healthy subjects.

Efficacy

Efficacy was examined in ten studies, three were nominated as pivotal. Supportive studies included an open-label study which examined maintenance of effect for up to 12 months; a comparison of the relative analgesic efficacy of tapentadol IR and tapentadol SR; and an assessment of efficacy in the management of neuropathic pain (painful diabetic peripheral neuropathy).

In all Phase III studies patients were required to have taken analgesics for at least three months and be dissatisfied with their treatment. If they were taking opioids the dissatisfaction could be due to either efficacy or tolerability issues. Non-opioids dissatisfaction had to be due to lack of efficacy. After a titration from 50 mg twice a day (bd), doses from 100 mg to 250 mg bd were given in the Phase III studies. Oxycodone CR doses were titrated to 20 to 50 mg bd.

The pivotal studies were randomised, double-blind, and active and placebo-controlled. All patients had moderate to severe chronic pain, due to osteoarthritis of the knee (Studies PAI-3008/KF11 and

PAI-3009/KF12) or chronic back pain (PAI-3011/KF23). A pre-specified meta-analysis of these studies was performed. The active comparator in all three studies was oxycodone CR.
In these studies patients had three weeks of flexible dose titration followed by 12 weeks of controlled dose adjustment maintenance. This allowed a comparison of the relative analgesic efficacy of doses of tapentadol SR and oxycodone CR. Paracetamol up to 1000 mg daily was allowed during dose titration but not during the maintenance period unless for reasons other than the study-related pain (and in that case for no more than three consecutive days).
The primary endpoint for the pivotal studies was change from baseline of the average pain intensity over the 12-week maintenance period, using an 11 point numerical rating scale. For the FDA submission, an alternative primary endpoint was used (change from baseline of average pain intensity over the last week of maintenance period at Week 12). The primary endpoint for one region was considered as a secondary endpoint for the other region (that is, centres outside the USA). Responder rates and time to treatment discontinuation due to lack of efficacy were also secondary endpoints. The primary analysis was ITT, LOCF with secondary analyses of BOCF and WOCF. Results for each of the pivotal studies are presented in the clinical evaluation report (CER).
Reasons for dissatisfaction with previous analgesic treatment were discussed in the clinical evaluation report. Inadequate analgesia was the overwhelming reason for dissatisfaction with previous analgesia in all groups in all three studies. The mean (SD) pain intensity score at baseline was 7.3 (1.31) in PAI-3008/KF11, 7.3 (1.10) in PAI-3009/KF12and 7.5 (1.29) in PAI-3011/KF23. Median baseline pain intensity scores were 7.2 to 7.5 across the three studies. The proportion of patients previously taking opioids in the three months prior to the screening visit was 32.4% in PAI-3008/KF11, 15.7% in PAI-3009/KF12 and 53.4% in PAI-3011/KF23.
The average mean total daily maintenance dose of tapentadol SR across the three pivotal studies was 351.4 mg compared with 65.4 mg for oxycodone CR. The median modal daily dose was 400 mg for tapentadol SR and 60 mg for oxycodone CR. All studies had very high discontinuation rates, mostly due to adverse effects or subject choice. This rate varied between study arms and across studies as shown below:

	Placebo	**Tapentadol SR**	**Oxycodone CR**
Study 11	39%	47%	65%
Study 12	36%	43%	67%
Study 23	51%	47%	58%

Lack of efficacy led to discontinuation in from 10 to 15% of patients in the placebo groups and was not a significant contributor to discontinuation in the active treatment groups. There were some differences in discontinuation rates between opioid experienced and naïve patients given oxycodone. In PAI-3008/KF11, only 31.2% of opioid naïve patients given oxycodone completed treatment compared with 44.4% of the opioid experienced patients.
Results for the primary endpoint and key secondary endpoints for these three studies and for their meta-analysis are summarised in Attachment 2 to this report. Study PAI-3009/KF12 was a “failed” study which did not show statistically significant efficacy for tapentadol SR or oxycodone CR.
In the meta-analysis the overall least squares (LS) mean difference from placebo in average daily pain intensity over the 12 week maintenance period was -0.5 (95% CI -0.73, -0.34; $p < 0.037$) for tapentadol SR and -0.3 (95%CI -0.52, -0.14; $p< 0.001$) for oxycodone CR. The secondary endpoint of pain intensity during Week 12 compared with baseline was statistically significant for tapentadol SR but not for oxycodone CR. Statistically significant differences between placebo and oxycodone CR were not consistently demonstrated for secondary endpoints, where the 30% responder rate for placebo was higher than the 30% responder rate for oxycodone CR. The individual studies demonstrated superiority of tapentadol SR over placebo or a trend towards superiority. There was a trend towards superiority for oxycodone CR over placebo for most efficacy endpoints, however in Studies PAI-3008/KF11 and PAI-3009/KF12 the 50% and 30% responder rates respectively were statistically significantly higher for placebo than for oxycodone CR.

Supportive studies for tapentadol SR included a study in patients with painful diabetic peripheral neuropathy. This study was open-label during the three week dose titration period then double-blind during a 12 week placebo-controlled period. Only those patients who had at least a one point reduction in pain intensity score during the titration period were randomised to double-blind treatment. The primary efficacy endpoint was change from baseline at randomisation in average pain intensity over the last week of the double-blind maintenance period (Week 12). Some 395/ 591 (67%) of patients enrolled in the open-label titration phase were randomised to the double-blind phase. This selected population of patients showed a robust response to tapentadol SR. An open-label, 12 month efficacy and safety study showed a continued analgesic effect of tapentadol SR over 12 months. A similar effect was seen for oxycodone CR, the active control in this study.
Relative analgesic efficacy of tapentadol IR and SR was examined in Study PAI-3019/KF39 described in the CER. This was a randomised, double-blind, 2-period crossover study in patients with moderate to severe low back pain. It was intended to demonstrate non-inferiority of tapentadol SR with tapentadol IR. Patients were titrated to an optimal dose of tapentadol IR (50, 75 or 100 mg every 4 – 6 hr) with a maximum total daily dose of 500 mg for 21 days. This was followed by two double-blind fixed dose (optimal daily dose from titration period) treatment crossover periods each of 14 days duration. The primary efficacy endpoint was the mean average pain intensity score during the last 3 days of each double-blind treatment period, using twice daily 11-point-NRS pain intensity evaluations.
The minimal difference for demonstration of non-inferiority was ± 2 on the 11-point-NRS pain scale. A post hoc analysis using equivalence margins of ±0.28 was also tested. A total of 116 patients were enrolled in the open-label titration period with 88 randomised and 87 (75%) included in the double-blind period. Reasons for discontinuation included: adverse event (n=16), non-compliance with study medication (n=6), subject choice (n=4) loss to follow-up (n=2) and lack of efficacy (n=1). The total mean pain intensity score decreased from 7.3 at pre-treatment to 4.2 after 3 weeks of open-label treatment. The estimated mean average pain intensity score over the last 3 days of treatment was 4.0 for tapentadol SR and 3.9 for tapentadol IR, with estimated difference of 0.1 (95%CI -0.09 to 0.28). This was within the specified range for non-inferiority.

Safety

A total of 1284 patients were given tapentadol SR in multi-dose Phase II/III studies, 494 patients took tapentadol SR for > 24 weeks and 243 took tapentadol for > 52 weeks. Mean treatment duration was 86.6 days (range 1 – 388 days) in these studies. Pooled adverse events occurring in ≥ 5% of patients for these combined studies are discussed in the CER.

The most frequently reported events were: nausea, vomiting, constipation, hyperhidrosis and dizziness. Nausea, vomiting, constipation, dizziness and pruritus were all more frequently reported with oxycodone CR (the main comparator) than with tapentadol SR. Hyperhidrosis was more frequent with tapentadol than with oxycodone (10.8% versus 5.1%).

There were no deaths in patients given tapentadol SR in the completed clinical trials. There was no clustering of serious adverse events. Respiratory depression was reported in two patients taking tapentadol SR. Withdrawal effects were seen between days 2 – 4 after ceasing study drug in 13.8% of patients given tapentadol SR and these were considered mild in 11.8% and moderate in 2%. This was similar to the reported withdrawal effects in patients given oxycodone CR. Hepatic enzyme abnormalities occurred with similar frequency in all treatment groups. Discontinuation rates, as previously discussed, were high in all groups but more so in groups receiving oxycodone CR.

Risk Management Plan

The RMP evaluator has noted that routine pharmacovigilance activities are proposed for tapentadol. While generally satisfactory the evaluator has identified areas for greater disclosure of risks in the Product Information. Areas of particular concern were the potential for interactions with other serotonergic medicines and monoamine oxidase inhibitors and the proposed reproductive toxicity

statement. An updated Risk Management Plan addressing the concerns raised by the nonclinical (low exposure levels obtained in nonclinical studies) and OPR evaluators (see *V. Pharmacovigilance* above) has been submitted to TGA.

Risk-Benefit Analysis

Delegate Considerations

There are no pharmacology issues of concern. Safety issues have been identified that can be adequately managed by the proposed S8 scheduling and by appropriate statements in the product literature and labelling as well as by modifications as requested to the Risk Management Plan. Hepatic enzyme abnormalities do not appear to be of concern though they were highlighted as potential effects in the nonclinical data.

Drug interactions with tapentadol are likely to be fewer than with morphine-based opioids due to the lack of CYP P450 metabolism of tapentadol. Gastrointestinal adverse events were generally less frequent with tapentadol than with oxycodone. The differences in proportion of patients who had withdrawal effects between tapentadol and other opioids may reflect differences in the dose strength rather than factors intrinsic to tapentadol. Use in patients with hepatic or renal impairment has been adequately investigated.

The indications requested for each dose form are consistent with the current indications for oxycodone IR and SR dose forms.

Tapentadol SR

The clinical evaluator recommended rejection of the SR dose form due to an inadequate demonstration of efficacy. The clinical evaluator considered that the pivotal studies should be required to show efficacy of both the active control (oxycodone CR) as well as of tapentadol SR to be considered a valid demonstration of efficacy. Of the three pivotal studies only one (PAI-3011/KF23) demonstrated statistically significant efficacy of oxycodone CR for the primary efficacy comparison. One, (PAI-3009/KF12) did not demonstrate a statistically significant difference between oxycodone CR and placebo or tapentadol SR and placebo for the primary efficacy endpoint.

The sponsor has responded to the effect that the lack of a statistically significant difference between the active comparator and placebo in a 3-arm study of test product, active control and placebo control does not mean it is a failed or invalid study. The sponsor cited ICH topic E10 *Note for Guidance on choice of control group in clinical trials* section 1.5.1[35] which states that when 2 treatments within a trial are shown to have different efficacy (that is, when one treatment is superior), that finding itself demonstrates that the trial had assay sensitivity. Therefore in those studies the comparison between the test product (tapentadol SR) and placebo can still be considered. This document has been adopted by the TGA.

The sponsor's response is accepted in that there is an acceptable demonstration of efficacy of tapentadol SR against placebo in treatment of chronic pain. The effect size does not however appear to be very large; the mean difference in change from baseline of the average pain intensity over the 12-week maintenance period, using an 11 point numerical rating scale was only 0.5 in the meta-analysis. The difference between tapentadol SR and placebo for 30% and 50% responder rates was 6.5% and 6.6% respectively. The difference in Patient Global Impression of Improvement was larger at 19.3%. The very high discontinuation rates in these studies are likely to have reduced the apparent differences between placebo and both actives in the pivotal studies.

The non-inferiority study between tapentadol IR and tapentadol SR gives limited assurance of similar efficacy. This was a small study with a wide margin for demonstration of non-inferiority.

[35] http://www.tga.gov.au/docs/pdf/euguide/ich/036496en.pdf

Both these factors would have contributed to the inability of the study to differentiate between the two products with respect to analgesic effect. Nevertheless the differences between treatments in this study were extremely small. On balance the Delegate considered that reasonable efficacy of tapentadol SR has been demonstrated.

Conclusion and recommendation

Subject to negotiation of amendments to the Product Information document, the Delegate proposed to approve the registration of:

- Palexia SR for the management of moderate to severe chronic pain unresponsive to non-narcotic analgesia.

The advice of the ACPM is requested, particularly concerning whether efficacy of Palexia SR (tapentadol) has been adequately demonstrated.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal.

ACPM recommended approval of the submission from CSL Pty Ltd to register the new chemical entity tapentadol (PALEXIA SR) sustained release tablets 50 mg, 100 mg, 150 mg, 200 mg, 250 mg for the indication:

For the relief of moderate chronic pain unresponsive to non-narcotic analgesia.

In making this recommendation, the ACPM considered the guidance on study design provided in the TGA accepted EU guideline on nociceptive and neuropathic pain and advised that the available studies did not adequately demonstrate efficacy in the appropriate population. In particular, the ACPM were concerned that data were not available for patients with malignancies in general and specifically those who experience severe chronic pain. The ACPM therefore did not support the broader indication as the risk benefit profile was not adequately assessed.

In addition to the recommended amendments to the Product Information (PI) and Consumer Medicines Information (CMI) for Palexia IR the following changes should be made prior to approval:

Provide detailed information in the Clinical Trials and the Precautions sections about the lack of evidence supporting the safe and efficacious use in patients with malignancy, including concomitant use in this population of other analgesics.

Response from Sponsor

The Sponsor provided comment on the omission of severe pain in the Indication recommended by the ACPM. The Sponsor contended that efficacy had been demonstrated in patients with severe chronic pain; the majority of patients in the Palexia SR Phase 3 clinical studies had severe pain at baseline.

The Sponsor contended that it was appropriate to maintain the proposed Palexia SR indication of moderate to severe pain:

Palexia SR - *For the relief of moderate to severe chronic pain unresponsive to non-narcotic analgesia*.

Outcome

Based on a review of quality, safety and efficacy, TGA approve the registration of Palexia SR tapentadol hydrochloride 50, 100, 150, 200 and 250 mg sustained release tablets blister packs indicated for:

> *The management of moderate to severe chronic pain unresponsive to non-narcotic analgesia. There is currently no clinical trial data available regarding the safety and efficacy of Palexia SR in patients with pain due to malignancy.*

The following special condition applies to this therapeutic good:

1. The full implementation of the Risk Management Plan version 1.1 for Australia dated September 2010, as agreed with the Office of Product Review, must be implemented.

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.

PALEXIA® SR PRODUCT INFORMATION
AUST R 165332, 165346, 165347, 165356, 165357

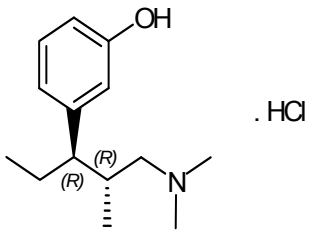
NAME OF THE MEDICINE

PALEXIA® SR 50 mg (tapentadol as hydrochloride) sustained release tablets
PALEXIA® SR 100 mg (tapentadol as hydrochloride) sustained release tablets
PALEXIA® SR 150 mg (tapentadol as hydrochloride) sustained release tablets
PALEXIA® SR 200 mg (tapentadol as hydrochloride) sustained release tablets
PALEXIA® SR 250 mg (tapentadol as hydrochloride) sustained release tablets

DESCRIPTION

PALEXIA® SR sustained release tablets contain tapentadol hydrochloride (HCl) which is a centrally acting synthetic analgesic combining mu agonist and noradrenaline re-uptake inhibition activity in a single molecule. Tapentadol is a white to off-white powder; freely soluble in water and methanol, and soluble in ethanol. The pKa_1 is 9.36 and pKa_2 is 10.37 determined in 0.15 M KCl solution. The partition coefficient is defined as the ratio of the equilibrium concentrations of a single neutral molecular species in a 1-octanol/aqueous buffered solution 2-phase system. The value of log P for tapentadol hydrochloride in 1-octanol/water is 2.89 ± 0.01. The chemical name for tapentadol HCl is 3-[(1*R*,2*R*)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol monohydrochloride. The molecular weight of tapentadol HCl is 257.80, and the empirical formula is $C_{14}H_{23}NO \bullet HCl$.

The structural formula of tapentadol HCl (CAS number: 175591-09-0) is:



PALEXIA® SR tablets contain 50, 100, 150, 200 and 250 mg tapentadol (as hydrochloride). Excipients are: hypromellose 100,000 mPa-s, microcrystalline cellulose, colloidal anhydrous silica and magnesium stearate. Excipients in the film coat are: hypromellose 6 mPa-s, lactose monohydrate, talc, macrogol 6000, propylene glycol, titanium dioxide (E171), iron oxide yellow (E172) (100, 150, 200 and 250 mg tablets only), iron oxide red (E172) (150, 200 and 250 mg tablets only), and iron oxide black (E172) (250 mg tablets only).

PHARMACOLOGY

Pharmacodynamics

Tapentadol is a centrally acting synthetic analgesic combining opioid and non-opioid activity in a single molecule. It has 18 times less binding affinity

than morphine to the human mu-opioid receptor but was only 2-3 times less potent in producing analgesia in animal models (on a dose per body weight basis). This low *in-vivo* potency difference is consistent with its two mechanisms of action. Tapentadol has been shown to inhibit noradrenaline reuptake in the brains of rats resulting in increased noradrenaline concentrations. In preclinical models, the analgesic activity due to the mu-opioid receptor agonist activity of tapentadol can be antagonized by selective mu-opioid receptor antagonists (e.g., naloxone), whereas the noradrenaline reuptake inhibition is sensitive to noradrenaline modulators. Tapentadol exerts its analgesic effects directly without a pharmacologically active metabolite.

Effects on the cardiovascular system: In ECG studies in conscious dogs, non-persistent QT/QTc interval prolongation was observed at exposures similar to or lower than the clinical plasma C_{max}. These effects were not observed in safety pharmacology studies with repeated ECG measurements. Heart rate was increased in conscious rats and dogs at peak plasma concentrations at least twice the clinical plasma C_{max}, but there was no clear effect on other ECG parameters (PR interval, QRS duration, T-wave or U-wave morphology). In a thorough QT trial in healthy subjects, no effect of multiple therapeutic and supratherapeutic doses of tapentadol on the QT interval was shown. Similarly, tapentadol had no relevant effect on other ECG parameters (heart rate, PR interval, QRS duration, T-wave or U-wave morphology).

Pharmacokinetics

The tapentadol PR formulation is a hydrophilic hypromellose-based matrix formulation that provides pH-independent *in-vitro* release of the drug substance over a time period of approximately 12 hours. An initial drug substance release of about 20% occurs over the first 30 minutes with ongoing drug release over the ensuing 12-hour period.

Absorption
Mean absolute bioavailability after single-dose administration (fasting) of PALEXIA® SR is approximately 32% due to extensive first-pass metabolism. Maximum serum concentrations of tapentadol are observed at between 3 and 6 hours after administration of PALEXIA® SR tablets.

Dose proportional increases for AUC (the most relevant exposure parameter for sustained-release formulations) have been observed after administration of PALEXIA® SR tablets over the therapeutic dose range.

A multiple dose study with twice daily dosing using 86 mg and 172 mg tapentadol administered as SR tablets showed an accumulation ratio of about 1.5 for the parent drug which is primarily determined by the dosing interval and apparent half-life of tapentadol.

Food Effect
The AUC and C_{max} increased by 8% and 18%, respectively, when PALEXIA® SR tablets were administered after a high-fat, high-calorie breakfast. PALEXIA® SR may be given with or without food.

Distribution
Tapentadol is widely distributed throughout the body. Following intravenous administration, the volume of distribution (Vz) for tapentadol is 540 +/- 98 L. The serum protein binding is low and amounts to approximately 20%.

Metabolism and Elimination
In humans, the metabolism of tapentadol is extensive. About 97% of the parent compound is metabolized. The major pathway of tapentadol metabolism is conjugation with glucuronic acid to produce glucuronides. After oral administration approximately 70% (55% glucuronide and 15% sulfate of tapentadol) of the dose is excreted in urine in the conjugated form. Uridine diphosphate glucuronyl transferase (UGT) is the primary enzyme involved in the glucuronidation (mainly UGT1A6, UGT1A9 and UGT2B7 isoforms). A total of 3% of drug was excreted in urine as unchanged drug. Tapentadol is additionally metabolized to N-desmethyl tapentadol (13%) by CYP2C9 and CYP2C19 and to hydroxy tapentadol (2%) by CYP2D6, which are further metabolized by conjugation. Therefore, drug metabolism mediated by cytochrome P450 system is of less importance than phase 2 conjugation.

None of the metabolites contributes to the analgesic activity.

Tapentadol and its metabolites are excreted almost exclusively (99%) via the kidneys.

The terminal half-life is on average 4 hours after oral administration. The total clearance is 1530 +/- 177 ml/min.

Elderly patients
The mean exposure (AUC) to tapentadol was similar in elderly subjects compared to young adults, with a 16% lower mean C_{max} observed in the elderly subject group compared to young adult subjects.

Renal Impairment
AUC and C_{max} of tapentadol were comparable in subjects with varying degrees of renal function (from normal to severely impaired). In contrast, increasing exposure (AUC) to tapentadol-O-glucuronide was observed with increasing degree of renal impairment. In subjects with mild, moderate, and severe renal impairment, the AUC of tapentadol-O-glucuronide are 1.5-, 2.5-, and 5.5-fold higher compared with normal renal function, respectively.

Hepatic Impairment
Administration of tapentadol resulted in higher exposures and serum levels to tapentadol in subjects with impaired hepatic function compared to subjects with normal hepatic function. The ratio of tapentadol pharmacokinetic parameters for the mild and moderate hepatic impairment groups in comparison to the normal hepatic function group were 1.7 and 4.2, respectively, for AUC; 1.4 and 2.5, respectively, for C_{max}; and 1.2 and 1.4, respectively, for $t_{1/2}$. The rate of formation of tapentadol-O-glucuronide was lower in subjects with increased liver impairment.

Pharmacokinetic Interactions

Tapentadol is mainly metabolized by Phase 2 glucuronidation, and only a small amount is metabolized by Phase 1 oxidative pathways.

As glucuronidation is a high capacity/low affinity system, any clinically relevant interactions caused by Phase 2 metabolism are unlikely to occur. This has been evidenced by clinical pharmacokinetic drug-drug interaction studies with probe drugs naproxen and probenecid with increases in AUC of tapentadol by 17% and 57%, respectively. No changes in the pharmacokinetic parameters of tapentadol were observed when paracetamol and acetylsalicylic acid were given concomitantly. Tapentadol was shown to be a weak inhibitor of human CYP2D6 activity *in vitro* but at concentrations 180- to 1400-fold higher than maximum concentrations in humans. *In vitro* induction experiments in human hepatocytes showed that CYP1A2, CYP2C9, and CYP3A4 activities were not markedly induced. Thus *in vitro* studies did not reveal any potential of tapentadol to either inhibit or induce cytochrome P450 enzymes. Tapentadol is an inducer of CYP1A, CYP2B and CYP2E in rats *in vivo*. The potential clinical relevance of this finding is unknown.

The pharmacokinetics of tapentadol were not affected when gastric pH or gastrointestinal motility were increased by omeprazole and metoclopramide, respectively.

Plasma protein binding of tapentadol is low (approximately 20%). Therefore, the likelihood of pharmacokinetic drug-drug interactions by displacement from the protein binding site is low.

CLINICAL TRIALS

The efficacy and safety of PALEXIA® SR in the treatment of moderate to severe chronic pain has been investigated in three pivotal Phase III randomised, double-blind, active- and placebo-controlled, parallel-group, multicentre studies; two in patients with moderate to severe chronic pain from osteoarthritis of the knee (clinical trials KF5503/11 and KF5503/12) and one in patients with moderate to severe chronic low back pain (clinical trial KF5503/23). These pain conditions were chosen as they usually present with moderate to severe pain that is often treated with opioids.

In all three studies, subjects were initially randomised to receive PALEXIA® SR (50 mg twice daily), placebo or oxycodone CR (10 mg twice daily) for the first 3 days. Subjects were then titrated upwards over the following 2 weeks (increments of PALEXIA® SR 50 mg, oxycodone CR 10 mg, or placebo twice daily) to achieve a stable optimum dose. Subjects were allowed paracetamol as rescue medication during the titration period. Subjects received the following maximum (minimum) doses: PALEXIA® SR 250 mg (100 mg) twice daily, oxycodone CR 50 mg (20 mg) twice daily, or placebo twice daily. The study drug was taken with or without food.

To enter the 12-week maintenance period, subjects had to be on a stable dose of the study drug for the last 3 days of the titration period without any rescue medication. If needed, subjects could request controlled adjustment of their dose based on their individual analgesia requirements and/or

tolerability experience however adjustments were to be kept to a minimum during the maintenance period.

All three studies had the same primary endpoints - change from baseline of the average pain intensity over the 12-week maintenance period of the daily pain intensity on an 11-point numerical rating scale (NRS), and change from baseline of the average pain intensity over the last week of the maintenance period at Week 12 of the daily pain intensity on an 11-point NRS. Secondary endpoints included 30% and 50% responder rates and Patient Global Impression of Change scale.

The results for these endpoints for all three studies are summarised in Table 1.

Meta-analysis of pivotal studies

A pre-specified meta-analysis of the data generated in the above three clinical trials was undertaken. The two main objectives of the meta-analysis were to assess the superior safety of PALEXIA® SR compared to oxycodone CR with regards to constipation (gastrointestinal tolerability), and to assess the non-inferior efficacy of PALEXIA® SR compared to oxycodone CR.

PALEXIA® SR was superior to oxycodone CR with regards to constipation, nausea and vomiting (gastrointestinal tolerability) ($p<0.001$). The non-inferiority of PALEXIA® SR to oxycodone CR in relation to the primary endpoint (change from baseline of the average pain intensity over the 12-week maintenance period or at Week 12) (using LOCF) was also demonstrated (both p-values ≤ 0.001) (Table 1).

Table 1. Meta-analysis of data generated in studies KF5503/11, KF5503/12 and KF5503/23 (ITT, LOCF); non-inferior efficacy of PALEXIA® SR compared to oxycodone CR.

	KF5503/11 (n=1023), Osteoarthritis			KF5503/12 (n=987), Osteoarthritis			KF5503/23 (n=958), Lower back pain			Meta-analysis		
	Placebo (n=336)	PALEXIA® SR (n=344)	Oxycodone CR (n=342)	Placebo (n=336)	PALEXIA® SR (n=319)	Oxycodone CR (n=331)	Placebo (n=316)	PALEXIA® SR (n=312)	Oxycodone CR (n=323)	Placebo (n=991)	PALEXIA® SR (n=978)	Oxycodone CR (n=999)
Baseline pain Mean (SD)	7.2 (1.29)	7.4 (1.35)	7.2 (1.29)	7.3 (1.12)	7.3 (1.09)	7.3 (1.10)	7.6 (1.32)	7.5 (1.32)	7.5 (1.22)	7.4 (1.25)	7.4 (1.26)	7.3 (1.21)
Wk 12 maintenance Mean (SD)	5.0 (2.61)	4.4 (2.48)	4.7 (2.35)	4.8 (2.47)	4.5 (2.48)	5.0 (2.44)	5.5 (2.57)	4.6 (2.66)	4.6 (2.56)	5.1 (2.56)	4.5 (2.54)	4.8 (2.45)
LS Means diff from placebo Baseline vs Wk 12[a]		-0.7 (0.18)	-0.3 (0.18)		-0.3 (0.18)	0.2 (0.18)		-0.8 (0.19)	-0.9 (0.19)		-0.6 (0.11)	-0.3 (0.11)
p-value 95% CI[b]		<0.001 (-1.04, -0.33)	0.069 (-0.68, 0.02)		0.152 (-0.61, 0.09)	0.279 (-0.16, 0.54)		<0.001 (-1.22, -0.47)	<0.001 (-1.24, -0.49)		<0.001 (-0.80, -0.39)	0.002 (-0.53, -0.12)
Overall maintenance Mean (SD)	5.1 (2.48)	4.4 (2.40)	4.7 (2.26)	5.0 (2.24)	4.7 (2.28)	5.1 (2.29)	5.5 (2.46)	4.7 (2.52)	4.6 (2.38)	5.2 (2.40)	4.6 (2.40)	4.8 (2.32)
LS Means diff from placebo Baseline vs overall[a]		-0.7 (0.17)	-0.3 (0.17)		-0.2 (0.16)	0.1 (0.16)		-0.7 (0.18)	-0.8 (0.18)		-0.5(0.10)	-0.3(0.10)
p-value 95% CI[b]		<0.001 (-1.00, –0.33)	0.049 (-0.67, -0.00)		0.135 (-0.55, 0.07)	0.421 (-0.18, 0.44)		<0.001 (-1.06, -0.35)	<0.001 (-1.16, -0.46)		<0.001 (-0.73, -0.34)	<0.001 -0.52, -0.14)
30% responder rate	35.9%	43.0%[c]	24.9%[c]	40.9%	41.1%	26.0%[d]	27.1%	39.7%[c]	36.5%	34.8%	41.3%[c]	27.0%[d]
50% responder rate	24.3%	32.0%[c]	17.3%[d]	27.0%	31.0%	22.1%	18.9%	27.0%[c]	17.4%	23.5%	30.1%[c]	20.8%
PGIC assessment of very much improved & much improved	35.5%	58.5%[c]	47.0%[c]	43.2%	56.0%[c]	42.5%	32.7%	55.5%[c]	60.0%[c]	37.4%	56.7%[c]	49.8%[c]

a: Change from baseline in average pain intensity scores based on numerical rating scale (NRS)[a], ITT population; LOCF = last observation carried forward Average pain scores are the averages of all scores recorded during the baseline period or during each time period (Week 12 of maintenance or overall maintenance).
b: Test for no difference between treatment from ANCOVA model with factor(s) treatment, pooled centre and baseline pain intensity as covariate (type III SS) unadjusted p-value.
c:Indicates statistically significant over placebo
d: Indicates statistical significance of placebo over active
LS = least square

Painful diabetic peripheral neuropathy
A randomised withdrawal Phase III clinical trial (KF5503/36 evaluating the efficacy and safety of orally administered PALEXIA® SR (100 to 250 mg twice daily) compared PALEXIA® SR to placebo in subjects with painful diabetic peripheral neuropathy.

The study consisted of two phases: an open label phase (n=588) during which all subjects received PALEXIA® SR and were titrated to an optimal dose, and a double-blind phase (n=389) during which subjects were randomised to receive PALEXIA® SR (n=196) or placebo (n=193).

During the open-label titration phase, subjects initially received PALEXIA® SR (50 mg twice daily) for the first 3 days. Subjects were then titrated upwards over the following 3 weeks (increments of PALEXIA® SR 50 mg twice daily) to achieve a stable optimum dose. The maximum (minimum) doses administered were: PALEXIA® SR 250 mg (100 mg) twice daily. The study drug was taken with or without food.

Following completion of the open-label titration phase, subjects who had at at least a 1-point improvement on an 11-point NRS in average pain intensity score were randomised into the double-blind maintenance phase to receive their individually determined open-label PALEXIA® SR dose or placebo for 12 weeks.

Subjects were allowed paracetamol as rescue medication during the titration period. Subjects were allowed PALEXIA® SR as supplemental analgesia during the double-blind maintenance phase (25 mg, twice daily for the first 4 days and 25 mg once daily for the remainder of the maintenance phase).

The primary efficacy endpoint was change from baseline at randomisation in average pain intensity over the last week (Week 12) of the double-blind maintenance period, as determined by twice-daily measurements on an 11-point NRS.

For the primary efficacy analysis, PALEXIA® SR showed a statistically significant difference in average pain intensity compared to placebo at Week 12 of the double-blind maintenance period ($p<0.001$, an LS mean difference compared to placebo: –1.3) (Table 2).

Table 2. Change in average pain intensity scores based on numerical rating scale (NRS)[a]- from start of double-blind phase to week 12 of double-blind phase baseline, ITT population

	Placebo	PALEXIA® SR
Start DB		
N	192	193
Mean (SD)	3.4 (1.88)	3.6 (1.90)
Median (Range)	3.3 (0 to 9)	3.8 (0 to 9)
Week 12 of Maintenance		
N	192	196
Mean (SD)	4.7 (2.46)	3.5 (2.13)
Median (Range)	4.8 (0 to 10)	3.2 (0 to 10)
Change from Start DB to Week 12 of		

Maintenance Period		
N	192	193
Mean (SD)	1.3 (2.41)	-0.1 (1.69)
Median (Range)	1.0 (-7 to 9)	-0.1 (-7 to 5)
LS Mean Change	1.4	0.0
LS Mean Difference versus Placebo (SE)		-1.3 (0.20)
95% CI (verses Placebo)		(-1.70, -0.92)
p value (versus Placebo)[b]		<0.001

a: LOCF=last observation carried forward
b: Test for no treatment difference based on the ANCOVA model with treatment, country, dose category and prior opioid use as factors and Start DB pain intensity as a covariate.
Average pain scores are the averages of all scores recorded during the 72-hour period before randomization or during each week.
Daily pain intensity is the average of pain scores over a 24-hour period, starting from time of randomization.
DB=double-blind

INDICATIONS

PALEXIA® SR is indicated for the management of moderate to severe chronic pain unresponsive to non-narcotic analgesia.

There is currently no clinical trial data available regarding the safety and efficacy of PALEXIA® SR in patients with pain due to malignancy.

CONTRAINDICATIONS

PALEXIA® SR is contraindicated:
- in patients with a known hypersensitivity to the active substance, tapentadol, or any component of the product,
- in situations where drugs with mu-opioid receptor agonist activity are contraindicated, i.e. patients with significant respiratory depression (in unmonitored settings or the absence of resuscitative equipment), and patients with acute or severe bronchial asthma or hypercapnia,
- in any patient who has or is suspected of having paralytic ileus,
- in patients with acute intoxication with alcohol, hypnotics, centrally acting analgesics, or psychotropic drugs (see **PRECAUTIONS**, **Interactions with other medicines**),
- in patients who are receiving MAO inhibitors or who have taken them within the last 14 days (see **PRECAUTIONS**, **Interactions with other medicines**).

PRECAUTIONS

Potential for Abuse
As with other drugs that have mu-opioid receptor agonist activity, PALEXIA® SR has a potential for abuse. This should be considered when prescribing or dispensing PALEXIA® SR in situations where there is concern about an increased risk of misuse, abuse, or diversion.

Drugs that have mu-opioid receptor agonist activity may be abused by crushing, chewing, snorting or injecting the product. Such practices pose a significant risk to the abuser and may result in overdose or death.

All patients treated with drugs that have mu-opioid receptor agonist activity should be carefully monitored for signs of abuse and addiction.

Drug Dependence
Tolerance: Repeated administration of opioids may lead to tolerance. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia, in the absence of disease progression or other external factors.

Withdrawal symptoms: In a study conducted over 12 months, 22.4% of patients given PALEXIA® SR had objective signs of opioid withdrawal compared with 27.3% given oxycodone CR when assessed between 2 - 5 days after the last dose of study drug. Only 4.8% of patients given PALEXIA® SR and 4.5% given oxycodone CR were considered by investigators to have moderate withdrawal. No subjects had moderately severe or severe withdrawal.

Use in patients with pain due to malignancy
There is currently no clinical trial data available regarding the safety and efficacy of PALEXIA® SR in patients with pain due to malignancy; therefore the use of PALEXIA® SR in patients with pain due to malignancy is not recommended.

Respiratory Depression
At high doses or in mu-opioid receptor agonist sensitive patients, PALEXIA® SR may produce dose-related respiratory depression. Therefore, PALEXIA® SR should be administered with caution to patients with impaired respiratory functions. Alternative non-mu-opioid receptor agonist analgesics should be considered and PALEXIA® SR should be employed only under careful medical supervision at the lowest effective dose in such patients. If respiratory depression occurs, it should be treated as any mu-opioid receptor agonist-induced respiratory depression (see **OVERDOSAGE**).

Head Injury and Increased Intracranial Pressure
Like other drugs with mu-opioid receptor agonist activity, PALEXIA® SR should not be used in patients who may be particularly susceptible to the intracranial effects of carbon dioxide retention such as those with evidence of increased intracranial pressure, impaired consciousness, or coma. Analgesics with mu-opioid receptor agonist activity may obscure the clinical course of patients with head injury. PALEXIA® SR should be used with caution in patients with head injury and brain tumors.

Seizures
PALEXIA® SR has not been systematically evaluated in patients with a seizure disorder, and such patients were excluded from clinical studies. However, like other analgesics with mu-opioid receptor agonist activity

PALEXIA® SR should be prescribed with care in patients with a history of a seizure disorder or any condition that would put the patient at risk of seizures.

Renal Impairment
For patients with mild or moderate renal impairment, no dosage adjustment is recommended (see **DOSAGE AND ADMINISTRATION**).

PALEXIA® SR has not been studied in controlled efficacy studies in patients with severe renal impairment, therefore use in this population is not recommended (see **DOSAGE AND ADMINISTRATION** and also **Pharmacokinetics**).

Hepatic Impairment
For patients with mild hepatic impairment, no dosage adjustment is recommended (see **DOSAGE AND ADMINISTRATION**).

A study of PALEXIA® SR in subjects with hepatic impairment showed higher serum concentrations than in those with normal hepatic function. PALEXIA® SR should be used with caution in patients with moderate hepatic impairment (see **DOSAGE AND ADMINISTRATION** and also **Pharmacokinetics**).

PALEXIA® SR has not been studied in patients with severe hepatic impairment and, therefore, use in this population is not recommended (see **DOSAGE AND ADMINISTRATION** and also **Pharmacokinetics**).

Use in Pancreatic/Biliary Tract Disease
Drugs with mu-opioid receptor agonist activity may cause spasm of the sphincter of Oddi. PALEXIA® SR should be used with caution in patients with biliary tract disease, including acute pancreatitis.

Effect on fertility
There were no apparent effects on the fertility of male rats at intravenous doses up to 12 mg/kg/day, although histopathology analyses were not conducted. In female rats, the numbers of corpora lutea and implantations were reduced, and pre- and post-implantation losses were increased, at intravenous tapentadol doses associated with maternal toxicity. The clinical relevance of these findings is unknown.

Use in pregnancy (Category C)
There are no adequate and well controlled studies of tapentadol in pregnant women. PALEXIA® SR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The effect of tapentadol on labor and delivery in humans is unknown. PALEXIA® SR is not recommended for use in women during and immediately prior to labor and delivery. Due to the mu-opioid receptor agonist activity of tapentadol, neonates whose mothers have been taking tapentadol should be monitored for respiratory depression.

Tapentadol crosses the placenta in pregnant rats. Tapentadol was evaluated for teratogenic effects in rats and rabbits following intravenous and subcutaneous administration during organogenesis. Embryofetal toxicity such

as delays in skeletal maturation and cerebral ventricular dilation was observed in rats concomitant with maternal toxicity at subcutaneous doses of 10 mg/kg/day or greater (plasma AUC exposure less than maximum anticipated clinical exposure). Subcutaneous administration of tapentadol to rabbits revealed embryofetal toxicity at doses of 10-24 mg/kg/day (AUC exposure 1 to 2 fold the maximum anticipated human exposure), along with reduced fetal viability, skeletal delays and other variations, and multiple malformations including gastroschisis/thoracogastroschisis, amelia/phocomelia and cleft palate at 10-24 mg/kg/day, and ablepharia, encephalopathy and spina bifida at 24 mg/kg/day. There were no teratogenic effects observed in similar studies conducted in rats and rabbits via the intravenous route (up to 15 mg/kg/day) Embryofetal toxicity, including malformations, may be secondary to maternal toxicity in these species.

Use in lactation
There is limited information on the excretion of tapentadol in breast milk. Tapentadol is excreted into milk in lactating rats following oral dosing. Oral tapentadol administration to rats during lactation resulted in increased postnatal pup mortality, at doses lower than those associated with maternal toxicity (exposure (AUC) less than maximum anticipated clinical exposure). The potential relevance to humans is unknown. Physicochemical and available pharmacodynamic/toxicological data on tapentadol point to excretion in breast milk and risk to the suckling child cannot be excluded. PALEXIA® SR should not be used during breast feeding.

Paediatric use
PALEXIA® SR is not recommended for use in children below 18 years of age due to insufficient data on safety and efficacy in this population.

Use in the elderly (persons aged 65 years and over)
In general, recommended dosing for elderly patients with normal renal and hepatic function is the same as for younger adult patients with normal renal and hepatic function. Because elderly patients are more likely to have decreased renal and hepatic function, care should be taken in dose selection as recommended (see **DOSAGE AND ADMINISTRATION** and also **Pharmacokinetics**).

Carcinogenicity
Tapentadol was administered to rats (diet) and mice (oral gavage) for two years. A significant trend towards increased hepatocellular tumours (adenoma and carcinoma) was observed in mice at oral doses of 100 mg/kg/day or greater. A dose-related increased incidence of hepatocellular hypertrophy (but not tumours) was observed in rats at dietary doses of 125 mg/kg/day or greater. Exposures (plasma AUC) in both species were less than that at the maximum recommended clinical dose. These findings may derive from adaptive changes following hepatic enzyme induction. The potential clinical relevance is unknown.

Genotoxicity
Tapentadol did not induce gene mutations in bacteria, but was clastogenic at cytotoxic concentrations in an *in vitro* chromosomal aberration test with metabolic activation in Chinese hamster V79 cells in 1 of 2 assays. The one

positive result for tapentadol was not confirmed *in vivo* in rats, using the two endpoints of chromosomal aberration and unscheduled DNA synthesis at extrapolated exposures (AUC) similar to the maximum anticipated human exposure. The weight of evidence indicates that tapentadol presents no significant genotoxic potential at clinical doses.

Effects on Ability to Drive and Use Machines
Like drugs with mu-opioid receptor agonist activity, PALEXIA® SR may have major influence on the ability to drive and use machines, due to the fact that it may adversely affect central nervous system functions (see **ADVERSE EFFECTS**). This has to be expected especially at the beginning of treatment, at any change of dosage as well as in connection with alcohol or tranquilizers (see **Interactions with other medicines**). Patients should be cautioned as to whether driving or use of machines is permitted.

Interactions with other medicines
Tapentadol is mainly metabolised by glucuronidation, a system with a very high capacity which is not easily saturated even in disease. As therapeutic concentrations of drugs that are subject to glucuronidation are generally well below the concentrations needed for potential inhibition of glucuronidation, the risk of clinically relevant interaction between these drugs is generally low. The following substances have been included in a set of interaction studies without any clinically significant finding: paracetamol, acetylsalicylic acid, naproxen, probenecid, omeprazole and metoclopramide (see **Pharmacokinetics**).

Only a small amount of tapentadol is metabolised by oxidative pathways (see **Pharmacokinetics**). Tapentadol was shown to be a weak inhibitor of human CYP2D6 activity in vitro but at concentrations 180- to 1400-fold higher than maximum concentrations in humans. *In vitro* induction experiments in human hepatocytes showed that CYP1A2, CYP2C9, and CYP3A4 activities were not markedly induced. Thus *in vitro* studies did not reveal any potential of tapentadol to either inhibit or induce cytochrome P450 enzymes. Tapentadol is an inducer of CYP1A, CYP2B and CYP2E in rats *in vivo*. The potential clinical relevance of this finding is unknown.Tapentadol was shown to be a weak inhibitor of human CYP2D6 activity *in vitro*, and an inducer of CYP1A, CYP2B and CYP2E in rats *in vivo.* The potential clinical relevance of this finding is unknown.

CNS depressants
Patients receiving other mu-opioid receptor agonist analgesics, general anesthetics, phenothiazines, other tranquilizers, sedatives, hypnotics or other CNS depressants (including alcohol and illicit drugs) concomitantly with PALEXIA® SR may exhibit an additive CNS depression. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with PALEXIA® SR. When such combined therapy is contemplated, the reduction of dose of one or both agents should be considered.

Monoamine oxidase (MAO) inhibitors
PALEXIA® SR is contraindicated in patients who are receiving monoamine oxidase (MAO) inhibitors or who have taken them within the last 14 days due

to potential additive effects on noradrenaline levels which may result in adverse cardiovascular events (see **CONTRAINDICATIONS**).

Serotonin Syndrome
PALEXIA® IR is a centrally acting synthetic analgesic combining mu-agonist and noradrenaline re-uptake inhibition activity

A causal relationship between tapentadol and serotonin syndrome has not been established, however there is a theoretical risk of serotonin syndrome when tapentadol is used in combination with serotonergic drugs such as selective serotonin re-uptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), SNRIs, tricyclic antidepressants (TCAs), MAOIs and triptans. Signs of serotonin syndrome may include confusion, agitation, fever, sweating, ataxia, hyperreflexia, myoclonus and diarrhoea. Withdrawal of the serotonergic drugs usually brings about a rapid improvement. Treatment depends on the nature and severity of the symptoms.

ADVERSE EFFECTS

Treatment emergent adverse events in the double-blind Phase 2/3 studies
In the pooled all Phase 2/3 PALEXIA® SR studies, the percentage of subjects administered PALEXIA® SR with at least 1 TEAE was 71.7%. This was higher when compared with the placebo group (54.5%) and lower than the oxycodone CR group (86.3%) (Table 3).

Compared with oxycodone CR there was better gastrointestinal tolerability with PALEXIA® SR. The incidence of nausea (19.5%), vomiting (7.4%) and constipation (13.6%) was lower with PALEXIA® SR than oxycodone CR (36.1%, 19.8% and 31.5%, respectively) (Table 3). PALEXIA® SR also had a beneficial safety profile over that of oxycodone CR for somnolence (11.3% vs 16.3%), dizziness (13.7% vs 19.8%), and pruritus (4.9% vs 12.4%). This suggests that the adverse event profile for PALEXIA® SR is similar to those of other opioid agonists, while at the same time exhibiting a lower incidence of a number of adverse events.
The majority of subjects in all treatment groups in the pooled all Phase 2/3 PALEXIA® SR studies experienced TEAEs that were mild to moderate in intensity. Less subjects in the all PALEXIA® SR group reported severe adverse events compared to those in the oxycodone CR group.

Table 5. TEAEs in at least 5% of subjects in any pooled treatment group (all studies) (PALEXIA® SR formulation Phase 2/3 studies integrated summary of safety: safety analysis set)[a]

System organ class/preferred term	Placebo (n=1498) n (%)	All PALEXIA® SR (n=3613) n (%)	All oxycodone CR (n=1472) n (%)
Number (n (%)) of subjects with TEAE	817 (54.5)	2589 (71.7)	1271 (86.3)
Gastrointestinal disorders	**370 (24.7)**	**1464 (40.5)**	**952 (64.7)**
Nausea	128 (8.5)	704 (19.5)	531 (36.1)
Constipation	85 (5.7)	493 (13.6)	464 (31.5)
Vomiting	44 (2.9)	269 (7.4)	292 (19.8)

Dry mouth	26 (1.7)	217 (6.0)	66 (4.5)
Diarrhoea	78 (5.2)	199 (5.5)	78 (5.3)
Nervous system disorders	**288 (19.2)**	**1308 (36.2)**	**662 (45.0)**
Dizziness	77 (5.1)	495 (13.7)	291 (19.8)
Headache	170 (11.3)	427 (11.8)	174 (11.8)
Somnolence	44 (2.9)	408 (11.3)	240 (16.3)
General disorders and administration site conditions	**138 (9.2)**	**583 (16.1)**	**290 (19.7)**
Fatigue	48 (3.2)	253 (7.0)	139 (9.4)
Skin and subcutaneous tissue disorders	**80 (5.3)**	**481 (13.3)**	**332 (22.6)**
Pruritus	20 (1.3)	176 (4.9)	183 (12.4)
Hyperhidrosis	16 (1.1)	160 (4.4)	75 (5.1)
Musculoskeletal and connective tissue disorders	**167 (11.1)**	**395 (10.9)**	**132 (9.0)**
Myalgia	9 (0.6)	42 (1.2)	10 (0.7)
Bone pain	2 (0.1)	16 (0.4)	1 (0.1)
Ear and labyrinth disorders	**23 (1.5)**	**109 (3.0)**	**49 (3.3)**
Vertigo	12 (0.8)	68 (1.9)	31 (2.1)

a: This summary of clinical safety includes clinical studies that vary in design (controlled dose adjustment, fixed dose, and open label) and subject population (lower back pain, pain due to OA, and pain due to peripheral neuropathy). Studies included: KF5503/09, KF5503/10, KF5503/19, KF5503/20, KF5503/24, KF5503/11, KF5503/12, KF5503/23, KF5503/36
MedDRA version 11.0 was used for coding.
TEAE = treatment emergent adverse events; MedDRA = Medical Dictionary for Regulatory Activities; N, n = number of subjects (total, per category).

The following adverse drug reactions (ADRs) were reported from clinical trials performed with PALEXIA® SR:

Very Common (≥ 1/10)

Nervous system disorders:	Dizziness, Somnolence, Headache
Gastrointestinal disorders:	Nausea, Constipation

Common (≥1/100 to <1/10)

Metabolism and nutrition disorders:	Decreased appetite
Psychiatric disorders:	Anxiety, Depressed mood, Sleep disorder, Nervousness, Restlessness
Nervous system disorders:	Disturbance in attention, Tremor, Muscle contractions involuntary
Vascular disorders:	Flushing
Respiratory, thoracic and mediastinal disorders:	Dyspnoea
Gastrointestinal disorders:	Vomiting, Diarrhoea, Dyspepsia
Skin and subcutaneous tissue disorders:	Pruritus, Hyperhidrosis, Rash

General disorders and administration site conditions:	Asthenia, Fatigue, Feeling of body temperature change, Mucosal dryness, Oedema

Uncommon (≥1/1,000 to <1/100)

Immune system disorders:	Drug hypersensitivity
Metabolism and nutrition disorders:	Weight decreased
Psychiatric disorders:	Disorientation, Confusional state, Agitation, Perception disturbances, Abnormal dreams, Euphoric mood
Nervous system disorders:	Depressed level of consciousness, Memory impairment, Mental impairment, Syncope, Sedation, Balance disorder, Dysarthria, Hypoaesthesia, Paraesthesia
Eye disorders:	Visual disturbance
Cardiac disorders:	Heart rate increased, Heart rate decreased
Vascular disorders:	Blood pressure decreased
Gastrointestinal disorders:	Abdominal discomfort
Skin and subcutaneous tissue disorders:	Urticaria
Renal and urinary disorders:	Urinary hesitation, Pollakiuria
Reproductive system and breast disorders:	Sexual dysfunction
General disorders and administration site conditions:	Drug withdrawal syndrome, Feeling abnormal, Irritability

Rare (≥1/10,000 to <1/1,000)

Psychiatric disorders:	Drug dependence, Thinking abnormal
Nervous system disorders:	Convulsion, Presyncope, Coordination abnormal
Respiratory, thoracic and mediastinal disorders:	Respiratory depression
Gastrointestinal disorders:	Impaired gastric emptying
General disorders and administration site conditions:	Feeling drunk, Feeling of relaxation

Treatment emergent adverse events with prolonged treatment

A total of 894 subjects with moderate to severe pain from low back pain or osteoarthritis of the knee or hip were treated with a flexible dosing regimen of PALEXIA® SR (100 mg to 250 mg twice daily) in a 1 year safety study (KF5503/24). The overall TEAE profile for prolonged treatment did not differ from the profile observed in short-term treatment. The overall incidence of TEAEs was lower in the PALEXIA® SR group (85.7%) compared to oxycodone CR (20 mg to 50 mg) (90.6%).

The most common TEAEs (incidence >10% in either treatment group) were constipation, nausea, vomiting, somnolence, dizziness, headache, fatigue and pruritus. Subjects administered PALEXIA® SR had a lower incidence of constipation, nausea, vomiting, dizziness, fatigue and pruritus compared to oxycodone CR (22.6% vs 38.6%, 18.1% vs 33.2%, 7.0% vs 13.5%, 14.8% vs 19.3%, 9.7% vs 10.3%, and 5.4% vs 10.3% respectively).

Post marketing experience
There have been no adverse reactions identified from spontaneous reports so far for PALEXIA® SR.

DOSAGE AND ADMINISTRATION

As with many centrally acting analgesic medications, the dosing regimen should be individualized according to the severity of pain being treated, the previous treatment experience and the ability to monitor the patient.

PALEXIA® SR should be taken twice daily, approximately every 12 hours. PALEXIA® SR may be administered with or without food.

Initiation of therapy
a) Initiation of therapy in patients currently not taking opioid analgesics:
Patients should start treatment with single doses of 50 mg tapentadol administered twice daily.

b) Initiation of therapy in patients currently taking opioid analgesics:
When switching from opioids to PALEXIA® SR and choosing the initial dose, the nature of the previous medication, administration and the mean daily dose should be taken into account.

Titration and maintenance
After initiation of therapy the dose should be titrated individually to a level that provides adequate analgesia and minimizes side effects under the close supervision of the prescribing physician.

Experience from clinical trials has shown that a titration regimen in increments of 50 mg tapentadol twice daily every 3 days was appropriate to achieve adequate pain control in most of the patients.

Total daily doses of PALEXIA® SR tablets greater than 500 mg tapentadol have not been studied and are therefore not recommended.

Discontinuation of treatment
Tapering of therapy is not required, but patients should be cautioned about the possibility of experiencing withdrawal symptoms (see **ADVERSE EFFECTS**).

Renal Impairment
No dosage adjustment is recommended in patients with mild or moderate renal impairment (see **Pharmacokinetics**).

PALEXIA® SR has not been studied in controlled efficacy studies in patients with severe renal impairment, and its use is not recommended. A pharmacokinetic study showed an increased level of an inactive metabolite in subjects with renal impairment (see **PRECAUTIONS** and also **Pharmacokinetics**).

Hepatic Impairment
No dosage adjustment is recommended in patients with mild hepatic impairment (see **Pharmacokinetics**).

PALEXIA® SR should be used with caution in patients with moderate hepatic impairment. Treatment in these patients should be initiated at 50 mg tapentadol and not be administered more frequently than once every 24 hours. Further treatment should reflect maintenance of analgesia with acceptable tolerability (see **PRECAUTIONS** and also **Pharmacokinetics**).

PALEXIA® SR has not been studied in patients with severe hepatic impairment and, therefore, use in this population is not recommended (see **PRECAUTIONS** and also **Pharmacokinetics**).

Elderly Patients (persons aged 65 years and over)
In general, recommended dosing for elderly patients with normal renal and hepatic function is the same as for younger adult patients with normal renal and hepatic function. Because elderly patients are more likely to have decreased renal and hepatic function, care should be taken in dose selection as recommended (see **PRECAUTIONS** and also **Pharmacokinetics**).

Paediatric Patients
PALEXIA® SR is not recommended for use in children below 18 years of age due to insufficient data on safety and efficacy in this population (see **PRECAUTIONS**).

OVERDOSAGE

Experience with PALEXIA® SR overdose is very limited. Preclinical data suggest that symptoms similar to those of other centrally acting analgesics with mu-opioid receptor agonist activity are to be expected upon intoxication with tapentadol. In the clinical setting, these symptoms may include miosis, vomiting, cardiovascular collapse, consciousness disorders up to coma, convulsions and respiratory depression up to respiratory arrest.

Management of overdose should be focused on treating symptoms of mu-opioid receptor agonism. Primary attention should be given to re-establishment of a patent airway and institution of assisted or controlled ventilation when overdose of PALEXIA® SR is suspected.

Pure opioid antagonists such as naloxone, are specific antidotes to respiratory depression resulting from opioid overdose. Respiratory depression following an overdose may outlast the duration of action of the opioid antagonist. Administration of an opioid antagonist is not a substitute

for continuous monitoring of airway, breathing, and circulation following an opioid overdose. If the response to opioid antagonists is suboptimal or only brief in nature, an additional antagonist should be administered as directed by the manufacturer of the product.

Gastrointestinal decontamination may be considered in order to eliminate unabsorbed drug. Gastrointestinal decontamination with activated charcoal or by gastric lavage may be considered within 2 hours after intake. Before attempting gastrointestinal decontamination, care should be taken to secure the airway.

Contact the Poisons Information Centre on 131 126 for further advice on overdosage management.

PRESENTATION AND STORAGE CONDITIONS

- PALEXIA® SR 50 mg sustained release tablets: white film-coated oblong shaped tablets with Grünenthal logo engraving on one side and "H1" engraving on the other side.
- PALEXIA® SR 100 mg sustained release tablets: pale yellow film-coated oblong shaped tablets with Grünenthal logo engraving on one side and "H2" engraving on the other side.
- PALEXIA® SR 150 mg sustained release tablets: pale pink film-coated oblong shaped tablets with Grünenthal logo engraving on one side and "H3" engraving on the other side.
- PALEXIA® SR 200 mg sustained release tablets: pale orange film-coated oblong shaped tablets with Grünenthal logo engraving on one side and "H4" engraving on the other side.
- PALEXIA® SR 250 mg sustained release tablets: brownish red film-coated oblong shaped tablets with Grünenthal logo engraving on one side and "H5" engraving on the other side.

Blister Packs of 7, 10, 14, 20, 28, 30, 40, 50, 56, 60, 90, 100 tablets.

Not all pack sizes may be available.

PALEXIA® SR 50 mg, 100 mg, 150 mg, 200 mg and 250 mg sustained release tablets have a shelf-life of 36 months when stored below 30°C. Protect from light.

NAME AND ADDRESS OF SPONSOR

CSL Limited ABN 99 051 588 348
45 Poplar Road
Parkville 3052
Australia

POISON SCHEDULE OF THE MEDICINE

Controlled Drug, S8

DATE OF TGA APPROVAL 24 December 2010

PALEXIA® is a registered trademark of Grunenthal GmbH, used under licence.

Attachment 2

Key efficacy results for tapentadol SR and oxycodone in pivotal studies

	KF5503/11 (n=1023), Osteoarthritis			KF5503/12 (n=987), Osteoarthritis			KF5503/23 (n=958), Lower back pain			Meta-analysis		
	Placebo (n=336)	**PALEXIA® SR (n=344)**	**Oxycodone CR (n=342)**	**Placebo (n=336)**	**PALEXIA® SR (n=319)**	**Oxycodone CR (n=331)**	**Placebo (n=316)**	**PALEXIA® SR (n=312)**	**Oxycodone CR (n=323)**	**Placebo (n=991)**	**PALEXIA® SR (n=978)**	**Oxycodone CR (n=999)**
Baseline pain Mean (SD)	7.2 (1.29)	7.4 (1.35)	7.2 (1.29)	7.3 (1.12)	7.3 (1.09)	7.3 (1.10)	7.6 (1.32)	7.5 (1.32)	7.5 (1.22)	7.4 (1.25)	7.4 (1.26)	7.3 (1.21)
Wk 12 maintenance Mean (SD)	5.0 (2.61)	4.4 (2.48)	4.7 (2.35)	4.8 (2.47)	4.5 (2.48)	5.0 (2.44)	5.5 (2.57)	4.6 (2.66)	4.6 (2.56)	5.1 (2.56)	4.5 (2.54)	4.8 (2.45)
LS Means diff from placebo Baseline vs Wk 12[a]		-0.7 (0.18)	-0.3 (0.18)		-0.3 (0.18)	0.2 (0.18)		-0.8 (0.19)	-0.9 (0.19)		-0.6 (0.11)	-0.3 (0.11)
p-value 95% CI[b]		<0.001 (-1.04, -0.33)	0.069 (-0.68, 0.02)		0.152 (-0.61, 0.09)	0.279 (-0.16, 0.54)		<0.001 (-1.22, -0.47)	<0.001 (-1.24, -0.49)		<0.001 (-0.80, -0.39)	0.002 (-0.53, -0.12)
Overall maintenance Mean (SD)	5.1 (2.48)	4.4 (2.40)	4.7 (2.26)	5.0 (2.24)	4.7 (2.28)	5.1 (2.29)	5.5 (2.46)	4.7 (2.52)	4.6 (2.38)	5.2 (2.40)	4.6 (2.40)	4.8 (2.32)
LS Means diff from placebo Baseline vs overall[a]		-0.7 (0.17)	-0.3 (0.17)		-0.2 (0.16)	0.1 (0.16)		-0.7 (0.18)	-0.8 (0.18)		-0.5(0.10)	-0.3(0.10)
p-value 95% CI[b]		<0.001 (-1.00, –0.33)	0.049 (-0.67, -0.00)		0.135 (-0.55, 0.07)	0.421 (-0.18, 0.44)		<0.001 (-1.06, -0.35)	<0.001 (-1.16, -0.46)		<0.001 (-0.73, -0.34)	<0.001 -0.52, -0.14)
30% responder rate	35.9%	43.0%[c]	24.9%[c]	40.9%	41.1%	26.0%[d]	27.1%	39.7%[c]	36.5%	34.8%	41.3%[c]	27.0%[d]
50% responder rate	24.3%	32.0%[c]	17.3%[d]	27.0%	31.0%	22.1%	18.9%	27.0%[c]	17.4%	23.5%	30.1%[c]	20.8%
PGIC assessment of very much improved & much improved	35.5%	58.5%[c]	47.0%[c]	43.2%	56.0%[c]	42.5%	32.7%	55.5%[c]	60.0%[c]	37.4%	56.7%[c]	49.8%[c]

a: Change from baseline in average pain intensity scores based on numerical rating scale (NRS)[a], ITT population**;** LOCF = last observation carried forward Average pain scores are the averages of all scores recorded during the baseline period or during each time period (Week 12 of maintenance or overall maintenance).
b: Test for no difference between treatment from ANCOVA model with factor(s) treatment, pooled centre and baseline pain intensity as covariate (type III SS) unadjusted p-value.
c:Indicates statistically significant over placebo
d: Indicates statistical significance of placebo over active
LS = least square