Summary of Safety Results and Conclusions

Exposure

A total of 3515 subjects were exposed to at least one dose of tapentadol IR during the development program, 467 during Phase 1 trials, 870 in Phase 2 single-dose trials, and 2178 in nine Phase 2/3 multiple-dose, double-blind trials. Phase 2/3 multiple-dose double-blind trials were carried out in the following populations: post-operative dental pain, post-operative bunionectomy pain, chronic non-malignant pain, end-stage joint disease, osteoarthritis, and chronic low back pain.

In the Phase 2/3 multiple-dose, double-blind trials, 2,034 subjects received 50mg-100mg per dose. A total of 449 subjects received flexible dosing of 50mg or 100mg every 4-6 hours as needed for at least 45 days, and 318 of these subjects received tapentadol IR for at least 90 days.

Therefore, in regard to the sought indication, an adequate number of subjects have been exposed to tapentadol IR to meet the ICH guidelines for exposure.

Deaths and Serious Adverse Events (SAEs)

No deaths were reported after treatment with tapentadol IR in any of the completed Phase 1 through 3 studies. Four deaths were reported in the Phase 3 tapentadol ER ongoing studies as of March 15, 2008. Details are located in Section 7.3.1.

There were a total of 21 nonfatal SAEs reported in 17 subjects from all phases of the completed studies in the tapentadol IR development program in subjects who received tapentadol IR. Serious adverse events occurred in 1% of subjects in the multiple-dose, double-blind safety analysis set treated with either tapentadol IR or oxycodone. The rate of SAEs in placebo treated patients was <1%.

The most commonly occurring SAEs (by System Organ Class (SOC) included cardiac disorders and nervous system disorders. All SOCs or individual preferred terms occurred in <1% of treated subjects in the tapentadol IR group. The occurrence of SAEs did not appear to be dose related. Details regarding all SAEs are located in Section 7.3.2.

Common Adverse Events

Treatment emergent adverse events (TEAEs) occurred in 76% of the "all" tapentadol group in the multiple-dose, double-blind safety analysis set, compared to 47% in the placebo group and 84% in the "all" oxycodone group. The most common TEAEs in the tapentadol IR group were nausea, dizziness, vomiting, somnolence, headache, constipation and pruritis. These occurred at a greater rate in the tapentadol IR group than in the placebo group. TEAEs related to asthenic conditions when combined (fatigue, lethargy, asthenia and malaise) were also common. The incidence of TEAEs appeared to be dose related.

There were no meaningful differences in adverse events reported with respect to age or racial groups. There was, however, an observation of a higher incidence of nausea, vomiting and dizziness in women compared to men treated with tapentadol IR or oxycodone IR compared to placebo.

A full discussion of TEAEs may be found in Section 7.4.1.

Adverse Events of Interest

The Division requested that SMQs be performed on the pooled TEAE data for 1) severe cutaneous reactions and 2) possible drug-related hepatic disorders. In the nine Phase 2/3 multiple-dose, double-blind studies, the percentage of subjects with TEAEs included in the severe cutaneous reactions SMQ was <1% in the "all" tapentadol group, similar to the percentage in the placebo group (<1%). The data do not point to a signal regarding severe cutaneous reactions of tapentadol IR.

The percentage of subjects with adverse events included in the possible drug-related hepatic disorders SMQ was 1% in both the "all" tapentadol group and the placebo group. The most commonly reported events in the "all" tapentadol group included increased GGT (<1%), ALT (<1%), and AST (<1%). In evaluation of laboratory abnormalities, no treatment-related laboratory findings were evident for liver function tests. Details of the SMQ analyses are located in Section 7.5.5, and laboratory evaluations in Section 7.4.2.

There was one report of seizure in the Phase 1 trial HF5503/10. This subject had a history of seizures ("grand-mal epilepsy) which was withheld during screening. He had stopped taking his seizure medication (valproic acid) a few months prior to enrollment in the study.

Laboratory Tests and Vital Signs

The only laboratory test result or vital sign measurement that showed consistent patterns that would indicate a potential for clinically relevant safety concerns in the Phase 1, 2, or 3 completed studies of tapentadol IR was oxygen saturation as measured by pulse oximetry. No consistent changes in cardiac parameters of heart rate or blood pressure were observed. In studies that measured oxygen saturation by pulse oximetry, a dose-dependent increase in the number of subjects with oxygen desaturation was detected with tapentadol IR. Similar findings were observed in with oxycodone IR; these findings reflect the mu-opioid agonist properties of tapentadol IR. Laboratory evaluations and vital signs are discussed in Sections 7.4.2 and 7.4.3 respectively.

ECG/QT Interval

In a thorough QT Phase 1 study, no effect of therapeutic (100 mg) and supratherapeutic (150 mg) doses of tapentadol IR on the QT interval was shown. Similarly, tapentadol IR had no relevant effect on other ECG parameters of heart rate, PR interval, QRS duration, T-wave or U-wave morphology. The assay sensitivity of the study was validated by the expected QTc prolongation observed in the moxifloxacin group.

There was no evidence of drug-related ECG abnormalities in the analysis of ECGs obtained during the Phase 1, 2, or 3 studies of tapentadol IR.

Evaluation of ECGs and the TQT study are discussed in Sections 7.4.4 and 7.4.5 respectively.

Drug-Disease Interactions

The results of the Phase 1 drug-disease interaction studies in subjects with hepatic impairment (HP5503/16) and in subjects with renal impairment (HP5503/15) demonstrated that, although there were effects on the pharmacokinetics of the parent compound or of the major metabolite, tapentadol IR was well tolerated with a safety profile similar to that observed in other single-dose tapentadol IR studies in healthy subjects. Nevertheless, the Applicant's dosing recommendations will reflect the results of the pharmacokinetic assessment in these populations, considering the potential outcomes in multiple-dosing situations

These studies are discussed in Section 7.5.3

Drug-drug interactions

No clinically relevant interactions were observed in the 4 Phase 1 drug-drug interaction studies when tapentadol IR was coadministered with metoclopramide (HP5503/19), probenecid (HP5503/21), naproxen and ASA (HP5503/22), or acetaminophen (HP5503/23). There was however approximately twice the percentage of reports of vomiting and somnolence in the group that received omeprazole plus tapentadol compared to tapentadol alone in Study (HP5503/20). There were not however changes in the PK parameters of tapentadol when coadministered with omeprazole.

These studies are discussed in Section 7.5.4.

Abuse liability, overdose, and withdrawal

Results from a Phase 1 study, conducted in opiate-experienced, nondependent subjects, showed that single doses of tapentadol IR (50, 100, and 200 mg) had a similar abuse liability profile to that of hydromorphone IR (4, 8, and 16 mg).

No cases of overdose were reported in the completed studies with tapentadol IR.

A small number of patients self-administered more than the intended daily dose of tapentadol IR, up to 1200mg/day for one or two days. All subjects had prior opioid experience and none reported an adverse event.

Withdrawal was evaluated in one study (KF5503/34). Seventeen percent of subjects in the tapentadol treatment group reported at least one withdrawal symptom. One percent (9/679) of subjects experienced drug withdrawal syndrome, one of which was coded as a serious adverse event (elevated systolic BP, irritability and anxiety).

It is clear that withdrawal can occur following abrupt cessation of tapentadol IR administration.

There were no reports of study drug diversion.

Abuse liability, overdose, and withdrawal are discussed in detail in Section 7.6.3.

Comparison with oxycodone

Throughout the Phase 2/3 multiple-dose double-blind studies, oxycodone was used as an active comparator to assess assay sensitivity. Safety data was collected on all subjects in the oxycodone treatment groups, and the rates of adverse events for tapentadol IR were compared to both placebo and oxycodone. The incidence of gastrointestinal events (nausea, vomiting, and constipation) was lower in the "all" tapentadol group compared to the "all" oxycodone group. The overall incidence of CNS effects of somnolence and dizziness was similar for tapentadol IR and oxycodone treated subjects, however in study KF5503/32 (post-operative bunionectomy pain), the incidence of somnolence was reported approximately twice as frequently in the tapentadol IR 100mg group (21%) than in the oxycodone 15mg IR group (10%).

The findings in the 2 pivotal Phase 3 studies are supported by the results of the Phase 3, 90-day safety study. In this study, comparisons between tapentadol IR (flexible doses of 50 mg or 100 mg) and oxycodone HCl IR (flexible doses of 10 mg or 15 mg) showed a lower likelihood of nausea, vomiting, nausea/vomiting (the composite nausea or vomiting), and constipation with tapentadol IR vs. oxycodone IR, and a similar likelihood of somnolence or dizziness between the tapentadol IR and oxycodone IR treatments.

Pertinent negatives

There were no reports of seizures during the development of tapentadol IR. This is relevant because of the known risk of seizures associated with Tramadol, and the similarity in the mechanisms of action of the two drugs.

Given that tapentadol is structurally related to tramadol whose labeling contains language warning about the risks of serotonin syndrome and tapentadol's selective norepinephrine reuptake inhibitor activity, tapentadol carries at least a theoretical risk of precipitating serotonin syndrome. Therefore, the following analysis was performed by Dr. Robert Shibuya.

The integrated database for the Phase 2/3 studies, excluding periods when subjects were not on study drug (screening, post-treatment), was searched for the following verbatim terms: serotonin, syndrome, myoclonus, tremor, fever, tachycardia, diaphoresis, mydriasis, hyperreflexia, hyperthermia, pyrexia, clonus, and hypertension. Patients treated with morphine or ibuprofen were also excluded due to small numbers. One hundred and four adverse events, occurring in 101 subjects were identified. These are summarized in Table 32b, below.

Table 32b: Adverse events associated with serotonin syndrome (tapentadol, placebo, and oxycodone-treated subjects only)

Sx/Si	Severity	Tapentadol	Placebo	Oxycodone
n (%)		2178	619	675
Diaphoresis	Total	41 (1.9)	1 (0.3)	11 (1.6)
	Mild	23	1	6
	Moderate	16		5
	Severe	2	1	
Fever	Total	14 (0.6)	0	3 (0.4)
	Mild	12		2
	Moderate	2		1
HTN	Total	16 (0.7)	2 (0.3)	0
	Mild	13	2	
	Moderate	3		
Tachycardia	Total	14 (0.6)	1 (0.3)	0
	Mild	8	1	
	Moderate	5		
	Severe	1		

Table 32b shows that the non-specific symptoms and signs associated with serotonin syndrome were observed more frequently in subjects treated with tapentadol than with the comparators. However, it should be noted that serotonin syndrome is a constellation of symptoms and signs. Three subjects experienced more than one adverse event associated with serotonin syndrome. Details are summarized in Table 32c.

Table 32c: Adverse events associated with serotonin syndrome reported more than once in a subject

Subject ID	Treatment	AE	Severity*	Related*
KF5504/04-005-5180	Tapentadol	HTN	Mild	No
KF5504/04-005-5180	Tapentadol	HTN	Mild	No
KF5504/04-005-5232	Placebo	Tachycardia	Mild	Possible
KF5504/04-005-5232	Placebo	Diaphoresis	Mild	Unlikely
KF5503/22-006-600001	Tapentadol	Diaphoresis	Mild	Probable
KF5503/22-006-600001	Tapentadol	Diaphoresis	Mild	Possible

*Severity and relationship to study drug administration were both in the investigator's judgment

Table 32c shows that three subjects experienced more than one serotonin syndrome-related adverse event. However, each subject only experienced two AEs and one of the subjects was treated with placebo. Therefore, it is extremely unlikely that any of these cases represented serotonin syndrome.

Overall, there was no evidence that tapentadol resulted in serotonin syndrome.

Overall conclusions

The safety profile of tapentadol IR was demonstrated in over 3500 subjects treated with tapentadol IR in the completed Phase 1, 2, and 3 studies. Tapentadol IR appears reasonably well tolerated across the intended marketed dose range (50mg, 75mg, or 100mg every 4 to 6 hours as needed) in both inpatient and outpatient settings. The profile

of adverse events is consistent with a centrally-acting compound with mu-opioid agonist activity. The data provided by the Applicant appears adequate, as does the exposure to study drug.

The Applicant has submitted a risk management proposal (Section 1.3) that includes both general pharmacovigilance and product specific activities to mitigate risks associated with the use of tapentadol IR. A complete review of this plan has been completed by DRISK (June 26, 2008). At this writing, the Eight Factor Analysis for scheduling is underway; however the Applicant has requested a Schedule II determination for tapentadol IR. As a Schedule II immediate-release opioid product for the treatment of acute pain, a pharmacovigilance plan rather than a REMS (Risk Evaluation and Mitigation Strategy) is likely sufficient to manage the risks associated with the use of tapentadol IR given the safety profile to date. The risks associated with the use of tapentadol IR are similar to the risks of other immediate-release opioids indicated for the treatment of pain. If post-marketing safety data reveals additional safety risks, the level of risk management will be reevaluated and augmented as needed.

Tapentadol IR has not been studied in subjects 18 years of age or younger. Studies must be administered to children prior to general use in this population. The Applicant has submitted a Pediatric Plan that is discussed in Section 1.4. A staged deferral has been requested, such that older age groups will be studied prior to younger ones. This plan will be reviewed by PERC on October 8, 2008.

7.1 Methods

7.1.1 Discussion of Clinical Studies Used to Evaluate Safety

Thirty-one clinical trials have been completed during the development of Tapentadol IR (20 Phase 1, and 11 Phase 2/3 double-blind studies). Two additional Phase 3 studies (KF5503/38 and KF5503/37) were ongoing at the time of the 4-month safety update, and are also included in the safety summary.

The Applicant pooled studies for the safety data as follows:

- Twenty-nine of the 31 completed clinical studies of tapentadol IR are presented in 5 separate pooled safety analysis sets.
    - Two pooled analysis sets (single-dose and multiple-dose studies) of 18 Phase 1 studies
    - Three pooled analysis sets (single-dose, multiple-dose double-blind, and open-label extension) of 11 Phase 2/3 studies.
- Safety results from 2 completed Phase 1 studies of Tapentadol IR (R331333-PAI-1027 in healthy Japanese subjects living in the USA; and HP5503/25, a thorough QT study) are presented separately.
- The Applicant provided references to safety data from other tapentadol formulations (ER, i.v. infusions, and oral solution) in the ISS.
- Adverse event data from four completed Phase 2 studies of tapentadol ER were integrated and presented in a single pooled analysis set.

The Applicant's figure below shows the pooling scheme:

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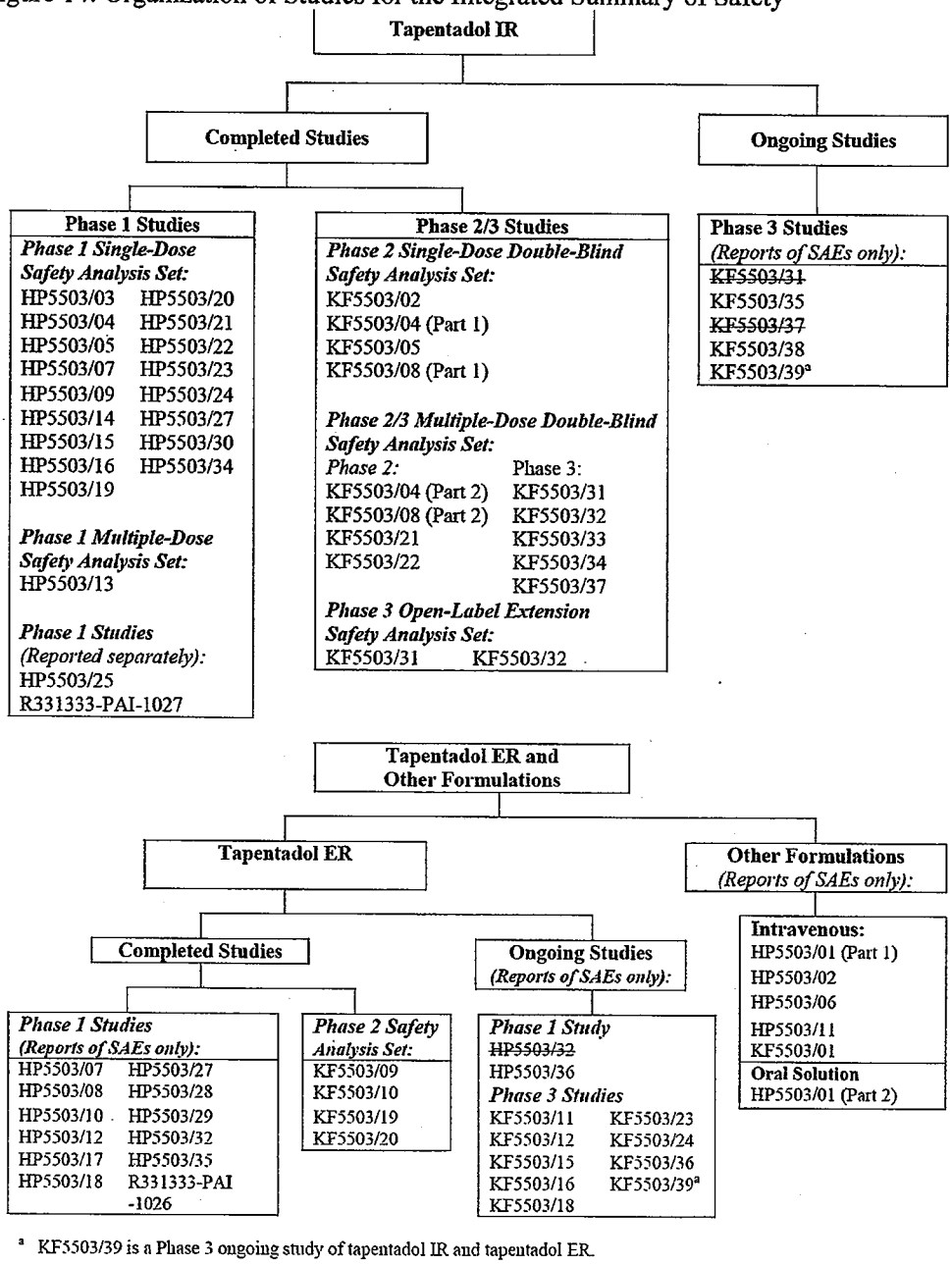
Figure 14: Organization of Studies for the Integrated Summary of Safety



[a] KF5503/39 is a Phase 3 ongoing study of tapentadol IR and tapentadol ER.

Source: Tapentadol ISS, 4-month safety update p. 46

A brief description of Phase 1 studies may be found in Section 9.4.

Safety data for subjects randomized at site 011006 in KF5503/31 were excluded from Phase 2/3 Multiple-dose Double-blind Safety Analysis Set and Open-label Extension

Safety Analysis Set in the integrated 4-month safety update database by the Applicant due to data irregularities discovered during an audit. Data for 35 subjects (1%, 35/3642) randomized in the double-blind treatment period and 26 subjects (5%, 26/537) enrolled in the open-label extension period at site 011006 in KF5503/31 are presented separately. According to the Applicant, the exclusion of these data from the main analysis populations did not impact the results of the integrated safety analysis. This will be assessed in the sections below.

The data irregularities were found as a result of an investigation of a single clinical investigator. On October 2-4, 2007, to assess concerns regarding duplicate ECG tracings across multiple subjects DSI performed an inspection of the study site. Details regarding the results of the investigation may be found in Section 3.2.

7.1.2 Adequacy of Data

In the individual study reports, adverse events were coded to preferred terms using various versions of Medical Dictionary of Regulatory Activities (MedDRA). MedDRA version 10.0 was used in the original NDA and updated to version 10.1 in the 4-month safety update. A review was performed comparing the verbatim terms to the preferred terms. The Applicant's approach to safety coding appeared adequate.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence.

The pooled data used in the review of safety is described in Section 7.1.1. This review of safety emphasizes the Phase 2/3 Multiple-Dose Double-Blind, and Phase 3 Open-Label Extension safety analysis sets. The double-blind safety analysis set allows for the comparison of adverse event rates between those receiving study drug and placebo, which is useful in determining possible causality. The Phase 3 Open-Label extension safety analysis set shows adverse events occurring after longer term use of tapentadol IR. Any important safety information obtained from the other safety analysis sets (Phase 1, Phase 2 single-dose, Phase 3 open-label) are also discussed in this review.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The exposure to Tapentadol IR in terms of numbers of subjects, dose and duration, and demographics was adequate. The details are delineated below by safety analysis set groupings.

Exposure

A total of 3515 subjects were exposed to at least one dose of tapentadol IR during the development program. The breakdown by study phase is shown below.

Table 33: Exposure to Tapentadol IR

Study Phase (Analysis set)	**Number of subjects exposed to tapentadol IR**
Phase 1 single and multiple-dose	467
Phase 2 single-dose	870
Phase 2/3 multiple-dose, double-blind	2178
Total	3515

Phase 1 single and multiple-dose

In the Phase 1 Single-dose Safety Analysis Set, 439 subjects received a single-dose of tapentadol IR (21 to 200 mg).

In the multiple-dose study (HP5503/13), 2 subjects received 4 doses, 15 subjects received 6 doses, and 8 subjects received 12 doses of tapentadol IR.

Phase 2 single-dose

A total of 870 subjects received a single dose of tapentadol IR in the Phase 2 single-dose Safety Analysis Set in 1 of the following dose groups: 0-30 mg (n=138), >30-60 mg (n=187), >60-90 mg (n=327), and >120 mg (n=218).

Phase 2/3 multiple-dose double-blind

Two-thousand, one-hundred seventy-eight subjects with moderate-to-severe pain received tapentadol IR (21-120mg) in nine clinical studies included in the Phase 2/3 Multiple-Dose, Double-Blind Safety Analysis Sets; 2034 of these subjects received tapentadol IR (50 to 100 mg every 4 to 6 hours as needed) for at least 45 days, and 318 received tapentadol IR for at least 90 days in study KF5503/34.

Table 34: Duration of Exposure: Phase 2/3 Multiple-Dose, DB Analysis Set

	Placebo (n=619)	"All" Tapentadol IR (n=2178)	"All" Oxycodone IR (n=675)
Treatment duration, days[a]			
N	619	2178	675
Mean (SD)	4.3 (3.47)	22.3 (34.35)	17.8 (30.98)
Median	3.0	4.0	4.0
Range	(1;10)	(1;105)	(1;106)
Treatment duration category, n (%)[a]			
N	619	2178	675
1 day	191 (31)	481 (22)	142 (21)
≥2-3 days	200 (32)	592 (27)	195 (29)
>3-10 days	228 (37)	535 (25)	211 (31)
>10-45 days	0	121 (6)	25 (4)
>45 days	0	449 (21)	102 (15)
Total duration, days[b]			
N	619	2178	675
Mean (SD)	4.3 (3.48)	22.7 (34.88)	18.1 (31.32)
Median	3.0	4.0	4.0
Range	(1;12)	(1;105)	(1;111)
Total duration category, n (%)[b]			
N	619	2178	675
1 day	191 (31)	481 (22)	141 (21)
≥2-3 days	199 (32)	586 (27)	192 (28)
>3-10 days	228 (37)	534 (25)	213 (32)
>10-45 days	1 (<1)	123 (6)	25 (4)
>45 days	0	454 (21)	104 (15)

Studies included: KF5503/04 (Part 2), KF5503/08 (Part 2), KF5503/21, KF5503/22, KF5503/31 (excluding site 011006), F5503/32, KF5503/33, KF5503/34, and KF5503/37.

[a] calculated based on the accumulative number of days on treatment during the treatment phase.

[b] calculated based on the number of days on study.

Subject R331333-PAI-3004-011002-400880 entered both KF5503/33 and KF5503/34 studies and was treated with tapentadol but was counted once in the "all" tapentadol IR group by using KF5503/34 study data with longer treatment duration.

SD = standard deviation.

Source: Tapentadol 4-Month Safety Update, p. 96

Among subjects in the "all" tapentadol IR pooled analysis treatment group, the mean total daily dose based on days on study drug (271.31) and the mean total daily dose while on study drug including days on and off study drug (269.42) were similar. The maximum mean total daily tapentadol IR dose taken was 800 mg.

The maximum total daily dose of tapentadol IR specified in the Phase 2/3 multiple-dose, double-blind protocols was 700 mg on Day 1 and 600 mg thereafter. Seven subjects in the Phase 3 study, KF5503/34, took a total daily dose of 1200 mg for 1 or 2 days. Further description of these subjects is provided in Section 7.6.4 (Overdose, Drug Abuse Potential/ Withdrawal and Rebound).

The Applicant's table below shows the extent of exposure by mean daily dose during the Phase 2/3 Multiple-Dose, Double-Blind Safety Analysis Set. The mean daily dose was 271 mg in the "all" tapentadol IR group, with a range of 50 to 800 mg.

Table 35: Extent of Exposure-Mean Total Daily Dose: Phase 2/3 Multiple-Dose, Double Blind

	Placebo (n=619)	"All" Tapentadol IR (n=2178)	"All" Oxycodone IR (n=675)
Mean total daily dose (mg) (days on drug only)[a]			
N	619	2178	675
Mean (SD)	0.00 (0.000)	271.31 (126.570)	40.24 (20.872)
Median	0.00	250.00	35.00
Range	(0.0;0.0)	(50.0;800.0)	(10.0;95.0)
Mean total daily dose (mg) (days on/off drug)[b]			
N	619	2178	675
Mean (SD)	0.00 (0.000)	269.42 (126.910)	40.04 (20.920)
Median	0.00	247.39	35.00
Range	(0.0;0.0)	(15.4;800.0)	(2.5;95.0)

Studies included: KF5503/04 (Part 2), KF5503/08 (Part 2), KF5503/21, KF5503/22, KF5503/31 (excluding site 011006), KF5503/32, KF5503/33, KF5503/34, and KF5503/37.

[a] Mean daily dose calculated based on the accumulative number of days on treatment during the treatment phase.

[b] Mean daily dose calculated based on the number of days on study.

Subject R331333-PAI-3004-011002-400880 entered both KF5503/33 and KF5503/34 studies and was treated with tapentadol IR in each study but was counted once in the "all" tapentadol IR group by using KF5503/34 study data with higher treatment dose.

Source: Tapentadol IR 4-Month Safety Update, p. 98

Phase 3 open-label

A total of 483 subjects received tapentadol IR (flexible dose 50 or 100 mg) during the Phase 3 open-label extension studies (KF5503/31 and KF5503/32). The mean duration of treatment was seven days, with a range of one to ten days.

The mean daily dose of tapentadol IR was 234.78 mg, with a range of 50 to 600 mg.

Demographics

Phase 1 single and multiple-dose safety analysis set

In the Phase 1 Single-dose Safety Analysis Set, demographic and baseline characteristics were similar in "all" tapentadol IR and the placebo pooled analysis treatment groups. The majority of subjects were female (60% in the "all" tapentadol IR group and 74% in the placebo group) and white (82% and 87%, respectively). The mean age was 39.6 years in the "all" tapentadol IR group and 32.7 years in the placebo group. Mean BMI was 24.39 kg/m2 in the "all" tapentadol IR group and 24.01 kg/m2 in the placebo group pooled analysis treatment groups. Table 93 in Section 9.4 illustrates the demographic characteristics.

In the Phase 1 multiple-dose study (HP5503/13), demographic and baseline characteristics were similar across the pooled analysis treatment groups. About half of subjects in the pooled analysis treatment groups were male (50% in the "all" tapentadol IR group and 59 % in the placebo group); the majority of subjects were white (66% and 71%).

Phase 2 single-dose

Demographic and baseline characteristics were similar in "all" tapentadol IR and placebo pooled analysis treatment groups in the Phase 2/ Single-dose Safety Analysis Set. Most subjects were White (78% in the "all" tapentadol IR group and 74% in the placebo group). The majority of subjects were women (68% and 69%, respectively); the median age of subjects was 26 years in the "all" tapentadol IR group and 25.0 years in the placebo group. Table 94 in Section 9.4 illustrates the demographic characteristics.

Phase 2/3 multiple-dose, double-blind

The demographic and baseline characteristics of sex, age, race, and BMI were similar across the placebo, "all" tapentadol IR, and "all" oxycodone IR pooled analysis treatment groups in the Phase 2/3 Multiple-dose Double-blind Safety Analysis Set. Approximately 70% of the subjects were women and 75% were Caucasian. The median age was 52 years of age with 81% of subjects less than 65 years of age.

The percentage of subjects who participated in outpatient (non-surgical) pain model studies was greater in the "all" tapentadol IR (48%) and "all" oxycodone IR (51%) groups than in the placebo group (27%). This is due to the fact that KF5503/08 and KF5503/34 were designed as outpatient pain model with no placebo treatment arms. The percentage of subjects who participated in studies in which rescue medications were allowed during the double-blind period was 30% in the placebo group, 45% in the "all" tapentadol IR group and 35% in the "all" oxycodone IR group; not all subjects in these studies took rescue medications.

The Applicant's table below illustrates the demographic characteristics of subjects in the Phase 2/3 Multiple-Dose, Double-Blind Safety Analysis Set.

Table 36: Demographic Characteristics: Phase 2/3 Multiple-Dose, Double-Blind Safety Analysis Set

	Placebo (n=619)	"All" Tapentadol IR (n=2178)	"All" Oxycodone IR (n=675)
Sex, n (%)			
N	619	2178	675
Female	463 (75)	1448 (66)	457 (68)
Male	156 (25)	730 (34)	218 (32)
Race/Ethnicity Group, n (%)			
N	619	2178	675
White	460 (74)	1644 (75)	509 (75)
Black	61 (10)	219 (10)	77 (11)
Hispanic	86 (14)	259 (12)	80 (12)
Other	12 (2)	56 (3)	9 (1)
Age (years)			
N	619	2178	675
Mean (SD)	49.3 (16.38)	51.0 (14.96)	52.6 (14.79)
Median	52.0	52.0	55.0
Range	(18;83)	(18;85)	(18;84)
Category			
<65	499 (81)	1759 (81)	524 (78)
≥65 to <75 years	92 (15)	316 (15)	119 (18)
≥75 years	28 (5)	103 (5)	32 (5)
Body mass index (kg/m^2)			
N	618	2176	674
Mean (SD)	29.1 (6.79)	29.8 (6.96)	30.3 (6.89)
Median	28.0	28.6	29.3
Range	(16;60)	(16;76)	(16;63)
Pain model, n (%)			
N	619	2178	675
Preoperative[a]	169 (27)	1048 (48)	342 (51)
Postoperative[b]	450 (73)	1130 (52)	333 (49)
Rescue medication allowed, n (%)			
N	619	2178	675
No	436 (70)	1204 (55)	438 (65)
Yes	183 (30)	974 (45)	237 (35)

Studies included: KF5503/04 (Part 2), KF5503/08 (Part 2), KF5503/21, KF5503/22, KF5503/31 (excluding site 011006), KF5503/32, KF5503/33, KF5503/34, and KF5503/37

[a] indicates an outpatient pain model.

[b] indicates an inpatient pain model

Subject R331333-PAI-3004-011002-400880 entered both KF5503/33 and KF5503/34 studies and was treated with tapentadol IR in each study but was counted once in the "all" tapentadol IR group.

Source: Tapentadol 4-Month Safety Update, p. 103

Phase 3 open-label

A total of 483 subjects received tapentadol IR (flexible dose 50 or 100 mg) during the open-label studies. The majority of subjects in the Phase 3 open-label studies were female (82%), Caucasian (61%), and less than 65 years of age (86%). The average age was 48.8 years.

7.2.2 Explorations for Dose Response

See Section 7.4.1

7.2.3 Special Animal and/or In Vitro Testing

The overall assessment of data from the preclinical development program of tapentadol did not identify human-relevant safety signals related to teratogenicity, fertility, genotoxicity or carcinogenicity.

Safety pharmacology studies analyzed potential side effects of tapentadol on vital organ systems. In general, side effects were consistent with opioid activity. At supra-antinociceptive doses, there were compound-related relevant effects on the CNS, cardiovascular, respiratory and gastrointestinal systems.

The cardiovascular effects were assessed clinically in a thorough QT study, which showed that tapentadol is not associated with QTc prolongation.

For details regarding preclinical studies and their results, the reader is referred to Dr. Kathleen Young's pharmacotoxicological review.

7.2.4 Routine Clinical Testing

The routine clinical testing performed during the development of tapentadol IR appears adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

The reader is referred to Section 4.4 and the Clinical Pharmacology Review (Dr. David Lee) for information regarding the metabolic, clearance and interaction workup.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Tapentadol is both a mu-opioid receptor agonist and an inhibitor of norepinephrine uptake. Expected adverse events include those related to the central nervous system, (i.e., sedation, dizziness, somnolence, headache, respiratory depression), the gastrointestinal system (i.e., nausea, vomiting, constipation), and others including pruritis and fatigue.

Adverse events were elicited from subjects in response to non-leading questions, were observed during examination of the subjects, or spontaneously reported by the subjects. In addition, laboratory data, vital signs, and ECGs were collected throughout the trials. An adequate TQT study was performed. The data collected allowed for adequate evaluation of the potential adverse events for similar drugs in this class (i.e., Tramadol).

Withdrawal symptoms were evaluated during Study KF5503/34. Drug accountability and compliance with study drug treatment was assessed during the longer Phase 3 trials (KF5503/33 [10 days], KF5503/34 [90 days], and KF5503/32 [9 days]). Results of these evaluations are discussed in Section 7.6.4.

SMQs were performed on the pooled TEAE data for 1) severe cutaneous reactions and 2) possible drug-related hepatic disorders. Results of these analyses may be found in Section 7.3.5.

7.3 Major Safety Results and Discussion

7.3.1 Deaths

No deaths were reported in any subject who received study drug as reported in the Phase 1 single-dose or multiple-dose Safety Analysis Sets, the Phase 2/3 single-dose Safety Analysis set, in the Phase 2/3 multiple-dose double-blind Safety analysis set, or in the Phase 3 open-label extension studies (KF5503/31 and 32).

One death was reported from study KF5503/34 in a subject (400187) who was a screen failure and not randomized. This subject did not receive any study drug.

As of March 15, 2008, there were 1007 subjects randomized in three Phase 3 ongoing multiple-dose, double-blind clinical studies of tapentadol IR (KF5503/35, 38, and 39). There was a report of one death in study KF5503/35. Treatment assignment remains blinded in this ongoing study. Possible treatments include tapentadol IR, morphine, or placebo. A summary of the narrative for the reported death provided by the Applicant follows.

A 55-year-old female subject (MCN# 2007-14044) started treatment with double blind study drug (tapentadol IR vs. morphine vs. placebo) on [redacted] at 6:45 h and stopped medication on [redacted] at 8:00 h. The subject had a medical history of arterial hypertension, two normal deliveries, one abortion, and uterine myomas. On [redacted] the subject had an operation for uterine myomas. The study drug was discontinued on [redacted] at 8:00 h because of the need for a repeat laparotomy due to bleeding from the surgical wound. The re-laparotomy was performed on [redacted] There were no post-operative complications reported and the subject had no complaints. On [redacted] at [redacted] the subject was found dead by a nurse. The last time the subject was seen by the nurse six hours prior, and at that time, the subject did not complain of adverse events and walked to the toilet without help. The cause of the subject's death was unknown. An autopsy was performed and the subject showed disseminated lung micro-embolism. According to the pathologist the emboli could have been a cause of the subject's sudden death. However, further results of the autopsy are still pending. The last dose of study drug was approximately two days prior to the patient's being found dead.

b(6)

The Applicant judged that there was no temporal relationship between the onset of pulmonary embolism and the administration of study drug, therefore the death was unrelated to the study drug.

Tapentadol ER Studies

There have been no deaths reported in the Phase 1 and 2 studies of tapentadol ER. Four deaths were reported in the Phase 3 tapentadol ER ongoing studies as of March 15, 2008.

None of the deaths occurred during treatment. Three of the deaths, cardiac arrest, lung cancer, and murder were considered unlikely or not related to study drug. The Applicant has requested follow-up information the fourth death, a case of death (cardiac arrest, patient received tapentadol). The treatment group assignment for the first three subjects in unknown since the blind has not been broken.

7.3.2 Nonfatal Serious Adverse Events

There were a total of 21 nonfatal SAEs reported from all phases of the completed studies in the Tapentadol IR development program in subjects receiving tapentadol IR. There were five SAEs reported in three Phase 3 studies that were ongoing at the time of the 4-month safety update, however the treatment assignments for these studies are still blinded.

Phase 1

There were two serious adverse events reported in one subject in the single-dose safety analysis set. There were also three serious adverse events reported in the subjects with hepatic impairment, and one in a subject with renal impairment. There were no SAEs reported in the multiple-dose safety analysis set in subjects receiving CG5503.

Phase 1 Single-Dose

In the Phase 1 Single-dose Safety Analysis set, two SAEs, loss of consciousness and respiratory arrest, were reported in one subject who received tapentadol. There were no reports of SAEs in those receiving placebo. Subject 101921 experienced serious adverse events of respiratory arrest and loss of consciousness approximately 1 hour after receiving a single dose of tapentadol IR 80 mg. The events occurred suddenly (2 minutes after a blood draw) and lasted approximately 30 seconds during which the subject received basic life support.

Narrative for subject 101921

Subject 101921, a 66-year-old white healthy female was consented and screened on 13 Sept 2006. The subject had a previous medical history of "appendectomy, sterilization, breast reduction both sides, and digit 1, 2, 3 correction right foot". Screening vital signs were as follows: temperature 36.0°C, pulse 57 bpm, respiration 10 breaths per minute, blood pressure 146/79 mmHg, and weight was 64.4 kg. The subject reported no prior medications. The subject had unremarkable laboratory values. A screening ECG showed "borderline PR interval" (PR 207 ms) as interpreted by the cardiologist from the central ECG provider.

The subject received a single dose of 80 mg of CG5503 base IR at 08:12 (Day 1). Prior to this dose, the subject had vital signs (temperature 35.7°C, pulse 57 bpm, respiration 16 breaths per minute, blood pressure 121/75 mmHg) and laboratory assessments that were unremarkable. An ECG performed at 07:12 showed "sinus bradycardia, first degree AV block (PR 215 ms), and non-specified ST-T abnormality" as interpreted by [ ]. At 09:13 the subject had a scheduled pharmacokinetic blood sample drawn via venous catheter. No abnormality was reported at the time of this sample. At 09:15, the subject experienced sudden loss of consciousness. The investigator

b(4)

described the subject as being unresponsive, pale, without spontaneous breaths and without a palpable pulse. Basic life support was started immediately, and the subject regained consciousness after 2 respiratory insufflations and initial cardiac massage. The duration of the event was reported as lasting approximately 30 seconds. The subject was able to speak fully and did not show any neurologic symptoms after regaining consciousness. The vital signs after the event were pulse 57 bpm, respiration 9 to 12 breaths per minute, and blood pressure 131/68 mmHg. The subject received intranasal oxygen, and pulse oximetry did not decrease below 95% for 7 hours after the event. Telemetry monitoring did not reveal any significant abnormality. Naloxone 200 mcg was administered four times at 12, 30, 94, and 180 minutes following the event. The only abnormalities from laboratories drawn at 10:25 were glucose 8.4 mmol/L and bicarbonate 24 mmol/L. An ECG performed at 11:52 revealed "sinus rhythm, first degree AV block (PR 249 ms), nonspecific T abnormality" as interpreted by [ ]. The subject experienced additional adverse events after the event: nausea (09:28), unsuitable feeling stomach (10:51) and vomiting (11:59), and dizziness (08:00 on 05 Oct 2006). b(4)

CG5503 base and CG5503-O-glucuronide pharmacokinetic parameters for this subject and comparison to the mean values for the elderly subject group are listed in the table below. The subject experienced the serious adverse event following the 1 hour blood draw. CG5503 base concentration at the 1 hour blood draw was 87.3 ng/mL

Table 37

	Subject 101921	Elderly Subjects (Mean ± SD)
CG5503 base		
C_{max}, ng/mL	87.30	62.6 ± 17.5
AUC_{last}, ng.h/mL	425.02	344 ± 98.0
AUC_{∞}, ng.h/mL	426.63	348 ± 97.1
CG5503-O-Glucuronide		
C_{max}, ng/mL	2760.00	2672 ± 267
AUC_{last}, ng.h/mL	13806.43	14319 ± 1508
AUC_{∞}, ng.h/mL	14088.43	14556 ± 1544

Source: study report 331333-pai-1019, p. 55

The subject was discharged two days after the event in stable condition. Vital signs at end of study were: temperature 34.8°, pulse 55 bpm, respiration 14 breaths per minute, and blood pressure 134/80 mmHg. Laboratory assessments showed no abnormal values. A final ECG was interpreted as "sinus rhythm, borderline PR interval" (PR 208 ms).

The subject was referred to a pulmonologist, who performed a detailed history and physical examination approximately one month later. There were no relevant abnormalities in pulmonary function test or blood gas analyses. From a pulmonologic point of view, there was no explanation found for the short period of respiratory arrest/loss of consciousness after intake of study drug. The subject appeared to be in good health. She had never smoked and the pulmonary function test showed no sign of COPD.

The subject was examined by a cardiologist approximately five weeks after the event, and was shown to be hemodynamically stable with a left ventricular ejection fraction of 61%, trace aortic insufficiency, mitral valve prolapse, mitral insufficiency grade I-II, and a large diameter aortic root. An exercise stress test was performed and was within normal limits.

The investigator considered the events to be severe and probably related to study drug. The Applicant considered the events to be consistent with vasovagal syncope, possibly associated with the drawing of the blood sample.

Reviewer's note: Although vasovagal syncope following a blood draw is not uncommon, it is not typically associated with cardio-respiratory arrest, although it has been described in the literature. In a patient without underlying cardiac or pulmonary conditions respiratory arrest associated with syncope is an unlikely scenario. The subject's Cmax for CG5503 base was higher than the mean for elderly patients as shown in the table above, which may have contributed to the event.

This event was reviewed by the Division at the time of the 15-day safety report, and discussed with the Applicant during a teleconference on November 2, 2006. The determination was made, in conjunction with the Applicant, that this event represented cardiopulmonary arrest. Dr. Shibuya performed an analysis comparing the incidence of sudden cardiac death in the general population (0.1-0.2%) and the incidence of this adverse event in the CG5503-exposed individuals, which at the time of the report was 1/3255 or 0.03%. Therefore, there does not appear to be excess risk of sudden cardiac death after exposure to CG5503 than in the general population.

In conclusion, the adverse event of cardiopulmonary arrest appears to be possibly related to the study drug.

Serious event adverse events were reported in three subjects who participated in Study HP5503/16 which was a single-center, open-label, parallel-group, single-dose, drug-disease interaction study conducted in 30 men and women with normal, mild, or moderate hepatic impairment. The SAEs were malignant bone neoplasm and tongue neoplasm in subjects with moderate and mild hepatic impairment, respectively, and a convulsion in a patient that was considered a screen failure and did not receive study drug. These events were determined by the Applicant to be unrelated to study drug. Upon review of the narratives, CRFs and additional data presented by the Applicant, this reviewer is in agreement with this determination.

One subject in study HP5503/15 (open-label, single-dose of 80 mg, PK), with moderate renal impairment, experienced the SAE of edematous pancreatitis at the end of the study that resulted in hospitalization.

Narrative for Subject 100608

Subject was a 69-year old white man with moderate renal impairment and a history of nephropathy, hyperuricemia, hypertension, and recurrent gastric pain for several years. He received a single, 93mg dose of CG5503 IR. Nausea and abdominal pain began five hours after administration of the single dose. Examination revealed epigastric pain on palpitation. Compared with predose clinical laboratory values, the End-of-Study (Day 3) tests showed elevated liver enzyme rates (AST 143 IU, ALT 247 IU, GGT 244 IU), leukocytosis (WBC count = 21140 cells/mm3), elevated urea (38.79 mg/dL), creatinine (2.86 mg/dL), bilirubin (1.11 mg/dL), alkaline phosphatase (180 IU), creatine phosphokinase (219 IU), LDH (273 IU), and uric acid (10.0 mg/dL). The subject was discharged from the study and was seen by his primary physician the following day. The subject reported abdominal pain and was hospitalized for further diagnostic tests and observation. Laboratory values described in hospital records were lipase (286 IU/L), C-reactive protein (25.8 mg/dL), uric acid (10.0 mg/dL), AST (66 IU/L), and GGT (192 IU/L). An ultrasound of the abdomen showed cholelithiasis without signs of cholecystitis. A CT scan of the abdomen showed a serous pancreatitis in the head of the pancreas without exudates or necrosis. An Endoscopic Retrograde Cholangiopancreatography showed non-dilated biliary ducts without stones, and swollen, erethematous papilla. The presence of cholecystolithiasis suggested a biliary etiology for the pancreatitis. The subject remained hospitalized for 7 days and was treated with i.v. ceftriaxone 2 g, oral pantoprazol 40 mg once daily, and oral Novalgin® (metamizol-sodium) 750 mg three times daily. The subject recovered and was discharged. The subject's liver enzymes were within normal limits when tested approximately 2 weeks later. The investigator considered the events to be serious and possibly related to study drug.

Reviewer comment: CG5503 as a contributing factor cannot be excluded. As a mu opioid receptor agonist, it is possible that CG5503 IR has an effect on the contractility of the sphincter of Oddi, which is a well described class effect. A contraction might have increased the pressure in the biliary duct and contributed to acute pancreatitis. Consequently, this event is considered possibly related to study drug.

Phase 1 Multiple-Dose

No serious adverse events were reported in subjects receiving CG5503 during the study or up to 7 days after the last dose of study drug in the Phase 1 multiple-dose study (HP5503/13).

Phase 2/3

Phase 2 Single-Dose

There were no serious adverse events reported for any subjects receiving tapentadol in the Phase 2/3 Single-dose safety analysis set. There was one SAE of chest pain (non-cardiac) reported in the morphine IR group, and one of pyrexia in the ibuprofen group.

Phase 2/3 Multiple Dose

A total of 17 SAEs were reported up to 30 days after the last dose of study drug for the Phase 2/3 double-blind multiple-dose analysis set, 11 occurring in subjects who received CG5503. Studies included in this analysis set are Studies included: KF5503/04 (Part 2),

KF5503/08 (Part 2), KF5503/21, KF5503/22, KF5503/31 (excluding site 011006), KF5503/32, KF5503/33, KF5503/34, and KF5503/37. The breakdown of the SAEs by treatment group, system organ class, and preferred term are shown in the table below.

Table 38: Serious Adverse Events Reported in the Phase 2/3 Multiple Dose Double Blind Safety Analysis Set

System organ class Preferred term	Placebo (n=619) n (%)	"All" Tapentadol IR (n=2178) n (%)	"All" Oxycodone IR (n=675) n (%)
No. (%) of Subjects with SAEs	2 (<1)	11 (1)	5 (1)
Cardiac disorders	1(<1)	4 (<1)	0
Acute myocardial infarction	0	1 (<1)	0
Cardiac failure congestive	0	1 (<1)	0
Myocardial infarction	0	1 (<1)	0
Supraventricular tachycardia	1 (<1)	1 (<1)	0
Nervous system disorders	1 (<1)	3 (<1)	0
Lethargy	0	1 (<1)	0
Thalamic infarction	0	1 (<1)	0
Transient ischemic attack	1 (<1)	1 (<1)	0
Gastrointestinal disorders	0	2 (<1)	1 (<1)
Ileus	0	1 (<1)	0
Small intestinal obstruction	0	1 (<1)	0
Pancreatitis, acute	0	0	1 (<1)
Infections and infestations	0	2 (<1)	1 (<1)
Bronchitis, viral	0	1 (<1)	0
Pneumonia	0	1 (<1)	0
Viral myocarditis	0	1 (<1)	0
appendicitis	0	0	1 (<1)
Respiratory, thoracic and mediastinal disorders	0	2 (<1)	0
COPD	0	1 (<1)	0
Pulmonary embolism	0	1 (<1)	0
Vascular disorders	0	1 (<1)	0
Deep vein thrombosis	0	1 (<1)	0
Psychiatric disorders	0	0	1 (<1)
Confusional state	0	0	1 (<1)
Renal and urinary disorders	0	0	1 (<1)
Renal failure, acute	0	0	1 (<1)
Surgical and medical procedures	0	0	1 (<1)
Spinal fusion surgery	0	0	1 (<1)

Studies included: KF5503/04 (Part 2), KF5503/08 (Part 2), KF5503/21, KF5503/22, KF5503/31 (excluding site 011006), KF5503/32, KF5503/33, KF5503/34, and KF5503/37
MedDRA version 10.1 was used for coding

"all" oxycodone dose of 10 or 15 mg;
Includes serious adverse events reported during treatment and up to 30 day after the last dose of study medication.
Source: tapentadol ISS-4 month safety update, p. 128

One percent of the subjects in the tapentadol and oxycodone groups experienced SAEs, and less than one percent in the placebo group. There was no SOC or PT for which there was greater than one percent incidence of any SAE in any treatment group.

The serious adverse events in the tapentadol group are shown below by SOC, preferred term and dosing group. Other than the fact that there were no SAEs reported in the lowest dosing group (0-30mg), the occurrence of SAEs does not appear to be dose dependent.

Table 39: SAES in the Multiple-Dose Double-Blind Safety Analysis Set by Tapentadol Dose

System Organ Class Preferred term	**Tapentadol IR Doses**				
	0-30 mg	**>30-60 mg**	**>60-90 mg**	**>90-120 mg**	**Flexible (50 or 100 mg)**
	(N=22) n (%)	(N=538) n (%)	(N=607) n (%)	(N=333) n (%)	(N=679) n (%)
Total no. subjects with SAEs	0	2 (<1)	2 (<1)	2 (1)	5(1)
Cardiac disorders	0	1 (<1)	1 (<1)	0	2 (<1)
Acute MI	0	0	0	0	1 (<1)
Cardiac failure, congestive	0	0	1 (<1)	0	0
MI	0	0	0	0	1 (<1)
SVT	0	1 (<1)	0	0	0
Nervous system disorders	0	0	0	1 (<1)	2 (<1)
Lethargy	0	0	0	1 (<1)	0
Thalamic infarction	0	0	0	0	1 (<1)
TIA	0	0	0	0	1 (<1)
Gastrointestinal disorders	0	1 (<1)	1 (<1)	0	0
Ileus	0	0	1 (<1)	0	0
Small intestine obstruction	0	1 (<1)	0	0	0
Infections and infestations	0	0	1 (<1)	0	1 (<1)
Bronchitis, viral	0	0	0	0	1 (<1)
Pneumonia	0	0	1 (<1)	0	0
Viral myocarditis	0	0	1 (<1)	0	0
Respiratory, thoracic and mediastinal disorders	0	1 (<1)	0	1 (<1)	0
COPD	0	0	0	1 (<1)	0

Pulmonary embolism	0	1 (<1)	0	0	0
Vascular disorders	0	1 (<1)	0	0	0
Deep vein thrombosis	0	1 (<1)	0	0	0
Total # SAEs	0	4	4	2	5

A line listing of the patients with SAEs may be found in Section 9.4.

The following narratives reflect SAEs that were determined to be either possibly or probably related to study drug following review of the patient narratives, CRFs and datasets provided by the Applicant.

Narratives

Subject 100321 (Ileus): The subject was a 66-year-old white man with a complex medical history of shortness of breath, sleep apnea, aortic thoracic aneurysm, bladder surgery, erectile dysfunction, inguinal hernia, kidney stones, ureter repair, hypothyroid, thyroidectomy, and depression. Prior medications included carvedilol, hydrochlorothiazide, levothyroxine, flouxetine, sildenafil, and paracetamol. Physical examination, vital signs, and laboratory values at baseline were unremarkable. ECG findings showed left axis deviation (at screening) and non-specific ST abnormality (at baseline). The subject received a total daily dose of 300 mg tapentadol IR on Day 1 and Day 2 of the double-blind period. On Day 2 the subject received one dose of the study drug and refused further dosing as he was not feeling well. The study medication was discontinued. The subject experienced abdominal pain, distension, and was very nauseated on Day 3. The subject continued to complain of abdominal pain and was given a laxative as well as an enema and rectal tube with no relief. The subject underwent decompressive colonoscopy that was only partially successful. The subject's condition improved after a nasal gastric tube was inserted and he was placed on all liquid diet. Ileus resolved on Day 7 and was considered possibly related to the study drug by the investigator. The subject was withdrawn from the study on Day 3 of the double blind period due to ileus.

Reviewer comment: I am in agreement with the Applicant that this SAE was possibly related to study drug. The patient's hypothyroidism could have also contributed.

Subject 100564 (Lethargy): The subject was a 64-year-old white woman with a medical history significant for asthma, hypercholesterolemia, hypertension, acid reflux, gastric bypass, hernia repair, cholecystectomy, instability and decreased range of motion in the left hip, mild depression, and seasonal allergies. Prior medications included lisinopril, pantoprazole sodium, simvastatin, sertraline hydrochloride, cetirizine hydrochloride, cefazolin sodium, and fluticasone propionate. Hydroxyzine, and fondaparinux sodium were also recorded as prior medications. Vital signs and laboratory values at baseline were unremarkable. Physical examination at baseline showed ankle edema. ECG findings showed sinus arrhythmia at screening, and non-specific T abnormality, ventricular premature systoles, and sinus tachycardia at baseline. The subject was randomized to the 100mg treatment group, and received a total daily dose of 600 mg tapentadol IR on Day 1

of the double blind period of the study. On Day 1 the subject experienced moderate pruritis and mild ventricular extrasystoles. The pruritis resolved on Day 2 and was considered probably related to the study drug by the investigator. On Day 2 the subject experienced "lethargy extreme" (verbatim) and showed decreased responses to external stimuli. The subject continued to have premature ventricular contractions and was transferred to the ICU for further evaluation and monitoring. Lethargy resolved on Day 3 and was considered probably related to the study drug. Ventricular systoles were reported as recovering and considered possibly related to the study drug by the investigator. Physical examination, vital signs, and laboratory values were unremarkable on Day 2. ECG findings on Day 2 showed an increase in heart rate to 124 bpm; all other ECG findings were unremarkable. The subject was withdrawn from the study on Day 2 of the double blind period due to lethargy.

Reviewer comment: I am in agreement with the Applicant that this SAE was probably associated with the study drug.

Phase 3 Open-Label Extension

Of the 537 subjects enrolled in the 9-day open-label extension periods of studies KF5503/31 and KF5503/32, there were SAEs reported for two subjects; one event of traumatic hematoma in subject 100064, and the events of anxiety and delirium in subject 100120. Additionally, the SAE of impaired healing was reported for one subject who entered the open-label extension phase at site 011006 in study KF5503/31 (Safety data for patients enrolled from this site were excluded from the open label safety analysis set by the Applicant due to results of an audit that showed data irregularities; details may be found in Section 3.2.

A summary of the review of the CRFs, narratives, and datasets provided by the Applicant are shown in the table below.

Table 40: SAEs Reported in the Open-label Extension Safety Analysis Set

Subject ID	Age/race/sex	Study/randomization group	SAE	Total daily dose	Day of AE	D/C Study drug due to SAE	Outcome	Relation to study drug according to reviewer's adjudication
100064	53/W/M	KF5503/ 31/75 mg	Traumatic hematoma/cellulitis in surgical wound	200-600mg Days 5-13	Day13	No	Unknown	Unrelated
100120*	63/W/M	KF5503/ 31/50 mg	Anxiety, delerium	200-550 days 4-11	Day 11	yes	Resolved	Possibly Probably
100145	70/W/F	KF5503/ 31/50 mg	Impaired healing	600-750 mg day	Day 12	No	Resolved	Unlikely

				4-12				

*narrative for this subject in body of text

Narrative

Subject 100120 (anxiety and delirium): The subject was a 63-year-old white man with a medical history of hypertension, murmur, contracture release left elbow, discectomy, herniated disc, right hip arthritis, hyperlipidemia, Hodgkins lymphoma, and mild depression. Prior medications included citalopram hydrobromide, atorvastatin calcium, lisinopril, ezetimibe, midazolam hydrochloride, cefazolin sodium, tobramycin, bupivacaine hydrochloride, propofol, paracetamol, enoxaparin sodium, polysaccharide-iron complex, and pantoprazole sodium. Physical examination, vital signs, and laboratory values at baseline were unremarkable. Baseline ECG findings showed minor ST depression, negative T waves, and prolonged QT interval. The subject received a total daily dose of 200 mg to 300 mg tapentadol IR on Day 1 to Day 3 of the double blind period. On Day 4 to Day 11 of the open label extension the subject received a total daily dose of 300 mg to 550 mg tapentadol IR. The subject experienced moderate confusion and hallucinations starting on Day 11 and continuing for 2 days. On Day 13 the subject went to a hospital by ambulance with complaints of tachypnea, diaphoresis, palpitations, nausea, and headache. His ECG was read as abnormal by the emergency room doctor. A myocardial infarction was ruled out. The subject also complained of disorientation. He was admitted to the hospital. On Day 14, the adverse events resolved. Psychiatric consultation on Day 15 revealed that the subject had appropriate affect, speech pattern, and logical thought process. His attention and memory were normal. The subject had no audio or visual hallucinations. The adverse event was assessed as delirium secondary to pain medication, which was resolved on admission. Physical examination in the discharge summary also revealed an anxious affect. The subject was discharged on Day 16. Discharge diagnoses included chest pain, anemia, anxiety, depression, and Hypophosphatemia. The anxiety was assessed by the investigator as possibly related and delirium as probably likely related to the study medication. The subject completed the double blind period of the study and was withdrawn from the open label extension on Day 14 due to delirium.

Reviewer comment: I am in agreement that the study drug was possibly related to the adverse events of anxiety and delirium.

Phase 3 Tapentadol IR Ongoing Studies

There have been six SAEs in five subjects reported during the ongoing Phase 3 trials for tapentadol IR. A total of 1007 subjects were randomized in the ongoing studies at the time of reporting. Since the studies are ongoing, treatment assignment remains blinded; possible treatment assignments are tapentadol IR, morphine IR or placebo for KF5503/35 and tapentadol IR/ER for KF5503/39. No events were reported for study KF5503/38. The table below shows the SAEs.

Table 41: SAEs Reported in Phase 3 Multiple-Dose Ongoing Studies of Tapentadol IR

System Organ Class Preferred Term	Number of Events in Any Treatment Group[a, b, c]
Total no. of events:	**6**
Total no. of subjects with AEs:	**5**
Cardiac disorders	
Sinus tachycardia	1
Infections and infestations	
Bronchopneumonia	1
Injury, poisoning and procedural complications	
Post procedural haemorrhage	1
Musculoskeletal and connective tissue disorders	
Back pain[d]	1
Psychiatric disorders	
Confusional state	1
Respiratory, thoracic and mediastinal disorders	
Pulmonary embolism	1

Source: tapentadol –ISS 4-month safety update, p. 175

Of the subjects with serious adverse events in the tapentadol IR ongoing double-blind studies, one subject (Subject 14590 in study KF5503/35) had serious adverse events of sinus tachycardia (severe) and confusional state (moderate) that were both considered probable/likely related to study drug by the investigator. Both adverse events resolved.

Tapentadol ER Studies

One SAE was reported (seizure) for one subject in study HP5503/10, a completed Phase 1 TQT study of tapentadol ER. The seizure occurred approximately three days post-dosing of 172 mg tapentadol ER. The event was determined to be possibly related to study drug.

SAEs occurring during the Phase 2 studies were hepatitis C, influenza, ankle fracture, radius fracture, myocardial ischemia, chest pain, and biliary colic reported for 1 subject each in the "all" tapentadol ER group.

SAEs occurring in the ongoing Phase 3 studies include cardiac disorders (MI, angina, CHF, arrhythmias), GI disorders (abdominal pain, constipation, nausea, vomiting), chest pain, infections, confusion, suicidal ideation, withdrawal syndrome, and others. These studies are currently ongoing, and the treatment assignments remain blinded.

7.3.3 Dropouts and/or Discontinuations

Subject Disposition

Phase 1 Single and Multiple-Dose Studies

The Applicant's table below illustrates the disposition of all randomized subjects in the Phase 1 single-dose studies.

Table 42: Subject Disposition: Phase 1 Single-Dose

	Placebo (n=97) n (%)	"All" Tapentadol IR (n=449) n (%)
Randomized	97 (100)	449 (100)
Randomized and dosed	91 (94)	439 (98)
Completed	90 (93)	425 (95)
Discontinued	7 (7)	24 (5)
Adverse event	2 (2)	9 (2)
Other	3 (3)	6 (1)
Pregnancy	0	1 (<1)
Protocol violation	1 (1)	5 (1)
Subject choice	1 (1)	3 (1)

Studies included: HP5503/03, HP5503/04, HP5503/05, HP5503/07, HP5503/09, HP5503/14, HP5503/15, HP5503/16, HP5503/19, HP5503/20, HP5503/21, HP5503/22, HP5503/23, HP5503/24, HP5503/27, HP5503/30, and HP5503/34

Source: Tapentadol IR: 4 Month Safety Update, p. 74

Thirty-two subjects were enrolled in the Phase 1 multiple-dose study (HP5503/13); 7 (22%) subjects were discontinued because of adverse events; 3 (9%) withdrew consent; and 22 (69%) were discontinued when the study was terminated. The sponsor temporarily stopped the study before continuing with the next dose level (200 mg every 6 hours), because the Agency did not feel that dosing in nonclinical toxicology studies was sufficient to support the safety of continued dose escalation in the clinical study until the Agency had the opportunity to review the pharmacokinetic data from completed studies with tapentadol IR. The requested information was submitted to the FDA, and the study remained suspended. Eventually, it was decided to terminate the study, as too much time had elapsed that prevented reconstitution of the cohorts

Phase 2/3 Multiple-Dose, Double-Blind Studies

The Applicant's table below illustrates the disposition of all randomized subjects in the Phase 2/3 multiple-dose, double-blind studies.

The overall percentage of subjects discontinuing after randomization is highest in the "all oxycodone IR" group (38%), and similar in the "all" tapentadol IR groups and placebo (34% and 33% respectively). Discontinuations due to lack of efficacy were greatest in the placebo group (28%), as would be expected, and similar in the tapentadol (13%) and oxycodone groups (12%). Discontinuations due to adverse events was highest in the oxycodone group (17%) followed by the tapentadol group (11%) and placebo (2%).

Table 43: Disposition: Phase 2/3 Multiple-Dose Double-Blind Analysis Set

	Placebo (n=630) n (%)	"All" Tapentadol IR (n=2228) n (%)	"All" Oxycodone IR (n=689) n (%)
Randomized	630 (100)	2228 (100)	689 (100)
Completed	424 (67)	1472 (66)	429 (62)
Discontinued	206 (33)	757 (34)	260 (38)
Lack of efficacy	179 (28)	284 (13)	86 (12)
Adverse event	11 (2)	247 (11)	115 (17)
Subject choice (subject withdrew consent)	10 (2)	112 (5)	29 (4)
Lost to follow-up	0	27 (1)	14 (2)
Other	6 (1)	88 (4)	16 (2)
Safety Analysis Set[a]	619 (98)	2178 (98)	675 (98)

Source: Tapentadol IR 4-Month Safety Update, p. 100

The discontinuations due to "other" reasons were reviewed using CRFs and datasets provided by the Applicant. The table below illustrates the results of this analysis.

Table 44: Reasons for Discontinuation for "Other" Reasons

Reason for discontinuation	Placebo	All Tapentadol IR	All Oxycodone IR
Total d/c because of "other" reasons	6	88	16
Non-compliance (with study drug or Visits)	0	24	2
Lack of efficacy	2	17	2
Randomized in error	2	11	2
No study drug available	0	9	1
Took prohibited medication	0	4	3
Adverse event	1	1	0
Discharge from hospital prior to Completion of dosing	1	7	3
Miscellaneous	0	15	3

Over 50% of the discontinuations in the "All" Tapentadol IR group were due to noncompliance, lack of efficacy, or randomization of the subject in error. It appears the reason that the number of lack of efficacy discontinuations deemed as "other" by the Applicant was large is that the coding for lack of efficacy was triggered by the use of rescue medication by the subject. The patients readjudicated did not request rescue medication, but did experience lack of efficacy of study drug.

As a result of the analysis, there was only one additional adverse event each in the tapentadol group and in the placebo group. There were no additional subjects in any treatment group that discontinued due to the reason "lost to follow-up". The table below shows the reasons for discontinuation in the Phase 2/3 multiple-dose, double-blind studies including the above readjudication.

Table 45: Disposition of Phase 2/3 Multiple-Dose, Double-Blind Subjects as Readjudicated

	Placebo (n=630) n (%)	"All" Tapentadol IR (n=2228) n (%)	"All" Oxycodone IR (n=689) n (%)
Randomized	630 (100)	2228 (100)	689 (100)
Completed	424 (67)	1472 (66)	429 (62)
Discontinued	206 (33)	757 (35)	260 (38)
Lack of Efficacy	181 (29)	301 (14)	88(13)
Adverse Event	12 (2)	248 (11)	115 (17)
Subject choice	10 (2)	112 (5)	29 (4)
Lost to follow-up	0	27 (1)	14 (2)
Non-compliance	0	24 (1)	2 (<1)
Randomized in error	2 (<1)	11 (<1)	2 (<1)
No study drug available	0	9 (<1)	1(<1)
Took prohibited medication	0	4 (<1)	3 (<1)
Discharge from hospital prior to Completion of dosing	1 (<1)	7 (<1)	3 (<1)
Miscellaneous	0	15 (1)	3 (<1)

An additional analysis was performed regarding subjects who discontinued treatment due to "subject choice". Using datasets provided by the Applicant (*kdispo.xpt and kae.xpt),* it was determined that a total of 93 subjects in all treatment groups who discontinued because of "subject choice" had at least one adverse event. Given the data presented, it was not possible to determine whether the adverse events lead to discontinuation. The breakdown by treatment group is as follows: "All tapentadol"-69, "All oxycodone"-20, and placebo-4. If one looks at the most extreme scenario (that these adverse events lead to discontinuation), then the proportion of discontinuations from each treatment group because of adverse events would be as follows: placebo-3%, "all tapentadol"-14%, and "all oxycodone"-20%. Although all treatment groups had an increase in the percentage of discontinuations due to adverse events using this analysis, the relative relationship of the proportions of discontinuations between treatment groups does not change.

Phase 3 Open-Label Extension

Five-hundred-thirty-seven subjects were enrolled in the nine-day open-label extension periods of studies KF5503/31 and KF5503/32. A total of 98% of subjects completed the study. The disposition of all subjects is shown in the table below.

Table 46: Disposition of Subjects in Phase 3 Open-Label Extension

Reason for Discontinuation	Number of subjects (%)
Total enrolled	537 (100)
Total completed	525 (98)
Total discontinued	12 (2)
Adverse events	4 (1)
Withdrew consent	4 (1)
Other	3 (<1)
Lost to follow-up	1 (<1)

Analysis of Discontinuation due to Adverse Events

Phase 1 Studies

In the Phase 1 Single-dose Safety Analysis Set, the percentage of subjects with TEAEs leading to discontinuation in the "all" tapentadol IR group was 1% (3/439) versus none in the placebo group. TEAEs leading to discontinuation were vomiting, vasovagal syncope and hypotension (1 subject each) in the "all" tapentadol IR group.

In the Phase 1 multiple-dose study (HP5503/13), the percentage of subjects with TEAEs leading to discontinuation was higher in the "all" tapentadol IR group (19%; 6/32) than in the placebo group (0%). TEAEs leading to discontinuation were vomiting (19%; 6/32), nausea (6%; 2/32), somnolence (3%; 1/32), syncope (3%; 1/32), and confusional state (3% 1/32).

The TEAEs leading to withdrawal appear dose related, with all of the withdrawals in dosing groups >60mg and none in the dosing groups receiving <60 mg of tapentadol.

No subjects in the Phase 2 single-dose safety analysis set discontinued treatment due to TEAE.

Phase 2/3 Double-Blind, Multiple-Dose Studies

In the Phase 2/3 Double-blind Multiple-dose Analysis Set, TEAEs that led to study discontinuation were reported in a higher percentage of subjects in the "all" tapentadol IR group (11%) compared with the placebo group (2%), and was lower than in the "all" oxycodone IR group (17%). The Applicant's table below shows the distribution of discontinuation by treatment group.

The SOCs with the highest percentage of TEAS leading to discontinuation of treatment are Nervous system disorders, Gastrointestinal disorders, Psychiatric disorders, and General Disorders. In all cases, the proportion in the "all tapentadol" group was higher than placebo. Nervous system disorders (5% vs. 1%) and Gastrointestinal system disorders (4% vs. 1%) showed the largest differences between "all tapentadol" and placebo.

Table 47: TEAEs Leading to Treatment Discontinuation in more than 3 Subjects in the "All" Tapentadol IR Group: Phase 2/3 Multiple-Dose DB

System organ class Preferred term	Placebo (n=619) n (%)	"All" Tapentadol IR (n=2178) n (%)	"All" Oxycodone IR (n=675) n (%)
Total no. subjects With TEAEs	11 (2)	243 (11)	113 (17)
Nervous system disorders	5 (1)	105 (5)	53 (8)
Dizziness	3 (<1)	57 (3)	27 (4)
Somnolence	1 (<1)	28 (1)	15 (2)
Headache	1 (<1)	19 (1)	8 (1)
Lethargy	0	7 (<1)	0
Gastrointestinal disorders	5 (1)	95 (4)	82 (12)
Nausea	4 (1)	51 (2)	46 (7)
Vomiting	1 (<1)	30 (1)	35 (5)
Constipation	0	13 (1)	18 (3)
Diarrhoea	0	10 (<1)	0
Dry mouth	0	7 (<1)	0
Abdominal pain	0	4 (<1)	3 (<1)
Psychiatric disorders	3 (<1)	48 (2)	11 (2)
Confusional state	0	10 (<1)	1 (<1)
Insomnia	1 (<1)	8 (<1)	2 (<1)
Euphoric mood	0	6 (<1)	1 (<1)
Depressive symptom	0	5 (<1)	0
Anxiety	0	5 (<1)	0
Hallucination, visual	1 (<1)	4 (<1)	2 (<1)
General disorders and administration site conditions	1 (<1)	37 (2)	12 (2)
Fatigue	1 (<1)	14 (1)	5 (1)
Irritability	0	7 (<1)	2 (<1)
Chest discomfort	0	4 (<1)	0
Skin and subcutaneous tissue disorders	0	25 (1)	17 (3)
Pruritus	0	8 (<1)	11 (2)
Hyperhidrosis	0	5 (<1)	5 (1)
Pruritus generalised	0	5 (<1)	1 (<1)
Musculoskeletal and connective tissue disorders	1 (<1)	12 (1)	2 (<1)
Muscle spasms	0	4 (<1)	0
Respiratory, thoracic and mediastinal disorders	0	8 (<1)	0
Dyspnoea	0	4 (<1)	0

Source: Tapentadol IR 4-month safety update; p. 131

Within the Nervous system disorders SOC, dizziness was the most common AE occurring in 3% of the subjects receiving tapentadol IR, compared to 1 % of placebo subjects and 8% of those receiving oxycodone. Somnolence, headache, and lethargy also occurred in a greater proportion of those receiving tapentadol IR compared with placebo. Those receiving oxycodone had a higher incidence of somnolence and lethargy leading to discontinuation than those receiving tapentadol.

The most common gastrointestinal disorders leading to discontinuation of study drug in the tapentadol group were nausea, vomiting and constipation. All occurred at a greater incidence than in the placebo subjects, and a lower incidence than the oxycodone subjects.

Psychiatric disorders occurred at only a slightly greater rate in the tapentadol group compared with the placebo group (2% vs. 1%) and at the same rate as tapentadol in the oxycodone group.

In terms of relatedness to study drug, the adverse events that occurred in a higher proportion of subjects in the tapentadol group compared to the placebo group may be related to study drug. They are as follows: dizziness, somnolence, headache, nausea, vomiting, constipation, and fatigue. For those TEAEs occurring in less than 1% of the tapentadol group, it is difficult to assign causality.

Discontinuation due to TEAE by dosage group was analyzed using dataset *kdispo.xpt.* The results are shown below.

Table 48: Discontinuation due to TEAE by Dosage Group

	Placebo	Tapentadol 0-30 mg	Tapentadol >30-60 mg	Tapentadol >60-90 mg	Tapentadol >90-120 mg	Tapentadol Flexible	"All" Oxycodone
Total enrolled	619	22	538	607	333	679	675
Discontinued due to AE # (%)	11 (2)	0	35 (6.5)	48 (8)	19 (6)	145 (21)	115 (17)

Discontinuations due to TEAEs does not appear to be dose-related, however the largest percentage of discontinuations occurred in the flexible dose tapentadol group.

Analysis of dropouts due to TEAEs and gender in subjects taking tapentadol showed that a slightly higher percentage of males (14%) discontinued due to TEAEs compared to females (10%). Of those subjects receiving tapentadol, 152/1759 (9%) of those less than 65 years of age discontinued due to TEAEs compared to 95/419 (23%%) of the subjects 65 years of age or greater.

Phase 3 Open-Label
Two subjects had TEAEs leading to discontinuation reported in the Phase 3 open-label extension analysis.

7.3.4 Significant Adverse Events

All adverse events are discussed in Sections 7.3 and 7.4.

7.4 Supportive Safety Results and Discussion

7.4.1 Common Adverse Events

This review of common adverse events will encompass all TEAEs reported in the Phase 2/3 Multiple-Dose, Double-Blind pooled analysis set unless otherwise stated. TEAEs

from the other analysis sets (Phase 1, Phase 2 single dose, and Phase 3 open-label) will be included as applicable.

The overall percentage of subjects with at least one TEAE in the "all" tapentadol IR group (76%) was higher than in the placebo group (47%) and lower than in the "all" oxycodone IR group (84%).

Treatment emergent adverse events reported by SOC occurred most commonly in the Gastrointestinal Disorders SOC and the Nervous System SOC. The percentage of subjects with TEAEs affecting the Gastrointestinal Disorders SOC was higher in the "all" tapentadol IR group (46%) than in the placebo group (21%) and lower than in the "all" oxycodone IR group (64%). The percentage of subjects with TEAEs affecting the Nervous System Disorders SOC was higher in the "all" tapentadol IR group (42%) than in the placebo group (21%) and similar in the "all" oxycodone IR group (41%).

A summary of TEAEs by preferred term reported for ≥3% of subjects in the "all" tapentadol IR pooled analysis treatment group is provided in Table X below. The most commonly reported (by ≥5% of subjects) TEAEs in the "all" tapentadol IR group were nausea, dizziness, vomiting, somnolence, headache, constipation, and pruritus. Nausea, dizziness, vomiting, somnolence, and constipation were reported in a higher percentage of subjects in the "all" tapentadol IR groups than for subjects in the placebo group. Nausea, vomiting, constipation, and pruritus were reported more often for subjects in the "all" oxycodone IR group than for subjects in the "all" tapentadol IR group.

Table 49: TEAEs in at Least 3% of Subjects in the "All" Tapentadol IR Group: Phase 2/3 Multiple-Dose, Double-Blind Safety Analysis Set

Preferred term	Placebo (n=619) n (%)	"All" Tapentadol IR (n=2178) n (%)	"All" Oxycodone IR (n=675) n (%)
Total no. subjects with TEAEs	289 (47)	1651 (76)	567 (84)
Nausea	80 (13)	663 (30)	298 (44)
Dizziness	48 (8)	516 (24)	168 (25)
Vomiting	26 (4)	397 (18)	208 (31)
Somnolence	17 (3)	320 (15)	86 (13)
Headache	66 (11)	239 (11)	69 (10)
Constipation	16 (3)	174 (8)	133 (20)
Pruritus	8 (1)	117 (5)	73 (11)
Dry mouth	2 (<1)	91 (4)	17 (3)
Fatigue	3 (<1)	72 (3)	29 (4)
Diarrhoea	17 (3)	68 (3)	12 (2)
Hyperhidrosis	4 (1)	59 (3)	31 (5)

Studies included: KF5503/04 (Part 2), KF5503/08 (Part 2), KF5503/21, KF5503/22, KF5503/31 (excluding site 011006), KF5503/32, KF5503/33, KF5503/34, and KF5503/37
Source: Tapentadol IR 4-month safety update; p. 110

A table listing TEAEs in at occurring in ≥1% of subjects in the "all" Tapentadol group may be found in Section 9.4.

Pruritis occurred in 5% of the "all tapentadol" group, and an additional preferred term "generalized pruritis" occurred in 2% (see Table X in Appendix X), bringing the total to 7%. Adding the percentages of generalized pruritis to pruritis for the other treatment groups resulted in a total of 2% for the placebo group and 15% for the "All" oxycodone group.

Further analysis of all TEAEs showed that there were a large number of adverse events under the HLT "asthenic conditions", including the preferred terms fatigue, malaise, lethargy, and asthenia. By combining these PTs, the incidence asthenic events became greater than 5% in the "all tapentadol" group, as shown in the table below, while the incidence in the placebo group is less than one percent. The proportion of asthenic events in the "all tapentadol" group was similar to that in the "all oxycodone" group, and given the difference from the placebo group, is likely due to the study drug.

Table 50: Incidence of "Asthenic Conditions" in the "All Tapentadol" Group Multiple-Dose Double-Blind Analysis Set

TEAE (PT)	Placebo N=619 n (%)	All Tapentadol N=2178 n (%)	All Oxycodone N=675 n (%)
Fatigue	3 (.5)	73 (3.4)	30 (4.4)
Lethargy	2 (.3)	25 (1.1)	0
Asthenia	0	17 (.8)	10 (1.5)
Malaise	0	2 (.1)	0
Total	5 (.8)	117 (5.4)	40 (5.9)

*each report represents a unique subject; duplicates were eliminated

An analysis of gastrointestinal events was also performed. The PTs abdominal pain, abdominal pain upper, abdominal pain lower, abdominal tenderness, stomach discomfort and abdominal discomfort were looked at as a group. The table below illustrates the results, comparing the "all tapentadol" group with placebo and oxycodone. The incidence of abdominal pain/discomfort in the "all tapentadol" group (2.7%) is greater than either the placebo (1%) or "all oxycodone" group (2.2%). This adverse event is likely due to the study drug.

Table 51: Incidence of Similar Abdominal Adverse Events in the "All Tapentadol Group": Multiple-Dose Double-Blind Analysis Set

TEAE (PT)	Placebo N=619 n (%)	All Tapentadol N=2178 n (%)	All Oxycodone N=675 n (%)
Abdominal pain	0	19 (0.9)	8 (1.1)
Abdominal pain, upper	7 (1)	19 (0.9)	4 (0.6)
Abdominal pain, lower	0	1 (.04)	0
Abdominal tenderness	0	1 (.04)	1 (0.1)
Stomach discomfort	0	17 (0.8)	2 (0.2)
Abdominal discomfort	0	3 (0.1)	0
Total	7 (1)	60 (2.7)	15 (2.2)

*each report represents a unique subject; duplicates were eliminated

The incidence of TEAEs reported in the Phase 3 open-label extension safety analysis set is similar in nature to those reported in the Phase 2/3 double-blind analysis set, however the incidence of all TEAEs is lower. The Applicant's table below shows the TEAEs reported in at least 2% of subjects in the OL Extension studies.

Table 52: TEAEs Reported in at Least 2% of Subjects: OL Extension Study

Preferred term	FLEX TAP IR (N=483) n (%)
Total no. subjects with TEAEs	166 (34)
Nausea	32 (7)
Headache	25 (5)
Dizziness	19 (4)
Somnolence	15 (3)
Vomiting	14 (3)
Constipation	12 (2)

Flex TAP: Tapentadol flexible dose of 50 or 100 mg
Source: Tapentadol IR 4-month safety update; p. 169

TEAEs in Phase 1 and 2 (single-dose)
TEAEs reported during Phase 1 and 2 (single-dose) studies were reviewed and present a similar profile to those reported during the Phase 2/3 multiple-dose, double-blind studies.

TEAEs by dose group
In the Phase 2/3 Double-blind Multiple-dose Analysis Set, the overall incidence of TEAEs increased with increased dose of tapentadol IR. Table X below shows the incidence of TEAEs by SOC and tapentadol IR dose. There do appear to be dose related trends for both the GI and nervous system SOC, with an increasing incidence of TEAEs occurring with increasing doses of Tapentadol IR.

Table 53: Incidence of TEAEs by SOC and Dose of Tapentadol IR

SOC	Placebo (N=619) n (%)	Dose of Tapentadol IR				
		0-30 mg (N=22)	>30-60 mg (N=538)	>60-90 mg (N=607)	>90-120 mg (N=333)	Flexible dose (N=697)
GI System	130 (21)	5 (23)	226 (42)	282 (46)	184 (55)	300 (44)
Nervous System	131 (21)	5 (23)	210 (39)	272 (45)	186 (56)	249 (37)

The Applicant's table below illustrates TEAEs by preferred term that occurred in at least 3% of subjects by tapentadol dosage group. Among subjects treated with tapentadol IR, the percentage of subjects with adverse events of nausea, dizziness, vomiting, somnolence, and pruritus increased with increased dosage. When the percentages for the preferred terms "pruritis" and "generalized pruritis" are added, there is a clear dose relationship as follows: 0-30mg: 0, 30-60mg: 5%, 60-90mg: 8%, 90-120mg: 16%, and flex dose: 5%.

Table 54: TEAEs in at Least 3% of Subjects by Tapentadol IR Dose Group

		Tapentadol IR				
Preferred Term	Placebo (n=619) n (%)	0-30 mg (n=22) n (%)	>30-60 mg (n=538) n (%)	>60-90 mg (n=607) n (%)	>90-120 mg (n=333) n (%)	Flex (n=679) n (%)
No. (%) of Subjects with TEAEs	289 (47)	13 (59)	372 (69)	466 (77)	282 (85)	518 (76)
Nausea	80 (13)	3 (14)	172 (32)	207 (34)	156 (47)	125 (18)
Dizziness	48 (8)	1 (5)	110 (20)	157 (26)	125 (38)	123 (18)
Vomiting	26 (4)	1 (5)	80 (15)	112 (18)	89 (27)	115 (17)
Somnolence	17 (3)	1 (5)	74 (14)	91 (15)	85 (26)	69 (10)
Headache	66 (11)	3 (14)	63 (12)	59 (10)	36 (11)	78 (11)
Constipation	16 (3)	2 (9)	30 (6)	30 (5)	25 (8)	87 (13)
Pruritus	8 (1)	0	18 (3)	39 (6)	31 (9)	29 (4)
Dry mouth	2 (<1)	0	15 (3)	26 (4)	14 (4)	36 (5)
Fatigue	3 (<1)	0	7 (1)	19 (3)	8 (2)	38 (6)
Diarrhoea	17 (3)	1 (5)	6 (1)	14 (2)	2 (1)	45 (7)
Hyperhidrosis	4 (1)	0	16 (3)	18 (3)	13 (4)	12 (2)
Pruritus generalised	4 (1)	0	13 (2)	14 (2)	23 (7)	4 (1)

Studies included: KF5503/04 (Part 2), KF5503/08 (Part 2), KF5503/21, KF5503/22, KF5503/31 (excluding site 011006), KF5503/32, KF5503/33, KF5503/34, and KF5503/37
TEAE = treatment-emergent adverse events.
MedDRA version 10.1 was used for coding
Flex = Tapentadol flexible dose of 50 or 100 mg.

Source: Tapentadol IR 4-Month Safety Update, p. 115

It is of interest that the incidences of nausea, dizziness, vomiting, somnolence, and pruritis were lower in the flexible-dose tapentadol group than the dosage groups receiving greater than 30mg of tapentadol IR per day. Subjects in the flexible dose group could receive 50 to 100mg every four to six hours as needed. This may reflect an effort of the subjects to minimize the adverse event incidence and severity through dose adjustment. The implication is that the ability to adjust the dosage of tapentadol IR results in better tolerance to the drug.

TEAEs by intensity

The majority of TEAEs were mild to moderate in intensity across the pooled analysis treatment groups in the Phase 2/3 Multiple-dose Double-blind Safety Analysis Set and in the Phase 2/3 Open-label Extension Safety Analysis Set. The majority of the occurrences of nausea, dizziness, somnolence, headache, constipation, and pruritus were considered to be mild or moderate in intensity across the pooled analysis treatment groups. The only TEAE with a higher proportion of severe occurrences compared to mild or moderate was vomiting

Table 55: Common Adverse Events by Intensity in all Subjects Receiving Tapentadol in the Phase 2/3 Double-Blind Safety Analysis Set

Adverse Event (PT)	Mild n(%)	Moderate n(%)	Severe n(%)
Nausea	595 (27)	545 (25)	123 (6)
Dizziness	531 (24)	345 (16)	7 (<1)
Somnolence	247 (11)	235 (11)	45 (2)
Headache	204 (9)	156 (7)	37 (2)
Vomiting	204 (9)	246 (11)	299 (13)
Pruritus	161 (7)	67 (3)	3 (<1)
Constipation	134 (6)	72 (3)	7 (<1)

Number of patients receiving tapentadol =2178

Table 56 below illustrates the severity of common adverse events by dosing group. Events of mild or moderate severity (M) are compared to those reported as severe (S). There appears to be a slight dose related trend of increased severity for nausea, dizziness, and somnolence. There is a marked trend towards an increasing proportion of severe vomiting related to increasing dose, ranging from zero in the lowest dosing group to 16% in the >90-120mg group. Additionally in the >90-120mg group, severe vomiting occurred at a greater rate than mild or moderate (16% vs. 11%). The only severe adverse event reported in >1% of subjects in the flexible dosing group was vomiting (2%).

Table 56: Common Adverse Events by Intensity and Dose in all Subjects Receiving Tapentadol in the Phase 2/3 Double-Blind Safety Analysis Set

TEAE (PT)	0-30mg n=22		>30-60mg n=538		>60-90mg n=607		>90-120mg n=333		Flex n=679	
	M*	S*	M	S	M	S	M	S	M	S
	# (%)	# (%)	# (%)	# (%)	# (%)	# (%)	# (%)	# (%)	# (%)	# (%)
Nausea	3 (13)	0	151 (28)	21 (4)	182 (30)	25 (4)	133 (40)	23 (7)	119(18)	6 (1)
Dizziness	1 (5)	0	0	0	145 (24)	12 (2)	116 (35)	9 (3)	118 (17)	5 (1)
Somnolence	1 (5)	0	1 (<1)	0	79 (13)	12 (2)	76 (23)	9 (3)	64 (9)	5 (1)
Headache	3 (13)	0	3 (1)	0	47 (8)	12 (2)	35 (11)	1 (<1)	70 (10)	8 (1)
Vomiting	1 (5)	0	40 (7)	40 (7)	57 (9)	55 (9)	35 (11)	54 (16)	104 (15)	11 (2)
Pruritis	0	0	31 (6)	0	53 (9)	0	52 (16)	2 (1)	31 (5)	1 (<1)
Constipation	0	2 (10)	30 (6)	0	21 (3)	1 (<1)	25 (8)	0	81 (12)	6 (1)

* M=mild or moderate severity, S=severe
Percentages represent percent of subjects in specified dosing group
Flex dose group received 50-100mg

TEAEs by selected concomitant medication usage

The incidence of selected common TEAEs is summarized below for all tapentadol IR doses combined in subjects who took the following concomitant medications: opioid analgesics, non-opioid analgesics, and antidepressants including SSRIs. The incidence of nausea, vomiting, dizziness, somnolence, and pruritis is highest in subjects who took concomitant opioid analgesics compared to those who received non-opioid analgesics or

antidepressants, and to all subjects receiving tapentadol IR. Since these are the typical opioid-associated adverse events, this is an expected finding, as these events may be additive. Interestingly, constipation occurred at a lower rate in subjects receiving concomitant opioids compared to those who did not. Patients receiving antidepressants had lower incidences of nausea, vomiting, dizziness, somnolence, and headache than all other groups. It is not possible to speculate on the reason for this finding with the available data.

Table 57: Percentage of Subjects Experiencing Common TEAEs by Concomitant Medication Usage for All Tapentadol IR Doses Combined

TEAE	All Tapentadol IR subjects n=2178	Opioid Analgesics n=660	Non-Opioid Analgesics n=1370	Antidepressants/SSRIS n=213
Nausea	30	41	30	16
Vomiting	18	21	18	14
Constipation	8	6	8	12
Dizziness	24	27	24	16
Somnolence	15	20	15	11
Headache	11	10	12	8
Pruritus	5	10	7	7

TEAEs by pain model

Six of the nine Phase 2/3 multiple-dose double-blind studies were conducted in postoperative subjects with moderate-to-severe pain (third molar extraction, bunionectomy, hip replacement) following surgery, and three studies were conducted in patients with moderate-to-severe pain in an out patient non-surgical setting (i.e., non-malignant pain, pain due to end-stage degenerative joint disease, low back pain, or OA of the hip or knee).

The Applicant's table below illustrates the incidence of TEAEs in post-surgical patients and outpatient, non-surgical patients. Nausea, vomiting, dizziness, and somnolence were reported in a higher percentage of subjects in postoperative studies than for subjects in outpatient studies in the "all" tapentadol IR pooled analysis treatment group. These are expected results given the fact that post-operative patients have received anesthetic and analgesic agents that may increase the number of adverse events.

Constipation was reported for a higher percentage of subjects in the outpatient studies than in the postoperative studies in the "all" tapentadol IR group. Nausea was reported in a higher percentage of subjects in postoperative studies than for subjects in the outpatient studies in the placebo group. There was no difference in the percentage of subjects with vomiting, dizziness, somnolence, or constipation based on the pain model in the placebo group, except for nausea, which was reported for a higher percentage of subjects in the postoperative studies. Again, these results are not unexpected.

Table 58: TEAEs of Nausea, Vomiting, Dizziness, Somnolence, and Constipation by Pain Model: Phase 2.3 Multiple-Dose Double-Blind Safety Analysis Set

	Placebo (n=619)		"All" Tapentadol IR (n=2178)	
Preferred Term	Nonsurgical[a] (n=169) n (%)	Postoperative (n=450) n (%)	Nonsurgical[a] (n=1048) n (%)	Postoperative (n=1130) n (%)
Total no. subjects with TEAEs	54 (32)	235 (52)	748 (71)	903 (80)
Nausea	9 (5)	71 (16)	197 (19)	466 (41)
Vomiting	7 (4)	19 (4)	151 (14)	246 (22)
Dizziness	8 (5)	40 (9)	199 (19)	317 (28)
Somnolence	2 (1)	15 (3)	97 (9)	223 (20)
Constipation	4 (2)	12 (3)	108 (10)	66 (6)

Source: 4-Month Safety Update, p. 113

Less Common Adverse Events

TEAEs occurring at a rate of <1% were reviewed. The following table shows the rates of TEAEs possibly related to the study drug. There are no unusual or unexpected findings.

Table 59: Adverse Drug Reactions Reported by <1% of Tapentadol IR Treated Subjects in Placebo-controlled Double-Blind, Phase 2/3 Multiple-Dose Clinical Studies.

System/Organ Class Referenced Preferred Term[a]	Tapentadol IR (21 mg to 120 mg) (n=2178) %	Placebo (n=619) %
Cardiac disorders		
Heart rate increased	0.7	0.8
Heart rate decreased	(<0.1)	0
Nervous system disorders		
Paresthesia	0.9	0.5
Hypoaesthesia	0.9	0.6
Disturbance in attention	0.8	0
Sedation	0.7	0.2
Dysarthria	0.6	0
* Depressed level of consciousness	0.5	0
Memory impairment	0.4	0
Ataxia	0.2	0
Presyncope	0.1	0
Coordination abnormal	<0.1	0
** Seizure	Unknown	Unknown
Respiratory, thoracic and mediastinal disorders		
Oxygen saturation decreased	0.8	0.5
Cough	0.6	0.3
Dyspnoea	0.6	0
Respiratory depression	0.4	0.2
Gastrointestinal disorders		
Impaired gastric emptying	<0.1	0
Renal and urinary disorders		
Urinary hesitation	0.6	0
Pollakuria	0.4	0
Skin and subcutaneous tissue disorders		
Urticaria	0.4	0
Musculoskeletal and connective tissue disorders		
Sensation of heaviness	0.2	0
Vascular disorders		
Blood pressure decreased	<0.1	0
General disorders and administration site conditions		
Abdominal discomfort	0.8	0.2
Irritability	0.6	0
Oedema	0.6	0
Feeling of relaxation	0.4	0.2
Drug withdrawal syndrome	0.3	0
Feeling abnormal	0.3	0
Feeling drunk	0.3	0
Immune system disorders		
Hypersensitivity	<0.1	0
Psychiatric disorders		
Euphoric mood	0.8	0
Disorientation	0.7	0.3
Restlessness	0.5	0.2
Agitation	0.4	0.3
Nervousness	0.2	0
Thinking abnormal	<0.1	0
~~Confusional state~~	~~0.5~~	~~0~~
~~Hallucination~~	~~0.1~~	~~0~~

[a] Referenced preferred term = sponsor defined aggregated MedDRA preferred terms.
Note: Adverse events were coded using MedDRA version 10.1
Percentages calculated using the number of subjects in each treatment group as a denominator.
The same subject may be counted in different categories. Within a category, a subject is only counted once.
ADRs were identified based on treatment-emergent adverse events.
* Occurred only in single-dose treated subjects. Not observed in multiple-dose studies
** Not observed in multiple-dose studies.
The data in this table also includes information from study KF5503/08 that was neither placebo- or oxycodone-controlled and included 47 subjects who were assessed for ADRs. The total number of studies, therefore, was 9.

Source: 4-Month Safety Update, p.

7.4.2 Laboratory Findings

Overview of laboratory testing in the development program

Laboratory assessments during Phase 1 and 2 (single-dose) were obtained at baseline and at various post-baseline time points. Labs included hematology, chemistry and urinalyses. These results are not pooled, but will be discussed below briefly.

A schedule of clinical laboratory data obtained during the 7 Phase 2/3 multiple-dose, double-blind studies included hematology, chemistry and urinalyses. The complete list of tests may be found in Table 91. Collection time points are provided in Table 88 in Section 9.4.

Laboratory summaries are also provided for the Phase 3 Open-label Extension Safety Analysis Set.

Selection of studies and analyses for drug-control comparisons of laboratory values

Laboratory data from Phase 1 and 2 (single-dose) studies were not pooled. Laboratory data were pooled in the Phase 2/3 Safety Analysis Set; however, according to the Applicant, due to the large variations in the laboratory normal ranges among the Phase 2/3 Multiple-dose Double-blind studies, only laboratory data for KF5503/21, KF5503/22, KF5503/32, KF5503/33, and KF5503/34 were summarized and are included in the summaries of clinical laboratory data for the Phase 2/3 Multiple-dose Double-blind Safety Analysis Set (omitted studies are: KF5503/4, KF5503/8). A request was made of the Applicant on July 31, 2008 to provide Shift tables for all Phase 2/3 studies, including studies KF5503/4 and KF5503/8. These tables were submitted by the Applicant on August 8, 2008. Laboratory data for subjects randomized at site 011006 in KF5503/31 (due to data irregularities, see Section 3.2) were summarized separately.

Analyses focused on measures of central tendency

Phase 1 and 2 (single-dose)

Based on a review of the individual study reports and the Applicant's analysis, there were no clinically relevant changes from baseline in mean laboratory values over time. Laboratory values showed fluctuations outside the normal ranges but did not reveal any consistent patterns that might indicate a potentially clinically important safety concern.

Phase 2/3 multiple-dose, double-blind analysis set

The datasets containing laboratory data for the Phase 2/3 multiple-dose, double-blind analysis set are *Klabs01.xpt* through *Klabs13.xpt.*

Upon request, the Applicant provided a table showing the mean changes from baseline for all laboratory examinations for all Phase 2/3 multiple-dose, double-blind studies. On review of the Applicant's table, there were no clinically relevant changes from baseline to endpoint in mean values for the pooled analysis treatment group in the Phase 2/3 Multiple-Dose Double-Blind Safety Analysis Set for subjects receiving study drug compared to placebo.

Analyses focused on outliers or shifts from normal to abnormal

Shift tables for all lab values were provided by the Applicant. There were no patterns of laboratory results that revealed concern regarding laboratory abnormalities.

The laboratory data from the open-label Phase 3 studies was reviewed. Results were similar to those found in the Phase 2/3 multiple-dose double-blind studies.

Marked outliers and dropouts for laboratory abnormalities

The Applicant provided predefined criteria used to identify potentially clinically important (PCI) laboratory values in the Phase 2/3 Multiple-dose, Double-blind safety analysis set. These are located in Table 95. The Applicant's table below shows the percentage of subjects with a potentially clinically important abnormal laboratory result at any time during treatment and with a normal baseline. The incidence for all lab tests, except creatine kinase (CK), was less than 1% for subjects in the "all tapentadol" group, and is similar to the placebo group. The incidence for clinically important abnormalities in CK was 1% in the "all" tapentadol group, and 2% in the placebo group.

Table 60: Potentially Clinically Important Abnormal Laboratory Results: Phase 2/3 Multiple-Dose, Double-Blind Analysis Set

	Placebo (n=602)			"All" Tapentadol IR (n=2113)			"All" Oxycodone IR (n=675)		
Laboratory type	Total	Abnormality, n (%)		Total	Abnormality, n (%)		Total	Abnormality, n (%)	
Parameter	n	Low	High	n	Low	High	n	Low	High
Chemistry	467	0	14 (3)	1681	12 (1)	48 (3)	483	3 (1)	11 (2)
Creatinine (umol/L)	466	0	1 (<1)	1679	0	3 (<1)	483	0	0
Alkaline phosphatase (U/L)	466	0	1 (<1)	1678	0	7 (<1)	483	0	2 (<1)
Chloride (mmol/L)	466	0	0	1672	2 (<1)	0	483	1 (<1)	0
Sodium (mmol/L)	466	0	0	1672	1 (<1)	0	483	0	0
Glucose (mmol/L)	463	0	0	1661	8 (<1)	0	482	1 (<1)	0
Creatine kinase (U/L)	463	0	8 (2)	1660	0	20 (1)	482	0	5 (1)
Phosphate (mmol/L)	454	0	2 (1)	1649	1 (<1)	5 (<1)	479	1 (<1)	1 (<1)
GGT (U/L)	454	0	0	1646	0	5 (<1)	479	0	1 (<1)
Potassium (mmol/L)	452	0	0	1641	0	3 (<1)	479	0	0
ALT (SGPT) (U/L)	449	0	1 (<1	1628	0	3 (<1)	477	0	2 (<1)
AST (SGOT) (U/L)	444	0	1 (<1)	1625	0	2 (<1)	476	0	1 (<1)
Bilirubin (umol/L)	445	0	0	1577	0	2 (<1)	465	0	1 (<1)
Triglycerides (mmol/L)	399	0	0	1548	0	3 (<1)	419	0	1 (<1)
Lipase (U/L)	321	0	0	1225	0	2 (<1)	338	0	0
Amylase (U/L)	223	0	0	1129	0	1 (<1)	338	0	0
Hematology	462	0	0	1648	1 (<1)	0	481	1 (<1)	0
Platelets (giga/L)	456	0	0	1608	1 (<1)	0	465	1 (<1)	0

Studies included: KF5503/21, KF5503/22, KF5503/31 (excluding site 011006), KF5503/32, KF5503/33, KF5503/34, and KF5503/37. Studies KF5503/04 and KF5503/08 were excluded from the analysis due to the large variation in the normal ranges used in these studies.

Potentially clinically important results at any time point during the treatment period and within normal range at baseline.

"n" under Total represents the number of subjects with at least 1 measurement at baseline and at least 1 measurement during the phase. Percentages of abnormality subgroup calculated with the number of subjects per parameter as denominator.

ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GGT = gamma-glutamyl transferase

Source: Tapentadol IR 4-Month Safety Update, p. 134

No subjects had a potentially clinically important (PCI) laboratory value for the following laboratory parameters: protein, calcium, uric acid, LDH, urea nitrogen, cholesterol, albumin, hemoglobin, RBC count, and WBC count.

During the Open-label extension studies, the percentage of subjects with a PCI abnormal value at any time during the open-label treatment period who had a normal baseline value ≤ 2%, as shown in the Applicant's table below. These results are not markedly different than those in the multiple-dose, double-blind analysis set, however there is not a placebo group for comparison.

Table 61: Potentially Clinically Important Laboratory Values: OL Extension Studies

		FLEX TAP IR (N=483)	
Laboratory type	Total	Abnormality, n (%)	
Parameter	n	Low	High
Chemistry	476	2 (<1)	11 (2)
Alkaline phosphate (U/L)	476	0	3 (1)
Chloride (mmol/L)	476	1 (<1)	0
GGT (U/L)	476	0	3 (1)
Triglycerides (mmol/L)	476	0	2 (<1)
ALT (SGPT) (U/L)	474	0	1 (<1)
Glucose (mmol/L)	473	1 (<1)	0
LDH (U/L)	469	0	5 (1)

Studies included: KF5503/31 (excluding site 011006) and KF5503/32
Flex Tap IR: Tapentadol flexible dose of 50 or 100 mg
Subjects may be included in more than one abnormality category
Abnormal values at any time post baseline with a normal baseline value
"n" under Total represents the number of subjects with at least one measurement at baseline and at least one measurement during the phase. Percentages of abnormality sub-group calculated with the number of subjects per parameter as denominator.
Source: Tapentadol IR 4-Month Safety Update, p. 171

Dropouts due to laboratory abnormalities
In the Phase 1 studies, two subjects and in Phase 3 studies, five subjects who received tapentadol IR discontinued treatment due to laboratory abnormalities.

Five of the seven subjects (two in Phase 1 and three in Phase 3) who discontinued did so due to abnormal liver functions. However two of the five subjects had abnormal liver function tests at baseline and in both cases, laboratory values returned to baseline level or lower while the subject was still receiving study drug. One subject discontinued due to an abnormal lipase level which was also abnormal at baseline, elevated slightly during treatment with study drug, and fell to below baseline levels while on study drug.

Overall, there does not appear to be substantial evidence of study drug related abnormalities in liver function based on subjects who discontinued treatment.

Additional analyses related to abnormal liver function may be found in hepatic reactions and in Section 7.5.6 (comprehensive search SMQ).

Narratives for subjects who discontinued treatment due to laboratory abnormalities follow:

Subject 107017 (Phase 1 study to evaluate abuse potential): Increased ALT
This 37-year-old Hispanic man had a normal medical history apart from a cholecystectomy two years before enrolling in the study. His history of recreational drug use included a moderate use of opioids, stimulants, and cannabinoids. At screening he received hydromorphone IR 8 mg during Period 1, and placebo during Period 2. He received CG5503 IR 116 mg, CG5503 IR 58 mg, CG5503 IR 233 mg, and hydromorphone IR 16 mg during Periods 1, 2, 3, and 4, respectively, of the double-blind treatment phase. His alanine aminotransferase (ALT) levels during the prescreening period, and on Day – 1 of Period 1 were 47 U/L and 79 U/L. Two days (53 hours) after receiving hydromorphone IR 16 mg, an adverse event of increased alanine aminotransferase (reported term elevated ALT) was reported (ALT value of 121 U/L). The adverse event did not resolve, and the subject was withdrawn from the study. A follow-up visit 8 days after the adverse event was reported revealed a high level of ALT (82 U/L). The investigator considered the elevated ALT to be of mild intensity, and unlikely to be related to the study medication

Reviewer comment: Since the subject received multiple different treatments during the study, it is unclear whether the laboratory abnormalities were due to tapentadol IR.

Subject 118066 (TQT study): AST and GGT elevation leading to study discontinuation:
A 60-year-old woman experienced moderate-intensity adverse events of aspartate aminotransferase (AST) and gamma-glutamyl transferase (GGT) increased on Day 3 of Period 3, leading to discontinuation from the study. The AST and GGT values, as well as alkaline phosphatase, lactate dehydrogenase (LDH), and alanine aminotransferase (ALT) values, had been within normal limits (0-30 U/L, 5-36 U/L, 533–1734 nkat/L, 135 – 214 U/L, and 0-35 U/L, respectively) at screening and on Day -1 of Periods 1 and 2. Prior and concomitant medications included Estreva (estradiol) and Surgestrone (promegestone) hormonal therapy. Study drug administration in Periods 1 and 2 included 5 doses of tapentadol IR 150 mg and 4 doses of placebo/1 dose of moxifloxacin 400 mg, respectively. The AST, GGT, LDH, and ALT values were elevated (40 U/L, 60 U/L, 591 U/L, and 40 U/L, respectively) on Day -1 of Period 3. Thereafter, the subject received a total of 5 doses of tapentadol IR 100 mg over Days 1 and 2 of Period 3 (the last dose about 20 hours before the liver function test adverse events were recorded). Repeat testing, on Days 3 and 5 of Period 3 showed increased AST (58 and 76 U/L), GGT (102 and 105 U/L), LDH (278 and 328 U/L), and ALT (58 and 68 U/L) values, respectively. The adverse events were assessed by the investigator as possibly related to the study drug. The subject did not continue to Period 4 of the study and underwent end-of-study/early withdrawal procedures on Day 10 of Period 3 at which time the AST, GGT, alkaline phosphatase, LDH, and ALT values remained elevated (77 U/L, 106 U/L, 2,501 nkat/L, 61 U/L, and 76 U/L, respectively). Since further follow-up of the subject was not

possible despite repeated attempts by the investigator, the adverse events were reported as not resolved.

Subject 400049 (Study KF5503/34-90 day safety study): liver function test abnormal
The subject was a 45-year-old white woman with a medical history of gastroesophageal reflux disease, hiatal hernia, intermittent vomiting, nausea, sensitive gag reflex, surgical stretching of esophageal stricture, bursitis of left hip, degenerative disc disease, left hip pain, low back pain, lumbar fracture, neck surgery, left ankle edema, allergy to surgical tape, and seasonal allergies. Prior and/or concomitant medications of Tramadol hydrochloride, vicoprofen, dyazine, lansoprazole, narine, and ibuprofen were reported. Physical examination at screening and baseline vital signs, and ECG findings were unremarkable. Laboratory values revealed abnormally elevated ALT (97 U/L), AST (105 U/L), Alkaline Phosphatase (166 U/L), GGT (115 U/L), and LDH (238 U/L). The subject received a total daily dose of 150 mg to 400 mg tapentadol IR on Day 1 to Day 54. The subject experienced "increased liver function tests" on Day 50. Abnormally elevated labs from baseline were further elevated: ALT (144 U/L), AST (170 U/L), Alkaline Phosphatase (175 U/L), GGT (127 U/L), and LDH (270 U/L). These lab tests decreased to a value at or lower than the baseline values by Day 60. The abnormal liver function tests were considered possibly related to the study drug by the investigator. The subject was withdrawn from the study on Day 60 due to abnormal liver function test.

Reviewer comment: The abnormal liver function tests are possibly related to study drug, and returned to baseline following discontinuation of treatment.

Subject 402025 (Study KF5503/34-90 day safety study): liver function test abnormal
The subject was a 45-year-old black woman with a medical history of hypertension, cholecystectomy, heartburn, post menopausal, degenerative joint disease spine, muscular spasms of low back and legs bilateral, osteoarthritis of right hip and spine, tension headaches, borderline diabetes, 2nd degree burn scars on waist and chest, acne, skin grafts of waist and chest, anxiety, depression, insomnia, and seasonal allergies. Prior and/or concomitant medications included ibuprofen, doxycycline, cyclobenzaprine hydrochloride, fluoxetine hydrochloride, diltiazem hydrochloride, calcium carbonate, diphenhydramine hydrochloride, antihistamines, vicodin, nortriptyline, and alprazolam. Laboratory values showed elevated ALT 47 U/L and 38 U/L (6 - 34 U/L), alkaline phosphatase 221 U/L and 205 U/L (31 – 106 U/L), GGT 271 U/L and 216 U/L (4 – 49 U/L), and LDH 307 U/L and 320 U/L (53 – 234 U/L) at screening and baseline, respectively. The AST was elevated at screening 40 U/L (9 – 34 U/L). Baseline ECG findings and vital signs were unremarkable. The subject received a total daily dose of 400 mg to 800 mg tapentadol IR on Day 1 to Day 55. The subject experienced abnormal liver function tests (ALT 89 U/L, AST 77 U/L, and alkaline phosphatase 216 U/L), elevated GGT 290 U/L, and elevated LDH 344 U/L on Day 42. The abnormal liver function test was reported as not resolved and considered probably related to the study drug by the investigator. Physical examination, ECG findings, and vital signs were unremarkable on Day 56. Laboratory values showed elevated ALT 47 U/L, AST 40 U/L, alkaline phosphatase 212 U/L, GGT 212 U/L, and LDH 297 U/L. The subject was withdrawn from the study on Day 59 due to liver function test abnormal.

Reviewer comment: This subject had markedly abnormal LFTs at baseline and screening. The subject was withdrawn from the study on Day 59 despite the fact that the LFTs had returned to or below the levels obtained at screening. It is unlikely the lab abnormalities were due to study drug.

Subject 400054 (Study KF5503/34-90 day safety study) ALT and AST Increased
The subject was a 54-year-old white man with a medical history of appendectomy, chronic low back pain, fracture of L4–L5, torn anterior cruciate ligament left knee, and anxiety. Prior and/or concomitant medications of vicodin and alprazolam were reported. Physical examination at screening and baseline laboratory values, vital signs, and ECG were unremarkable, including ALT (31 U/L) and AST (27 U/L). The subject received a total daily dose of 600 mg to 800 mg tapentadol IR on Day 1 to Day 57. The subject experienced increase alanine aminotransferase (50 U/L) and increased aspartate aminotransferase (62 U/L) on Day 44. The increased alanine aminotransferase and increased aspartate aminotransferase resolved (36 U/L and 42 U/L, respectively) on Day 61 and were considered possibly related to the study drug by the investigator. Physical examination, laboratory values, vital signs, and ECG findings were unremarkable on Day 61. The subject was withdrawn from the study on Day 61 due to increased alanine aminotransferase and aspartate aminotransferase.

Reviewer comment: It is of note that the lab abnormalities returned to normal while subject was receiving study drug.

Subject 400383 (Study KF5503/34-90 day safety study) lipase increased
The subject was a 79-year-old white man with a history of cataracts both eyes, hearing loss left ear, hyperlipidemia, hypertension, cholecystectomy, colon surgery, low back pain, osteoarthritis right knee, right knee severe pain, intermittent headaches, non insulin diabetic, and venous stenosis changes with edema on both feet. Prior and/or concomitant medications included quinapril hydrochloride, chondroitin/glucosamine, multivitamins, paracetamol, metformin, and glibenclamide. Physical examination at screening was unremarkable except for old cholecystectomy surgical scar, silver arterioles on funduscopy, and sensation of loss in lower limb distally. Baseline laboratory values showed elevated lipase 440 U/L (0 – 130 U/L) and normal amylase. ECG findings showed old inferior infarct and right bundle branch block. Vital signs were unremarkable. The subject received a total daily dose of 150 mg to 400 mg tapentadol IR on Day 1 to Day 50 except on Day 8, Day 26, and Day 39 when no study drug was taken. The subject experienced "elevated lipase level" (verbatim) of 440 U/L (0 – 130 U/L) with normal amylase on Day 18. The increased lipase was reported as not resolved and considered possibly related to the study drug by the investigator. Physical examination and vital signs were unremarkable including a normal abdominal examination. Laboratory values showed elevated lipase 170 U/L on Day 57. ECG findings were unchanged from baseline. The subject was withdrawn from the study on Day 59 due to increased lipase.

Reviewer note: Again, the subject's laboratory value, in this case lipase, was abnormal at baseline, elevated slightly during treatment with study drug, and fell to below baseline

levels while on study drug. Although it is possible this was due to study drug, it is not clear given the abnormal baseline value.

Subject 100567 (Study KF5503/31) elevated troponin level
Subject was a 62 year-old white male with medical history of hypertension, left anterior fascicular block, and MI 12 years prior. The patient was on no cardiac medications. PE, VS, and labs at baseline were normal. Screening ECG at baseline showed a first degree A-V block, left anterior hemiblock and non-specific T wave abnormalities. The subject received seven doses of tapentadol IR 100mg on Day 1, 4 doses on Day 2, and 1 dose on Day 3. On Day 3 the subject experienced abdominal distension and chest pain, and had an increased troponin. Troponin resolved on the same day and was considered unlikely related to study drug by the investigator. Chest pain was treated with isosorbide dinitrate. The subject was withdrawn from the study due to increased troponin. End of study ECG showed tachycardia (103), left anterior fascicular block, and late transition. A chest x-ray showed no active process.

Reviewer comment: There is no evidence in the narrative that the increased troponin level was definitely related to study drug.

Additional analyses and explorations

Hepatic Reactions
No subjects had elevations in liver function parameters that met the criteria for the composite hepatotoxicity analysis (i.e., an ALT or AST value >3 x ULN and alkaline phosphatase value below the normal reference range and a total bilirubin above the normal reference range), and no subject had an ALT or AST value >10 x ULN in any pooled analysis treatment group in the Phase 2/3 Multiple-dose Double-blind Safety Analysis Set.

There was no apparent difference between the placebo and "all" tapentadol IR pooled analysis treatment groups in the percentage of subjects with ALT or AST values >3 X ULN or >5 X ULN, as shown in the Applicant's table below.

Table 62: Elevations in Liver Function Parameters at Any Time During Treatment: Phase 2/3 Multiple-Dose, DB Analysis Set

Parameter Category	Placebo (N=602) n (%)	"All" Tapentadol IR (N=2113) n (%)	"All" Oxycodone IR (N=675) n (%)
ALT (SGPT) (U/L)			
n	449	1628	477
>3 x ULN	2 (<1)	9 (1)	2 (<1)
>5 x ULN	0	4 (<1)	1 (<1)
AST (SGOT) (U/L)			
n	444	1625	476
>3 x ULN	1 (<1)	5 (<1)	1 (<1)
>5 x ULN	0	1 (<1)	0

Studies included: KF5503/21, KF5503/22, KF5503/31 (excluding site 011006), KF5503/32, KF5503/33, KF5503/34, and KF5503/37.

KF5503/04 and KF5503/08 were excluded from the analysis due to the large variation in the normal ranges used in these studies.

"n" represents the number of subjects with at least 1 measurement at baseline and at least 1 measurement during the phase. Percentages of abnormality subgroup calculated with the number of subjects per parameter as denominator.

For possible drug related hepatic reactions based on the comprehensive search SMQ, see Section 7.5.6.

Reviewer's conclusion: There do not appear to be any consistent laboratory abnormalities related to study drug administration.

7.4.3 Vital Signs

Overview of vital signs testing in the development program

Vital sign data in the Phase 1 studies were not pooled. Vital sign assessments were obtained at baseline and at various post-baseline time points in the Phase 1 studies. Based on the vital sign measurements in the Phase 1 single- and multiple- dose studies in healthy subjects, no systematic effect on vital signs was observed.

A schedule of vital sign time points in the 9 Phase 2/3 multiple-dose double-blind studies is provided in Section 9.4. For the Phase 2 Single-dose Safety Analysis Set; the Phase 2/3 Multiple-dose Double-blind Safety Analysis Set; and the Phase 3 Open-label Extension Safety Analysis Set, descriptive statistics (N, mean, SD, median, and range) were provided by pooled analysis treatment group for heart rate, systolic and diastolic blood pressure, respiration rate, and oxygen saturation for the absolute values and the change from baseline at numerous time points.

Selection of studies and analyses for overall drug-control comparisons

The Phase 2/3 multiple-dose double-blind analysis set is appropriate for overall drug-control comparisons of vital sign data.

Analyses focused on measures of central tendencies

There were no clinically relevant changes in mean values for pulse rate, systolic or diastolic blood pressure, respiratory rate, and pulse oximetry for any of the pooled

analysis treatment groups at endpoint in the Phase 2/3 Multiple-Dose Double-blind Safety Analysis Set. (Applicant's attachment 3.11.1SU)

Analyses focused on outliers or shifts from normal to abnormal

Vital sign shift tables were provided by the Applicant upon a request submitted July 31, 2008. There were no findings of note discovered upon review of these tables.

Marked outliers and dropouts for vital sign abnormalities

The criteria used to assess potentially clinically important abnormal vital sign measurements are provided in Table 63.

Table 63: Criteria for Identifying Potentially Clinically Important Vital Sign Values in the Phase 2/3 Studies

Parameter	Abnormally Low Post Baseline	Abnormally High Post Baseline
Systolic blood pressure (mmHg)	Value ≤90 with baseline >90	Value ≥180 with baseline <180
Diastolic blood pressure (mmHg)	Value ≤50 with baseline >50	Value ≥105 with baseline <105
Heart rate (beats per minute [bpm])	Value ≤45 with baseline >45	Value ≥115 with baseline <115
Respiration rate (breaths per minute)	Value <7 with baseline ≥7	Value >25 with baseline ≤25
Oxygen saturation (%)	Value <90 with baseline ≥90	--

-- No abnormally high limit

Source: ISS, p. 68

The percentage of subjects with one or more potentially clinically important vital sign measurement at any time during the treatment phase and who had a normal baseline value is shown below in Table 64.

Table 64: Potentially Clinically Important Abnormal Vital Sign Values: Phase 2/3 Multiple-Dose Double-Blind Studies

	Placebo (N=619)			"All" Tapentadol IR (N=2178)			"All" Oxycodone IR (N=675)		
	Total	Abnormality n (%)		Total	Abnormality n (%)		Total	Abnormality n (%)	
Parameter	n	Low	High	n	Low	High	n	Low	High
Pulse rate (bpm)	591	6 (1)	7 (1)	2010	11 (1)	21 (1)	588	5 (1)	13 (2)
SBP (mmHg)	591	30 (5)	1 (<1)	2010	118 (6)	14 (1)	588	36 (6)	4 (1)
DBP (mmHg)	591	27 (5)	0	2010	128 (6)	10 (<1)	588	36 (6)	2 (<1)
Respiration (/min)	589	0	1 (<1)	2006	0	6 (<1)	588	0	1 (<1)
Pulse oximetry (%)	433	1 (<1)	NA	1147	26 (2)	NA	329	6 (2)	NA

Studies included: KF5503/04, KF5503/08, KF5503/21, KF5503/22, KF5503/31 (excluding site 011006), KF5503/32, KF5503/33, KF5503/34, and KF5503/37.
DBP = diastolic blood pressure; NA = not applicable; no abnormaly high criteria was applied for pulse oximetry;
SBP = systolic blood pressure
Subjects may be counted in more than one abnormal category.
Pulse oximetry was not assessed in KF5503/33 or KF5503/34
"n" under Total represents the number of subjects with at least 1 measurement at baseline and at least 1 measurement during the phase. Percentages of abnormality subgroup calculated with the number of subjects per parameter as denominator.

Source: ISS, p. 143

The percentage of subjects with PCI abnormal vital sign values was similar to the percentage in the placebo group. Among subjects in the tapentadol IR dose groups, the percentage of subjects with abnormally low oxygen concentration, measure by pulse oximetry, tended to increase with increasing doses: tapentadol IR 0-30mg (0%), >30-

60mg (2%), >60-90mg (2%), and >90-120mg (4%). Overall, the incidence for the "all tapentadol IR group (2%) the same as the "all" oxycodone group (2%) suggesting that the finding reflects the mu-opioid agonist property of tapentadol IR.

There were no subjects in the Phase 1 or Phase 2/3 safety datasets that were coded as discontinuing treatment due to abnormal vital signs. The Applicant conducted a search of adverse events identified as potentially associated with abnormal vital signs or abnormal ECGs. See results of that search in Section 7.4.4.

Additional analyses and explorations

Subgroup analyses were carried out for PCI abnormal vital signs by sex, age group, and race. The only finding of note is that the percentage of subjects with PCI abnormally low systolic blood pressure measurement was higher for female subjects that for male in the placebo group (7% in females vs. 0% in males), and the "all" tapentadol group (8% vs. 1%).A similar pattern was observed for low diastolic blood pressure measurements. The presence of these findings in the placebo group indicates it may not be related to study drug.

Reviewer's conclusion: According to the above data, the only vital sign abnormality that may be related to the administration of study drug is oxygen saturation as measured by pulse oximetry. This effect appears to be dose-related within the tapentadol IR treatment groups, and similar in incidence to the oxycodone treatment groups. This finding may represent a mu-opioid effect of tapentadol IR.

7.4.4 Electrocardiograms (ECGs)

Overview of ECG testing in the development program

Electrocardiogram (ECG) data for subjects in the Phase 1 studies were not integrated. A 12-lead ECG was obtained at baseline and at various post baseline time points in each study. In HP5503/03, HP5503/04, HP5503/05, and HP5503/07, the investigator assessed clinically significant changes in ECG findings. In all other Phase 1 single-dose studies and in the Phase 1 multiple-dose study, potentially clinically significant criteria were applied to the ECG parameters.

Based on the ECG measurements in the Phase 1 single- and multiple-dose studies, no systematic effect on ECGs can be determined.

A schedule of ECG time points in the 9 Phase 2/3 multiple-dose double-blind studies is provided in Section 9.4. Electrocardiograms were not performed in the Phase 2 single-dose study, KF5503/02. Because ECG laboratories for the remaining 3 Phase 2 single-dose studies (KF5503/04, KF5503/05, and KF5503/08) used methodologies that differed from the rest of the Phase 2/3 studies, ECG data for these 3 studies were not pooled.

Centralized ECG interpretation was provided by 2 ECG laboratories: [ ] b(4)
[ ] provided centralized interpretation of the ECG data in the Phase 2 multiple-dose studies (KF5503/21 and KF5503/22) and [ ] provided centralized interpretation of the ECG data in the Phase 3 studies (KF5503/31, KF5503/32, KF5503/33, KF5503/34,

and KF5503/37). ECG assessments from [ ] were analyzed separately. b(4)

Selection of studies and analyses for overall drug-control comparisons

Phase 2/3 multiple-dose, double-blind studies were selected to assess drug-control comparisons of ECG findings. These include studies KF5503/21, KF5503/22, KF5503/31, KF5503/32, KF5503/33, KF5503/34, and KF5503/37. These studies were not designed to provide a thorough evaluation of the effect of tapentadol IR on QT/QTc intervals. A thorough QT study (HP5503/25) was conducted. Those results are discussed in Section 7.4.5.

Standard analyses and explorations of ECG data

Centralized ECG assessments included heart rate, PR interval, RR interval (not collected in KF5503/21 and KF5503/22), QRS interval, QT interval, QTcB (Bazett's), QTcF (Fridericia's), QTlc, and QTcLD.

The ECG assessments were evaluated by descriptive statistics and frequency tabulations. The Applicant's analyses summarized values at baseline, endpoint, and changes from baseline to endpoint. In addition, abnormalities for heart rate, PR interval, QRS interval, and QT interval during the treatment period were identified using the criteria in Table 65. The incidence of the abnormalities was summarized by pooled analysis treatment group.

Table 65: Criteria for Identifying Abnormal ECG Heart Rate and Interval Values in the Phase 2/3 Single-dose and Multiple-dose Studies

	Outside of Normal Limit if	
ECG parameter	Abnormally low	Abnormally high
Heart Rate (bpm)	≤45	≥115
PR interval (msec)	--	≥200
QRS interval (msec)	≤50	≥120
QT interval (msec)	≤200	≥500

Source: ISS, p. 69

Analyses focused on measures of central tendency

There were no clinically meaningful changes in heart rate or mean ECG values across the pooled analysis treatment groups in the Phase 2/3 Multiple-Dose, Double-Blind Safety Analysis Set.

Vital sign data from the Phase 3 open-label extension study was reviewed and revealed no significant findings.

Analyses focused on outliers or shifts from normal to abnormal

The percentage of subjects with abnormalities in heart rate, PR interval, QRS interval, or QT interval values at any time point during the double-blind treatment period was similar for subjects in the placebo and "all" tapentadol IR groups. The results are illustrated in Table 66.

Table 66: Abnormalities in Heart Rate and ECG Parameters During Treatment: Phase 2/3 Multiple-Dose Double-Blind Studies

	Placebo			"All" Tapentadol IR		
	Total	Abnormality, n (%)		Total	Abnormality, n (%)	
Parameter	n	Low	High	n	Low	High
Phase 2 Studies						
Heart rate (beats/min)	146	2 (1)	0	455	5 (1)	0
PR interval (ms)	146	0	10 (7)	455	0	15 (3)
QRS interval (ms)	146	0	0	455	0	1 (<1)
QT interval (ms)	146	0	0	455	0	0
Phase 3 Studies						
Heart rate (beats/min)	423	4 (1)	2 (<1)	1374	3 (<1)	3 (<1)
PR interval (ms)	421	0	29 (7)	1361	0	89 (7)
QRS interval (ms)	423	0	16 (4)	1374	0	51 (4)
QT interval (ms)	423	0	1 (<1)	1374	0	4 (<1)

Studies included: Phase 2 studies (KF5503/21, KF5503/22) and Phase 3 studies (KF5503/31 [excluding site 011006], KF5503/32, KF5503/33, KF5503/34, and KF5503/37). KF5503/04 and KF5503/08 are excluded from the analysis due to the difference in methodologies used to measure the ECG.
Centralized ECG review provided by [redacted] in Phase 2 studies (KF5503/21 and KF5503/22) and by [redacted] in Phase 3 studies (KF5503/31, KF5503/32, KF5503/33, KF5503/34, and KF5503/37). b(4)
"n" under Total represents the number of subjects with at least 1 measurement at baseline and at least 1 measurement during the phase. Percentages of abnormality subgroup calculated with the number of subjects per parameter as denominator.
Source: ISS, p. 145

Seven percent of placebo-treated subjects in the Phase 2 and 3 trials had abnormally high PR intervals. Of those subjects treated with tapentadol in Phase 3, 7% showed PR interval prolongation, the same as the placebo group, and in Phase 2, 3% showed PR prolongation. QRS interval prolongation occurred in 4% of the placebo and tapentadol IR groups in the pooled Phase 3 trials. None of the abnormalities appear to be related to study drug, given the similar proportions found in the placebo groups.

The incidence of any abnormal QTc values during the treatment phase was tabulated using shift tables and presented by pooled analysis treatment groups. The normal limits were derived from the European Agency for the Evaluation of Medicinal Products, Committee for Propriety Medicinal Products concept paper. The criteria for classifying QTc values are provided in the Table 67.

Table 67: Criteria for Classifying QTc Values in the Phase 2/3 Single and Multiple-Dose Studies

	Classification	Adult Males	Adult Females
QTc Value (msec)	Normal	<430	<450
	Borderline	430 to 450	450 to 470
	Prolonged	>450	>470
Clinically Important QTc Value (msec)	No	<500	<500
	Yes	≥500	≥500

Source: ISS, p. 70

Among subjects in the Phase 2 studies (KF5503/21 and KF5503/22), 1 subject (<1%; 1/441) in the "all" tapentadol IR group with a normal baseline QTcB interval value had a prolonged QTcB interval value at endpoint. No subject in the "all" tapentadol IR or placebo group with a normal QTcF interval value at baseline had a prolonged QTcF interval value at endpoint.

Among subjects in the Phase 3 studies (KF5503/31, KF5503/32, KF5503/33, KF5503/34, and KF5503/37), 4 subjects (1%; 4/386) in the placebo group and 16 subjects (1%; 16/1246) in the "all" tapentadol IR group, using the Bazett correction for QTc intervals, with a normal QTcB interval value at baseline had a prolonged QTcB interval value at endpoint. Results were similar using the Fridericia correction for QTc intervals.

The percentage of subjects with a prolonged QTcB or QTcF value greater than 500msec at any time point during the double-blind treatment period in the Phase 2/3 Multiple-Dose Double-Blind studies was low and similar for subjects in the placebo and "all" tapentadol IR groups. Three subjects in the "all" tapentadol IR group (<1%; 3/1374) with a baseline value <500 msec had a postbaseline QTc interval ≥ 500msec. Two other subjects with baseline values > 500msec had post base line measurements ≥ 500msec. No subject had an adverse event reported of QTc prolonged. Two subjects in the placebo group (<1%; 2/423) had postbaseline QTc values ≥ 500msec; for one subject baseline values were ≥500msec and for the other <500msec.

The results of the TQT study are discussed below in 7.4.5 Special Safety Studies.

Marked outliers and dropouts for ECG abnormalities

Please see below.

Dropouts potentially due to abnormal vital signs and/or ECGs

No subjects were identified who were coded as discontinuing treatment due to an abnormal ECG and/or vital sign in the Phase 1 or Phase 2/3 safety analysis sets. The Applicant conducted a wider search using selected preferred terms in order to identify subjects who potentially dropped out due to an ECG and/or vital sign abnormality. The results of this search follow.

The following preferred terms were identified by the Applicant as potentially associated with abnormal vital signs or abnormal ECG.

- Acute myocardial infarction
- Heart rate irregular
- Hypertension
- Hypotension
- Hypoxia
- Myocardial infarction
- Oxygen saturation decreased
- Palpitations
- Syncope
- Supraventricular tachycardia
- Tachycardia
- Vasovagal syncope

In Phase 1 studies, there were four subjects who received tapentadol IR who dropped because of a reason noted in the list above, two because of syncope, one hypotension, and one because of a first degree atrioventricular block. Upon review of the narratives provided by the Applicant, 2 episodes of syncope were possibly related to study drug. The episodes of hypotension and A-V block were unlikely related.

In the Phase 2/3 safety data set, there were 14 subjects who received tapentadol IR who dropped out due to adverse events potentially related to vital sign or ECG abnormalities as follows: palpitations-3 subjects, MI/Acute MI-2 subjects, hypoxia-2 subjects, hypertension-2 subjects, and one subject each reporting SVT, irregular heart rate, hypotension, presyncope, and tachycardia. Upon review of the narratives provided by the Applicant, the SVT, irregular heart rate and the two myocardial infarctions are considered not related to study drug. The remainder of the events are possibly or probably related. The rates of these events are included in the analysis of discontinuations due to adverse events in the Phase 2/3 multiple-dose double blind safety analysis set in Section 7.3.3. Each preferred term occurred at a rate of <1%.

Additional analyses and explorations

A thorough QT study (HP5503/10), conducted with tapentadol ER 86 mg twice daily and 172 mg twice daily for 5 consecutive dose administrations, demonstrated no influence on myocardial repolarization in the dose range examined.

7.4.5 Special Safety Studies

Thorough QT Study

Study HP5503/25 is entitled "A Single-Center, Double-Blind, Randomized, Placebo- and Positive-Controlled Four-Way Crossover Study to Evaluate Electrocardiogram Parameters in Healthy Men and Women Receiving Multiple Dosing of an Immediate-Release Formulation of CG5503 (Tapentadol HCl) at Therapeutic and Supratherapeutic Doses. The study report was reviewed by Biopharmaceutics reviewer Christine Garnett. The following is a brief summary of her review.

No significant QT prolongation effect of tapentadol HCl (100 mg q6h and 150 mg q6h) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between tapentadol HCl (100 mg and 150 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidance.

The study was a Phase 1, single-center, double-blind, randomized, placebo- and positive controlled, 4-way crossover study to evaluate the electrocardiogram parameters in healthy men and women (n=68) receiving multiple dosing of an immediate-release (IR) formulation of tapentadol HCl at therapeutic and supratherapeutic doses. Overall findings are summarized in Table 68 from Dr. Garnett's review.

Table 68: The Point Estimates and the 90% CIs corresponding to the Largest Upper Bounds for Tapentadol HCl (100 mg and 150 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time, h	ΔΔQTcF, ms	90%CI, ms
Tapentadol HCl IR 100 mg q6h	26	-0.7	(-3.3, 2.0)
Tapentadol HCl IR 150 mg q6h	26	1.1	(-1.8, 3.8)
Moxifloxacin 400 mg *	1.5	10.2	(6.2, 14.3)

The supratherapeutic dose is only 50% higher than the highest therapeutic dose administered q6h and similar to the expected exposure when 100 mg is administered q4h (assuming an accumulation of 2 based on T1/2 of 4 h). The sponsor did not evaluate higher doses of tapentadol HCl because "the results from Study HP5503/13 suggest that higher doses than tapentadol IR 150 mg would lead to an unacceptably high rate of mainly gastrointestinal adverse events in healthy subjects which would not be acceptable for this pharmacodynamic study." To support the supratherapeutic dose, the sponsor performed PK simulations in women with mild hepatic impairment and probenecid as concomitant medication, over a range of body-weight observed in the pooled database used to develop the PPK model. According to the simulation, 1 in 1000 patients dosed with tapentadol HCl 100 mg are expected to achieve exposures greater than that achieved with tapentadol HCl 150 mg IR.

Moderate hepatic impairment leads to 1.8-fold increase in Cmax. The sponsor is proposing dose and regimen adjustment for moderate hepatic impaired patients. The proposed dosing in moderate hepatic impaired patients is:

b(4)

The supra-therapeutic dose of 150 mg q6h covers the range of exposures expected with the modified dosing regimen in moderately hepatic impaired patients. There was no relationship between tapentadol concentrations and ΔΔQTcF.

7.4.6 Immunogenicity

This category is not applicable to this study drug.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Findings

Among subjects treated with tapentadol IR, the percentage of subjects with TEAEs of nausea, dizziness, vomiting, somnolence, and pruritis increased with increasing doses of tapentadol IR. A similar pattern was observed for the overall incidence of TEAEs and TEAEs of dizziness and somnolence in the Phase 2/3 Single-dose Safety Analysis Set. Subjects in the flexible tapentadol IR dosing group had lower incidences of adverse

events than those subjects receiving greater than 30mg tapentadol IR as fixed dose regimens, likely due to the fact that they could adjust their dose as needed, for both improved efficacy and adverse event profile.

Table 69: Incidence of Selected TEAEs by Tapentadol IR Dose: Phase 2/3 MD, DB Studies

		Tapentadol IR				
Preferred Term	Placebo (n=619) n (%)	0-30 mg (n=22) n (%)	>30-60 mg (n=538) n (%)	>60-90 mg (n=607) n (%)	>90-120 mg (n=333) n (%)	Flex (n=679) n (%)
No. (%) of Subjects with TEAEs	289 (47)	13 (59)	372 (69)	466 (77)	282 (85)	518 (76)
Nausea	80 (13)	3 (14)	172 (32)	207 (34)	156 (47)	125 (18)
Dizziness	48 (8)	1 (5)	110 (20)	157 (26)	125 (38)	123 (18)
Vomiting	26 (4)	1 (5)	80 (15)	112 (18)	89 (27)	115 (17)
Somnolence	17 (3)	1 (5)	74 (14)	91 (15)	85 (26)	69 (10)
Pruritus	8 (1)	0	18 (3)	39 (6)	31 (9)	29 (4)

Studies included: KF5503/04 (Part 2), KF5503/08 (Part 2), KF5503/21, KF5503/22, KF5503/31 (excluding site 011006), KF5503/32, KF5503/33, KF5503/34, and KF5503/37
TEAE = treatment-emergent adverse events
Flex Tap IR: Tapentadol flexible dose of 50 or 100 mg
Source: ISS, p. 226

Refer to Section 7.4.1 for a more detailed discussion of dose-response as it relates to TEAEs.

7.5.2 Drug-Demographic Interactions (gender, race)

Gender

Among the healthy subjects treated with tapentadol IR in the Phase 1 Single-dose Safety Analysis Set, TEAEs of nausea, vomiting, dizziness, somnolence, and headache were reported more often for women than for men. The percentage of subjects in the placebo groups with nausea, vomiting, dizziness, and somnolence was similar for women and men in the placebo group. TEAEs of headache were reported more often for women than men in the placebo group. There was a higher incidence of somnolence, vomiting, dizziness, and nausea in women compared to men in the "all" tapentadol group.

In the Phase 2/3 Multiple-dose Double-blind Safety Analysis Set, the overall percentage of subjects with at least 1 TEAE was greater for female subjects than for male subjects in the placebo group (48% for women versus 43% for men) and the "all" tapentadol IR (81% versus 66%, respectively) pooled analysis treatment groups. A higher percentage of women experienced TEAEs of nausea, vomiting, and dizziness compared with men in the "all" tapentadol IR group.

In the Phase 2/3 Open-label Extension Safety Analysis Set, the overall percentage of TEAEs and the percentages of women and men with TEAEs of nausea, vomiting, dizziness, somnolence, and constipation were generally similar.

Race

Among the healthy subjects treated with tapentadol IR in the Phase 1 Single-dose Safety Analysis Set, TEAEs of nausea, dizziness, somnolence, headache, and fatigue were reported more often for subjects categorized as white than for subjects categorized as other races. No differences in the percentage of subjects with TEAEs by race groups were noted in the placebo pooled analysis treatment group. The number of subjects categorized as other races was too small to make any comparisons in the Phase 1 multiple-dose Safety Analysis Set.

In the Phase 2/3 Multiple-dose Double-blind Safety Analysis Set, the overall percentage of subjects with TEAEs was greater for Hispanic subjects (85%; 221/259) than for White (75%; 1225/1644) or Black (72%; 157/219) subjects in the "all" tapentadol IR group. Nausea, vomiting, dizziness, and somnolence were reported more often for Hispanic subjects than for White subjects or Black subjects. There is not enough information to determine the reason for this finding.

No differences in the overall percentage of subjects with TEAEs or in the percentage of subjects with nausea, vomiting, dizziness, and somnolence were noted by race group for subjects in the placebo pooled analysis treatment group.

A randomized, double-blind, placebo-controlled, single-center, dose-ascending Phase 1 study was conducted to evaluate the safety and tolerability of tapentadol IR (10 mg, 20 mg, and 40 mg) in healthy male Japanese subjects in support of the development of the tapentadol IR in Japan. Twelve Japanese subjects who have resided outside of Japan for no more than 5 years and whose parents and maternal and paternal grandparents are Japanese were randomized to receive tapentadol IR (10 mg, 20 mg, or 40 mg) and placebo in 1 of 3 treatment sequences.

Most adverse events were mild, of short duration, and resolved spontaneously. The most common TEAE was headache. There were no deaths, serious adverse events, or discontinuations due to adverse events. There were no clinically relevant changes in laboratory values, vital signs, or ECG findings, and the adverse event profile was consistent with that reported in other Phase 1 studies in healthy subjects. Tapentadol IR 10 mg, 20 mg, and 40 mg was well tolerated in healthy male Japanese subjects.

Age

Study HP5503/30 was a parallel-group, single-center, open-label Phase 1 study to compare the single-dose pharmacokinetics of tapentadol and its metabolite tapentadol-O-glucuronide between healthy elderly (>65 years) and young adult (18 to 45 years) men and women (16 subjects per age group). The tolerability profile of a single 80-mg dose of tapentadol IR administered to healthy subjects was comparable between young adult and elderly subjects.

In the Phase 2/3 Multiple-dose Double-blind Safety Analysis Set, the overall percentage of TEAEs reported for subjects <65 years and ≥65 years of age was similar in the "all" tapentadol IR pooled analysis treatment group. Among subjects treated in the "all" tapentadol IR group, nausea and vomiting were reported more often for subjects <65

years of age than for subjects ≥65 years of age; the percentage of subjects with of TEAEs of dizziness and somnolence were generally similar for the 2 age groups. The incidence of constipation was slightly higher in subjects ≥65 years of age The results are shown in the Table 70.

Table 70: Selected TEAES by Age Group: Phase 2/3 Multiple-Dose, Double-Blind

	Placebo (n=619)		"All" Tapentadol IR (n=2178)		"All" Oxycodone IR (n=675)	
Preferred Term	<65 years (n=499) n (%)	≥65 years (n=120) n (%)	<65 years (n=1759) n (%)	≥65 years (n=419) n (%)	<65 years (n=524) n (%)	≥65 years (n=151) n (%)
Total no. subjects with TEAEs	241 (48)	48 (40)	1343 (76)	308 (74)	434 (83)	133 (88)
Nausea	70 (14)	10 (8)	576 (33)	87 (21)	241 (46)	57 (38)
Vomiting	17 (3)	9 (8)	341 (19)	56 (13)	165 (31)	43 (28)
Dizziness	45 (9)	3 (3)	405 (23)	111 (26)	134 (26)	34 (23)
Somnolence	15 (3)	2 (2)	254 (14)	66 (16)	70 (13)	16 (11)
Constipation	11 (2)	5 (4)	124 (7)	50 (12)	83 (16)	50 (33)

Studies included: KF5503/04 (Part 2), KF5503/08 (Part 2), KF5503/21, KF5503/22, KF5503/31 (excluding site 011006), KF5503/32, KF5503/33, KF5503/34, and KF5503/37.
TEAE = treatment-emergent adverse events
MedDRA version 10.1 was used for coding.

Source: ISS, p. 183

The number of subjects ≥65 years of age was too small to make any comparisons in the Phase 1 Single- and Multiple-dose, Phase 2/3 Single-dose, and Phase 2/3 Open-label Extension Safety Analysis Sets.

7.5.3 Drug Disease Interactions

Safety in subjects with hepatic impairment

A single-center, open-label, parallel-group, drug-disease interaction study (HP5503/16) was conducted in 30 men and women with normal hepatic function, mild hepatic impairment, or moderate hepatic impairment, who were 39 to 68 years of age, inclusive. Ten subjects in each hepatic-function group received a single, oral dose of tapentadol IR 80 mg. Using Child-Pugh classification, subjects were categorized at screening on the basis of 2 clinical features (encephalopathy and ascites) and 3 laboratory-based parameters (albumin, bilirubin, and prothrombin time) as shown in Table 71 and according to the scoring criteria below:

Table 71: Child-Pugh Classification of Liver Impairment

Clinical and Biochemical Measurements	Points Scored for Increasing Abnormality		
	1	2	3
Encephalopathy (grade)[a]	None	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate
Bilirubin (mg/100 mL)	<2	2-3	>3
Albumin (g/mL)	>3.5	2.8-3.5	<2.8
Prothrombin time (%)	>70	40-70	<40

[a] Subjects with encephalopathy grades 3 and 4 were to be excluded

Child-Pugh's classification is applicable exclusively to hepatically impaired subjects to characterize the degree of impairment of a proven chronic condition or cirrhosis of any pathology (misleadingly, healthy matches would have a score of 5 as with the mild hepatically impaired).

Source: ISS, p. 186

- total score of 5 to 6 = Mild hepatic impairment
- total score of 7 to 9 = Moderate hepatic impairment
- total score of 10 to 15 = Severe hepatic impairment

The overall incidence of adverse events was higher for subjects with mild (90.0%) or moderate (90.0%) hepatic impairment than for subjects with normal hepatic function (60.0%). The most commonly reported adverse events were dizziness, fatigue, nausea, and feeling abnormal. TEAEs are summarized in the table below.

Table 72: TEAEs in at Least Two Subjects in any Group by Hepatic Function Group HP5503/16

System Organ Class Dictionary-derived Term	Hepatic Function Group		
	Normal Hepatic Function (N=10) n (%)	Mild Hepatic Impairment (N=10) n (%)	Moderate Hepatic Impairment (N=10) n (%)
Total no. subjects with adverse events	6 (60.0)	9 (90.0)	9 (90.0)
Nervous system disorders	5 (50.0)	4 (40.0)	8 (80.0)
Dizziness	3 (30.0)	4 (40.0)	6 (60.0)
Headache	3 (30.0)	0	2 (20.0)
Gastrointestinal disorders	3 (30.0)	1 (10.0)	4 (40.0)
Nausea	2 (20.0)	1 (10.0)	4 (40.0)
Vomiting	0	0	2 (20.0)
General disorders and administration site conditions	4 (40.0)	9 (90.0)	3 (30.0)
Fatigue	4 (40.0)	5 (50.0)	2 (20.0)
Feeling abnormal	0	4 (40.0)	0

Note: Incidence is based on the number of subjects, not the number of events

Source: ISS, p. 187

There were no deaths or discontinuations due to a TEAE. SAEs were reported for two subjects who received study drug: malignant bone neoplasm in a subject with moderate hepatic impairment, and tongue neoplasm in subject with mild hepatic impairment.

There were no clinically relevant treatment related changes in laboratory values, vital signs, or ECG findings.

Conclusion: The percentage of TEAEs in the subjects with mild and moderate hepatic impairment was greater than in healthy subjects, although there were no deaths or discontinuations due to TEAEs, and no SAEs attributable to study drug. Administration of a single 80-mg dose of tapentadol IR resulted in higher exposures and serum levels of tapentadol base in subjects with impaired hepatic function compared to subjects with normal hepatic function. The ratio of tapentadol IR base 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 Cmax; and 1.2 and 1.4, respectively, for t1/2. The rate of formation of CG5503-O-glucuronide was lower in subjects with increased liver impairment, resulting in lower peak, serum concentrations with no changes in exposure or renal elimination.

Safety in subjects with renal impairment

The effects of varying degrees of renal impairment on the safety of tapentadol were investigated in a single study. HP5503/15 was an open-label, parallel-group, single-dose, pharmacokinetic study of tapentadol IR in 40 men and women between 25 and 70 years of age, inclusive, with normal renal function or mild, moderate, or severe renal impairment. Serum creatinine samples obtained during screening were used for the determination of the creatinine clearance according to the Cockcroft-Gault formula. Subjects were allocated to 1 of 4 renal-function groups:

- Group 1: Normal renal function (creatinine clearance [CLCR] ≥80 mL/min);
- Group 2: Mild renal impairment (CLCR = 50 to <80 mL/min);
- Group 3: Moderate renal impairment (CLCR = 30 to <50 mL/min);
- Group 4: Severe renal impairment (CLCR <30 mL/min)

The study included 40 subjects (10 per renal-function group). To balance the treatment groups, group matching was applied to the renal-function groups to assure demographic comparability with respect to age, weight, sex, and ethnicity.

Safety assessments included adverse events, clinical laboratory tests, vital signs, 12-lead ECGs, and physical examinations. The safety analysis set included all 40 subjects who were enrolled and received at least 1 dose of tapentadol IR. All subjects received a single dose of 80-mg tapentadol IR on Day 1.

Safety Results: Tapentadol IR was generally well tolerated when administered as a single 80mg dose. Most subjects experienced at least 1 adverse event (overall: 87.5%) regardless of their renal impairment group (normal, mild, moderate, or severe). The most commonly reported adverse events were fatigue, dizziness, nausea, feeling abnormal, and headache. There were no consistent patterns in the occurrence of adverse events across the renal impairment groups. Most adverse events were mild, of short duration, and resolved spontaneously. The Applicant's table below shows the frequency of TEAEs.

Table 73: TEAEs in at Least 2 Subjects in Any Group for Subjects With Renal Function Group: Study HP5503/15

	Renal Function Group			
System Organ Class Preferred term	Normal Function (N=10) n (%)	Mild Impairment (N=10) n (%)	Moderate Impairment (N=10) n (%)	Severe Impairment (N=10) n (%)
Total no. subjects with adverse events	9 (90)	10 (100)	9 (90)	7 (70)
General disorders and administration site conditions	8 (80)	9 (90)	5 (50)	4 (40)
Fatigue	5 (50)	7 (70)	4 (40)	3 (30)
Feeling abnormal	3 (30)	3 (30)	1 (10)	1 (10)
Nervous system disorders	4 (40)	3 (30)	6 (60)	5 (50)
Dizziness	2 (20)	1 (10)	5 (50)	4 (40)
Headache	2 (20)	1 (10)	2 (20)	2 (20)
Gastrointestinal disorders	4 (40)	1 (10)	3 (30)	2 (20)
Nausea	4 (40)	0	2 (20)	2 (20)
Vomiting	2 (20)	0	1 (10)	1 (10)
Psychiatric disorders	2 (20)	1 (10)	0	0
Euphoric mood	2 (20)	0	0	0

Study included: HP5503/15
Source: ISS, p. 189

There were no deaths or SAEs due to adverse events. One subject (100608) in the moderate renal impairment group experienced an SAE of edematous pancreatitis that required hospitalization. The investigator and this reviewer considered the event to be possibly related to study drug. The narrative for this subject is located in Section 7.3.2.

Two subjects experienced 1 or more adverse events related to abnormal laboratory values. One subject with moderate renal impairment experienced leukocytosis and elevated hepatic enzyme values related to pancreatitis. One subject with mild hepatic impairment and pre-existing elevated ALT and who was taking concomitant glimepiride, also experienced elevated ALT and gamma-glutamyl transferase. These adverse events were mild in intensity and were considered by the investigator to be possibly related to study drug administration.

There were no clinically relevant changes from baseline in mean supine values for blood pressure, pulse, or respiratory rate. However, 1 subject with normal renal function experienced a decreased oxygen saturation adverse event that was rated as mild and considered by the investigator to be probably or likely related to study drug. The subject's oxygen saturation values returned to normal within approximately 1 minute, with verbal stimulation. There were no associated symptoms reported for this event.

Conclusion: The tolerability profile of a single dose of tapentadol IR 80 mg administered to subjects with varying degrees of renal function was consistent with the profile observed in other single-dose tapentadol IR studies. Exposure to the parent drug following a single 80-mg oral dose of tapentadol IR was comparable in subjects with varying degrees of renal function (from normal to severely impaired). In contrast, increasing exposure to CG5503-O-glucuronide was observed with increasing degree of renal impairment. This was not unexpected since elimination of this metabolite mainly occurs via the renal route. In subjects with severe renal impairment, the elimination of the CG5503-Oglucuronide is clearly reduced. In mild, moderate, and severe renal impairment, the AUC (CG5503-O-glucuronide) values are 1.5-, 2.5-, and 5.5-fold higher compared with normal renal function, respectively.

7.5.4 Drug-Drug Interactions

Five Phase 1 drug-drug interaction studies were carried out with tapentadol IR co-administered with metoclopramide (HP5503/19), omeprazole (HP5503/20), probenecid (HP5503/21), naproxen and ASA (HP5503/22), or acetaminophen (HP5503/23). The following is a summary of the findings for these studies. Details may be found in the Biopharmaceutics review by Dr. David Lee.

HP5503/19-Metoclopramide

The safety and tolerability of tapentadol IR 80mg alone and when coadministered with metoclopramide in healthy subjects was assessed in a randomized, open-label, 2-way crossover, drug-drug interaction study, which enrolled 30 (24 completers) healthy subjects between 25 and 55 years of age. Subjects either received a single dose of tapentadol IR 80 mg or 6 doses of 20-mg metoclopramide (once every 6 hours on Day –1 and Day 1) with a single dose of tapentadol IR 80 mg 1 hour after the fifth dose of metoclopramide.

The overall incidence of adverse events was comparable between tapentadol IR alone or with metoclopramide. Most adverse events were mild, of short duration, and resolved spontaneously. The most common TEAEs included dizziness, somnolence, headache, nausea, vomiting, and feeling hot. There were no deaths and no serious adverse events. Three subjects discontinued due to adverse events (gastrointestinal infection; headache; dizziness, restlessness, diarrhea, and nausea) with metoclopramide treatment prior to receiving tapentadol IR. There were no clinically relevant changes in laboratory values, vital signs, or ECG findings, and the adverse event profile was consistent with previous experience with tapentadol IR in other Phase 1 studies in healthy subjects. In addition, there were no clinically relevant differences in PK parameters of tapentadol IR or its metabolite Tapentadol –O-glucuronide when tapentadol IR 80 mg was administered alone or with 20 mg metoclopramide.

HP5503/20-Omeprazole

The safety and tolerability of tapentadol IR 80 mg alone and when coadministered with multiple doses of omeprazole 40 mg in healthy subjects was assessed in a single-center, randomized, open-label, 2-way crossover, drug-drug interaction study. The study was

conducted in 32 healthy subjects (16 men and 16 women) between 25 and 55 years of age, inclusive. Subjects received tapentadol IR 80 mg alone and tapentadol IR 80 mg coadministered with omeprazole (40 mg once daily for 4 days) with tapentadol IR administered 2 hours after the last dose of omeprazole in 1 of 2 randomized treatment sequences.

All adverse events were mild or moderate in intensity. The most common adverse events were dizziness, headache, somnolence, nausea, and vomiting. This adverse event profile was consistent with previous studies conducted in healthy subjects. The incidence of reported adverse events was similar in each treatment group, except for vomiting and somnolence. The percentages of subjects with vomiting and somnolence were approximately 2 times greater with omeprazole (vomiting 26%, somnolence 35%), than without omeprazole treatment (vomiting 13%, somnolence 19%). There were no clinically relevant differences in the pharmacokinetic parameters of tapentadol or its metabolite, tapentadol-O-glucuronide, when tapentadol IR was administered alone and when coadministered with 40-mg omeprazole, therefore based on the results obtained from this study, the increased incidence of vomiting and somnolence cannot be attributed to changes in the pharmacokinetic parameters of tapentadol IR when coadministered with omeprazole.

There were no deaths and no serious adverse events in this study.. There were no clinically relevant changes in laboratory values, vital signs, or ECG findings.

HP5503/21 (Probenecid)
The coadministration of tapentadol IR and probenecid was studied because probenecid is an inhibitor of the glucuronidation system, which is the main metabolizing pathway for tapentadol IR.

The pharmacokinetics, safety and tolerability of tapentadol IR 80 mg alone and when coadministered with probenecid in healthy subjects was assessed in a single-center, randomized, open-label, 2-way crossover, drug-drug interaction study. The study was conducted in 28 healthy subjects (14 men and 14 women) between 26 to 55 years of age, inclusive. Subjects received tapentadol IR 80 mg alone and tapentadol IR 80 mg coadministered with probenecid (500 mg twice daily for 2 days) with tapentadol IR administered with the third dose of probenecid in 1 of 2 randomized treatment sequences.

The most common adverse events were dizziness, nausea, and vomiting. This adverse event profile was consistent with previous studies conducted in healthy subjects. The incidence of dizziness, vomiting, and pruritus was greater in subjects who received tapentadol IR 80 mg following probenecid treatment compared to subjects who received the tapentadol IR 80 mg alone. The limited sample size allows only for reporting of differences between treatment groups, but clinical relevance cannot be attributed to these observational differences. There were no deaths, serious adverse events, or adverse events leading to discontinuation in this study.

There were no clinically relevant changes in laboratory values, vital signs, or ECG findings, and the adverse event profile was consistent with previous experience with tapentadol IR in other Phase 1 studies in healthy subjects.

The pharmacokinetic data suggested that the metabolism of tapentadol IR was decreased when coadministered with probenecid. The maximum serum concentration (Cmax) and area under the serum concentration versus time curve (AUC) of tapentadol IR increased by 30% and 57%, respectively, when tapentadol IR was coadministered with probenecid. There was no evidence of any substantial changes in renal elimination of tapentadol IR and its major metabolite, tapentadol-O-glucuronide when tapentadol IR was coadministered with probenecid.

HP5503/22 Naproxen and Acetylsalicylic acid

The safety and tolerability of tapentadol IR 80 mg alone and when coadministered with naproxen (500 mg twice daily for 2 days) or with (ASA 325 mg once daily for 2 days) was assessed in a single-center, randomized, open-label, 3-way-crossover, drug-drug-interaction study. The study was conducted in 38 healthy subjects (19 men and 19 women) between 25 and 54 years of age, inclusive. Subjects received tapentadol IR 80 mg alone, tapentadol IR 80 mg coadministered with naproxen 500 mg twice daily for 2 days (with tapentadol IR administered with the last dose of naproxen), tapentadol IR 80 mg coadministered with ASA 325 mg twice daily for 2 days (with tapentadol IR administered with the last dose of ASA) in 1 of 6 randomized treatment sequences.

Overall, there was a higher incidence of adverse events in the tapentadol IR /naproxen treatment group than in the tapentadol IR /ASA or tapentadol IR alone treatment groups (83% vs 58% vs 60% respectively). A higher proportion of subjects in the tapentadol/naproxen group had dizziness, nausea, feeling hot, and euphoric mood than in the other two treatment groups. The most common adverse events for all groups were dizziness, nausea, and headache. Most adverse events were mild, of short duration, and resolved spontaneously. There were no deaths, serious adverse events, or discontinuations among subjects receiving tapentadol during this study.

There were no clinically relevant changes in laboratory values, vital signs, or ECG findings, and the adverse event profile of tapentadol IR was consistent with previous experience in other Phase 1 studies in healthy subjects.

There were no clinically relevant differences in the pharmacokinetic parameters of tapentadol or its metabolite, tapentadol-O-glucuronide, when tapentadol IR was administered alone and when coadministered with ASA (325 mg once daily for 2 days). Coadministration of naproxen (500 mg twice daily for 2 days) with a single oral dose of tapentadol IR 80 mg resulted in a 17% increase in the AUC, but did not show any significant effect on the Cmax of tapentadol IR.

HP5503/23 Acetaminophen

The safety and tolerability of a single dose of tapentadol IR administered alone and when

coadministered with acetaminophen was assessed in a single-center, randomized, open-label, 2-way-crossover, drug-drug interaction study. The study was conducted in 24 healthy subjects (12 men and 12 women) between 25 to 55 years of age, inclusive. Subjects received tapentadol IR 80 mg alone and tapentadol IR 80 mg coadministered with acetaminophen 1000 mg every 6 hours for 7 doses (with tapentadol IR administered with the fifth dose of acetaminophen) in 1 of 2 randomized treatment sequences.

The incidence of adverse events was comparable between tapentadol IR alone or with acetaminophen. The most common adverse events were dizziness, headache, somnolence, nausea, and feeling hot. Most adverse events were mild, of short duration, and resolved spontaneously. There were no deaths, serious adverse events, or discontinuations due to adverse events. There were no clinically relevant changes in laboratory values, vital signs, or ECG findings, and the adverse event profile of tapentadol IR was consistent with previous experience in other Phase 1 studies in healthy subjects.

There were no clinically relevant differences in the pharmacokinetic parameters of tapentadol or its metabolite, tapentadol-O-glucuronide, when tapentadol IR was administered alone and when coadministered with acetaminophen.

7.5.5 SMQs

At the Division's request, the Applicant performed SMQs for Possible Drug Related Serious Cutaneous Reactions and Hepatic Reactions.

Hepatic Reactions

Possible drug related hepatic reactions were assessed by the Applicant based on the comprehensive search SMQ.

In the Phase 2/3 Single-dose Safety Analysis Set, the percentage of subjects with possible drug-related hepatic disorders based on the comprehensive search SMQs was (1%) in the "all" tapentadol IR and placebo pooled analysis treatment groups (The most common possible drug-related hepatic disorder in the "all" tapentadol IR group was blood bilirubin increased, which was reported by 4 (<1%) subjects. The table below was provided by the Applicant.

Table 73a: Subjects with Possible Drug-Related Hepatic Disorders-Comprehensive Search SMQ: Phase 2/3 Single Dose Safety Analysis Set.

SMQ SMQ Subcategory Preferred term (SMQ Scope)	Placebo (n=165) n (%)	"All" Tapentadol IR (n=870) n (%)
Number (%) of Subjects with TEAE SMQs	2 (1)	8 (1)
Possible drug related hepatic disorders – comprehensive search (SMQ)	2 (1)	8 (1)
Liver related investigations, signs and symptoms (SMQ)	2 (1)	8 (1)
Blood bilirubin increased (broad)	2 (1)	4 (<1)
Alanine aminotransferase increased (broad)	0	1 (<1)
Aspartate aminotransferase increased (broad)	0	1 (<1)
Gamma-glutamyl transferase increased (broad)	0	1 (<1)
Hepatic function abnormal (broad)	0	1 (<1)

Studies included: KF5503/02, KF5503/04 (Part 1), KF5503/05, and KF5503/08 (Part 1)
SMQ = Standard MedDRA Queries; TEAE = treatment-emergent adverse events.
MedDRA version 10.0 was used for the search.
Source: Tapentadol IR 4-Month Safety Update, p. 220

In the Phase 2/3 Multiple-dose Double-blind Safety Analysis Set, the percentage of subjects with possible drug-related hepatic disorders based on the comprehensive search SMQs was (1%) in the "all" tapentadol IR and placebo pooled analysis treatment groups. The most common possible drug-related hepatic disorders were gamma-glutamyltransferase increased, alanine aminotransferase increased, and aspartate aminotransferase increased; each was reported by <1% of subjects in the "all" tapentadol IR pooled analysis treatment group. The Applicant's table below illustrates these results.

Table 74: Number (%) of Subjects with Possible Drug-Related Hepatic Disorders Comprehensive Search SMQs: Phase 2/3 Multiple-Dose, Double-Blind

SMQ SMQ Subcategory SMQ Subcategory2 Preferred Term (SMQ Scope)	Placebo (n=619) n (%)	"All" Tapentadol IR (n=2178) n (%)	"All" Oxycodone IR (n=675) n (%)
Total no. subjects with TEAE SMQs	7 (1)	22 (1)	7 (1)
Possible drug related hepatic disorders - comprehensive search (SMQ)	7 (1)	22 (1)	7 (1)
Liver related investigations, signs and symptoms (SMQ Scope)	7 (1)	21 (1)	7 (1)
Gamma-glutamyltransferase increased (broad)	5 (1)	10 (<1)	4 (1)
Alanine aminotransferase increased (broad)	3 (<1)	9 (<1)	1 (<1)
Aspartate aminotransferase increased (broad)	3 (<1)	9 (<1)	1 (<1)
Blood alkaline phosphatase increased (broad)	1 (<1)	4 (<1)	1 (<1)
Liver function test abnormal (broad)	0	3 (<1)	1 (<1)
Blood bilirubin increased (broad)	0	1 (<1)	1 (<1)
Hepatic enzyme increased (broad)	0	1 (<1)	1 (<1)
Hyperbilirubinemia (broad)	0	0	1 (<1)
Transaminases abnormal (broad)	1 (<1)	0	0
Possible drug related hepatic disorders - severe events only (SMQ)	0	1 (<1)	0
Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ)	0	1 (<1)	0
Liver disorder (broad)	0	1 (<1)	0
Cholestasis and jaundice of hepatic origin (SMQ)	0	0	1 (<1)
Hyperbilirubinaemia (broad)	0	0	1 (<1)

Studies included: KF5503/04 (Part 2), KF5503/08 (Part 2), KF5503/21, KF5503/22, KF5503/31 (excluding site 011006), KF5503/32, KF5503/33, KF5503/34, and KF5503/37.
SMQ = Standard MedDRA Queries; TEAE = treatment-emergent adverse events.
MedDRA version 10.1 was used for the search.
Source: Tapentadol IR 4-Month Safety Update, p. 222

One subject (Subject 401280), treated with tapentadol IR in KF5503/34, had a TEAE of liver disorder, which reflected an increase in gamma-glutamyltransferase on Day 88. The subject's GGT was elevated at baseline (67 U/L), high on day 88 (177.0 U/L), and returning toward baseline when assessed 16 days after the end of treatment. Other liver enzymes remained within the normal limits throughout the study. The event was assessed as possibly related to study drug by the investigator and was moderate in intensity. No countermeasures were used and the event was reported as not resolved.

Reviewer comment: I am in agreement with the Applicant's interpretation.

In the Phase 2/3 Open-label Extension Safety Analysis Set, 2 (<1%, 2/483) subjects treated with tapentadol IR had possible drug-related hepatic disorders SMQs (1 subject had gamma-glutamyltransferase increased and 1 subject had hepatic enzyme increased).

Tapentadol ER

In the Phase 2 Tapentadol ER Safety Analysis Set, the percentage of subjects with possible drug-related hepatic disorders based on the comprehensive search SMQs was

similar across the "all" tapentadol IR and placebo groups (1%). None of the possible drug-related hepatic disorders were reported for more than 2 subjects in the "all" tapentadol IR group. All preferred terms for possible drug-related hepatic disorders SMQs were broad in scope. The percentage of subjects with possible drug-related hepatic disorders was similar across the treatment groups. The Applicant's table below illustrates the results.

Table 75: Subjects with Possible Drug-Related Hepatic Disorders-Comprehensive Search SMQs: Tapentadol ER

SMQ SMQ Subcategory 1 SMQ Subcategory 2 Preferred term (SMG Scope)	Placebo (n=512) n (%)	"All" Tapentadol ER (n=1168) n (%)
Number (%) of Subjects with Possible drug related hepatic disorders – comprehensive search (SMQ)	3 (1)	10 (1)
Liver related investigations, signs and symptoms (SMQ)	3 (1)	8 (1)
Alanine aminotransferase increased (broad)	1 (<1)	2 (<1)
Gamma-glutamyl transferase increased (broad)	0	2 (<1)
Aspartate aminotransferase increased (broad)	1 (<1)	1 (<1)
Blood bilirubin increased (broad)	0	1 (<1)
Hepatic enzyme increased (broad)	2 (<1)	1 (<1)
Hepatic function abnormal (broad)	0	1 (<1)
Transaminase increased (broad)	0	1 (<1)
Blood alkaline phosphatase increased (broad)	0	0
Possible drug-related hepatic disorders - severe events only (SMQ)	0	2 (<1)
Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ)	0	2 (<1)
Hepatic steatosis (broad)	0	2 (<1)
Asterixis (broad)	0	0

Studies included: KF5503/09, KF5503/10, KF5503/19, and KF5503/20
SMQ = Standard MedDRA Queries
MedDRA version 10.0 was used for the search.
Source: Tapentadol IR 4-Month Safety Update, p. 223

Conclusion regarding hepatic SMQ
The percentage of subjects with adverse events included in the SMQ with possible drug-related hepatic disorders was low (1%) in the "all" tapentadol IR group, with a similar percentage reported in the placebo group (1%). The most common possibly drug-related hepatic disorders were gamma-glutamyltransferase increased, alanine aminotransferase increased, and aspartate aminotransferase increased; each was reported by <1% of subjects in the "all" tapentadol IR pooled analysis treatment group. Overall, the results of this SMQ and the laboratory data (Section 7.4.2) do not point to a signal of drug-related hepatic disorders. The percentage of subjects with possible drug-related hepatic disorders was similar across the placebo, "all" tapentadol IR, and "all" oxycodone IR treatment groups.

Severe Cutaneous Reactions
Possible drug related severe cutaneous reactions were assessed by the Applicant based on the comprehensive search SMQ.

There were no reports of severe cutaneous adverse reaction SMQs for subjects in the Phase 2/3 Single-dose Tapentadol IR Safety Analysis Set.

In the Phase 2/3 Multiple-dose Double-blind Safety Analysis Set, 10 (<1%) subjects in the "all" tapentadol IR group, 2 (<1%) subjects in the placebo group, and 2 (<1%) subjects in the "all" oxycodone IR group had at least 1 TEAE that was included in the severe cutaneous adverse reactions SMQ.

Blister was reported for 9 subjects and stomatitis was reported for 1 subject in the "all" tapentadol IR group, conjunctivitis and mouth ulcer were reported for 1 subject each in the placebo group, and conjunctivitis and blister were reported for 1 subject each in the "all" oxycodone IR group. All reports of blister occurred in a localized area. The Applicant's table below illustrates these results.

Table 76: Subjects with Severe Cutaneous Reactions SMQ: Phase 2/3 Multiple-Dose DB Safety Analysis Set

Preferred Term (SMQ Scope)	Placebo (n=619) n (%)	"All" Tapentadol IR (n=2178) n (%)	"All" Oxycodone IR (n=675) n (%)
Total no subjects with TEAE SMQs	2 (<1)	10 (<1)	2 (<1)
Severe cutaneous adverse reactions (SMQ)	2 (<1)	10 (<1)	2 (<1)
Blister (broad)	0	9 (<1)	1 (<1)
Stomatitis (broad)	0	1 (<1)	0
Conjunctivitis (broad)	1 (<1)	0	1 (<1)
Mouth ulceration (broad)	1 (<1)	0	0

Studies included: KF5503/04 (Part 2), KF5503/08 (Part 2), KF5503/21, KF5503/22, KF5503/31 (excluding site 011006)KF5503/32, KF5503/33, KF5503/34, and KF5503/37.
SMQ = Standard MedDRA Queries.
MedDRA version 10.1 was used for the search.
Source: Tapentadol IR 4-month safety update, p. 219

Conclusion regarding severe cutaneous reaction SMQ
There does not appear to be a safety signal regarding severe cutaneous reactions for tapentadol IR.

7.6 Additional Safety Evaluations

7.6.1 Human Reproduction and Pregnancy Data

There were seven reports of positive pregnancy tests in the Applicant's safety database among subjects who received at least one dose of tapentadol; four subjects who participated in the tapentadol IR studies, 2 subjects in the tapentadol ER studies, and 1 subject who received tapentadol via intravenous infusion. The table below is a summary of the above subjects. There have been no reports of abnormal pregnancies or infants up to this point in time.

Table 77: Pregnancies

Subject	Study	Formulation	Dose	Outcome
101101	HP5503/22	Tapentadol IR	single	voluntary termination of pregnancy
301010	KF5503/32	Tapentadol IR	multiple	normal male infant
302165	KF5503/32	tapentadol IR	multiple	unknown
7379/574	KF5503/04	Tapentadol IR	multiple	normal infant
5006/0379	KF5503/10	Tapentadol ER	single	false positive urine pregnancy test
112169	KF5503/23	blinded Tx	?	?
0026	HP5503/02	Tapentadol IV	4 single doses	normal female infant

7.6.2 Pediatrics and Assessment and/or Effects on Growth

No studies have been carried out in pediatric patients. As part of this NDA submission, the Applicant has submitted a Pediatric Plan and staged deferral request. They propose to begin clinical studies in the oldest age group ([ ] years of age) approximately [ ] following approval of the adult indications in acute pain, to take advantage of available safety information from both the preclinical juvenile program and the adult postmarketing database. Trials will be conducted in a step-wise manner to gather adequate pharmacokinetic, safety and efficacy information in the older children before exposing younger age groups. This staged deferral proposal will expose the minimum number of children while allowing the ability to perform the necessary clinical studies that will support information on dosing tapentadol in the pediatric population.

b(4)

The Pediatric Plan and deferral request will be reviewed by PERC on October 8, 2008.

7.6.3 Overdose, Drug Abuse Potential/ Withdrawal and Rebound

A complete review of the abuse liability studies will be completed by the Controlled Substance Staff (CSS) and the Office of Safety and Epidemiology (OSE).

Abuse liability and overdose

Since tapentadol IR has mu-opioid receptor agonist properties, it is expected that there will be a positive finding for abuse liability.

The results from a Phase 1 study, HP5503/14, conducted in 40 opiate-experienced, non-dependent subjects, showed that single doses of tapentadol IR (50 mg, 100 mg, and 200 mg) had a similar abuse liability profile of subjective effects to that of calculated equianalgesic, single doses of hydromorphone IR (4, 8, and 16 mg).

No case of overdose has been reported in the completed studies with tapentadol IR. One subject who received tapentadol ER in an ongoing 1-year, open-label, Phase 3 clinical study (KF5503/24) reported an overdosage with euphoric mood and visual disturbance.

Drug accountability and compliance with study drug treatment was assessed for the 3 longer-term Phase 3 clinical studies (KF5503/33 [10 days], KF5503/34 [90 days], and the open-label extension period in KF5503/32 [9 days]). For the 3-day, double-blind KF5503/32 study as well as the Phase 1 studies, study drug administration was carried out in the controlled environment of clinical research sites and direct observation of the dose administration by study staff assured compliance.

In the Phase 3 study, KF5503/34, 7 subjects in the tapentadol IR group reportedly took a total daily dose of 1,200 mg for 1 day (n=6) or 2 days (n=1). These subjects had prior opioid experience, and none of the subjects had an adverse event for at least 5 days after reporting to have taken a 1,200-mg dose. In Study KF5503/34, fewer subjects in the tapentadol IR group (9%) than in the oxycodone IR group (12%) took more than 14 capsules on any day) for 1 or more days. Of those in KF5503/34, 2 subjects taking tapentadol IR (0.1%) and 1 subject taking oxycodone HCl IR exceeded 14 capsules for ≥5 days during the study.

Withdrawal

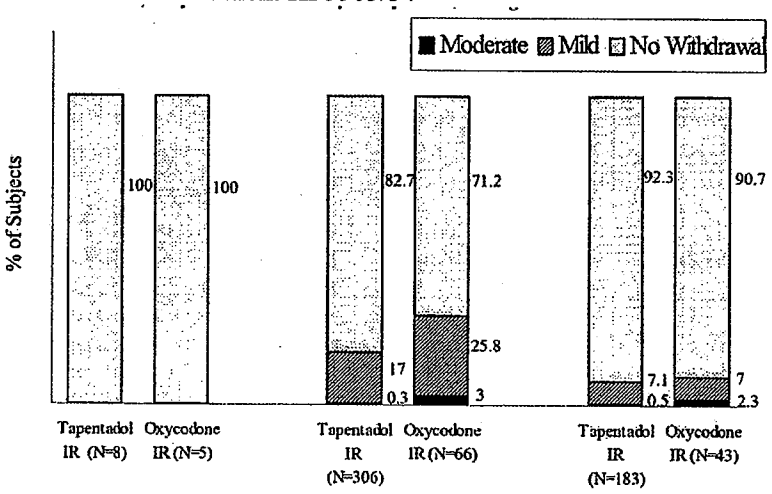
The withdrawal effect of tapentadol IR was evaluated by the COWS and SOWS questionnaires and by reports of TEAEs of withdrawal syndrome in the Phase 3 multiple-dose, double-blind study, KF5503/34. In this study, treatment was terminated without tapering and subjects were asked to refrain from restarting other opioid medication during the time between the end of treatment visit and the follow-up visit. Two standard opiate withdrawal scales (COWS and SOWS) were administered, and TEAEs of withdrawal syndrome were recorded.

In KF5503/34, subjects completed the COWS questionnaire two to four days after treatment cessation at the follow-up visit. A summary of COWS total score (calculated as a sum of 11 individual items based on categories of withdrawal symptoms: 0 to 4 = no withdrawal, 5 to 12 = mild, 13 to 24 = moderate, 25 to 36 = moderately severe, and 37 to 48 = severe withdrawal) is presented in the figure below for subjects who did not take opioid medication after discontinuation of the study drug until the day of the assessment.

The majority of the subjects who did not take opioid medication after discontinuation of study drug had COWS assessed between 2 and 4 days from the discontinuation of study medication. Most subjects reported no withdrawal symptoms; the percentage of subjects with objective signs of opioid withdrawal in the tapentadol IR group (17%) was lower than in the oxycodone group (29%).

Of all subjects with COWS assessments who did not take opioid medication after discontinuation of the study medication and during the day of COWS assessment, five subjects had moderate withdrawal symptoms (2 in the tapentadol IR [0.3%] group and 3 in the oxycodone HCl IR group [3%]). All remaining withdrawal symptoms were mild.

Figure 15: COWS Withdrawal Categories in Subjects Without Opioid Medication After Discontinuation: KF5503/34



In KF5503/34, subjects completed the SOWS 2 to 4 days after treatment at the follow-up visit. Mean total score of SOWS for subjects who had assessment between 2 to 4 days for the tapentadol IR group (6.9) was lower than in the oxycodone HCl IR group (8.7). An ANOVA model was applied to analyze the SOWS total score. The corresponding nominal p-value revealed no significant difference between the tapentadol IR and oxycodone IR groups in the withdrawal symptom severity assessed with SOWS total score.

For those who had assessments 5 or more days after discontinuation from the study drug, the mean total score for SOWS was 6.3 in the tapentadol IR group and 7.0 for the oxycodone HCl IR group and that difference between groups was not significant

Nine (1%) of 679 tapentadol IR-treated subjects and 2 (1%) of 170 oxycodone IR-treated subjects experienced drug withdrawal syndrome. Of these, a single case of withdrawal symptoms (elevated systolic blood pressure, irritability, and anxiety) was listed as a serious adverse event for a subject who had received treatment with tapentadol IR (250 mg to 600 mg total daily dose) for 94 days.

Among the 9 subjects in the tapentadol IR group with drug withdrawal syndrome, all events were mild or moderate in intensity, and all resolved. A total of 5 cases were assessed as probably related to the study drug, and 1 was a serious adverse event. Seven subjects reported this syndrome following the last dose of tapentadol and one subject reported a drug withdrawal syndrome while continuing daily treatment with tapentadol IR. Of the 2 subjects in the oxycodone IR group with drug withdrawal syndrome TEAEs, 1 subject had a mild event assessed as probably related to the study drug and 1 subject had a severe event assessed as unrelated to study drug. For both subjects, the events were reported following the last dose of study drug and both events resolved.

The following is the narrative for subject 401540 who reported the SAE of drug withdrawal syndrome.

> Subject 401540, randomized to tapentadol IR, was a 52-year-old Asian man. The subject received a total daily dose of 250 mg to 600 mg tapentadol IR on Day 1 to Day 92. During the last 5 days in the study, the subject took the following daily doses: 300 mg, 300 mg, 300 mg, 300 mg, and 100 mg. On Day 95, the subject experienced opiate withdrawal. The subject developed nervousness, tremors, and hypertension 3 days after the discontinuation of the study drug. The subject was treated in a hospital emergency room with codeine. Relevant physical symptoms reported included high SBP (190 mmHg) and pulse rate 81 to 100 bpm (CIOMS). The drug withdrawal syndrome resolved on Day 96. The event was assessed as probably/likely related to the study drug.

Although most subjects reported no withdrawal symptoms, it is clear that withdrawal symptoms can occur upon cessation of tapentadol IR treatment.

7.7 Additional Submissions

There were no additional safety submissions. The 120-day safety update has been integrated into the review of safety.

8. POSTMARKETING EXPERIENCE

There is no postmarketing experience with this drug.

9. APPENDICES

9.1 Literature Review and other Important Relevant Materials/References

The Applicant provided adequate references for review of this submission.

9.2 Labeling Recommendations

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Other issues are likely to arise during the labeling sessions and will be addressed as needed. The completed label will be attached to this review.

9.3 Advisory Committee Meeting

There was no Advisory Committee held related to this NDA submission.

9.4 Additional Tables

Table 78: Efficacy Measurements

Pain Intensity – 11-Point Numerical Rating Scale

The subject will indicate the current pain intensity on the following numeric rating scale in response to the following question: "What is your pain level at this time?"

0	1	2	3	4	5	6	7	8	9	10
No Pain										**Pain as bad as you can imagine**

Pain Relief – 5-Point Numerical Rating Scale

Subject will indicate their pain relief (PAR) at the same time points as PI in response to the following question: "How much relief have you had from your starting pain?"

- None = 0
- A little = 1
- Some = 2
- A lot = 3
- Complete = 4

Patient Global Impression of Change Scale

The subject will indicate their status by completing the following statement: "Since I began study medication, my overall status is:

- Very Much Improved = 1
- Much Improved = 2
- Minimally Improved = 3
- No Change = 4
- Minimally Worse = 5
- Much Worse = 6
- Very Much Worse = 7

Table 79: Laboratory panels

Hematology Panel

hemoglobin	platelet count
hematocrit	red blood cell (RBC) count
white blood cell (WBC) count with differential	

Serum Chemistry Panel

sodium	alkaline phosphatase (AP)
potassium	creatine phosphokinase (CK)
chloride	lactate dehydrogenase (LDH)
bicarbonate	uric acid
blood urea nitrogen (BUN)	calcium
creatinine	phosphate
glucose	albumin
AST	total protein
ALT	cholesterol
gamma-glutamyltransferase (GGT)	triglycerides
bilirubin	amylase
lipase	

Table 80: Concomitant Medication (Excluding Analgesics and Rescue Medication) in at Least 5% of Subjects in Any Group: Double-Blind Period (Study R331333-PAI 3003; KF5503/32: Intent-to-Treat Analysis Set)

	Placebo (N=120) n (%)	Tapentadol IR 50 mg (N=119) n (%)	Tapentadol IR 75 mg (N=120) n (%)	Tapentadol IR 100 mg (N=118) n (%)	Oxycodone HCl IR 15 mg (N=125) n (%)
Total Number of Subjects with Concomitant Medication	87 (73)	93 (78)	92 (77)	99 (84)	107 (86)
Metoclopramide Hydrochloride	3 (3)	26 (22)	32 (27)	43 (36)	57 (46)
Cefalexin	20 (17)	24 (20)	28 (23)	27 (23)	31 (25)
Multivitamins	19 (16)	14 (12)	13 (11)	15 (13)	15 (12)
Ondansetron Hydrochloride	0	6 (5)	6 (5)	11 (9)	17 (14)
Bisacodyl	0	7 (6)	3 (3)	8 (7)	13 (10)
Diphenhydramine Hydrochloride	0	1 (1)	10 (8)	7 (6)	7 (6)
Fish Oil	1 (1)	5 (4)	4 (3)	7 (6)	3 (2)
Levothyroxine Sodium	4 (3)	4 (3)	2 (2)	6 (5)	7 (6)
Ascorbic Acid	2 (2)	11 (9)	4 (3)	5 (4)	4 (3)
Calcium	13 (11)	4 (3)	8 (7)	5 (4)	3 (2)
Estradiol	2 (2)	3 (3)	3 (3)	3 (3)	6 (5)
Estrogens Conjugated	6 (5)	1 (1)	2 (2)	2 (2)	1 (1)
Promethazine Hydrochloride	0	2 (2)	1 (1)	2 (2)	6 (5)
Docusate Sodium	3 (3)	2 (2)	1 (1)	1 (1)	7 (6)
Tocopherol	6 (5)	4 (3)	2 (2)	1 (1)	6 (5)

Percentages calculated with the number of subjects in each group as denominator.
Terms sorted based on percentages in the 100 mg group.

Source: CSR R331333-PAI-3003 (KF5503/32), p. 73

Table 81

Bowel Movement Questionnaire

Subjects will answer the following questions in the diary every evening during the run in and the double-blind periods:

1. If you had no bowel movement today, please check this box and stop at this question.
   a. No bowel movement today
2. Describe your bowel movement
   a. watery
   b. loose
   c. normal
   d. very hard (little balls)
3. How severe was your straining?
   a. no straining
   b. mild straining
   c. moderate straining
   d. severe straining
4. Did the stool make you feel like you completely emptied your bowels?
   a. yes
   b. no

Vomiting Questionnaire:

Subjects will answer the following question in the diary every evening during the double-blind period:

Have you vomited in the past 24 hours? Yes/No

Table 82

Attachment 2: Sleep Evaluation Questionnaire

Instructions:
Please answer these questions about how you slept *last night*. Mark all answers in the boxes.

Example:
If you think that it took you *half an hour* to fall asleep last night after you turned out the lights last night, your answer to Question 1 would look like this:

1. How long after bedtime/lights out did you fall asleep last night?
   [0] hour(s) [30] minutes

Sleep Questions:

1. How long after bedtime/lights out did you fall asleep last night?
   [ ] hour(s) [ ] minutes

2. How many times did you wake up during the night?
   [ ][ ] (number of times)

3. How long did you sleep last night?
   [ ] hour(s) [ ] minutes

4. Please rate the overall quality of your sleep last night
   (Mark *an "X" in the box that best describes your answer*)

Excellent	Good	Fair	Poor
▼	▼	▼	▼
[ ] 1	[ ] 2	[ ] 3	[ ] 4

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ON ORIGINAL

Table 83: Brief Description of Phase 1 Single-Dose Tapentadol IR Completed Studies

GRT/J&JPRD Study No.	Brief Description of Study
HP5503/03 0000\Mod5.3.1.1\HP5503/03	Randomized, double-blind, placebo-controlled, 4-way crossover, dose-escalation study to evaluate safety, tolerability, pharmacokinetics, and pharmacodynamics of tapentadol IR 64, 86, 129, and 172 mg in healthy male and female subjects.
HP5503/04 0000\Mod5.3.1.1\HP5503/04	Randomized, open-label, 3-way crossover study to evaluate the absolute bioavailability and food effect on the bioavailability of tapentadol IR 86 mg (fasted and fed) capsule and 15-minute i.v. infusion of tapentadol 34 mg in healthy male subjects.
HP5503/05 0000\Mod5.3.3.1\HP5503/05	Non-randomized, open-label, excretion balance and pharmacokinetic study of tapentadol IR 86 mg healthy male subjects.
HP5503/07 0000\Mod5.3.1.1\HP5503/07	Randomized, open-label, 4-way crossover study to determine the relative bioavailability of tapentadol IR (21.5 mg and 86 mg) tapentadol ER (86 and 172 mg).
HP5503/09 0000\Mod5.3.4.1\HP5503/09	Randomized, double-blind, placebo- and active-controlled, 4-way crossover study to determine the effect on orocaecal transit time of 2 doses of tapentadol IR (43 mg and 86 mg) compared to morphine sulfate (30 mg) and placebo in healthy subjects.
HP5503/14 R331333-PAI-1007 0000\Mod5.3.4.1\HP5503/14	Randomized, double-blind, placebo-controlled, 7-way crossover study to evaluate the abuse potential of tapentadol IR (50 mg, 100 mg, and 200 mg) compared to placebo and hydromorphone HCl IR (4 mg, 8 mg, and 16 mg) in opiate-experienced but nondependent recreational drug users.
HP5503/15 R331333-PAI-1006 0000\Mod5.3.3.3\HP5503/15	Non-randomized, open-label, parallel-group study to evaluate the pharmacokinetics, safety, and tolerability of tapentadol IR (80 mg) in subjects with varying degrees of renal impairment (mild, moderate, or severe) compared with subjects with normal renal function.
HP5503/16 R331333-PAI-1002 0000\Mod5.3.3.3\HP5503/16	Non-randomized, open-label, parallel-group study to evaluate the pharmacokinetics, safety, and tolerability of tapentadol IR (80 mg) in subjects with varying degrees of hepatic impairment (mild or moderate) compared with subjects with normal hepatic function.
HP5503/19 R331333-PAI-1008 0000\Mod5.3.3.4\HP5503/19	Randomized, open-label, 2-way crossover, drug-drug interaction study in healthy subjects to determine the effect of metoclopramide (6 doses of 20 mg each every 6 hours and a single tapentadol IR dose 1 hour after the fifth dose of metoclopramide) on the pharmacokinetics of tapentadol IR (80 mg) when tapentadol IR and metoclopramide were coadministered in healthy subjects.
HP5503/20 R331333-PAI-1009 0000\Mod5.3.3.4\HP5503/20	Randomized, open-label, 2-way crossover, drug-drug interaction study in healthy subjects to determine the effect of omeprazole (40 mg once daily for 4 days and a single tapentadol IR dose with the fourth dose of omeprazole) on the pharmacokinetics of tapentadol IR (80 mg) when tapentadol IR and omeprazole were coadministered in healthy subjects.
HP5503/21 R331333-PAI-1010 0000\Mod5.3.3.4\HP5503/21	Randomized, open-label, 2-way crossover, drug-drug interaction study in healthy subjects to determine the effect of probenecid (500 mg twice daily for 2 days and a single tapentadol IR dose with the third dose of probenecid) on the pharmacokinetics of tapentadol IR (80 mg) when tapentadol IR and probenecid were coadministered in healthy subjects.

GRT/J&JPRD Study No.	Brief Description of Study
HP5503/22 R331333-PAI-1011 0000\Mod5.3.3.4\HP5503/22	Randomized, open-label, 3-way crossover, drug-drug interaction study in healthy subjects to determine the effect of naproxen (500 mg twice daily for 2 days and a single tapentadol IR dose with the third dose of naproxen) and acetylsalicylic acid (325 mg once daily for 2 days and a single tapentadol IR dose with the second dose of acetylsalicylic acid) on the pharmacokinetics of tapentadol IR (80 mg) when each is coadministered with tapentadol IR in healthy subjects.
HP5503/23 R331333-PAI-1013 0000\Mod5.3.3.4\HP5503/23	Randomized, open-label, 2-way crossover, drug-drug interaction study in healthy subjects to determine the effect of acetaminophen (seven doses of 1000 mg each every 6 hours and a single tapentadol IR dose with the fifth dose of acetaminophen) on the pharmacokinetics of tapentadol IR (80 mg) when tapentadol IR and acetaminophen were coadministered in healthy subjects
HP5503/24 R331333-PAI-1016 0000\Mod5.3.1.2\HP5503/24	Randomized, open-label, 3-way crossover study to evaluate the bioequivalence of tapentadol IR capsules (80 mg) with the to-be-marketed tapentadol IR tablet (80 mg) in healthy male and female subjects.
[redacted]	[redacted]
HP5503/30 R331333-PAI-1019 0000\Mod5.3.3.3\HP5503/30	Non-randomized, open-label, parallel-group study to evaluate the pharmacokinetics, safety, and tolerability of tapentadol IR (80 mg) in healthy elderly (≥65 years) and young (18 to 45 years) subjects.
HP5503/34 R331333-PAI-1014 0000\Mod5.3.1.1\HP5503/34	Randomized, open-label, 2-way crossover study to investigate the effect of a high-fat, high-caloric meal on the bioavailability of tapentadol IR (100 mg) in healthy male and female subjects.
R331333-PAI-1027 0000\Mod5.3.3.3\R331333-PAI-1027	Randomized, double-blind, placebo-controlled, single-center, dose-ascending study conducted to evaluate the safety and tolerability of tapentadol IR (10 mg, 20 mg, and 40 mg) in healthy male Japanese subjects

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Table 84: Brief Description of Phase 1 Multiple-Dose Tapentadol IR Completed Studies

GRT/J&JPRD Study No.	Brief Description of Study
HP5503/13 R331333-PAI-1005 0000\Mod5.3.3.1\HP5503/13	Randomized, double-blind, placebo-controlled, dose-escalation study to assess the highest tolerable tapentadol IR dose within the range of doses planned for this study (75 mg to 249 mg)[a] in healthy male and female subjects.
HP5503/25 R331333-PAI-1018 0000\Mod5.3.4.1\HP5503/25	Randomized, double-blind, placebo-and positive-controlled, 4-way crossover study to evaluate the effect of tapentadol IR (100 mg or 150 mg five doses every 6 hours) on the measured 12-lead ECG QT intervals corrected for heart rate (QTc) in healthy male and female subjects.

[a] The highest dose administered in this study was 175 mg. The sponsor temporarily stopped the study before continuing with the next dose level (200 mg every 6 hours), because the FDA did not feel that dosing in nonclinical toxicology studies was sufficient to support the safety of continued dose escalation in the clinical study until the agency had the opportunity to review the pharmacokinetic data from completed studies with tapentadol IR. The requested information was submitted to the FDA, and the study remained suspended. Eventually, it was decided to terminate the study, as too much time had elapsed that prevented reconstitution of the cohorts (which would have required major protocol amendments) and due to the desire not to restart titration of dose from the initial dose level in new cohorts. Moreover, with the highest administered dose (175 mg every 6 hours), it was felt that sufficient data was available to continue the development of tapentadol IR.

Source: Tapentadol ISS, p. 49

Table 85: Brief Description of Phase 2 Studies Providing Basis for Efficacy

Study	Brief description of study	Treatment Regimen	Number of subjects in ITT analysis set	Rescue Analgesic Medication Allowed during Double-Blind period	Conclusions
KF5503/21 (GRT); R331333-PAI-2004 (J&JPRD) Mod5.3.5.1\KF5503/21	Randomized, double-blind, placebo- and active-controlled, parallel-group, multi-center study to evaluate the efficacy, safety, and tolerability of tapentadol IR for the relief of post-operative pain following a bunionectomy	Fixed dose every 4 to 6 hours for 3 days with an option for an early second dose on Study Day 2[a] Tapentadol IR 50 mg Tapentadol IR 100 mg Oxycodone HCl IR 10 mg Placebo	269 -Tapentadol IR 50 mg: 67 -Tapentadol IR 100 mg: 68 -Oxycodone HCl IR 10 mg: 67 -Placebo: 67	Yes, rescue medication permitted after the second dose of study drug[b]	Both the 50 mg and 100 mg tapentadol IR groups were statistically superior to placebo for the Study Day-3 SPI-24 primary endpoint. The analysis result was based on an ANOVA model
KF5503/22 (GRT); R331333-PAI-2003 (J&JPRD) Mod5.3.5.1\KF5503/22	Randomized, double-blind, placebo- and active-controlled, parallel-group, multi-center study to evaluate the efficacy and safety of tapentadol IR for the relief of post-operative pain following a bunionectomy	Fixed dose every 4 hours for 12 hours Tapentadol IR 80 mg/80 mg/80 mg Tapentadol IR 120 mg/120 mg/120 mg Tapentadol IR 120 mg/60 mg/60 mg Tapentadol IR 160 mg/80 mg/80 mg Oxycodone HCl IR 10 mg/10 mg/10 mg Placebo	480 -Tapentadol IR 80 mg/80 mg/80 mg: 80 -Tapentadol IR 120 mg/120 mg/120 mg: 79 -Tapentadol IR 120 mg/60 mg/60 mg: 82 -Tapentadol IR 160 mg/80 mg/80 mg: 79 –Oxycodone HCl IR 10 mg/10 mg/10 mg: 81 –Placebo: 79	No	All tapentadol IR dose regimens were significantly superior compared with placebo

[a] Early second dose was allowed as early as 1 hour but no later than 6 hours after the first dose.

[b] 1st line: 1 g acetaminophen (maximum of 4000 mg per day), oral; 2nd line: 400 mg ibuprofen, oral or ≤30 mg ketorolac, intravenous; 3rd line: 5 mg hydrocodone and 500 mg acetaminophen, oral

Source: ISE, p. 33

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Table 86: SAEs Reported in Multiple-Dose, Double-Blind Safety Analysis Set in Subjects Receiving Tapentadol

Subject ID	Age/race/sex	Study/randomization group	SAE	Tapentadol Total daily dose	Day of AE	D/C Study drug due to SAE	Outcome	Relation to study drug according to reviewer's adjudication
100004	76/W/F	KF5503/31/100 mg	COPD exacerbation	500-600mg on day 1-3 50-200mg days 5-12	Day 2	No	Resolved	Unlikely
100045	48/W/M	KF5503/31/50 mg	SVT PE DVT	100 mg day 1 0 0	Day 1 Day 2 Day 2	Yes	Resolved Resolved Resolved	Unlikely
100321*	66/W/M	KF5503/31/75mg	Ileus	300 mg day 1 75 mg day 2	Day 3	Yes	Resolved	Possible
100564*	64/W/F	KF5503/31/100mg	Lethargy	600mg day1	Day 2	Yes	Resolved	Probable
100363	72/W/M	KF5503/31/100 mg	Atrial fibrillation Visual hallucination	200-400mg on days 1-3	Day 1	Yes	Resolved	Unlikely
301021	60/H/F	KF5503/32/75mg	Pneumonia CHF Viral myocarditis	300-375 mg days 1-3	Day 3 End of DB pd	No	Resolved	Unlikely
305056	54/W/F	KF5503/32/50 mg	Small intestine obstruction	200 mg days 1-3	Day 4	No	Resolved (surgery)	Not related
401300	60/W/M	KF5503/ 34/flexible	MI	50 mg days 1-9	Day 10	No	Resolved	Unlikely
401450	68/W/M	KF5503/ 34/flexible	TIA	50-350mg days 1-20	Day 21	Yes (17 days after event)	Resolved	Unlikely
400102	74/W/F	KF5503/ 34/flexible	Thalamic infarction	50-100 mg days 1-31	Day 31	Yes (7 days after	Resolved	Unlikely

						even t)		
400984	71/W/M	KF5503/ 34/flexible	Acute MI	600mg day 1-3 400 mg day 4 500 mg day 5	Day 2	Yes	Resolved	Unlikely
402026	69/W/F	KF5503/ 34/flexible	Viral bronchitis	300-500 mg days 1-28	Day 26	Yes (day 38)	Resolved	Unrelated

*Narrative in body of text

Table 87: Number (%) of Subjects with TEAEs in ≥ 1% of Subjects in the "All" Tapentadol Group by Preferred Term for Phase 2/3 Multiple-Dose, Double-Blind Studies

Preferred Term	PLACEBO (N=619) n (%)	All Tapentadol IR (N=2178) n (%)	All OXY IR (N=675) n (%)
Total no. subjects with TEAEs	289 (47)	1651 (76)	567 (84)
Nausea	80 (13)	663 (30)	298 (44)
Dizziness	48 (8)	516 (24)	168 (25)
Vomiting	26 (4)	397 (18)	208 (31)
Somnolence	17 (3)	320 (15)	86 (13)
Headache	66 (11)	239 (11)	69 (10)
Constipation	16 (3)	174 (8)	133 (20)
Pruritus	8 (1)	117 (5)	73 (11)
Dry mouth	2 (<1)	91 (4)	17 (3)
Fatigue	3 (<1)	72 (3)	29 (4)
Diarrhoea	17 (3)	68 (3)	12 (2)
Hyperhidrosis	4 (1)	59 (3)	31 (5)
Pruritus generalised	4 (1)	54 (2)	24 (4)
Pyrexia	11 (2)	48 (2)	16 (2)
Dyspepsia	2 (<1)	37 (2)	13 (2)
Decreased appetite	0	36 (2)	14 (2)
Insomnia	4 (1)	36 (2)	11 (2)
Nasopharyngitis	1 (<1)	30 (1)	5 (1)
Tremor	2 (<1)	30 (1)	7 (1)
Confusional state	0	28 (1)	3 (<1)
Feeling hot	4 (1)	28 (1)	11 (2)
Muscle spasms	7 (1)	28 (1)	9 (1)
Upper respiratory tract infection	1 (<1)	28 (1)	9 (1)
Anxiety	4 (1)	27 (1)	7 (1)
Body temperature increased	12 (2)	27 (1)	5 (1)
Lethargy	2 (<1)	24 (1)	4 (1)
Hot flush	3 (<1)	23 (1)	8 (1)
Arthralgia	5 (1)	22 (1)	5 (1)
Blood creatine phosphokinase increased	12 (2)	22 (1)	6 (1)
Rash	5 (1)	22 (1)	12 (2)
Abnormal dreams	2 (<1)	21 (1)	3 (<1)
Urinary tract infection	4 (1)	21 (1)	2 (<1)
Abdominal pain	2 (<1)	20 (1)	9 (1)

Preferred Term	PLACEBO (N=619) n (%)	All Tapentadol IR (N=2178) n (%)	All OXY IR (N=675) n (%)
Abdominal pain upper	7 (1)	19 (1)	4 (1)
Hypotension	7 (1)	19 (1)	7 (1)
Muscle twitching	3 (<1)	19 (1)	6 (1)
Disturbance in attention	0	18 (1)	6 (1)
Hypoaesthesia	3 (<1)	18 (1)	3 (<1)
Vision blurred	2 (<1)	18 (1)	6 (1)
Euphoric mood	0	17 (1)	12 (2)
Oxygen saturation decreased	3 (<1)	17 (1)	5 (1)
Asthenia	2 (<1)	15 (1)	10 (1)
Disorientation	2 (<1)	15 (1)	5 (1)
Hallucination, visual	2 (<1)	15 (1)	2 (<1)
Paraesthesia	2 (<1)	15 (1)	6 (1)
Sedation	1 (<1)	15 (1)	5 (1)
Stomach discomfort	0	15 (1)	2 (<1)
Cough	2 (<1)	14 (1)	2 (<1)
Hypertension	2 (<1)	14 (1)	0
Irritability	0	14 (1)	3 (<1)
Sinusitis	1 (<1)	14 (1)	2 (<1)
Bronchitis	1 (<1)	13 (1)	5 (1)
Influenza	0	13 (1)	4 (1)
Oedema peripheral	0	13 (1)	4 (1)
Back pain	1 (<1)	12 (1)	6 (1)
Dysarthria	0	12 (1)	0
Dyspnoea	0	12 (1)	5 (1)
Flushing	1 (<1)	12 (1)	4 (1)
Pain in extremity	4 (1)	12 (1)	3 (<1)
Chest pain	1 (<1)	11 (1)	0
Contusion	1 (<1)	11 (1)	2 (<1)
Dysuria	1 (<1)	11 (1)	3 (<1)
Flatulence	6 (1)	11 (1)	5 (1)
Nasal congestion	0	11 (1)	3 (<1)
Pharyngolaryngeal pain	4 (1)	11 (1)	4 (1)
Restlessness	1 (<1)	11 (1)	4 (1)
Vertigo	0	11 (1)	3 (<1)

Time Schedule for Phase 2/3 Tapentadol IR Studies
Laboratory Tests

Protocol No.	Scr	Initial Exam	Base	T_0	H0.5	H 1	H1.5	H2	H3	H 4	H 5	H6	H7	H8	H 10	H 12	H16, 20	H24	D2	D3	D4	D6	D43	D91	End Trt/ DC	FU
KF5503/02 (Single Dose)		X																X								
KF5503/04 (Single - Multiple Dose)		X																X[1]			X(H 90)					
KF5503/05 (Single Dose)	X	X																X								
KF5503/08[2] (Single - Multiple Dose)	X	X																				X (H146, 150)				X
KF5503/21	X	X	X																		X				X	
KF5503/22 (PAI-2003)	X															X									X[4]	X
PAI-3002 (KF5503/33)	X		X																						X	
PAI-3003 (KF5503/32)	X		X																						X	X
PAI-3004 (KF5503/34)	X		X																				X	X	X	

Scr: Screening period. Base: Last assessment prior to dosing. T_0: The time of oral intake of investigational product.
[1]24 hours represent the end of single-dose period for KF5503/04 study.
[2]Single-dose period ended at hour 36 for KF5503/08 study.
[4]This occurs at discharge.

Source: ISS, p. 217

Time Schedule for Phase 2/3 Tapentadol IR Studies
Vital Signs

Protocol No.	Scr	Int	Base	T_0	H0.5	H 1	H1. 5	H2	H 3	H 4	H 5	H 6	H 7	H 8	H 10	H 12	H24	D2	D3	D4	D5	D6	D7	D8	D15	D29	D43	D57	D71	D91
KF5503-02 (Single Dose)		X	X		X	X		X	X	X	X			X		X	X													
KF5503-04 (Single + Multiple Dose)		X	X		X	X	X	X	X	X	X			X			X[1]	X (H30, 36,42, 48)	X (H54, 60, 66)	X (H78, 90)										
KF5503-05 (Single Dose)		X	X		X	X	X	X	X	X	X			X			X													
KF5503-08[2] (Single + Multiple Dose)	X	X						X								X		X (H36, 37,38, 42,43, 44, 48)	X (H49, 50,54, 55, 56,60, 72,84)	X (H96, 108)	X (H120, 132)	X (H1 44,1 56)	X (H168)	X (H192)						
KF5503-21[3]	X	X	X	X		X		X			every 4-6 hours, after preceding dose							X	X	X										
KF5503-22 (PAI-2003)	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X														
PAI-3002 (KF5503-33)	X		X																			X							
PAI-3003 (KF5503-32)	X		X	X												X	X	X	X										
PAI-3004 (KF5503-34)	X		X																						X	X	X	X	X	X

Scr: Screening period. Base: Last assessment prior to dosing. T_0: The time of oral intake of investigational product.
[1]24 hours represent the end of single-dose period for KF5503-04 study.
[2]Single-dose period ended at hour 36 for KF5503-08 study.
[3]The treatment period is 4 days (starts at T_0 and ends at D4). The hours 0.5, 1, 1.5, 2, 3 are considered post-initial dose, but there are measurements done at remedication, which occurs every 4-6 hours after preceding dose.
[4]This occurs at discharge.

Source: ISS, p. 216

Time Schedule for Phase 2/3 Tapentadol IR Studies
12-Lead Electrodiagram

Protocol No.	Scr	Initial Exam	Base	T_0	H0.5	H 1	H1.5	H 2	H3	H4	H 5	H 6	H 7	H 8	H 10	H12	H16, 20	H 24	D2	D3	D4	D5	D6	D7	D8	D43	End Trt/ DC	F U
KF5503/04 (Single + Multiple Dose)		X				X		X		X								X[1]		X (H67, 68,70)	X (H90)	X						
KF5503/05 (Single Dose)		X				X		X		X								X										
KF5503/08[2] (Single + Multiple Dose)	X	X						X															X (H 144, 146, 150)		X (H192)			X
KF5503/21[3]	X		X			X													X	X	X						X	
KF5503/22 (PAI-2003)	X		X				X									X											X[4]	
PAI-3002 (KF5503/33)	X		X																				X				X	
PAI-3003 (KF5503/32)	X		X																								X	
PAI-3004 (KF5503/34)	X		X																							X	X	

Scr: Screening period. Base: Last assessment prior to dosing. T_0: The time of oral intake of investigational product.
[1]24 hours represent the end of single-dose period for KF5503/04 study.
[2]Single-dose period ended at hour 36 for KF5503/08 study.
[3]The treatment period is 4 days (starts at T_0 and ends at D4). The hours 0.5, 1, 1.5, 2, 3 are considered post-initial dose, but there are measurements done at remedication, which occurs every 4-6 hours after preceding dose.
[4]This occurs at discharge.

Source: ISS p. 215

Table 91: List of Laboratory Tests Obtained during Phase 2/3 Studies

- **Hematology:** hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differential, and platelet count.
- **Biochemistry:** sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, amylase, AST, ALT, gamma-glutamyl transferase (GGT), bilirubin, alkaline phosphatase (AP), creatine phosphokinase, lactate dehydrogenase, uric acid, calcium, phosphorus, albumin, total protein, cholesterol, triglycerides, and lipase.
- **Urinalysis:** specific gravity and dipstick analysis of pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase. If the dipstick showed pathologic results, a microscopic examination of the sediment (including RBC, WBC, epithelial cells, crystals, casts, and bacteria) was performed.

Table 92: Criteria for Identifying Potentially Clinically Important Laboratory Values in the Phase 2/3 Multiple-Dose Studies

Laboratory Parameter (Standard International Units)	Low Potentially Clinically Important Levels	High Potentially Clinically Important Levels
Albumin (g/L)	<20	>2 x ULN
Alkaline phosphatase (U/L)	NA	>1.5 x ULN
Alanine transaminase[a] (U/L)	NA	>3 x ULN
Aspartate transaminase[a] (U/L)	NA	>3 x ULN
Blood urea nitrogen (mmol/L)	NA	>3 x ULN
Calcium (mmol/L)	<1.75	>3
Chloride (mmol/L)	<90	>120
Cholesterol (mmol/L)	NA	>2 x ULN
Creatine phosphokinase (U/L)	NA	>3 x ULN
Creatinine (umol/L)	NA	>1.5 x ULN
Gamma glutamyl transferase (U/L)	NA	>3 x ULN
Glucose (mmol/L)	<3.33	>3 x ULN
Lactic dehydrogenase (U/L)	NA	>1.5 x ULN
Phosphorus (Phosphate) (mmol/L)	<0.484	>1.5 x ULN
Potassium (mmol/L)	<2.8	>5.80
Sodium (mmol/L)	<125	>155
Total bilirubin (umol/L)	NA	>1.5 x ULN
Total protein (g/L)	NA	>2 x ULN
Triglycerides (mmol/L)	NA	>2 x ULN
Uric acid (umol/L)	NA	>1.5 x ULN
Hematocrit (%)	NA	N/A
Hemoglobin (g/L)	<75	>1.1 x ULN
Platelet count (giga/L)	<100	>3 x ULN
Red Blood Cell Count (tera/L)	<3	>2 x ULN
White blood cell count (giga/L)	<2.5	>2.5 x ULN
Amylase (U/L)	NA	>3 x ULN
Lipase (U/L)	NA	>3 x ULN

Source: Module 2.7 Clinical Summary; 2.7.4 Clinical Safety/Integrated Summary of Safety, p. 51

Table 93: Demographic Characteristics: Phase 1 Single-Dose Safety Analysis Set

	Placebo (n=91) n (%)	"All" Tapentadol IR (n=439) n (%)
Sex, n (%)		
N	91	439
Female	67 (74)	262 (60)
Male	24 (26)	177 (40)
Race/Ethnicity Group, n (%)		
N	91	439
White	79 (87)	359 (82)
Other	12 (13)	80 (18)
Age (years)		
N	91	439
Mean (SD)	32.7 (7.68)	39.6 (11.67)
Median	33.0	38.0
Range	(18;49)	(18;78)
Category		
<65 years	91 (100)	418 (95)
≥65 years	0	21 (5)
Body mass index (kg/m^2)		
N	91	439
Mean (SD)	24.01 (2.697)	24.39 (2.362)
Median	24.10	24.40
Range	(18.5;30.0)	(18.5;31.8)

Studies included: HP5503/03, HP5503/04, HP5503/05, HP5503/07, HP5503/09, HP5503/14, HP5503/15, HP5503/16, HP5503/19, HP5503/20, HP5503/21, HP5503/22, HP5503/23, HP5503/24, HP5503/27, HP5503/30, and HP5503/34

Source: Tapentadol IR 4-Month Safety Update, p. 75

Table 94: Demographic Characteristics: Phase 2 Single-Dose Safety Analysis Set

	Placebo (n=165)	"All" Tapentadol IR (n=870)
Sex, n (%)		
N	165	870
Female	114 (69)	588 (68)
Male	51 (31)	282 (32)
Race/Ethnicity Group, n (%)		
N	165	870
White	122 (74)	676 (78)
Black	15 (9)	76 (9)
Hispanic	25 (15)	99 (11)
Other	3 (2)	19 (2)
Age (years)		
N	165	870
Mean (SD)	30.2 (11.14)	30.5 (11.42)
Median	25.0	26.0
Range	(18; 64)	(18; 65)
Category		
<65 years	165 (100)	868 (99.8)
65 to <75 years	0	2 (0.2)
Body mass index (kg/m^2)		
N	165	870
Mean (SD)	25.6 (4.59)	26.0 (5.21)
Median	24.5	24.6
Range	(18; 40)	(17; 51)
Pain model, n (%)		
N	165	870
Preoperative[a]	0	47 (5)
Postoperative[b]	165 (100)	823 (95)
Rescue medication allowed, n (%)		
N	165	870
Yes	165 (100)	870 (100)

Studies included: KF5503/02, KF5503/04 (Part 1), KF5503/05, and KF5503/08 (Part 1)
"all" tapentadol IR includes tapentadol IR 21 mg to 172 mg
[a] indicates a nonsurgical/outpatient pain model.
[b] indicates an inpatient pain model.

Source: Tapentadol IR 4-Month Safety Update, p. 84

Table 95: Criteria for Identifying Potentially Clinically Important Laboratory Values in the Phase 2/3 Multiple-dose Studies

Laboratory Parameter (Standard International Units)	Low Potentially Clinically Important Levels	High Potentially Clinically Important Levels
Albumin (g/L)	<20	>2 x ULN
Alkaline phosphatase (U/L)	NA	>1.5 x ULN
Alanine transaminase[a] (U/L)	NA	>3 x ULN
Aspartate transaminase[a] (U/L)	NA	>3 x ULN
Blood urea nitrogen (mmol/L)	NA	>3 x ULN
Calcium (mmol/L)	<1.75	>3
Chloride (mmol/L)	<90	>120
Cholesterol (mmol/L)	NA	>2 x ULN
Creatine phosphokinase (U/L)	NA	>3 x ULN
Creatinine (umol/L)	NA	>1.5 x ULN
Gamma glutamyl transferase (U/L)	NA	>3 x ULN
Glucose (mmol/L)	<3.33	>3 x ULN
Lactic dehydrogenase (U/L)	NA	>1.5 x ULN
Phosphorus (Phosphate) (mmol/L)	<0.484	>1.5 x ULN
Potassium (mmol/L)	<2.8	>5.80
Sodium (mmol/L)	<125	>155
Total bilirubin (umol/L)	NA	>1.5 x ULN
Total protein (g/L)	NA	>2 x ULN
Triglycerides (mmol/L)	NA	>2 x ULN
Uric acid (umol/L)	NA	>1.5 x ULN
Hematocrit (%)	NA	N/A
Hemoglobin (g/L)	<75	>1.1 x ULN
Platelet count (giga/L)	<100	>3 x ULN
Red Blood Cell Count (tera/L)	<3	>2 x ULN
White blood cell count (giga/L)	<2.5	>2.5 x ULN
Amylase (U/L)	NA	>3 x ULN
Lipase (U/L)	NA	>3 x ULN

[a] Alanine aminotransferase (ALT)/ serum glutamic pyruvic transaminase (SGPT); aspartate aminotransferase (AST)/ serum glutamic oxaloacetic transaminase (SGOT)

NA = not applicable; ULN = upper limit of normal

Source: Tapentadol IR 4-Month Safety Update, p. 66

Table 96: Laboratory Reference Ranges for Phase 2/3 Studies

Parameter	Units	Normal Range	
		Male	Female
Albumin	g/l	36-50	36-50
Alk phos	U/L	35-123	36-118
ALT	U/L	8-45	8-43
AST	U/L	11-39	11-37
Bilirubin	umol/l	3.8-21.9	3.8-21.9
Calcium	mmol/l	2.1-2.5	2.1-2.5
Chloride	mmol/l	97-110	97-110
Creatine Kinase	U/L	31-197	23-179
Creatinine	umol/l	64-115	50-94
GGT	U/L	11-61	8-49
Glucose	mmol/l	3.8-6.1	3.8-6.1
LDH	U/L	135-225	135-214
Phosphate	mmol/l	0.8-1.5	0.8-1.5
Potassium	mmol/l	3.5-5	3.5-5
Protein	g/l	62.3-82.8	62.3-82.8
Sodium	mmol/l	135-146	135-146
Uric acid	umol/l	189-451	143-385
Hematocrit	vol-%	39-51	35-45
Hemoglobin	g/l	116-154	132-173
Platelets	giga/l	145-420	145-420
RBC	tera/l	4.4-5.8	3.9-5.2
WBC	giga/l	3.9-10.3	4-10.3

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/s/

Ellen Fields
9/18/2008 05:28:19 PM
MEDICAL OFFICER

Robert Shibuya
9/22/2008 10:28:19 PM
MEDICAL OFFICER

Interdisciplinary Review Team for QT Studies Consultation:

Thorough QT Study Review

NDA	22-304
Generic Name	Tapentadol HCl tablets
Sponsor	Johnson and Johnson
Indication	Treatment of moderate to severe acute pain
Dosage Form	Immediate Release (IR) film-coated tablet
Drug Class	Analgesic
Therapeutic Dose	50, 75 or 100 mg IR tablets every 4-6 hrs
Duration of Therapeutic Use	Acute [redacted] b(4)
Maximum Tolerated Dose	Unknown. Highest tested doses: 200 mg Single dose and 175 mg every 6 hrs multiple dose
Application Submission Date	22 January 2008
Review Classification	Standard
Date Consult Received	17 April 2008
Clinical Division	DAARP / HFD 170
PDUFA Date	23 November 2008

1 SUMMARY

1.1 Overall Summary of Findings

No significant QT prolongation effect of tapentadol HCl (100 mg q6h and 150 mg q6h) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between tapentadol HCl (100 mg and 150 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidance.

This was a Phase 1, single-center, double-blind, randomized, placebo- and positive-controlled, 4-way crossover study to evaluate the electrocardiogram parameters in healthy men and women (n=68) receiving multiple dosing of an immediate-release (IR) formulation of tapentadol HCl at therapeutic and supratherapeutic doses. Overall findings are summarized in Table 1.

Table 1: The Point Estimates and the 90% CIs corresponding to the Largest Upper Bounds for Tapentadol HCl (100 mg and 150 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time, h	ΔΔQTcF, ms	90%CI, ms
Tapentadol HCl IR 100 mg q6h	26	-0.7	(-3.3, 2.0)
Tapentadol HCl IR 150 mg q6h	26	1.1	(-1.8, 3.8)
Moxifloxacin 400 mg *	1.5	10.2	(6.2, 14.3)

** CIs are adjusted for 11 post-baseline time points. See* Table 8.

The supratherapeutic dose is only 50% higher than the highest therapeutic dose administered q6h and similar to the expected exposure when 100 mg is administered q4h (assuming an accumulation of 2 based on $T_{1/2}$ of 4 h). The sponsor did not evaluate higher doses of tapentadol HCl because "the results from Study HP5503/13 suggest that higher doses than tapentadol IR 150 mg would lead to an unacceptably high rate of mainly gastrointestinal adverse events in healthy subjects which would not be acceptable for this pharmacodynamic study." To support the supratherapeutic dose, the sponsor performed PK simulations in women with mild hepatic impairment and probenecid as concomitant medication, over a range of body-weight observed in the pooled database used to develop the PPK model. According to the simulation, 1 in 1000 patients dose with tapentadol HCl 100 mg are expected to achieve exposures greater than that achieved with tapentadol HCl 150 mg IR.

Moderate hepatic impairment leads to 1.8-fold increase in C_{max}. The sponsor is proposing dose and regimen adjustment for moderate hepatic impaired patients. The proposed dosing in moderate hepatic impaired patients is:

b(4)

The supra-therapeutic dose of 150 mg q6h covers the range of exposures expected with the modified dosing regimen in moderately hepatic impaired patients.

There was no relationship between tapentadol concentrations and ΔΔQTcF.

2 PROPOSED LABEL

The lack of drug effect on the prolongation of QT interval has been mentioned under the pharmacodynamics section. However, the sponsor did not include a description of study results in the proposed label.

b(4)

The following text is our suggestions for labeling. We defer all labeling decisions to the clinical review team.

12.2 Pharmacodynamics

b(4)

b(4)

3 BACKGROUND

Tapentadol HCl, also known as CG5503 or R331333, is a centrally active analgesic (antinociceptive) agent that is being investigated for the treatment of acute pain. It has an apparently dual mode of action, being both a μ-opioid receptor agonist and an inhibitor of norepinephrine uptake.

3.1 MARKET APPROVAL STATUS

Tapentolol is not approved for marketing in the USA or elsewhere.

3.2 PRECLINICAL INFORMATION

Source: IB, Dec 2006

The results of safety pharmacology studies are summarized in Table 2.

Table 2: Safety Pharmacology Studies

Issue/Model Species, number, gender	Route	CG5503 Dose/concentration	Results
Cardiovascular system – in vitro			
Ikr/HERG, CHO cells (SP21; SP101; SP131)	*In vitro*	1 – 100 μM	CG5503: threshold concentration for HERG inhibition = 10 μM (2210 ng/ml); IC_{50} = 36.1 μM (7978 ng/ml*) The O-glucuronide (E01472), N-methyl (GRT3451Z) and sulfate (GRT3793H) metabolites were even less active with IC_{50} values of >300, 264 and >300 μM, respectively.
Action potential, rabbit papillary muscle (SP70)	*In vitro*	3 – 100 μM	≤10 μM (2210 ng/ml): no effect on APD; concentration-dependent APD prolongation at 30 and 100 μM (6630 and 22100 ng/ml); no reverse-use dependency
Action potential, guinea pig papillary muscle (SP122; SP144)	*In vitro*	0.1 – 100 μM	10 and 100 μM (2210 and 22100 ng/ml): slight shortening of the APD by 3 and 9%; reduction in upstroke velocity and AP potential at 100 μM No effect on the AP of the glucuronide up to 300 μM
Isolated perfused guinea pig heart (SP154)	*In vitro*	1 – 30 μM	30 μM: decrease in HR, prolongations in PR and QRS times, no effect on QTc
Isolated atrium and papillary muscle, guinea pig (PH379)	*In vitro*	215 – 1000 μM	Weak negative chronotropic (IC_{50} = 408 μM/90168 ng/ml) and inotropic effects (IC_{50} = 508 μM/112268 ng/ml)
Isolated aortic stri-ps, Sprague Dawley rat (SP220)	*In vitro*	100 – 316 μM	Vasorelaxant effect in K^+-depolarized aortic strip preparations: IC_{50} = 153 μM (corresp. 33813 ng/ml)

Issue/Model Species, number, gender	Route	CG5503 Dose/concentration	Results
Cardiovascular system – in vivo			
Anesthetized New Zealand White rabbits, 6 m (PH323)	i.v.	1.0 – 10 mg/kg	1.0 mg/kg: decrease in LV contractility and central venous pressure 4.64 and 10 mg/kg: additionally decreases in BP, HR and respiratory rate, slight prolongations of PQ and QRS 10 mg/kg: decreases in CO and SV No effect on QTc whatever the dose
Anesthetized Beagle dog, 3 m, 3 f (SP103/A)	i.v.	0.5 – 4.5 mg/kg	Dose-dependent hypotensive effect (significant at 4.5 mg/kg) related to a negative inotropic effect (decreases in LV contractility, CO and SV); slight widening of QRS; 1.5 mg/kg and 4.5 mg/kg: disappearance of P wave and change in T wave morphology; no change of QTc at any dose Serum exposure: 1177 (f) and 1717 (m) ng/ml at 4.5 mg/kg
Conscious Beagle dog, 6 m (SP35/A)	i.v.	3 – 9 mg/kg	Reversible increases in HR, CO and BP (dose-related); LV ejection fraction decreased at 6 and 9 mg/kg; high variability in respiratory rate (panting, abdominal respiration); transient shortening of PQ (9 mg/kg), decrease of QT in parallel to tachycardia, no change in QTc Serum exposure: 665/1,105/2,531 ng/ml in 3/6/9 mg/kg groups
Conscious Sprague Dawley rat, 6 m (PH371)	i.v.	4.64 – 14.6 mg/kg	4.64 mg/kg: increase in BP; 10 mg/kg: increase in BP and HR; 14.7 mg/kg: increase in BP and HR (preceded by an initial decrease in HR)

Source: Sponsor's Table 5.8 in the IB

Reviewer's Comment: We note that negative inotropic effects (such as prolongation of the QRS, decrease in LV contractility, LV ejection fraction, cardiac output and stroke volume) were noted at higher doses in the in vivo studies.

3.3 PREVIOUS CLINICAL EXPERIENCE

Source: Clinical Overview (module 2.5) and Response to FDA information request dated 25 Mar 2008

> "More than 3200 subjects have received tapentadol IR in Phase 1, 2, and 3 clinical studies completed as of 03 October 2007.
>
> No deaths were reported following treatment in the Phase 1, 2, or 3 completed studies included in this submission as of 03 October 2007.
>
> In a search of the Phase 1,2,3 completed clinical studies examining tapentadol IV, IR or ER (Table 1) for the adverse event preferred terms of syncope, syncope vasovagal, ventricular tachycardia, ventricular fibrillation, and convulsion, a total of 36 subjects who experienced these treatment-emergent adverse events were identified. Of these subjects, 21 reported at least one of these adverse events during tapentadol treatment (7 with IV, 8 with IR, and 6 with ER)."

Reviewer's Comment: On review of the narratives, most cases of syncope were vasovagal and not associated with QT prolongation. One 64 yr old male with known CAD experienced of ventricular fibrillation during cardiac catheterization.

3.4 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of tapentadol's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The sponsor submitted data from a single 'thorough QT' (TQT) study to evaluate the effect of tapentadol on cardiac conduction (repolarization). Digital ECGs were submitted to the ECG Warehouse.

4.2 TQT STUDY

4.2.1 Title

A Single-Center, Double-Blind, Randomized, Placebo- and Positive-Controlled Four-Way Crossover Study to Evaluate Electrocardiogram Parameters in Healthy Men and Women Receiving Multiple Dosing of an Immediate-Release Formulation of CG5503 (Tapentadol HCl) at Therapeutic and Supratherapeutic Doses

4.2.2 Protocol Number

R331333-PAI-1018; HP5503/25

4.2.3 Study Dates

07 May 2007 - 31 August 2007

4.2.4 Objectives

The primary objective of the study was to assess the effects of tapentadol on the measured 12-lead ECG QT intervals corrected for heart rate (QTc) in healthy men and women receiving multiple dosing of an immediate-release (IR) formulation of tapentadol at therapeutic and supratherapeutic doses.

4.2.5 Study Description

4.2.5.1 Design

This was a Phase 1, single-center, double-blind, randomized, placebo- and positive controlled, 4-way crossover study. The study consisted of a screening phase of approximately 3 weeks (maximum of 21 days; minimum of 7 days), a baseline assessment phase (Days -2 and -1) in each of the 4 treatment periods, and a double-blind treatment phase consisting of 4 treatment periods that were separated by a washout period of 7 to 14 days.

4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

The positive (moxifloxacin) control was blinded.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

- **Treatment A**: 5 doses of tapentadol IR 100 mg every 6 hours and a single dose of placebo (matching moxifloxacin) given with the 5th dose of tapentadol IR 100 mg
- **Treatment B**: 5 doses of tapentadol IR 150 mg every 6 hours and a single dose of placebo (matching moxifloxacin) given with the 5th dose of tapentadol IR 100 mg

- **Treatment C**: 5 doses of placebo (matching tapentadol) every 6 hours and a single dose of placebo (matching moxifloxacin) given with the 5th dose of placebo (matching tapentadol)
- **Treatment D**: 5 doses of placebo (matching tapentadol) every 6 hours and a single dose of moxifloxacin 400 mg given with the 5th dose of placebo (matching tapentadol).

4.2.6.2 Sponsor's Justification for Doses

"Tapentadol exposure after oral intake of 100 mg IR every 4 hours (Q4h) irrespective of food intake was simulated for a scenario where high steady state C_{max} and AUCτ after tapentadol IR intake was expected. To characterize high clinical exposure scenario, simulations were performed in women with mild hepatic impairment (using total bilirubin and total protein concentrations in serum of mild hepatic impaired patients as surrogate) and probenecid as concomitant medication, over a range of body-weight observed in the pooled database used to develop the PPK model.

"The simulated steady-state C_{max} values fall largely within the range of the C_{max} values observed following tapentadol IR 150 mg dose given every six hours (Q6h) in the TQT study. Only one simulated subject exhibited C_{max} value slightly higher than the maximum observed C_{max} following the 150 mg Q6h dose regimen.

"Based on the simulation results, it can be concluded that the simulated maximum serum concentrations, C_{max}, are contained within the range of maximum serum concentration observed (HP5503/25, Module 5.3.4.1\HP5503/25) in the supra-therapeutic dose group of TQT study."

Reviewer's Comment: The choice of the supratherapeutic dose based on the simulation study is reasonable. The range of exposures achieved with tapentadol 150 mg IR administered q6h reasonably covers the range of exposures seen with the therapeutic dosing (based from Population PK analysis). However, it should be noted that 1 in 1000 patients in the simulations resulted in exposures beyond the range of that observed with tapentadol 150 mg IR.

Since tapentadol hydrochloride IR is labeled to be administered every 4-6 hr, the maximum proposed therapeutic dose is 100 mg q4h. The accumulation with q6h at steady-state is reported to be 1.6, while the accumulation expected with q4h is approximately 2. This results in a 40% increased exposure for the 100-mg dose with q4h regimen compared to q6h regimen. The exposures achieved with 100-mg q4h regimen are covered by the range of exposures with a 150-mg q6h regimen.

Further moderate hepatic impairment leads to 1.8-fold increase in C_{max}. However, the sponsor is proposing dose and regimen adjustment for moderate hepatic impaired patients. The proposed dosing in moderate hepatic impaired patients is:

b(4)

b(4)

The supra-therapeutic dose of 150 mg q6h covers the range of exposures expected with the modified dosing regimen in moderately hepatic impaired patients.

4.2.6.3 Instructions with Regard to Meals

In each treatment period, subjects were provided an evening snack, and thereafter fasted from food for at least 10 hours before the baseline assessments on Day –1, and before the first study drug administration on Days 1 and 2. Study drug was to be swallowed whole with 240 mL of noncarbonated water.

4.2.6.4 ECG and PK Assessments

Table 3: Sampling Schedule

Study Day	-2 to -1	1	2
Intervention	No treatment (Baseline)	Placebo (for Tapentadol) Tapentadol IR 100 mg Tapentadol IR 150 mg Placebo (for Tapentadol) Every 6 hours (A total of 3 doses)	Placebo (for Tapentadol) Tapentadol IR 100 mg Tapentadol IR 150 mg Moxifloxacin 400 mg Placebo (for Moxifloxacin with 5th dose) Every 6 hours (A total of 2 doses)
12-Lead ECGs	Record ECGs###	Pre-dose	Record ECGs****
PK Samples for drug	None collected	Collected+++	

-24, -23.5, -23, -22.5, -22, -21.5, -21, -20, -18, -15, -14, -12, -10.5, -10
**** 24, 24.5, 25, 25.5, 26, 27, 28, 30 33, 34, 36
+++ Pre-dose, 1.5, 6, 12, 18, 24, 24.5, 25, 25.5, 26, 27, 28, 30 33, 34, 36
NOTE: Between the periods a 7 – 14 day washout was performed.

4.2.6.5 Baseline

The sponsor collected same day pre-dose baseline at visits -1 and 2.

4.2.7 ECG Collection

Source: Clinical protocol R331333-PAI-1018 (HP5503/25) Amendment INT-2

Serial 12-lead triplicate ECGs were to be recorded [3 ECG recordings at each specified time point (see above) until 10 regular consecutive complexes were available; consecutive recordings had to be separated by at least 1 minute, with recording of the complete triplicate ECGs not to exceed 5 minutes] in each treatment period on Day –1,

Day-1and on Day 2. Prior to each ECG recording, each subject had to rest in a supine position in bed for at least 20 minutes.

The electronic record was forwarded to a central ECG facility [ ] r evaluation. Trained and certified ECG readers, operating from a centralized ECG laboratory, will measure the ECG intervals. The ECG readers will read all ECG recordings, with 1 reader reading all ECGs per subject. The ECG readers will be blinded to time, treatment, and subject identifier. The degree of inter- and intra-reader variability will be established by having the assessors reread a subset of the data (both normal and abnormal) under blinded conditions. b(4)

Safety ECGs were obtained at screening and at time of study completion (or withdrawal).

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

75 subjects, (39 males, 36 females) 25-65 yrs of age, with a normal baseline ECG and a BMI between 20-30 kg/m^2 were enrolled in this study. 59 subjects completed the study. Sixteen subjects withdrew from the study. Twelve subjects discontinued the study due to adverse events. Seven of these subjects withdrew after screening but *prior to* receiving any study drug due to microscopic hematuria (n=2), eosinophilia/neutropenia, atrio-ventricular block (n=2), anoxic seizure/vasovagal syncope, and increased liver function test values. Five subjects discontinued from the study due to TEAE's of non-sustained ventricular tachycardia, urticaria (n=2), first degree A-V block, elevated AST and GGT. Four subjects withdrew due to other reasons.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary analysis was performed on all time-points for ΔQTcF using mixed-effect model with treatment, sequence, period, time point of measurement and treatment by time point of measurement interaction as fixed effects, and subject as a random effect. The upper bounds of the one-sided 95% CIs for the mean differences between tapentadol IR (doses of 100 mg and 150 mg) and placebo in QTcF at each time point were below 10 ms. Table 4 presents mixed model analysis results in ΔQTcF.

Table 4: Mixed Model Analysis in ΔQTcF

	Pairwise Comparison Tapentadol IR 100 mg Minus Placebo			Pairwise Comparison Tapentadol IR 150 mg Minus Placebo			Pairwise Comparison Moxifloxacin 400 mg Minus Placebo		
	L.S.Mean	SE	90% CI	L.S.Mean	SE	90% CI	L.S.Mean	SE	90% CI
QTcF (ms)									
DB Treatment									
Day 2, 24 H	-3.9	1.72	(-6.76; -1.11)	-4.1	1.71	(-6.87; -1.24)	-0.6	1.70	(-3.41; 2.20)
Day 2, 24 H 30 min	-2.0	1.72	(-4.83; 0.83)	-2.2	1.71	(-4.98; 0.65)	0.4	1.70	(-2.40; 3.20)
Day 2, 25 H	-3.2	1.72	(-6.00; -0.34)	-1.9	1.71	(-4.77; 0.87)	8.5	1.70	(5.69; 11.30)
Day 2, 25 H 30 min	-0.9	1.72	(-3.68; 1.97)	-0.1	1.71	(-2.91; 2.72)	11.4	1.70	(8.59; 14.20)
Day 2, 26 H	2.5	1.72	(-0.34; 5.34)	2.4	1.71	(-0.38; 5.26)	12.3	1.70	(9.52; 15.12)
Day 2, 26 H 30 min	-0.5	1.72	(-3.29; 2.37)	-2.1	1.72	(-4.89; 0.75)	9.5	1.70	(6.65; 12.26)
Day 2, 27 H	-0.2	1.72	(-3.06; 2.60)	0.4	1.71	(-2.46; 3.17)	12.6	1.71	(9.74; 15.37)
Day 2, 28 H	-0.6	1.72	(-3.38; 2.28)	-0.6	1.71	(-3.41; 2.22)	12.2	1.70	(9.41; 15.02)
Day 2, 30 H	2.7	1.72	(-0.10; 5.55)	-0.7	1.71	(-3.51; 2.12)	9.1	1.70	(6.25; 11.86)
Day 2, 33 H	-1.8	1.72	(-4.62; 1.03)	-2.2	1.71	(-5.03; 0.60)	7.8	1.70	(4.95; 10.56)
Day 2, 36 H	-0.6	1.72	(-3.45; 2.21)	-2.3	1.71	(-5.09; 0.54)	9.0	1.70	(6.23; 11.84)

LS Means and CIs are based on mixed model: change = arm aperiod window trtgrp window*trtgrp / ddfm=kr
tpd30_qtcf_mod_p1.rtf generated by tpdmodels51.sas.

Source: Sponsor' Table 14 on page 72 of CG5503: Clinical Study Report R331333-PAI-1018(HP5503/25)

The sponsor claims that the assay sensitivity was established as the lower limits of the 90% confidence intervals for mean ΔQTcF between moxifloxacin 400 mg and placebo were above zero for all time points between 24 and 36 hours postdose.

Reviewer's Comment: To claim assay sensitivity, at least one 1-sided 95% lower bound has to be greater than 5 ms (not 0 ms as stated by the sponsor).

4.2.8.2.2 Categorical Analysis

Categorical analysis was used to summarize QTc > 450 ms, > 480 ms and > 500 ms, and QTc interval absolute changes from baseline ≥ 30 and < 60 ms. No subject observed a QTc > 480 ms or a change from baseline QTc > 60 ms. There were 6 subjects with QTc > 450 ms (4 subjects with moxifloxacin 400 mg, and one subject with each of tapentadol IR 100 mg and 150 mg). There were 16 subjects with change from baseline 30ms ≤ ΔQTcF < 60 ms (12 subjects with moxifloxacin 400 mg, and 4 subjects with tapentadol IR 150 mg).

4.2.8.2.3 Additional Analyses

The sponsor also performed analyses of QTcB and QTcI correction methods.

4.2.8.3 Safety Analysis

There were no deaths or treatment-emergent serious adverse events in this study.

One subject withdrew from the study *prior to* randomization and study drug administration following the serious adverse events of severe syncope vasovagal and seizure-anoxic after screening (see section 4.2.8.1).

As mentioned earlier, 12 subjects discontinued due to adverse events, 7 prior to receiving any study drug. 5 subjects discontinued due to TEAE's. Subject 118011 a 25-year-old white man experienced mild-intensity adverse events of palpitations and ventricular tachycardia (reported terms: cardiac palpitations and non-sustained ventricular

tachycardia), that were noted via continuous ECG monitoring prior to scheduled ECG and vital signs measurements and the first dose of study drug in Period 2, 14 days after receiving the last dose of study drug (placebo) on Day 2 of Period 1.

Subject 118033, a 39-year-old white man experienced moderate-intensity adverse event of atrio-ventricular block (AVB) first degree (reported term: AVB first degree), 13 days after receiving 5 doses of tapentadol IR 150 mg in Period 3. The event resolved after 26 hours. The subject was withdrawn from the study the day after the event.

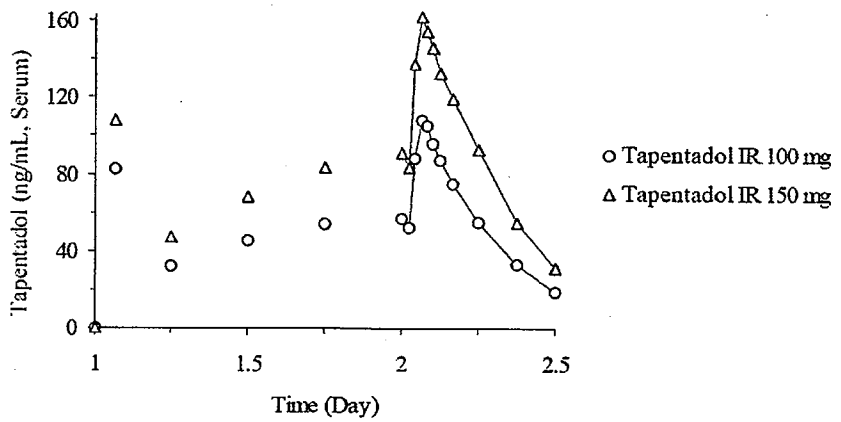
Overall the adverse event profile of tapentadol IR was consistent with the previous experience in healthy subjects. The most common adverse events (>10%) in either of the 4 treatments were vertigo CNS origin, headache, somnolence, dizziness, nausea, vomiting, and feeling drunk.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

With every 6 hr dosing regimen, near steady-state condition were reached as evidenced by the mean trough concentrations at 6, 12, 18, 24 and 30 hr for both the doses as shown in Figure 1.

Figure 1: Mean Serum Concentration-Time Profiles of Tapentadol (Day 1 and Day 2)



Source: Sponsor's Figure 2 of Clinical Study Report R331333-PAI-1018 (HP5503/25)

A summary of the mean±SD PK parameters for tapentadol as calculated from the concentration-time profile on Day 2 are presented in Table 5.

Table 5: Summary of Descriptive Statistics of the Pharmacokinetic Parameters of Tapentadol

PK parameters	n	Tapentadol IR 100 mg	Tapentadol IR 150 mg
C_{trough}, ng/mL	55	55.2 ± 25.2	93.3 ± 50.7
$C_{tmax,ss}$, ng/mL	58	129 ± 42.0	197 ± 89.1
$t_{max,ss}$, h	58	1.45 (0.87-6.00)	1.49 (0.40-6.02)
AUC_{τ}, h.ng/mL	58	465 ± 146	729 ± 282
$C_{avg,ss}$, ng/mL	58	78.4 ± 24.3	122 ± 48.0
$t_{1/2}$, h	53	3.7 ± 0.9	3.7 ± 0.9
CL_{ss}/F, mL/min	58	3969 ± 1351	3820 ± 1176

t_{max}: median (min-max)

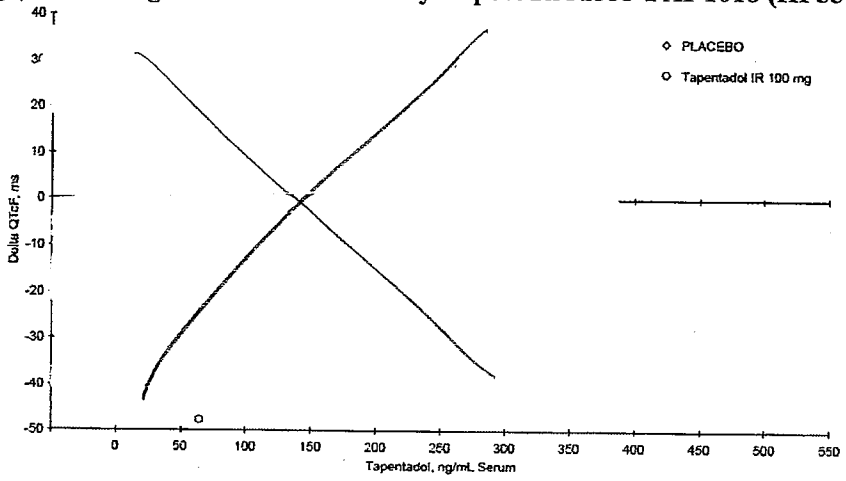
Source: Table 9 of Clinical Study Report R331333-PAI-1018 (HP5503/25)

Mean peak tapentadol-O-glucuronide serum concentrations were reached after 2 hours and the terminal half-life averaged 3.4 hours for both treatments. On average for tapentadol-O-glucuronide, $C_{max,ss}$ was 4,663 and 6,791 ng/mL after administration of the 5th dose of tapentadol IR 100 mg and tapentadol IR 150 mg, respectively. These results were similar to those observed in previous studies with the tapentadol IR formulation.

4.2.8.4.2 Exposure-Response Analysis

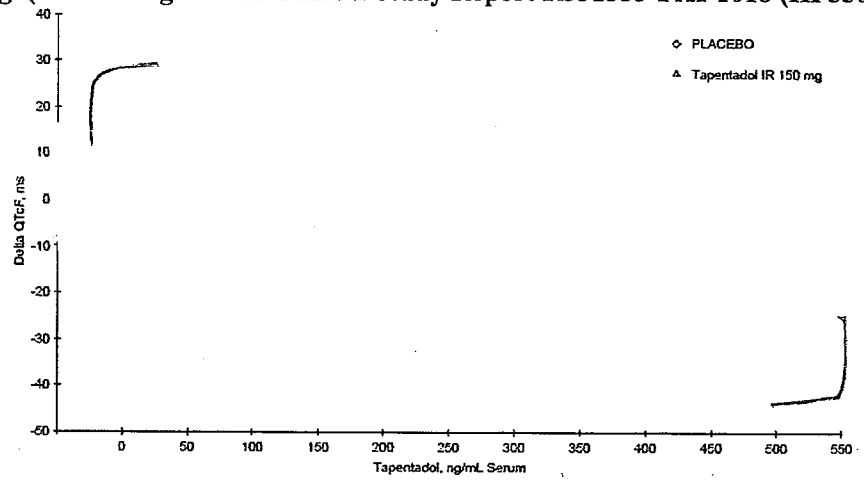
The potential relationship between serum tapentadol concentration and change in QTcF interval was examined graphically by plotting the ΔQTc for all subjects at each time point of measurement against the corresponding individual tapentadol serum concentration as shown in Figure 2 and Figure 3.

Figure 2: Scatterplot of the Individual ΔQTcF Against the Corresponding Tapentadol Serum Concentrations on Day 2 After Administration of Tapentadol IR 100 mg (Source: Figure 6 of Clinical Study Report R331333-PAI-1018 (HP5503/25))



b(4)

Figure 3: Scatterplot of the Individual ΔQTcF Against the Corresponding Tapentadol Serum Concentrations on Day 2 After Administration of Tapentadol IR 150 mg (Source: Figure 7 of Clinical Study Report R331333-PAI-1018 (HP5503/25))



b(4)

The graphical evaluation shows no relationship between the change in QTcF from baseline and the corresponding serum concentration of tapentadol in either of the 2 treatments compared with placebo treatment.

Reviewer's Comment: No formal exposure-response analyses were performed.

5 REVIEWERS' ASSESSMENT

5.1 STATISTICAL ASSESSMENTS

QTcF Analysis

The ECG data were submitted electronically and included all subjects who received study drug, and had adequate baseline and post-dose digital ECG data for all treatment period. The dataset contains one record for each scheduled ECG-related data-point of the study.

The results are summarized in **Table 6** and Table 7 for tapentadol IR 100 mg and 150 mg, respectively. The upper bounds of the two-sided 90% CIs for the mean differences between tapentadol IR and placebo in the pre-dose ΔQTcF change from baseline at each time point are below 10 ms. The largest upper bounds for tapentadol IR 100 mg and 150 mg are 1.99 ms and 3.84 ms, respectively. They occurred at 26 hour after dosing. Table 8 summarizes the results of the mean difference between moxifloxacin and placebo in QTcF with and without multiplicity adjustments. With multiplicity adjustment, the largest lower bound for moxifloxacin is 6.17 ms. It occurred on Day 2 at 1.5 hour after dosing. Figure 4 present the time-course ΔΔQTcF for tapentadol IR 100 mg, 150 mg and moxifloxacin 400 mg.

Table 6: Placebo adjusted, Mean QTcF Change from Baseline (used Pre-Dose as Baseline) Tapentadol IR 100 mg

Day	Time (hr)	ΔQTcF N	ΔQTcF Mean	ΔQTcF (SD)	Placebo N	Placebo Mean	Placebo (SD)	ΔΔQTcF N	ΔΔQTcF Diff	ΔΔQTcF (SD)	ΔΔQTcF 90% CI
2	24	60	-5.84	(9.20)	60	0.31	(8.67)	60	-6.14	(13.94)	(-9.15,-3.14)
	24.5	60	-4.4	(9.12)	60	-0.8	(9.50)	60	-3.6	(13.81)	(-6.58,-0.62)
	25	60	-4.87	(9.96)	60	-0.62	(8.62)	60	-4.26	(13.54)	(-7.18,-1.34)
	25.5	60	-3.08	(7.91)	60	-1.82	(8.13)	60	-1.26	(12.11)	(-3.87, 1.35)
	26	60	-1.65	(8.66)	60	-0.98	(8.75)	60	-0.67	(12.36)	(-3.34, 1.99)
	26.5	60	-2.58	(9.30)	60	-0.84	(8.56)	60	-1.74	(12.30)	(-4.39, 0.91)
	27	60	-3.31	(8.90)	60	-1.05	(8.42)	60	-2.25	(12.19)	(-4.88, 0.38)
	28	60	-3.8	(9.51)	60	-1.26	(7.58)	60	-2.54	(11.49)	(-5.02,-0.06)
	30	60	-6.03	(9.43)	60	-3.56	(9.02)	60	-2.47	(11.75)	(-5.00, 0.07)
	33	60	-7.82	(9.36)	60	-2.97	(8.42)	60	-4.86	(11.22)	(-7.28,-2.44)
	36	60	-8.78	(9.77)	60	-3.91	(8.25)	60	-4.87	(12.62)	(-7.59,-2.15)

Note: ΔQTcF: mean change from baseline in QTcF interval
ΔΔQTcF: Placebo-adjusted, mean change from baseline in QTcF interval
CI: Confidence Interval, Diff: Test drug - Placebo

Table 7: Placebo adjusted, Mean QTcF Change from Baseline (used Pre-Dose as Baseline) Tapentadol IR 150 mg

Day	Time (hr)	ΔQTcF N	ΔQTcF Mean	ΔQTcF (SD)	Placebo N	Placebo Mean	Placebo (SD)	ΔΔQTcF N	ΔΔQTcF Diff	ΔΔQTcF (SD)	ΔΔQTcF 90% CI
2	24	61	-2.62	(9.88)	61	0.2	(8.64)	61	-2.81	(13.92)	(-5.79, 0.16)
	24.5	61	-2.68	(9.42)	61	-0.77	(9.42)	61	-1.92	(14.46)	(-5.01, 1.18)
	25	61	-2.36	(9.42)	61	-0.69	(8.56)	61	-1.66	(14.82)	(-4.83, 1.51)
	25.5	61	-2.01	(8.55)	61	-1.83	(8.06)	61	-0.18	(12.73)	(-2.90, 2.54)
	26	61	0	(8.98)	61	-1.05	(8.70)	61	1.05	(13.06)	(-1.75, 3.84)
	26.5	61	-1.56	(9.55)	61	-0.85	(8.49)	61	-0.7	(13.23)	(-3.53, 2.12)
	27	61	-0.87	(10.38)	61	-1.13	(8.37)	61	0.26	(14.08)	(-2.75, 3.27)
	28	61	-1.87	(10.05)	61	-1.24	(7.52)	61	-0.64	(12.10)	(-3.22, 1.95)
	30	61	-5.34	(8.42)	61	-3.57	(8.94)	61	-1.77	(13.08)	(-4.57, 1.03)
	33	61	-6.06	(8.07)	61	-3.15	(8.47)	61	-2.92	(11.83)	(-5.45,-0.39)
	36	61	-7.4	(8.98)	61	-3.88	(8.19)	61	-3.52	(12.46)	(-6.19,-0.86)

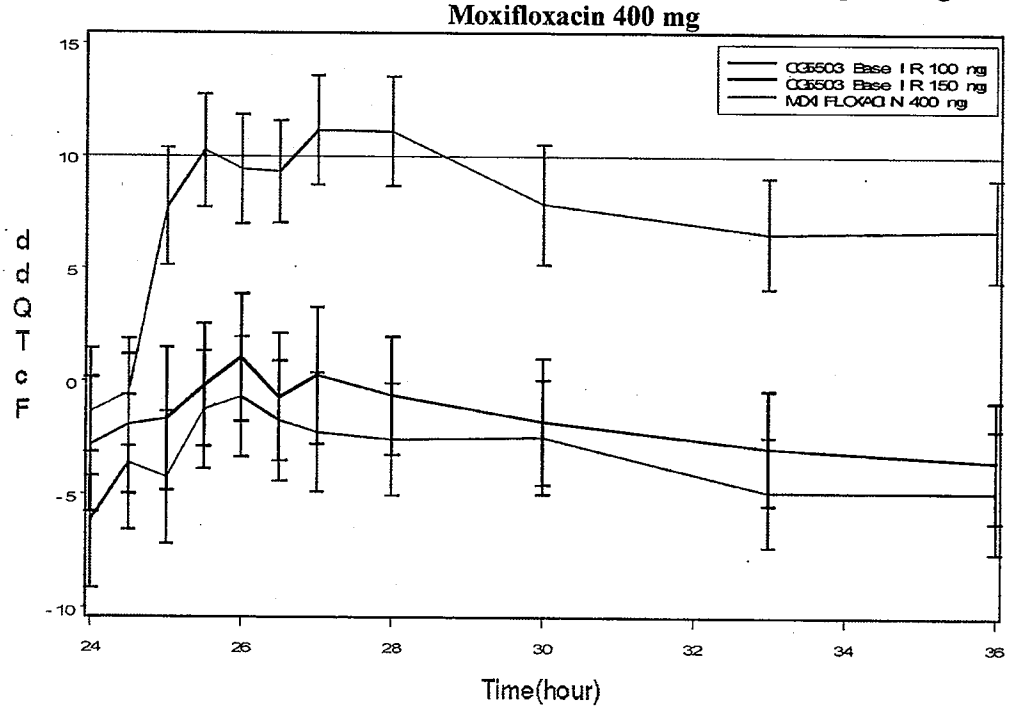
Note: ΔQTcF: mean change from baseline in QTcF interval
ΔΔQTcF: Placebo-adjusted, mean change from baseline in QTcF interval
CI: Confidence Interval, Diff: Test drug - Placebo

Table 8: Placebo adjusted, Mean QTcF Change from Baseline (Used Pre-Dose as Baseline) Moxifloxacin 400 mg

Day	Time (hr)	Moxifloxacin N	Moxifloxacin Mean	Moxifloxacin (SD)	Placebo N	Placebo Mean	Placebo (SD)	Diff N	Diff (M - P)	90% CI	Adjusted 90% CI*
2	24**	61	-1.08	(8.10)	61	0.3	(8.70)	61	-1.38	(-4.18, 1.43)	(-5.91, 3.15)
	24.5	61	-1.22	(7.91)	61	-0.7	(9.46)	61	-0.52	(-2.89, 1.85)	(-4.35, 3.31)
	25	61	7.16	(9.21)	61	-0.56	(8.68)	61	7.72	(5.12,10.32)	(3.52,11.92)
	25.5	61	8.48	(9.39)	61	-1.74	(8.14)	61	10.22	(7.71,12.72)	(6.17,14.26)
	26	61	8.54	(8.71)	61	-0.84	(8.94)	61	9.38	(6.96,11.80)	(5.46,13.29)
	26.5	61	8.58	(7.82)	61	-0.71	(8.62)	61	9.28	(7.02,11.55)	(5.62,12.94)
	27	61	10.1	(8.52)	61	-1.02	(8.45)	61	11.12	(8.69,13.55)	(7.19,15.04)
	28	61	10.05	(8.74)	61	-1.04	(7.78)	61	11.08	(8.66,13.50)	(7.17,14.99)
	30	61	4.33	(9.16)	61	-3.52	(8.99)	61	7.84	(5.19,10.49)	(3.56,12.12)
	33	61	3.36	(9.51)	61	-3.2	(8.44)	61	6.56	(4.12, 9.01)	(2.61,10.52)
	36	61	2.84	(9.20)	61	-3.86	(8.21)	61	6.7	(4.44, 8.95)	(3.05,10.35)

*CIs are adjusted with 11 post-baseline time points
Diff (M - P): Moxifloxacin-Placebo
** In this table, hour 24 indicates hour 0 on Day 2.

Figure 4: Time Course ΔΔQTcF for Tapentadol IR 100 mg, 150 mg and Moxifloxacin 400 mg



Categorical analysis was used to summarize QTc > 450, > 480 and > 500 ms, and changes from baseline > 30, 30 ms < QTc < 60 ms, and ≥ 60 ms as shown in Table 9.

Table 9: Frequency for QTcF and Absolute ΔQTcF

Category	Treatment	# of Subjects	total # Subjects	% of Subjects
450ms≤QTcF<480 ms	Placebo	0	63	0.0%
	Moxifloxacin	2	63	4.8%
	Tapentadol IR 100-mg	2	61	3.3%
	Tapentadol IR 150-mg	1	64	1.6%
30ms ≤ ΔQTcF < 60 ms	Placebo	2	63	3.2%
	Moxifloxacin	2	63	3.2%
	Tapentadol IR 100-mg	3	61	4.9%
	Tapentadol IR 150-mg	1	64	1.6%

PR Analysis

We performed the same statistical analyses of PR interval. The results are summarized in Table 10 and Table 11 for tapentadol IR 100 mg and 150 mg, respectively. The upper bounds of the two-sided 90% CIs for the mean differences between tapentadol IR and placebo in the pre-dose ΔPR change from baseline at each time point for tapentadol IR 100 mg and 150 mg are 1.96 ms and 4.57 ms, respectively. They occurred at 30 hours after dosing.

Table 10: Placebo adjusted, Mean PR Change from Baseline (used Pre-Dose as Baseline) Tapentadol IR 100 mg (Day 2)

Time	ΔPR			Placebo			ΔΔPR			
(hr)	N	Mean	(SD)	N	Mean	(SD)	N	Diff	(SD)	90% CI
24	60	-1.21	(8.45)	60	0.22	(7.50)	60	-1.42	(10.50)	(-3.69, 0.84)
24.5	60	-1.9	(6.18)	60	0.64	(7.83)	60	-2.54	(9.67)	(-4.62,-0.45)
25	60	-1.08	(7.48)	60	0.74	(8.17)	60	-1.82	(11.31)	(-4.26, 0.62)
25.5	60	-2.33	(7.94)	60	0.12	(8.76)	60	-2.45	(12.35)	(-5.11, 0.22)
26	60	-3.08	(7.36)	60	-0.87	(8.68)	60	-2.21	(11.91)	(-4.78, 0.36)
26.5	60	-3.02	(9.08)	60	-1.21	(8.55)	60	-1.81	(11.76)	(-4.35, 0.73)
27	60	-2.2	(7.73)	60	0.06	(9.15)	60	-2.27	(12.37)	(-4.94, 0.40)
28	60	-2.26	(7.71)	60	-0.91	(9.66)	60	-1.35	(11.72)	(-3.88, 1.17)
30	60	-7.11	(9.90)	60	-6.3	(10.78)	60	-0.81	(12.82)	(-3.57, 1.96)
33	60	-4.7	(8.67)	60	-3.5	(8.56)	60	-1.19	(9.13)	(-3.16, 0.78)
36	60	-5.53	(9.80)	60	-3	(11.34)	60	-2.53	(11.16)	(-4.94,-0.13)

Note: ΔPR: mean change from baseline in QTcF interval
ΔΔPR: Placebo-adjusted, mean change from baseline in PR interval
CI: Confidence Interval, Diff: Test drug - Placebo

Table 11: Placebo adjusted, Mean PR Change from Baseline (used Pre-Dose as Baseline) Tapentadol IR 150 mg (Day 2)

Time	ΔPR			Placebo			ΔΔPR			
(hr)	N	Mean	(SD)	N	Mean	(SD)	N	Diff	(SD)	90% CI
24	61	-1.06	(8.46)	61	0.12	(7.47)	61	-1.19	(10.73)	(-3.48, 1.11)
24.5	61	-0.86	(8.38)	61	0.72	(7.80)	61	-1.59	(11.69)	(-4.09, 0.92)
25	61	-0.24	(9.24)	61	0.73	(8.11)	61	-0.97	(11.70)	(-3.47, 1.53)
25.5	61	-1.19	(7.26)	61	0.11	(8.68)	61	-1.3	(10.81)	(-3.62, 1.01)
26	61	-2.33	(8.59)	61	-0.8	(8.62)	61	-1.53	(11.57)	(-4.00, 0.95)
26.5	61	-1.6	(8.67)	61	-1.27	(8.50)	61	-0.33	(11.25)	(-2.73, 2.08)
27	61	-1.78	(8.92)	61	0.02	(9.08)	61	-1.79	(12.10)	(-4.38, 0.79)
28	61	-1.69	(7.55)	61	-0.99	(9.61)	61	-0.69	(10.53)	(-2.95, 1.56)
30	61	-4.1	(7.44)	61	-6.47	(10.77)	61	2.37	(10.30)	(0.17, 4.57)
33	61	-3.5	(7.83)	61	-3.71	(8.65)	61	0.21	(10.07)	(-1.94, 2.36)
36	61	-5.47	(9.46)	61	-3.09	(11.26)	61	-2.38	(12.60)	(-5.08, 0.31)

Note: ΔPR: mean change from baseline in QTcF interval
ΔΔPR: Placebo-adjusted, mean change from baseline in PR interval
CI: Confidence Interval, Diff: Test drug - Placebo

QRS Analyses

We performed the same statistical analyses of QRS correction. The results are summarized in Table 12 and Table 13 for tapentadol IR 100 mg and 150 mg, respectively. The upper bound of the two-sided 90% CIs for the mean differences between tapentadol IR and placebo in the pre-dose ΔQRS change from baseline at each time point for tapentadol IR 100 mg is 2.39 ms at 36 hours and tapentadol IR 150 mg is 4.23 ms at 26 hours after dosing,

Table 12: Placebo adjusted, Mean QRS Change from Baseline (used Pre-Dose as Baseline) Tapentadol IR 100 mg

Time	ΔQRS			Placebo			ΔΔQRS			
(hr)	N	Mean	(SD)	N	Mean	(SD)	N	Diff	(SD)	90% CI
24	60	-1.36	(5.34)	60	-0.76	(4.78)	60	-0.6	(6.80)	(-2.06, 0.87)
24.5	60	-0.1	(5.21)	60	-0.03	(5.40)	60	-0.06	(7.42)	(-1.66, 1.54)
25	60	-0.33	(5.21)	60	0.11	(6.12)	60	-0.44	(7.95)	(-2.16, 1.27)
25.5	60	-0.66	(5.79)	60	-0.86	(5.42)	60	0.2	(7.12)	(-1.34, 1.73)
26	60	-0.76	(5.17)	60	-1.21	(6.12)	60	0.46	(8.15)	(-1.30, 2.21)
26.5	60	-0.86	(5.62)	60	-1.22	(5.93)	60	0.36	(7.02)	(-1.16, 1.87)
27	60	-0.45	(5.63)	60	-1.05	(5.22)	60	0.6	(6.83)	(-0.87, 2.07)
28	60	-1.64	(5.69)	60	-1.26	(5.32)	60	-0.37	(7.18)	(-1.92, 1.17)
30	60	0.15	(6.26)	60	-0.54	(5.08)	60	0.69	(7.30)	(-0.89, 2.26)
33	60	-1.44	(6.16)	60	-1.26	(4.44)	60	-0.18	(6.90)	(-1.67, 1.31)
36	60	-0.38	(6.33)	60	-1.24	(4.64)	60	0.86	(7.12)	(-0.68, 2.39)

Note: ΔQRS: mean change from baseline in QTcF interval
ΔΔQRS: Placebo-adjusted, mean change from baseline in QRS interval
CI: Confidence Interval, Diff: Test drug - Placebo

Table 13: Placebo adjusted, Mean QRS Change from Baseline (used Pre-Dose as Baseline) Tapentadol IR 150 mg

Time	ΔQRS			Placebo			ΔΔQRS			
(hr)	N	Mean	(SD)	N	Mean	(SD)	N	Diff	(SD)	90% CI
24	61	0.5	(5.34)	61	-0.79	(4.75)	61	1.29	(7.17)	(-0.25, 2.82)
24.5	61	0.7	(5.32)	61	-0.06	(5.36)	61	0.76	(7.68)	(-0.89, 2.40)
25	61	0.72	(5.03)	61	0.13	(6.07)	61	0.59	(7.93)	(-1.10, 2.29)
25.5	61	0.73	(4.77)	61	-0.85	(5.37)	61	1.58	(7.82)	(-0.09, 3.25)
26	61	1.13	(5.72)	61	-1.25	(6.07)	61	2.38	(8.64)	(0.54, 4.23)
26.5	61	-0.3	(5.83)	61	-1.21	(5.88)	61	0.91	(9.24)	(-1.06, 2.89)
27	61	0.18	(5.85)	61	-1.03	(5.18)	61	1.21	(7.55)	(-0.40, 2.83)
28	61	0.48	(5.41)	61	-1.21	(5.29)	61	1.69	(7.96)	(-0.01, 3.39)
30	61	0.6	(6.24)	61	-0.52	(5.04)	61	1.12	(6.81)	(-0.34, 2.58)
33	61	-0.52	(5.85)	61	-1.28	(4.41)	61	0.76	(7.24)	(-0.79, 2.30)
36	61	-0.67	(6.02)	61	-1.21	(4.60)	61	0.54	(7.16)	(-0.99, 2.08)

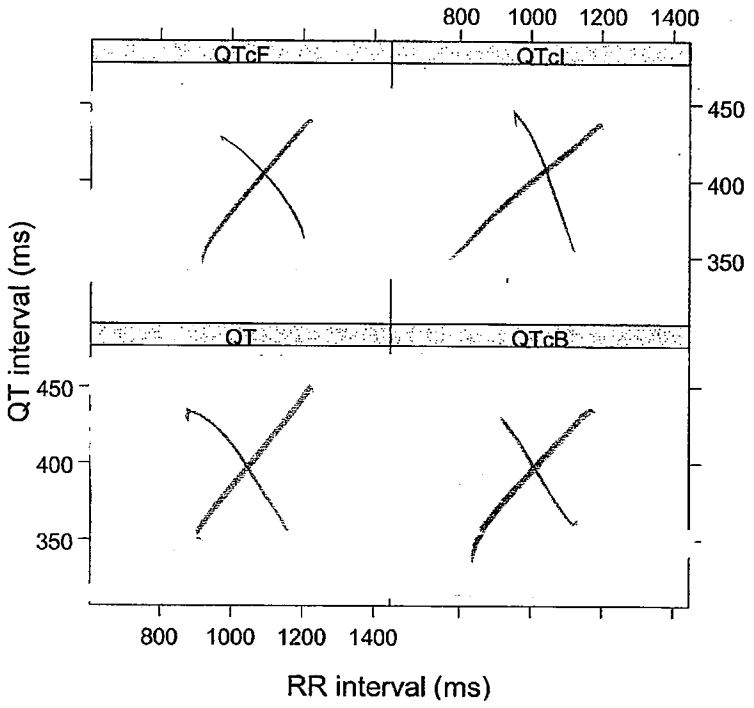
Note: ΔQRS: mean change from baseline in QTcF interval
ΔΔQRS: Placebo-adjusted, mean change from baseline in QRS interval
CI: Confidence Interval, Diff: Test drug - Placebo

5.2 CLINICAL PHARMACOLOGY ASSESSMENTS

5.2.1 QT Corrections

The observed QT-RR interval relationship is presented in Figure 5 together with the Bazett's (QTcB), Fridericia (QTcF), and individual correction (QTcI).

Figure 5: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line).



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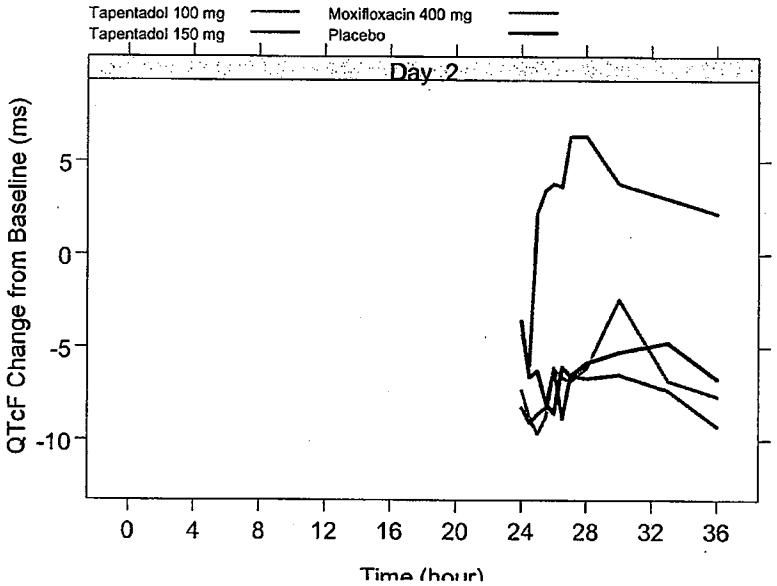
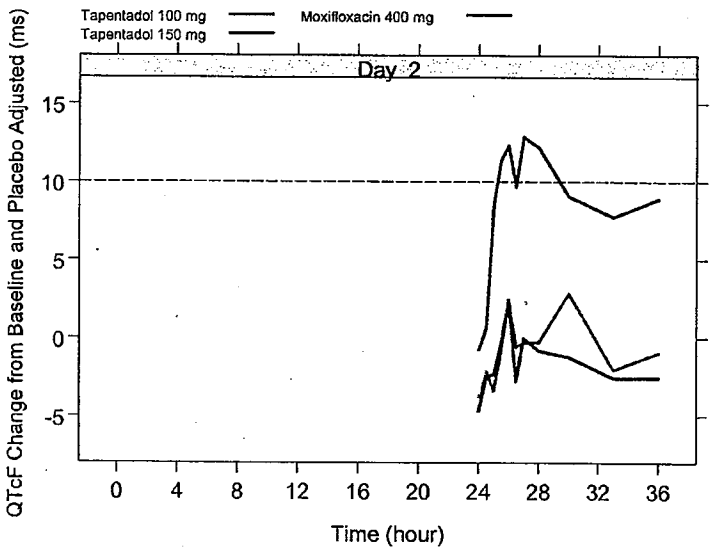
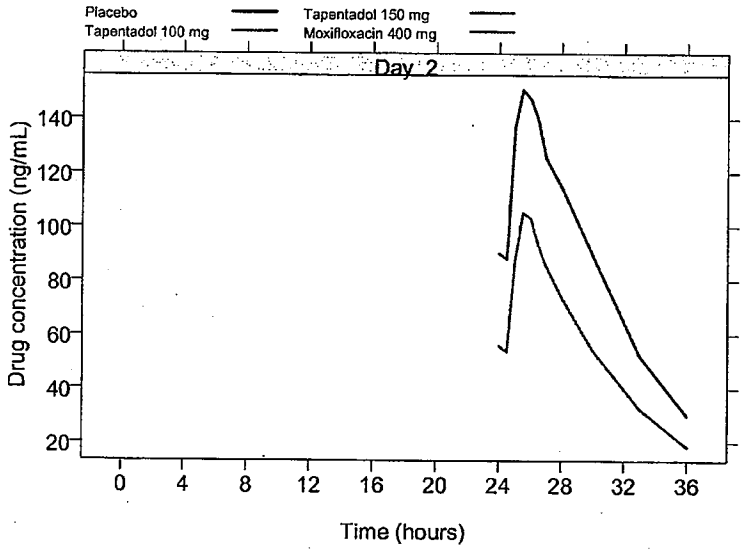
5.2.2 QTcF and Tapentadol Concentration Time Profiles

Figure 6: Mean Δ QTcF (change from time-matched baseline) (top), ΔΔ QTcF (placebo-adjusted change from baseline) (middle), Drug concentration (bottom) time profiles for Tapentadol 100 mg (blue line), Tapentadol 150 mg (red line), moxifloxacin (green line), and placebo (black line).



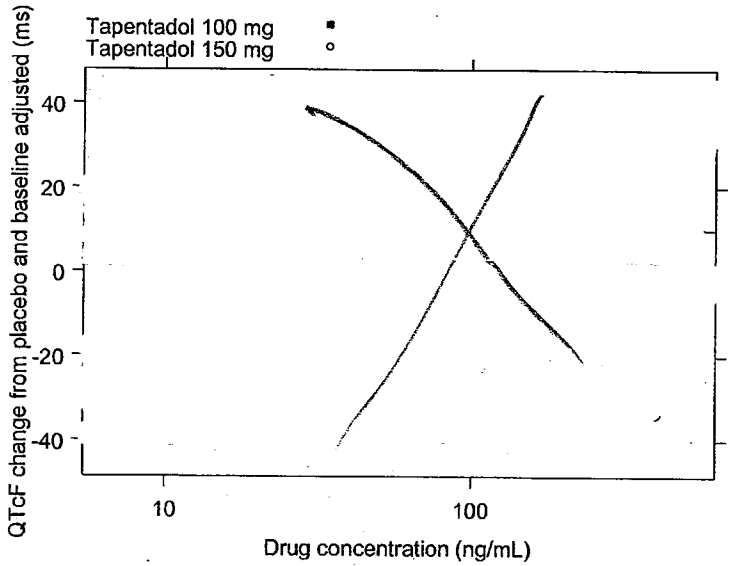




5.2.3 Drug Concentration-QTcF Analysis

The relationship between ΔΔQTcF and tapentadol concentrations is visualized in Figure 7 with no evident exposure-response relationship.

Figure 7 : ΔΔ QTcF vs. Tapentadol concentration.



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5.3 CLINICAL ASSESSMENTS

5.3.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e. sudden death, syncope, seizures, significant ventricular tachycardia) occurred in this study after administration of tapentadol.

In addition to the QTc interval, there were no clinically significant effects on the PR and QRS intervals (see Tables 10, 11 12 and 13 in section 5.1).

5.3.2 ECG assessments

Waveforms submitted to the ECG warehouse were reviewed. Lead II was used as the primary lead. More than 99% of ECGs were annotated in primary lead. According to ECG warehouse statistics less than 0.1% of ECGs had any significant QT bias.

T-wave offset high frequency noise and poor T-wave signal were noted in 20% and 5% of ECGs respectively. However, on review of a subset of the ECGs there were no changes in T wave morphology (notching, inversion, etc.). Also, given the fact that less than 0.1% of ECGs had any significant QT or T-wave offset bias, the sponsor's conclusion that tapentadol did not cause any significant changes in T- or U-wave morphology appears acceptable.

Overall ECG acquisition and interpretation in this study was acceptable.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	The recommended oral starting dose is 50 mg, 75 mg, or 100 mg immediate-release tablet (IR) every 4 to 6 hours depending upon the initial pain intensity. On the first day of dosing, the second dose may be administered as soon as 1 hour after the first dose, if adequate pain relief is not attained with the first dose. Subsequent dosing is 50 mg, 75 mg, or 100 mg every 4 to 6 hours and should be adjusted to maintain adequate analgesia with acceptable tolerability. (2.5 Clinical Overview, Section 6.1 page 74)	
Maximum tolerated dose	Although study HP5503/13 was set up to define the highest tolerable dose of tapentadol IR in healthy subjects, the highest tolerable dose was not reached. The sponsor temporarily stopped the study before continuing with the next dose level (232 mg every 6 hours), because the FDA did not feel that dosing in nonclinical toxicology studies was sufficient to support the safety of continued dose escalation in the clinical study until the Agency had the opportunity to review the pharmacokinetic data from completed studies with CG5503 (tapentadol HCl). The requested information was submitted to the FDA, and the study remained suspended. Eventually, it was decided to terminate the study, as too much time had elapsed that prevented reconstitution of the cohorts (which would have required major protocol amendments) and due to the desire not to restart titration of dose from the initial dose level in new cohorts. Moreover, with the highest administered dose (203 mg every 6 hours), it was felt that sufficient data was available to continue the development of CG5503. In study HP5503/14, single oral doses up to 200 mg tapentadol IR were administered and these were well tolerated. In animal studies, NOAEL values vary by study type, species and duration. NOEL/NOAEL values for preclinical toxicology studies are available in 2.6.7.1 (Toxicology Overview).	
Principal adverse events	Among 1880 tapentadol-IR treated subjects in the Phase 2/3 multiple-dose, double-blind, completed studies, the most commonly reported TEAEs were nausea, dizziness, vomiting, somnolence, headache, constipation, and pruritus. (2.5 Clinical Overview, Section 6, page 73)	
Maximum dose tested	Single Dose	200 mg tapentadol (HP5503/14)
	Multiple Dose	175 mg tapentadol every 6 hours (HP5503/13)
Exposures Achieved at Maximum Tested Dose	Single Dose	C_{max} = 166 ± 58.5 ng/mL AUC_∞ = 969 ± 304 ng.h/mL (2.7.2 Summary of ClinPharm Studies, Section 2.5.5, page 57)
	Multiple Dose	$C_{max,ss}$ = 162 ± 42.2 ng/mL AUC_τ = 737 ± 166 ng.h/mL (2.7.1 Summary of BioPharmaceutical Studies, Section 2.2.3, page 25)
Range of linear PK	Dose proportionality of the PK of tapentadol was investigated in a cross-study comparison across studies and was statistically confirmed for doses between 50 mg and 150 mg, inclusive, for C_{max} and for doses between 50 mg and 129 mg for AUC_∞, inclusive. The investigated dose range fully covers the therapeutic	

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	dose range of 50 mg to 100 mg. (2.5 Clinical Overview, Section 2.3, page 12)	
Accumulation at steady state	The mean accumulation ratio observed in study HP5503/13 ranged from 1.44 ± 0.41 (28%) at the lowest dose (75 mg) to 1.70 ± 0.30 (18%) at the highest dose (175 mg). This is in accordance with the predicted accumulation ratio of 1.6 ($t_{1/2}$: 4.3h and τ: 6h) for a Q6h dosing scheme. (2.7.2 Summary of Clinical Pharmacology Studies, Section 3.5, Table 34, page 67)	
Metabolites	After oral administration approximately 70% of the dose is excreted in urine in the conjugated form (55% as tapentadol-O-glucuronide and 15% as tapentadol-O-sulfate). Uridine diphosphate glucuronyl transferases (UGT) are the primary isoenzymes involved in the glucuronidation (mainly UGT1A6, UGT1A9 and UGT2B7 isoforms). Only 3% of the orally administered drug was excreted in urine as unchanged drug. Tapentadol is additionally metabolized via phase 1 oxidative pathways to N-desmethyl tapentadol (13%) primarily by CYP2C9, and to hydroxy tapentadol (2%) primarily by CYP2D6; these compounds are further metabolized by conjugation. Therefore, drug metabolism mediated by cytochrome P450 system is of minor importance compared to phase 2 metabolism (conjugation). Tapentadol has no clinically relevant active metabolites. Tapentadol and its metabolites are excreted almost exclusively (99%) via the kidneys.. (2.5 Clinical Overview, Section 3.1.3, page 13)	
Absorption	Absolute/Relative Bioavailability	F, % (95% CI) = 32.0 (29.4-34.8) (fasted) (2.7.1 Summary of BioPharmaceutical Studies, Section 2.1.1 , page 20, Table 5)
	t_{max}	tapentadol: 1.25 h (0.50-6.27)-cross study (2.7.2 Summary of Clinical Pharmacology Studies, Section 3.1.1 , page 62, Table 32) tapentadol-O-glucuronide: 1.50 h (1.00-4.00) (2.7.2 Summary of Clinical Pharmacology Studies, Section 2, various studies)
Distribution	V_{dF} or V_d	V_{ss} = 540 ± 98 L (2.7.2 Summary of Clinical Pharmacology Studies, Section 3.2, page 64)
	% bound	Protein binding: 20% (2.7.2 Summary of Clinical Pharmacology Studies, Section 3.2, page 64)
Elimination	Route	phase-2 conjugation: glucuronidation and sulphation to tapentadol-conjugates (96%) followed by renal elimination; renal clearance as parent (3%) (2.7.2 Summary of Clinical Pharmacology Studies, Section, 3.3.2, page 65)
	Terminal t½	The mean cross study t½ for tapentadol was 4.3 ± 0.8 h (CV 16%) (2.7.2 Summary of Clinical Pharmacology Studies, Section 3.4, page 66) The mean cross study t½ for tapentadol-O-glucuronide was 3.9 ± 0.5 h (CV 13%) (2.7.2 Summary of Clinical Pharmacology Studies, Section 3.6.2, page 74)

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	CL/F or CL	CL/F was calculated based on compiled study data at 4470 ± 1519 mL/min (CV 34%) (2.7.2 Summary of Clinical Pharmacology Studies, Section 3.4, page 65)
Intrinsic Factors	Age	The AUC of tapentadol was similar in elderly subjects (>65 years of age) compared to young adults (18 to 45 years of age), with a 16% lower mean C_{max} observed in the elderly subject group compared to young adult subjects; this was investigated in a Phase I clinical pharmacology study. This observation was confirmed by an analysis of pooled Phase I data, which showed only a negligible difference between the C_{max} and AUC values for elderly and younger subjects. (2.5 Clinical Overview, Section 3.1.4.1.1, page 13)
	Sex	The estimated mean cross study C_{max} and total systemic exposure (AUC) of tapentadol were approximately 20% higher in women than in men. After bodyweight correction, the estimated mean CL/F was similar in both sexes, indicating no relevant difference in the PK of tapentadol between men and women. (2.7.2 Summary of Clinical Pharmacology Studies, Section 3.6.3, page 76)
	Race	No clinical studies were conducted for the sole reason to evaluate the effects of race on the PK of tapentadol. In healthy Japanese men, the PK of tapentadol is similar to that observed in Phase I studies in non-Japanese subjects. The population PK model predicted clearance of tapentadol in Black subjects, Hispanic-Latinos, and other combined non-White racial groups, was approximately 17%, 11%, and 15% lower, respectively as compared to that in White subjects. The race effect is of no clinical relevance. (2.7.2 Summary of Clinical Pharmacology Studies, Section 3.6.6, page 79)

	Hepatic & Renal Impairment	Effect of Hepatic Impairment (cross study comparison): *mild impairment*: C_{max} is similar and AUC_∞ is 1.4-fold higher compared to normal subjects. *moderate impairment*: C_{max} is 1.8-fold higher and AUC_∞ is 3.5-fold higher compared to normal subjects. (2.7.2 Summary of Clinical Pharmacology Studies, Section 3.6.1, page 68) Effect of Renal Impairment (cross study comparison): C_{max} and AUC_∞ were similar in all groups. (2.7.2 Summary of Clinical Pharmacology Studies, Section 3.6.2, page 72)
Extrinsic Factors	Drug interactions	Metoclopramide: C_{max} and AUCs were comparable Omeprazole: C_{max} and AUCs were comparable Probenecid: C_{max} was 30% higher and AUC_∞ was 57% higher in the presence of probenecid Naproxen: C_{max} was comparable and AUC_∞ was 17% higher in the presence of naproxen Acetylsalicylic Acid C_{max} and AUCs were comparable Acetaminophen: C_{max} and AUCs were comparable (2.7.2 Summary of Clinical Pharmacology Studies, Section 2.4, page 42)
	Food Effects	high-fat, high-calorie breakfast (pivotal study): C_{max} was 16% higher and AUC_∞ was 25% higher in the presence of food continental breakfast (exploratory study): C_{max} was 25% higher and AUC_∞ was 32% higher in the presence of food (2.7.1 Summary of BioPharmaceutical Studies, Section 3.3 , page 33)
Expected High Clinical Exposure Scenario	• Please refer to the separate document entitled "Simulation of Expected High Clinical Exposure Scenario".	

6.2 TABLE OF STUDY ASSESSMENTS

Table 3: Time and Events Schedule
(Study R331333-PAI-1018; HP5503/25)

Procedure and Evaluations	Screening Phase	Treatment Periods 1 through 4[a] Baseline Assessments		Double-Blind Treatment Phase			End-of-Study/Early Withdrawal[b]
Day	-21 to -3	-2	-1	1	2	3	
Screening/Administrative Procedures[c]							
Informed consent	X						
Inclusion/exclusion criteria	X	X					
Medical history, including smoking habits	X	X					
Weight, height, calculated BMI	X						X[d]
Electroencephalogram (EEG)	X						
Prestudy therapy	X	X					
Randomization			X				
Confinement to study center[e]		X	X	X	X	X	X
Study Drug Administration							
Study drug administration[f]				X	X		
Pharmacokinetics							
Pharmacokinetic blood sample[g]				X	X		
Safety							
Physical examination	X						X
Vital signs[h]	X	X	X	X	X	X	X
Pulse oximetry[h]				X	X		
12-lead ECG[i]	X		X	X	X		X
Clinical laboratory tests	X		X[j]				X
Serology tests[k, l]	X						
Urine drug screen[l]	X	X					
Alcohol breath test[l]	X	X					
Pregnancy test[l, m]	X		X				X
Ongoing subject review							
Concomitant therapy[n]	←----------						----------→
Adverse event monitoring[o]	←----------						----------→

(continued)

Table 3: Time and Events Schedule (Continued)
(Study R331333-PAI-1018; HP5503/25)

[a] Each treatment period begain in the evening of Day-2 with confinement to the study center and start of the fasting period. On Day –1, baseline ECG assessments were followed by the double-blind treatment phase (Days 1 to 3). Treatment periods were separated by a washout period of at least 7 but no more than 14 days.

[b] End-of-study assessments were performed on Day 3 of Period 4, or at the time of early withdrawal, for all subjects who received study drug.

[c] Results of the screening evaluations had to be available to the investigator for review before the first dose of study drug is administered on Day 1.

[d] Body weight only was measured at the end of the study or at early withdrawal.

[e] In each period, subjects was admitted to the study center on the evening of Day –2 at least 36 hours before study drug administration was scheduled to occur and remained confined to the study center until the morning of Day 3.

[f] Subjects fasted for at least 10 hours overnight. The first study drug administration in each period occurred at approximately 8:00 am in the morning of Day 1. Subjects continued to fast until lunch (4 hours after study drug administration). Noncarbonated water was allowed during this time, except from 2 hours before until 2 hours after study drug administration. Study drug was administered every 6 hours (total of 5 doses in each period), each with 240 mL of noncarbonated water. Study drug had to be swallowed whole and could not be chewed, divided, or crushed.

[g] Pharmacokinetic blood samples (4 mL each) were collected on Day 1 at 0 (predose), 1.5, 6, and 12 hours, and on Day 2 at 18, 24 (predose), 24.5, 25, 25.5, 26, 26.5, 27, 28, 30, 33, and 36 hours after the first administration of study drug in each period.

the first administration of study drug in each period.

[h] Vital signs were measured after a subject had been in the supine position for 5 minutes and before study drug administration (where applicable). If ECGs, vital signs and PK blood samples were scheduled at the same time, the ECG was to be done before vital signs, and vital signs before collection of the PK blood sample and timed so that the ECG was collected at the specified time. Pulse oximetry was to be continuously monitored from just before the first dosing on Day 1 until approximately 36 hours thereafter.

[i] Standard 12-lead triplicate ECGs were to be performed on Day –1/ Day 1 (baseline ECG assessments) and on Day 2 of each treatment period at protocol specified times after subjects had been in a supine position, and had rested for at least 20 minutes. In addition, safety 12-lead ECGs were to be done at screening and at the end of study or at early withdrawal.

[j] Blood and urine samples for clinical laboratory tests (hematology, chemistry, serum pregnancy test, urinalysis) were to be collected on Day -1 of each treatment period.

[k] Serology consisted of testing for human immune-deficiency virus 1 and 2 (HIV 1 and 2), Hepatitis B antigens, and Hepatitis C antibodies.

[l] If the results were positive, the subject was deemed ineligible for study entry.

[m] Serum pregnancy tests were to be performed for all female subjects at screening, on Day -1 of each treatment period, and at the end of the study or at early withdrawal.

[n] Concomitant therapy was monitored throughout the study beginning from the time of the signing of the informed consent before the first study-related procedure until the end of the study including the washout periods.

[o] Adverse events were monitored throughout the study beginning from the time of the signing of the informed consent before the first study-related procedure until the end of the study including the washout periods.

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