CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-123

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA: 21-123

Drug Class: Synthetic, Centrally-acting Analgesic

Drug Name: Ultracet™ tablets (Tramadol hydrochloride/acetaminophen)
[37.5 mg Tramadol and 325 mg acetaminophen]

Indication: [redacted] acute [redacted] pain

Sponsor: RW Johnson Pharmaceutical Research Institute
920 Route 202 South, Raritan, NJ 08869 (908) 704-4033
Contact Person: Sandra Cottrell, Regulatory Affairs

Clinical Studies: 4 Selected Controlled, Domestic (Volumes 1 through 177)
TRAMAP-ANAG-010 and -013 (Single Dose, Oral Surgery);
-005 (Single Dose, Orthopedic Surgery);
-006 (Multiple Dose, Chronic Pain of Benign Origin)

Statistical Reviewer: Lillian Patrician, MS, MBA

Submitted: 08/31/99
Review Date: 04/07/00
PDUFA Date: 07/02/00

I. Background

This submission is an application for the new combination product, 37.5 mg tramadol hydrochloride/325 mg acetaminophen tablets, also designated as (1) tramadol hydrochloride/acetaminophen; (2) tramadol/acetaminophen; (3) Tramadol/APAP; and (4) TRAM/APAP.

This statistical reviewer was assigned to examine a select 4 Phase 3 studies from this clinical program. Three (Studies -005, -010, and -013) were conducted to "demonstrate the efficacy of the fixed-dose Tramadol/APAP combination in providing effective relief of [redacted] pain, and to show that each component of the combination contributes to its analgesic efficacy". [redacted]

The proposed dosage and administration schedule is 1 to 2 tablets every 4 to 6 hours as needed for pain relief up to a maximum of 8 tablets per day. [redacted]

The sponsor reports that tramadol hydrochloride is a centrally acting synthetic analgesic originally developed by [redacted] and through licensing agreement, is developed in the U.S. by R.W. Johnson Pharmaceutical Research Institute (RWJPRI). In 1995, it was approved in the U.S. for the management of moderate to moderately severe pain.

Tramadol's pharmacokinetic and pharmacodynamic profile shows peak activity in 2 to 3 hours with an elimination half-life and duration of analgesia of 6 hours. That of acetaminophen indicates a rapid onset of action (0.5 hours) and half-life of 2 hours.

The sponsor expected that combining the 2 products would provide for the rapid onset of action of APAP and the prolonged effect of Tramadol in both short- and long-term pain, with enhanced analgesia and improved side effect profile compared to Tramadol alone. The sponsor expanded, "the clinical development program for Tramadol to include investigations of its effects when administered as a fixed-dose combination. These have been useful in pain management because they provide analgesia with a reduction in the required dose of each active component, and presumably an improved safety profile". *[Vol 49 of 380 - page 57]*

II. Phase 3 Study TRAMAP-ANAG-010 - Single Dose Oral Surgery

1. Study Design: Efficacy Study TRAMAP-ANAG-010 was a Phase 3, randomized, double-blind, active-controlled, single center, parallel-group, factorial design study with a placebo control conducted to demonstrate the safety and 8-hour analgesic superiority of Tramadol/APAP to each component alone and to Placebo in patients experiencing moderate to severe pain from an oral

surgical procedure. Ibuprofen 400 mg was included as an active reference control to establish sensitivity of the clinical endpoints in this pain model. The Placebo control was used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active treatment.

The study was conducted from December, 1997 to August, 1998 at one investigational site, Kiersch in Tucson, AZ with subinvestigators at Sierra Vista, AZ. The protocol date is October 28, 1997 with 3 amendments.

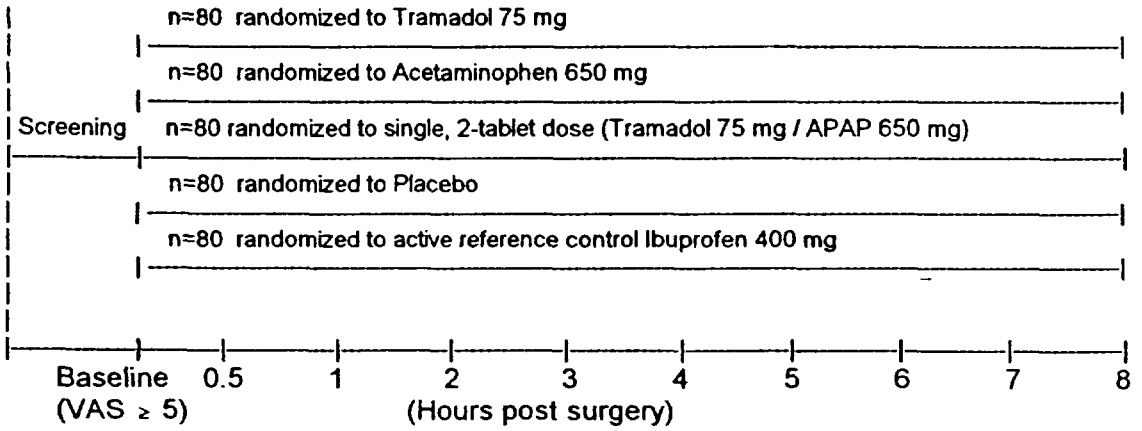
The first amendment, dated Dec 19, 1997, was added after 18 patients entered trial, to redefine allowed surgical procedures to include only those involving extraction of 2 or more impacted third molars requiring bone removal rather than at least 2 impacted mandibular third molars. In addition, this amendment specified that if only 2 molars were extracted, they must have been ipsilateral and required bone removal. Other revisions to the protocol made by this amendment included the specification of a VAS to measure baseline pain, modification of the guidelines for use of ice packs after dosing, and revision to the list of excluded concomitant medications.

The second amendment, dated June 19, 1998, was added after 273 patients were enrolled and provided further clarification of the number of molar extractions which required bone removal.

According to the Appendix 1.1 of Item 8 / Vol 56 / Page 124, the third amendment is dated July 22, 1999, however, the sponsor's study report states that only 2 amendments were made. No documentation on the content of amendment 3 could be located.

A total of 400 patients were to be randomized by a 1:1:1:1:1 schema of 80 per treatment group, balanced by permuted blocks, and stratified on baseline pain severity (moderate pain assigned to lowest patient numbers and severe pain to highest patient numbers). Sample size was based on 80% power at alpha level of 0.05 to detect a between-group difference in TOTPAR of about 4 units, assuming a standard deviation of 9 units, as determined in the pilot dental studies.

TRAMAP-ANAG-010 STUDY SCHEDULE



Screening Phase: To qualify for study entry, patients were required to show evidence of good physical health, minimum age of 16 to 18 years, and moderate to severe pain following an oral surgical procedure that involved extraction of 2 or more impacted molars, 2 of which required bone removal.

Double-blind Phase: At the time patients reported a moderate or severe pain of at least 5 on the VAS scale (as a result of the oral surgery procedure), they were randomized in equal numbers to one of 5 treatment groups to receive a single dose of medication consisting of 2 tablets and 2 capsules:

Tramadol/APAP	[2 tablets TRAM 37.5/APAP 325 + 2 capsules Placebo]
Tramadol 75 mg	[2 tablets Tramadol 37.5 mg + 2 capsules Placebo]
Acetaminophen 650 mg	[2 tablets Placebo + 2 capsules APAP 325 mg]
Ibuprofen 400 mg	[2 tablets Placebo + 2 capsules Ibuprofen 200 mg]
Placebo	[2 tablets Placebo + 2 capsules Placebo]

Baseline pain scores were recorded and followed by the patients' pain and relief scores recorded at 30 minutes, 1, 2, 3, 4, 5, 6, 7, and 8 hours after receiving the dose of study medication. Current pain was scored on a 4-point scale (0=none through 3=severe). Pain relief was scored on a 5-point scale (0=none through 4=complete).

If needed, supplemental analgesic medication was allowed during the 8-hour assessment period. A final assessment of pain and relief was recorded before supplemental medication was taken. The final overall assessment of study medication (5-point scale of 1=poor through 5=excellent) was recorded at the end of the 8-hour period or at the time supplemental analgesia was needed.

Primary Efficacy Analysis: The objective of the efficacy analysis was to demonstrate the 8-hour analgesic superiority of TRAM/APAP to either of its components alone and to Placebo. The sponsor reports that the trial was designed to "allow adequate characterization of the onset, peak, and duration of analgesic activity for the combination product".

The sponsor planned analysis of variance to compare treatment differences for change in pain from that at baseline, and pain relief scores at each time point. Missing values were to be replaced according to the last-observation-carried-forward. The primary analysis would be based on the Intent-to-treat population of all patients randomized.

Primary Efficacy Measures: The protocol identifies efficacy evaluations in the Statistical Methods section of Planned Analysis as (1) pain intensity; (2) pain relief at each observation point (PR) compared to baseline; (3) overall assessment of therapy; (4) time to remedication; (5) rate of remedication; (6) time to onset of perceptible pain relief; (7) time to onset of meaningful pain relief; (8) pain intensity difference from baseline (PID); (9) sum of pain intensity differences (SPID); and (10) total pain relief (TOTPAR).

These efficacy measures are scales of patient self-reporting ratings for pain relief and pain intensity differences from pre-treatment baseline levels for times 0.5, 1, 2, 3, 4, 5, 6, 7, and 8 hours after administration of trial medication. Patients also reported the time at which supplemental analgesic medication was taken. Patients used the double-stopwatch procedure to record the time to onset of meaningful pain relief and onset of perceptible pain relief. At the end

of the 8-hour observation period, or after taking rescue medication, patients made an overall assessment of study therapy. The summary variables of total pain relief (TOTPAR) and sum of pain intensity differences (SPID) were derived from scores summed over the 8 hours.

Time to onset of pain relief for each treatment group was obtained by linear interpolation based on the group's mean pain relief + pain intensity difference (PRID) to estimate the time when that group would have first reached a PRID score of 1. The protocol states, "the equation for calculating time of onset of pain relief is: onset of pain relief in minutes = (30 minutes) / (mean PRID at 30 minutes)". Duration of relief was defined as the earliest time when half of the patients in a treatment group had remedicated. Time to onset of perceptible pain relief and time to onset of meaningful pain relief were also measured via the stopwatch technique. The time to remedication with supplemental analgesic medication was also recorded.

2. Patient Disposition: A total of 400 patients were enrolled in 1 center (80 randomized to each treatment group); 151 were male and 249 were female; patients ranged in age from 16 to 46 years (mean±sd, 21.5±4.91).

STUDY TRAMAP-ANAG-010 *Table A-010*
SPONSOR'S SUMMARY OF PATIENT DISPOSITION

Sponsor's Results	Total	Placebo (N=79)	Ibuprofen 400 mg (N=80)	Tramadol 75 mg (N=78)	APAP 650 mg (N=80)	TRAM/APAP 75mg/650mg (N=80)
# ITT - All Randomized	400	80	80	80	80	80
# Completions	287	44	60	50	67	66
- No Remedication (%)	60 (21)	3 (07)	19 (32)	9 (18)	8 (12)	21 (32)
- Required Remed (%)	227 (79)	41 (93)	41 (68)	41 (82)	59 (88)	45 (68)
# Withdrew	113	36	20	30	13	14
- Due to AE	7	2	2	3	0	0
- Other Reason	2	0	0	1	0	1
- & Req Remed	104	34	18	26	13	13
Sex						
- Females (%)	249 (62)	54 (67)	48 (60)	55 (69)	50 (62)	42 (52)
- Males (%)	151 (38)	26 (33)	32 (40)	25 (31)	30 (38)	38 (48)
Race						
- Caucasian (%)	304 (76)	60	63	63	57	61
- Other (%)	96 (24)	20	17	17	23	19
Age Range in Years	16-46	16-35	16-41	16-39	16-39	16-46
Baseline Pain						
- Moderate	275 (69)	54 (67)	55 (69)	55 (69)	56 (70)	55 (69)
- Severe	125 (31)	26 (33)	25 (31)	25 (31)	24 (30)	25 (31)
Mean Baseline Pain (VAS)		6.2 ±1.19	6.1 ±1.06	6.1 ±1.00	6.2 ±1.15	6.1 ±1.09

3. Sponsor's Evaluation: Testing was at the 0.05 level with no adjustments for multiplicity issues. The sponsor reports, "For all efficacy comparisons, TRAM/APAP was significantly superior to Placebo ($p<0.001$). Ibuprofen 400 mg was significantly superior to Placebo for all efficacy comparisons ($p<0.001$) with the exception of time to onset of perceptible pain relief. Tramadol 75 mg and APAP 650 mg provided significantly greater pain relief for TOTPAR and SPID compared to Placebo for all time intervals ($p<0.05$). With the exception of PID at Hours 7 and 8, TRAM/APAP was statistically superior to Tramadol 75 mg at each evaluation time point for pain relief, PID, and PRID. TRAM/APAP was statistically superior to APAP 650 mg at Hours 3 to 8 for pain relief and PRID, and between Hours 4 and 8 for PID. At the 0-4, 4-8, and 0-8 hour intervals, TRAM/APAP was statistically superior to Tramadol 75 mg for TOTPAR and SPID, and to APAP 650 mg for TOTPAR. TRAM/APAP showed a statistically significant difference over its Tramadol component with regard to patients' overall assessment of the trial medication ($p<0.001$)", but not for the other component, APAP 650 mg". *[Table B-010 on page 7]*

With regard to mean pain relief (PR) at Hours 1 and 2, statistically significant differences were found between TRAM/APAP and Placebo; and TRAM/APAP and Tramadol 75 mg. However, TRAM/APAP did not separate from APAP 650 mg. At this time 1 hour post-dose, Ibuprofen 400 mg was statistically different from Placebo, and the sensitivity of this pain model was established. At Hours 3 through 8, statistically significant differences were found between TRAM/APAP and Placebo; TRAM/APAP and Tramadol 75 mg; and TRAM/APAP and APAP 650 mg. At this time post-dose, Ibuprofen 400 mg was statistically different from Placebo.

The sponsor found the median time to onset of perceptible pain relief following a single dose of TRAM75/APAP650 (27.9 minutes) to be later than those following a single dose of APAP 650 mg (25.4), and earlier than those in the Ibuprofen 400 mg (38.6); Tramadol 75 mg (30.7); and Placebo (43.5) groups. Time to onset of perceptible and meaningful pain relief were analyzed jointly as bivariate survival times using the Wei, Lin, and Weissfeld marginal distribution method Results of the analysis of the times to onset of perceptible pain relief indicated a significant difference between the TRAM/APAP group and the Placebo, Tramadol 75 mg, and Ibuprofen 400 mg groups ($p\leq 0.001$), but not for APAP 650 mg.

The median time to onset of meaningful pain relief following a single dose of TRAM75/APAP650 (103.0 minutes) were also later than those following a single dose of APAP 650 mg (99.8), and earlier than those in the Ibuprofen 400 mg group (121.0). Less than half of the patients in the Tramadol 75 mg and Placebo groups experienced meaningful pain relief. The sponsor reports that results of the bivariate analysis of the times to onset of meaningful pain relief indicated a significant difference between the TRAM/APAP group and the Placebo, Tramadol 75 mg, and Ibuprofen 400 mg groups ($p\leq 0.001$), but again, not for APAP 650 mg.

The duration of pain relief, defined as the earliest time when half of the patients in the treatment group had remedicated, was longer for the TRAM/APAP (326 minutes) and Ibuprofen 400 mg (301) groups compared to APAP 650 mg (184), Tramadol 75 mg (124), and Placebo (122).

The percentage of patients remedicating was comparable for the TRAM/APAP and Ibuprofen 400 mg groups. Over the 8 hours of assessment, 28% of patients in the TRAM/APAP group did not remedicate compared to 26% in the Ibuprofen 400 mg group. Results significantly favored TRAM/APAP over each component ($p<0.001$); 14% in the Tramadol 75 mg group, 10% in the APAP 650 mg group, and 5% in the Placebo group.

STUDY TRAMAP-ANAG-010 *Table B-010*
SPONSOR SUMMARY OF EFFICACY RESULTS

Final Efficacy Measures Using ITT Population with LOCF Sponsor's Results	Placebo (N=79)	Ibuprofen 400 mg (N=80)	Tramadol 75 mg (N=78)	APAP 650 mg (N=80)	TRAM/APAP 75mg/650mg (N=80)
Mean Pain Relief over Time (PR)					
- at 30 minutes	0.595	0.763	0.782	1.438	1.250 [A]
- at 1 hour	0.709	1.625	0.923	2.100	1.963 [A]
- at 2 hours	0.620	2.175	1.141	1.900	2.113 [A]
- at 3 hours	0.468	2.213	1.154	1.563	2.050 [B]
- at 4 hours	0.430	2.000	1.103	1.288	1.950 [B]
- at 5 hours	0.392	1.838	1.077	1.050	1.738 [B]
- at 6 hours	0.392	1.525	1.000	0.913	1.525 [B]
- at 7 hours	0.380	1.375	0.936	0.813	1.375 [B]
- at 8 hours	0.380	1.288	0.859	0.763	1.313 [B]
Mean Total Pain Relief over Time (TOTPAR): 0-8 hour TOTPAR scale: 0=no relief through 32=complete.					
- at 0-4 hours	2.17	7.58	4.25	6.52	7.72 [C]
- at 4-8 hours	1.54	6.03	3.87	3.54	5.95 [D]
- at 0-8 hours	3.72	13.61	8.12	10.06	13.67 [D]
Treatment vs. Placebo		<0.001	<0.001	<0.001	<0.001
TRAM/APAP vs. Component			<0.001	0.002	
Mean Pain Intensity Difference over Time (PID)					
- at 30 minutes	0.051	0.250	0.192	0.500	0.500 [E]
- at 1 hour	0.063	0.675	0.244	0.850	0.750 [E]
- at 2 hours	-0.076	0.963	0.333	0.713	0.863 [E]
- at 3 hours	-0.139	0.988	0.295	0.588	0.825 [E]
- at 4 hours	-0.177	0.863	0.244	0.413	0.775 [F]
- at 5 hours	-0.177	0.788	0.231	0.288	0.663 [F]
- at 6 hours	-0.177	0.600	0.205	0.200	0.500 [F]
- at 7 hours	-0.203	0.488	0.180	0.125	0.413 [F]
- at 8 hours	-0.203	0.450	0.140	0.088	0.363 [F]
Mean Sum of Pain Intensity Difference (SPID): 0-8 hours SPID scale: -8 to 24					
- 0-8 Hours	-1.1	5.6	1.8	3.1	5.0
Treatment vs. Placebo		<0.001	0.001	<0.001	<0.001
TRAM/APAP vs. Component			<0.001	0.017	

A: At hours 0.5, 1, and 2, TRAM/APAP found statistically different from Placebo and Tramadol 75 mg.

B: At hours 3 through 8, TRAM/APAP found statistically different from Placebo, Tramadol 75 mg, and APAP 650 mg. Ibuprofen 400 mg separated from Placebo.

C: At 0-4 hours, TRAM/APAP found statistically different from Placebo and Tramadol 75 mg.

D: At 4-8 and 0-8 hours, TRAM/APAP found statistically different from Placebo, Tramadol 75 mg, and APAP 650 mg. Ibuprofen 400 mg separated from Placebo.

E: At hours 0.5, 1, 2, and 3, TRAM/APAP found statistically different from Placebo and Tramadol 75 mg.

F: At hours 4 through 8, TRAM/APAP found statistically different from Placebo, Tramadol 75 mg, and APAP 650 mg. Ibuprofen 400 mg separated from Placebo.

The above results on pairwise comparisons of treatment means reflect p-values computed using Fisher's LSD, statistically significant if $p<0.05$, with no *adjustment for multiplicity issues.*

Reviewer's Evaluation: To evaluate the 8-hour analgesic superiority of Tramadol/APAP to each component and to Placebo, the analyses used the ITT population of all patients randomized, using LOCF for imputation of missing values and assessments after remedication. The sponsor based sample size estimations of 80 per treatment group on total pain relief (TOTPAR) to detect differences of 4 units, which would be equivalent to ½ unit mean differences. However, the Division of Analgesia, Anti-inflammatory, and Ophthalmic Drug Products (DAAODP) recommends 30 to 50 patients per group to provide sufficient power to detect clinically meaningful, as well as statistically significant, differences between treatment groups at the 0.05 level. Even with the increased sample size of 80 patients per treatment, TRAM/APAP provided only marginal improvement in pain intensity and pain relief over the 8 hours, and failed to show a separation from the individual component of APAP 325 mg. Furthermore, 95% confidence intervals on differences between combination and APAP 650 mg includes zero, which demonstrates that the hypothesis of equal mean pain relief for these treatment groups cannot be rejected. ***[Table C-010 and Graphs A-010, B-010, and C-010 on pages 9-12].***

Change in Pain Intensity: With regard to mean change in pain intensity assessed over 8 hours, the combination product did not distinguish itself from each of its components. An analysis of variance on mean baseline pain intensity found no evidence of statistically significant differences among treatment groups. An analysis of covariance on change in pain intensity per time point of assessment, using baseline pain intensity as a covariate, determined statistically significant differences between active control Ibuprofen 400 mg and Placebo ($p<0.001$), thus validating the pain model in this study. The TRAM/APAP combination also separated statistically from Placebo ($p<0.001$). However, when adjusting for multiplicity issues at a 1.25% level, the TRAM/APAP combination demonstrated statistically significant differences between APAP 650 mg only at Hours 4 and 5 ($p<0.0125$), and between Tramadol 75 mg from 30 minutes through Hour 5 ($p<0.0125$).

Pain Relief: An analysis of covariance on mean pain relief, per time point of assessment, using baseline pain intensity as a covariate, determined statistically significant differences between active control Ibuprofen 400 mg and Placebo ($p<0.001$), thus further validating the pain model in this study. However, when adjusting for multiplicity issues at a 1.25% level, the TRAM/APAP combination demonstrated statistically significant differences between APAP 650 mg only at Hours 4 through 8 ($p<0.0125$), and between Tramadol 75 mg from 30 minutes through Hour 6 ($p<0.0125$). There was insufficient evidence to determine statistically significant differences at all other time points.

Time to Onset of Pain Relief: The protocol states, "the equation for calculating time of onset of pain relief is: onset of pain relief in minutes = (30 minutes) / (mean PRID at 30 minutes)". Other submissions for this indication have calculated this efficacy measure as time to onset of perceptible pain relief as first stopwatch time and time to meaningful pain relief as second stopwatch time, with extensions of this made for situations when rescue medication was taken or no stopwatch time taken. According to the sponsor's calculation, the median time to onset of perceptible pain relief following a single dose of TRAM75/APAP650 (27.9 minutes) was later than those following a single dose of APAP 650 mg (25.4), and earlier than those in the Ibuprofen 400 mg (38.6); Tramadol 75 mg (30.7); and Placebo (43.5) groups.

Treatment Pairwise Comparisons in Postsurgical Dental Pain
ITT using LOCF
Reviewer's Results
Time-Specific Change in Pain Intensity (PID) and Pain Relief (PR)

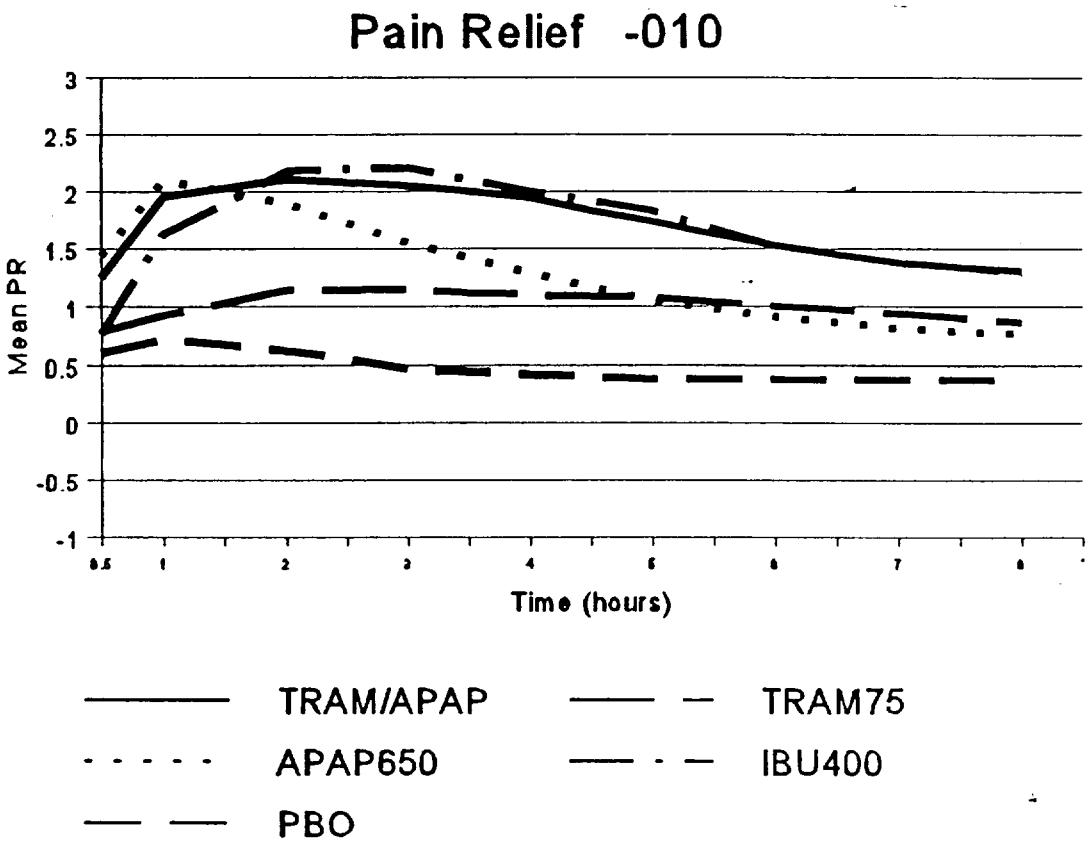
TRAM/APAP vs APAP650	p-value **	95% CI [Diff]	TRAM/APAP vs APAP650	p-value **	95% CI [Diff]
PID - Hour 0.5	0.958	[-0.18, 0.18] ^	PR - Hour 0.5	0.216	[-0.22, 0.16]
PID - Hour 1	0.327	[-0.32, 0.11] ^	PR - Hour 1	0.432	[-0.48, 0.21] ^
PID - Hour 2	0.278	[-0.12, 0.40] ^	PR - Hour 2	0.274	[-0.17, 0.59] ^
PID - Hour 3	0.086	[-0.03, 0.49] ^	PR - Hour 3	0.015	[0.10, 0.88]
PID - Hour 4	0.007 **	[0.10, 0.61]	PR - Hour 4	<0.001 **	[0.27, 1.05]
PID - Hour 5	0.004 **	[0.12, 0.62]	PR - Hour 5	<0.001 **	[0.31, 1.07]
PID - Hour 6	0.018	[0.05, 0.54]	PR - Hour 6	<0.001 **	[0.26, 0.98]
PID - Hour 7	0.018	[0.06, 0.51]	PR - Hour 7	0.002 **	[0.22, 0.90]
PID - Hour 8	0.018	[0.04, 0.49]	PR - Hour 8	0.001 **	[0.22, 0.88]
TRAM/APAP vs TRAM75	**p-value ****	**95% CI [Diff]**	**TRAM/APAP vs TRAM75**	**p-value ****	**95% CI [Diff]**
PID - Hour 0.5	<0.001 **	[0.13, 0.49]	PR - Hour 0.5	0.002 **	[0.44, 0.50]
PID - Hour 1	<0.001 **	[0.30, 0.72]	PR - Hour 1	<0.001 **	[0.70, 1.38]
PID - Hour 2	<0.001 **	[0.27, 0.79]	PR - Hour 2	<0.001 **	[0.59, 1.35]
PID - Hour 3	<0.001 **	[0.28, 0.80]	PR - Hour 3	<0.001 **	[0.51, 1.28]
PID - Hour 4	<0.001 **	[0.28, 0.80]	PR - Hour 4	<0.001 **	[0.46, 1.24]
PID - Hour 5	<0.001 **	[0.19, 0.69]	PR - Hour 5	<0.001 **	[0.28, 1.04]
PID - Hour 6	0.017	[0.05, 0.54]	PR - Hour 6	0.005 **	[0.16, 0.88]
PID - Hour 7	0.047	[0.005, 0.47]	PR - Hour 7	0.014	[0.10, 0.78]
PID - Hour 8	0.048	[0.004, 0.45]	PR - Hour 8	0.007	[0.12, 0.78]

** *The above are p-values (2-sided testing) using analysis of covariance with baseline pain intensity as the covariate.*

** *Shaded cells represent statistically significant differences between treatment groups for post dose assessment times adjusted for the multiplicity of testing issues (at alpha level of 1.25%).*

^ *Confidence intervals that include zero indicate a null hypothesis of equal treatment means cannot be rejected.*

STUDY TRAMAP-ANAG-010 *Graph A-010*
Postsurgical Dental Pain (Single Dose Study)
Reviewer's Results
Mean Pain Relief
Intent-to-treat Population using Last Observation Carried Forward (LOCF)

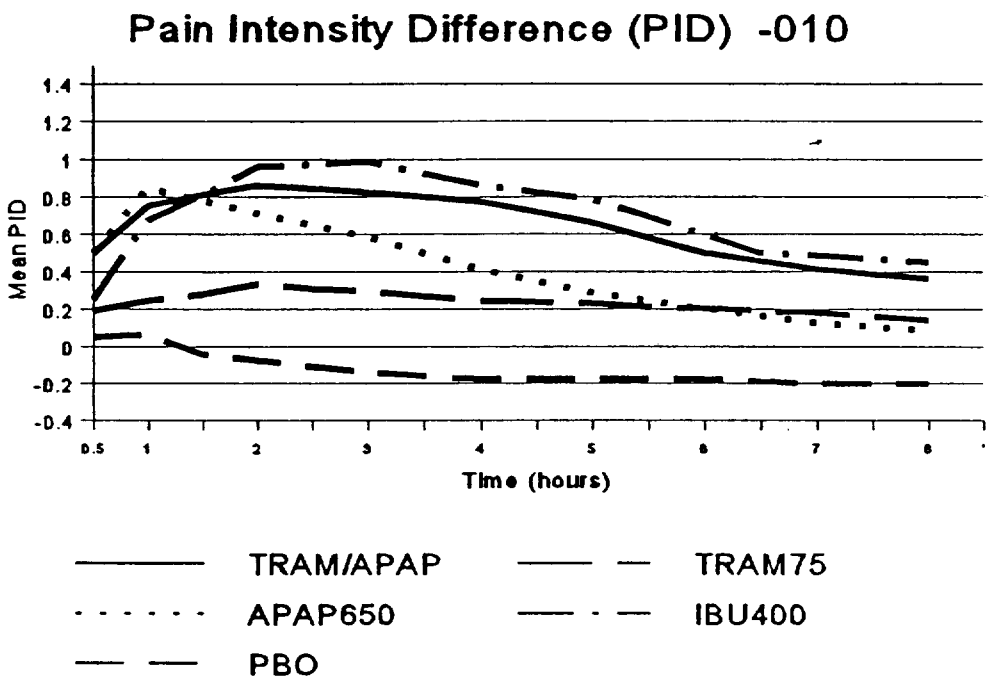


TRAM/APAP = Tramadol 75 mg / Acetaminophen 650 mg
TRAM75 = Tramadol 75 mg
APAP650 = Acetaminophen 650 mg
IBU400 = Ibuprofen 400 mg
PBO = Placebo

** *Pain Relief (PR) Scores: 0=none; 1=little; 2=some; 3=lot; 4=complete*

The above graphical representation of mean pain relief illustrates a close parallel between the TRAM75/APAP650 combination treatment and Ibuprofen 400 mg. In the TRAM/APAP combination treatment group, it appears that Acetaminophen 650 mg contributes to the first 2 hours of pain relief while the Tramadol 75 mg then helps to sustain that relief through Hour 8. This demonstrates what the sponsor expected, i.e. combining the 2 products would provide for the rapid onset of action of APAP and the prolonged effect of Tramadol.

STUDY TRAMAP-ANAG-010 *Graph B-010*
Postsurgical Dental Pain (Single Dose Study)
Reviewer's Results
Mean Pain Intensity Difference (PID)
Intent-to-treat Population using Last Observation Carried Forward (LOCF)

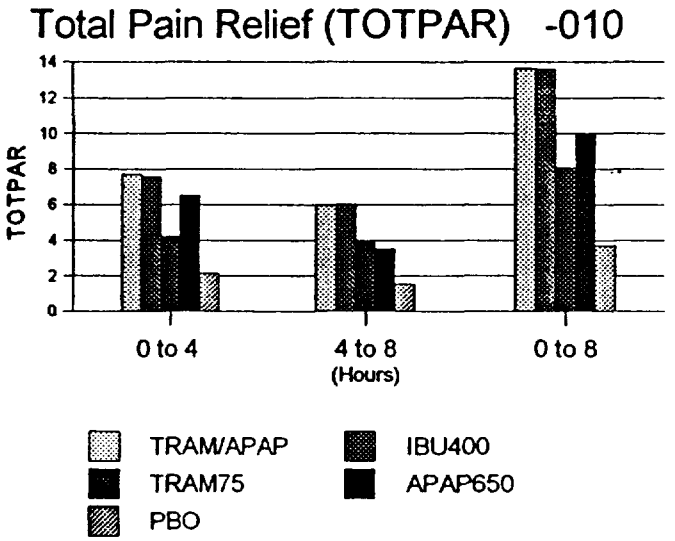


TRAM/APAP = Tramadol 75 mg / Acetaminophen 650 mg
TRAM75 = Tramadol 75 mg
APAP650 = Acetaminophen 650 mg
IBU400 = Ibuprofen 400 mg
PBO = Placebo

** *Pain Intensity Difference (PID): -3 to -1 = pain increase; 0= no change; 1 to 3* = pain decrease

The above graphical representation of mean change in pain intensity from baseline (PID) illustrates a greater mean decrease in pain intensity for the Ibuprofen 400 mg group. As is shown in the previous graph for mean pain relief, In the TRAM/APAP combination treatment group, it appears that Acetaminophen 650 mg contributes to the first 2 hours of change in pain while the Tramadol 75 mg then helps to sustain that decrease through Hour 8.

STUDY TRAMAP-ANAG-010 *Graph C-010*
Postsurgical Dental Pain (Single Dose Study)
Reviewer's Results
Total Pain Relief (TOTPAR) at 0 to 4 hours; 4 to 8 hours; and 0 to 8 hours
Intent-to-treat Population using Last Observation Carried Forward (LOCF)



TRAM/APAP = Tramadol 75 mg / Acetaminophen 650 mg
TRAM75 = Tramadol 75 mg
APAP650 = Acetaminophen 650 mg
IBU400 = Ibuprofen 400 mg
PBO = Placebo

TOTPAR Scores: *0= no pain relief; 2= little; 3= some; 4=complete*
max (0 to 4 hours) = 16 (complete relief at every evaluation)
max (0 to 8 hours) = 32 (complete relief at every evaluation)

The above graphical representation of total pain relief scores over time (TOTPAR) illustrates the overall sum of pain relief scores across the 8 hours of assessment. The TRAM/APAP combination and Ibuprofen 400 mg provided comparable overall total pain relief. APAP 650 mg appears to be contributing to the total pain relief during the first 4 hours of assessment, and then for the remaining 4 to 8 hours, each component (Tramadol 75 mg and APAP650 mg) appear to provide comparable total pain relief. For TRAM/APAP, Ibuprofen 400 mg, and APAP 650 mg, more total pain relief is realized during the first 4 hours post surgery.

III. Phase 3 Study TRAMAP-ANAG-013 - Single Dose Oral Surgery

1. Study Design: This was a randomized, double-blind, parallel-group, active-controlled, factorial design trial with a placebo control. The objective of this trial was to evaluate the safety and 8-hour single-dose analgesic superiority of combination Tramadol 75 mg with APAP 650 mg (TRAM/APAP) to each component alone and to Placebo in patients with pain from an oral surgical procedure. Four hundred patients were to be randomized, 80 patients per treatment group. The study was conducted from March to July of 1998 at one site, [redacted]. One amendment, dated June 19, 1998, was added after 320 patients entered trial to redefine the allowed surgical procedures. The study followed the same protocol, study schedule, and methodology as described in Study TRAMAP-ANAG-010. ***[Section II on page 2 of this review].***

2. Patient Disposition: A total of 400 patients were enrolled in 1 center (80 randomized to each treatment group); 147 were male and 253 were female; patients ranged in age from 16 to 45 years (mean±sd, 21.1±4.71).

The sponsor reports that the demographic and baseline characteristics were comparable across the 5 treatment groups. All patients were required to have moderate or severe pain before administering trial medication; 281 (70%) of the patients reported having moderate pain at baseline. The mean baseline pain rating was similar in all treatment groups [redacted]. Three hundred and eight (77%) of the 400 patients completed the trial as planned. A total of 92 patients were considered to have withdrawn from the trial; 89 withdrew because they did not complete at least the two-hour evaluation before remedicating.

STUDY TRAMAP-ANAG-013 *Table A-013*
SPONSOR'S SUMMARY OF PATIENT DISPOSITION

Sponsor's Results	Total	Placebo (N=80)	Ibuprofen 400 mg (N=80)	Tramadol 75 mg (N=80)	APAP 650 mg (N=80)	TRAM/APAP 75mg/650mg (N=80)
# ITT - All Randomized	400	80	80	80	80	80
# Completions %)	308	35	74	54	70	75
- No Remedication (%)	99 (33)	7 (20)	35 (47)	22 (41)	12 (17)	23 (31)
- Required Remed (%)	209 (67)	28 (80)	39 (53)	32 (59)	58 (83)	52 (69)
# Withdrew	92	45	6	26	10	5
Sex						
- Females (%)	253 (63)	53 (66)	52 (65)	47 (59)	49 (61)	52 (65)
- Males (%)	147 (37)	27 (34)	28 (35)	33 (41)	31 (39)	28 (35)
Race						
- Caucasian (%)	299 (75)	60	62	62	55	60
- Other (%)	101 (25)	20	18	18	25	20
Age Range in Years	16-46	16-42	16-29	16-34	16-44	16-46
Baseline Pain						
- Moderate	281 (70)	56 (70)	56 (70)	56 (70)	56 (70)	57 (71)
- Severe	119 (30)	24 (30)	24 (30)	24 (30)	24 (30)	23 (29)
Mean Baseline Pain (VAS)		6.0 ±1.04	6.2 ±1.04	6.1 ±1.02	6.0 ±1.04	6.0 ±1.04

3. Sponsor's Evaluation: Testing was at the 0.05 level with no adjustments for multiplicity issues. The sponsor reports that TRAM/APAP and Ibuprofen 400 mg were statistically superior to Placebo and APAP 650 mg for the summary efficacy variables of TOTPAR and SPID. With regard to mean pain relief (PR) at 30 minutes through Hour 8, statistically significant differences were found between TRAM/APAP and Placebo, and between Ibuprofen 400 mg and Placebo. At 30 minutes through Hour 3, TRAM/APAP was found statistically different from Tramadol 75 mg. However, TRAM/APAP did not separate statistically from APAP 650 mg for the 8-hour assessment. ***[Table B-013 on page 15]***

The median time to onset of perceptible pain relief could not be calculated for the Placebo group because more than half of the patients did not experience perceptible or meaningful pain relief and were therefore censored and coded as 8 hours plus 1 minute, longer than all of the uncensored observations. However, the median time following a single dose of TRAM/APAP (21.1 minutes) was earlier than that following a single dose of APAP 650 mg (23.5); Tramadol 75 mg (74.3); and Ibuprofen 400 mg groups (27.1). Time to onset of perceptible and meaningful pain relief were analyzed jointly as bivariate survival times using the Wei, Lin, and Weissfeld marginal distribution method Results of the analysis of the times to onset of perceptible pain relief indicated a significant difference between the TRAM/APAP group and the Placebo and Tramadol 75 mg groups ($p \leq 0.001$).

The median time to onset of meaningful pain relief following a single dose of TRAM/APAP (54.5 minutes) was comparable to that following a single dose of APAP 650 mg (51.8) and Ibuprofen 400 mg (61.5). Results of the bivariate analysis indicated a significantly faster onset for TRAM/APAP compared to the Tramadol 75 mg and Placebo groups ($p<0.001$); with no significant difference in onset as compared to the APAP 650 mg and Ibuprofen 400 mg groups ($p=0.316$).

The estimated onset of pain relief is defined as the time required after dose administration to achieve a mean PRID rating of 1. The onset of pain relief was similar for TRAM/APAP (14 minutes) and APAP 650 mg (14 minutes), with the onset of pain relief for both of these groups numerically faster than that for Ibuprofen 400 mg (27), Placebo (83), and Tramadol 75 mg (100).

The duration of pain relief, defined as the earliest time when half of the patients in the treatment group had remedicated, was longer for the TRAM/APAP (245 minutes) and Ibuprofen 400 mg (423 minutes) groups compared to the APAP 650 mg (165 minutes), Tramadol 75 mg (123 minutes), and Placebo (105 minutes) groups.

The percentage of patients remedicating was lowest in the Ibuprofen group. Over the 8 hours of assessment, 44% of patients in the Ibuprofen 400 mg group did not remedicate compared to 29% in the TRAM/APAP group; 28% in the Tramadol 75 mg; 15% in the APAP 650 mg; and 9% in the Placebo group.

With regard to patients' overall assessment of the trial medication, TRAM/APAP showed a significant difference over Tramadol 75 mg ($p<0.001$), but not for APAP 650 mg. Thirty percent of the patients in the TRAM/APAP group and 39% of patients in the Ibuprofen 400 mg group rated their medication as very good or excellent compared to 14% in the Tramadol group, 29% in the APAP group, and 13% in the Placebo group.

STUDY TRAMAP-ANAG-013
SPONSOR SUMMARY OF EFFICACY RESULTS

Table B-013

Final Efficacy Measures Using ITT Population with LOCF Sponsor's Results	Placebo (N=80)	Ibuprofen 400 mg (N=80)	Tramadol 75 mg (N=80)	APAP 650 mg (N=80)	TRAM/APAP 75mg/650mg (N=80)	
Mean Pain Relief over Time (PR)						
- at 30 minutes	0.463	0.838	0.400	1.538	1.500	A C
- at 1 hour	0.413	1.900	0.688	2.100	2.025	A C
- at 2 hours	0.588	2.288	0.863	1.613	2.075	A B C
- at 3 hours	0.600	2.350	0.925	1.150	1.713	A B C
- at 4 hours	0.538	2.188	0.963	1.038	1.450	C
- at 5 hours	0.513	1.963	0.963	0.788	1.325	B C
- at 6 hours	0.413	1.763	0.938	0.663	1.100	C
- at 7 hours	0.338	1.438	0.913	0.563	0.988	C
- at 8 hours	0.338	1.238	0.863	0.525	0.950	C
Mean Total Pain Relief over Time (TOTPAR): 0-8 hour TOTPAR scale: 0=no relief through 32=complete						
- at 0-4 hours	2.14	8.73	3.44	5.90	7.26	D E
- at 4-8 hours	1.60	6.40	3.68	2.54	4.36	D
- at 0-8 hours	3.74	15.13	7.11	8.44	11.63	D E
Treatment vs. Placebo		<0.001	0.020	0.002	<0.001	
TRAM/APAP vs. Component			0.002	0.020		
Mean Pain Intensity Difference over Time (PID)						
- at 30 minutes	-0.100	0.288	-0.100	0.588	0.638	E G
- at 1 hour	-0.163	0.813	-0.038	0.950	0.888	E G
- at 2 hours	-0.238	1.075	0.038	0.550	0.888	E F G
- at 3 hours	-0.225	1.125	0.075	0.338	0.700	E F G
- at 4 hours	-0.250	1.088	0.138	0.300	0.550	E G
- at 5 hours	-0.250	0.950	0.125	0.163	0.513	E G
- at 6 hours	-0.300	0.825	0.125	0.088	0.338	G
- at 7 hours	-0.338	0.625	0.088	0.013	0.325	G
- at 8 hours	-0.338	0.463	0.050	0.000	0.313	F G
Mean Sum of Pain Intensity Difference (SPID): 0-8 hours SPID scale: -8 to 24						
- 0-8 Hours	-2.1	6.7	0.6	2.2	4.4	
Treatment vs. Placebo		<0.001	0.012	<0.001	<0.001	
TRAM/APAP vs. Component			<0.001	0.032		

A: At hours 0.5, through 3, TRAM/APAP found statistically different from Tramadol 75 mg.
B: At hours 2, 3, and 5, TRAM/APAP found statistically different from APAP 650 mg.
C: At hours 0.5 through 8, TRAM/APAP and Ibuprofen 400 mg separated from Placebo.
D: At 0-4, 4-8, and 0-8 hours, TRAM/APAP and Ibuprofen statistically different from Placebo and APAP 650 mg.
E: At 0-4 and 0-8 hours, TRAM/APAP statistically different from Tramadol 75 mg.
E: At hours 0.5 through 5, TRAM/APAP found statistically different from Tramadol 75 mg.
F: At hours 2, 3, and 8, TRAM/APAP found statistically different from APAP 650 mg.
G: At hours 0.5 through 8, TRAM/APAP and Ibuprofen 400 mg separated from Placebo.

The above results on pairwise comparisons of treatment means reflect p-values computed using Fisher's LSD, statistically significant if $p<0.05$, with no *adjustment for multiplicity issues.*

4. Reviewer's Evaluation: To evaluate the 8-hour analgesic superiority of Tramadol/APAP to each component alone and to Placebo, the analyses used the ITT population of all patients randomized. Last-observation-carried-forward was the method of imputation for missing values and assessments after remedication. Even with the increased sample size of 80 patients per treatment, the TRAM/APAP combination provided only marginal improvement in pain intensity and pain relief over the 8 hours, and failed to show a separation from the individual component of APAP 650 mg. Furthermore, 95% confidence intervals on differences between combination and APAP 650 mg include zero, which demonstrates that the hypothesis of equal mean pain relief for these treatment groups cannot be rejected. ***[Table C-013 and Graphs A-013, B-013, and C-013 on pages 17-20]***

Change in Pain Intensity: With regard to mean change in pain intensity assessed over 8 hours, the combination product did not distinguish itself from each of its components. An analysis of variance on mean baseline pain intensity found no evidence of statistically significant differences among treatment groups. An analysis of covariance on change in pain intensity per time point of assessment, using baseline pain intensity as a covariate, determined statistically significant differences between active control Ibuprofen 400 mg and Placebo ($p<0.001$), thus validating the pain model in this study. The TRAM/APAP combination also separated statistically from Placebo ($p<0.001$). However, when adjusting for multiplicity issues at a 1.25% level, TRAM/APAP combination separated from Tramadol 75 mg only from 30 minutes through Hour 3. There was insufficient evidence to determine statistically significant differences at all other time points. There was no evidence of statistically significant differences between TRAM/APAP and APAP 650 throughout the 8-hour interval.

Pain Relief: An analysis of covariance on mean pain relief, per time point of assessment, using baseline pain intensity as a covariate, determined statistically significant differences between active control Ibuprofen 400 mg and Placebo ($p<0.001$), thus further validating the pain model in this study. The TRAM/APAP combination also separated statistically from Placebo ($p<0.001$). However, when adjusting for multiplicity issues at a 1.25% level, the TRAM/APAP combination demonstrated statistically significant differences between Tramadol 75 mg only from 30 minutes through Hour 3 ($p<0.0125$); there was insufficient evidence to determine statistically significant differences at all other time points. There was no evidence of statistically significant differences between TRAM/APAP and APAP 650 throughout the 8-hour interval.

Time to Onset of Pain Relief: The protocol states, "the equation for calculating time of onset of pain relief is: onset of pain relief in minutes = (30 minutes) / (mean PRID at 30 minutes)". Other submissions for this indication have calculated this efficacy measure as time to onset of perceptible pain relief as first stopwatch time and time to meaningful pain relief as second stopwatch time, with extensions of this made for situations when rescue medication was taken or no stopwatch time taken. According to the sponsor's calculation, the median time to onset of perceptible pain relief following a single dose of TRAM/APAP (21.1 minutes) was earlier than that following a single dose of APAP 650 mg (23.5); Tramadol 75 mg (74.3); and Ibuprofen 400 mg groups (27.1).

Table C-013

Study TRAMAP-ANAG -013
Treatment Pairwise Comparisons in Postsurgical Dental Pain
ITT using LOCF
Reviewer's Results
Time-Specific Change in Pain Intensity (PID) and Pain Relief (PR)

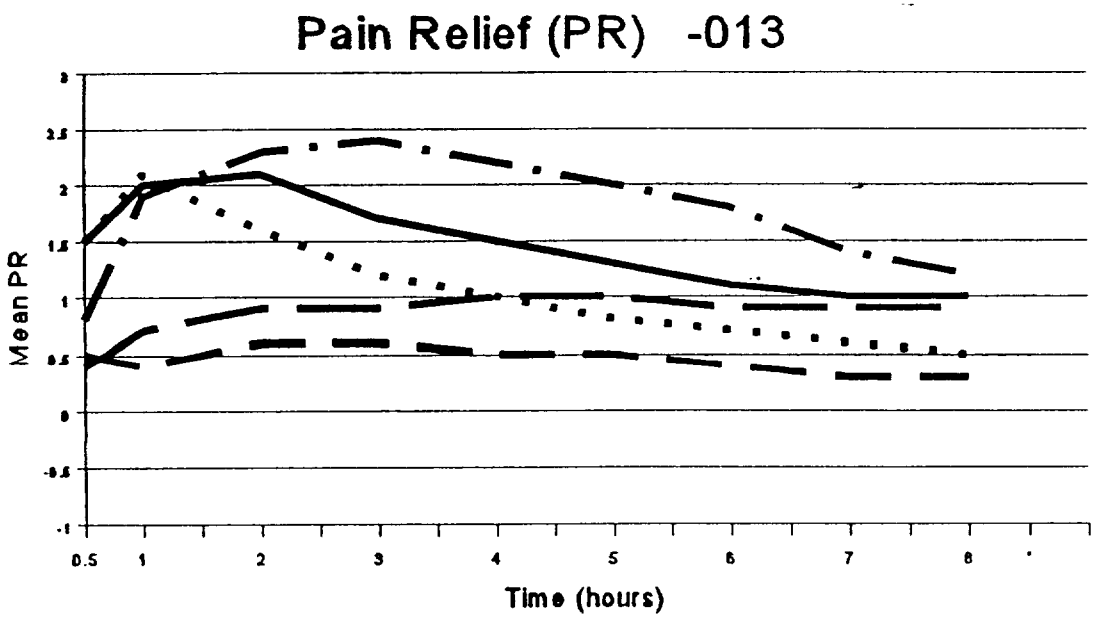
TRAM/APAP vs APAP650	p-value **	95% CI [Diff]	TRAM/APAP vs APAP650	p-value **	95% CI [Diff]
PID - Hour 0.5	0.604	[-0.15, 0.27] ^A	PR - Hour 0.5	0.812	[-0.35, 0.27] ^A
PID - Hour 1	0.675	[-0.30, 0.20] ^A	PR - Hour 1	0.690	[-0.45, 0.29] ^A
PID - Hour 2	0.024	[0.05, 0.65]	PR - Hour 2	0.041	[0.02, 0.90]
PID - Hour 3	0.027	[0.04, 0.70]	PR - Hour 3	0.019	[0.09, 1.03]
PID - Hour 4	0.135	[-0.08, 0.60] ^A	PR - Hour 4	0.100	[-0.08, 0.90] ^A
PID - Hour 5	0.036	[0.02, 0.70]	PR - Hour 5	0.029	[0.06, 1.02]
PID - Hour 6	0.110	[-0.06, 0.58] ^A	PR - Hour 6	0.062	[-0.02, 0.90] ^A
PID - Hour 7	0.038	[0.02, 0.62]	PR - Hour 7	0.059	[-0.02, 0.87] ^A
PID - Hour 8	0.034	[0.02, 0.62]	PR - Hour 8	0.054	[-0.005, 0.86] ^A
TRAM/APAP vs TRAM75	p-value **	95% CI [Diff]	TRAM/APAP vs TRAM75	p-value **	95% CI [Diff]
PID - Hour 0.5	< 0.001 **	[0.53, 0.95]	PR - Hour 0.5	< 0.001 **	[0.79, 1.41]
PID - Hour 1	< 0.001 **	[0.68, 1.18]	PR - Hour 1	< 0.001 **	[0.97, 1.71]
PID - Hour 2	< 0.001 **	[0.56, 1.16]	PR - Hour 2	< 0.001 **	[0.77, 1.65]
PID - Hour 3	< 0.001 **	[0.30, 0.96]	PR - Hour 3	< 0.001 **	[0.32, 1.25]
PID - Hour 4	0.015	[0.08, 0.76]	PR - Hour 4	0.050	[-0.01, 0.97] ^A
PID - Hour 5	0.021	[0.06, 0.74]	PR - Hour 5	0.140	[-0.12, 0.84] ^A
PID - Hour 6	0.170	[-0.10, 0.55] ^A	PR - Hour 6	0.487	[-0.30, 0.62] ^A
PID - Hour 7	0.111	[-0.05, 0.55] ^A	PR - Hour 7	0.738	[-0.37, 0.52] ^A
PID - Hour 8	0.074	[-0.03, 0.57] ^A	PR - Hour 8	0.691	[-0.35, 0.50] ^A

** *The above are p-values (2-sided testing) using analysis of covariance with baseline pain intensity as the covariate.*

** *Shaded cells represent statistically significant differences between treatment groups for post dose assessment times adjusted for the multiplicity of testing issues (at alpha level of 1.25%).*

^A *Confidence intervals that include zero indicate a null hypothesis of equal treatment means cannot be rejected.*

STUDY TRAMAP-ANAG-013 *Graph A-013*
Postsurgical Dental Pain (Single Dose Study)
Reviewer's Results
Mean Pain Relief
Intent-to-treat Population using Last Observation Carried Forward (LOCF)

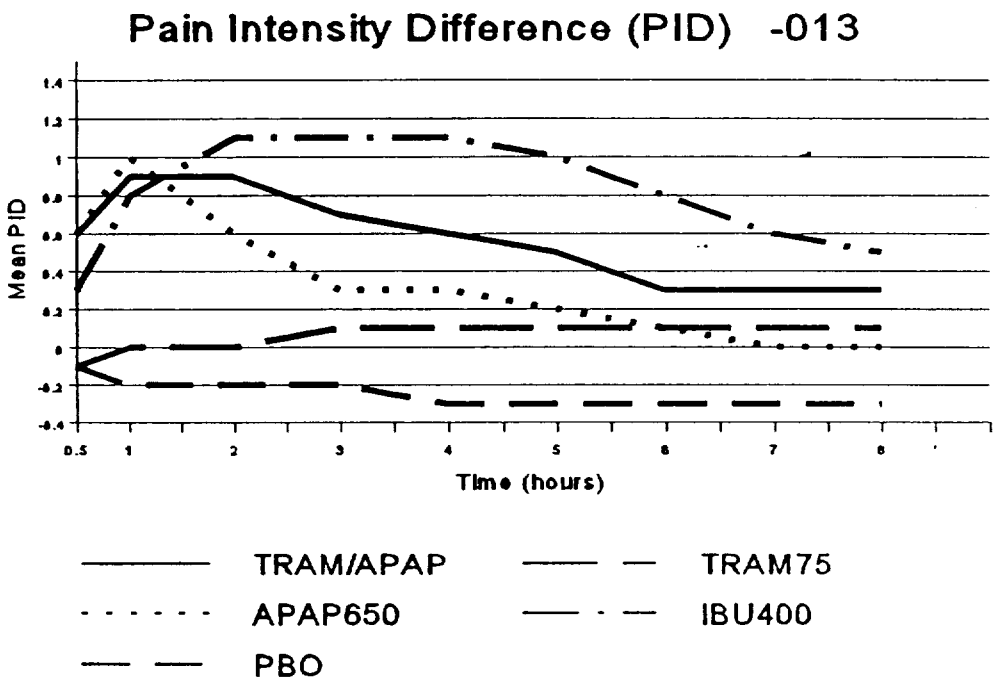


TRAM/APAP = Tramadol 75 mg / Acetaminophen 650 mg
TRAM75 = Tramadol 75 mg
APAP650 = Acetaminophen 650 mg
IBU400 = Ibuprofen 400 mg
PBO = Placebo

** *Pain Relief (PR) Scores: 0=none; 1=little; 2=some; 3=lot; 4=complete*

The above graphical representation of mean pain relief illustrates earlier onset of action for TRAM75/APAP650 combination treatment, but overall, Ibuprofen 400 mg demonstrated greater pain relief over a longer period of time. As was seen in Studies -010 and -012, in the TRAM/APAP combination treatment group, it appears that Acetaminophen 650 mg contributes to the first 2 hours of pain relief while the Tramadol 75 mg then helps to sustain that relief through Hour 8.

STUDY TRAMAP-ANAG-013 *Graph B-013*
Postsurgical Dental Pain (Single Dose Study)
Reviewer's Results
Mean Pain Intensity Difference (PID)
Intent-to-treat Population using Last Observation Carried Forward (LOCF)



TRAM/APAP = Tramadol 75 mg / Acetaminophen 650 mg
TRAM75 = Tramadol 75 mg
APAP650 = Acetaminophen 650 mg
IBU400 = Ibuprofen 400 mg
PBO = Placebo

** *Pain Intensity Difference (PID): -3 to -1 = pain increase; 0= no change; 1 to 3* = pain decrease

The above graphical representation of mean change in pain intensity from baseline (PID) illustrates a greater mean decrease in pain intensity for the Ibuprofen 400 mg group, as was seen in Studies -010 and -012. Once again, in the TRAM/APAP combination treatment group, it appears that Acetaminophen 650 mg contributes to the first 2 hours of change in pain while the Tramadol 75 mg then helps to sustain that decrease through Hour 8.

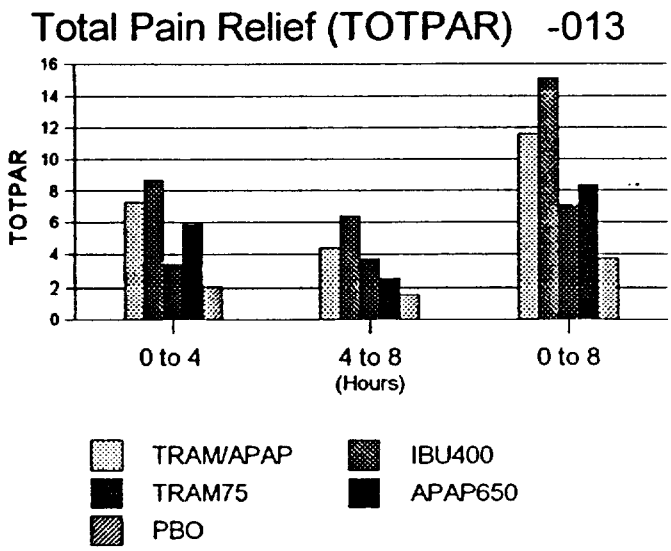
STUDY TRAMAP-ANAG-013 *Graph C-013*

Postsurgical Dental Pain (Single Dose Study)

Reviewer's Results

Total Pain Relief (TOTPAR) at 0 to 4 hours; 4 to 8 hours; and 0 to 8 hours

Intent-to-treat Population using Last Observation Carried Forward (LOCF)



TRAM/APAP = Tramadol 75 mg / Acetaminophen 650 mg *IBU400 = Ibuprofen 400 mg*
TRAM75 = Tramadol 75 mg *PBO = Placebo*
APAP650 = Acetaminophen 650 mg

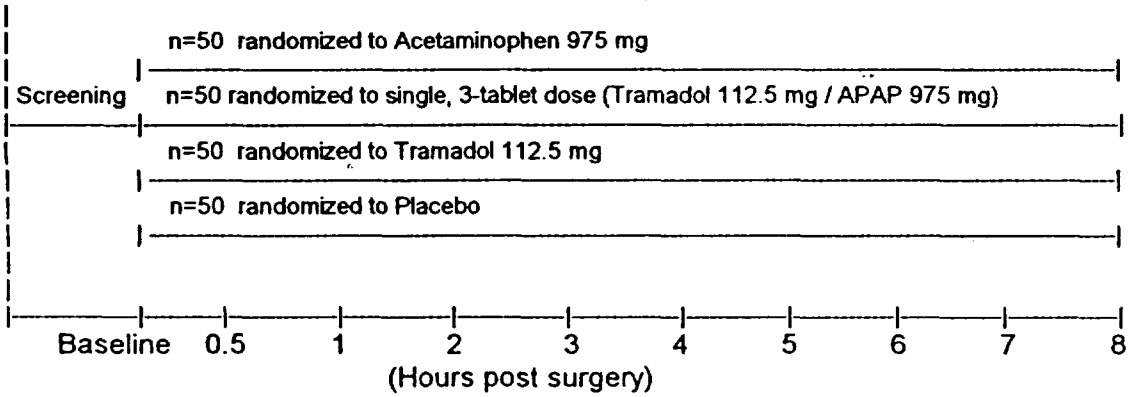
TOTPAR Scores: *0= no pain relief; 2= little; 3= some; 4=complete*
max (0 to 4 hours) = 16 (complete relief at every evaluation)
max (0 to 8 hours) = 32 (complete relief at every evaluation)

The above graphical representation shows greatest total pain relief scores over time (TOTPAR) for Ibuprofen 400 mg followed by TRAM/APAP. APAP 650 mg appears to be contributing to the total pain relief during the first 4 hours.

IV. Phase 3 Study TRAMAP-ANAG-005 - Single Dose Orthopedic Surgery

1. Study Design: Efficacy Study TRAMAP-ANAG-005 was a Phase 3, randomized, double-blind, single center, parallel-group, factorial design study with Placebo control conducted to evaluate the efficacy and safety of single dose of combination Tramadol ~~112~~ 112.5 mg with Acetaminophen 975 mg (TRAM 112.5/APAP 975) as compared to each component alone and to Placebo in patients experiencing pain from a orthopedic surgical procedure. The study was conducted from June, 1996 to March, 1997 at one investigational site, Black, in Austin, TX

TRAMAP-ANAG-005 STUDY SCHEDULE



Patients who experienced moderate or severe pain following an orthopedic surgical procedure were eligible for trial participation. A total of 200 qualified patients were to be randomized by a 1:1:1:1 schema of 50 per treatment group to a single dose of TRAM 112.5/APAP 975, Tramadol 112.5 mg, APAP 975 mg, or Placebo.

Following the recording of baseline pain intensity and administration of study medication, patients evaluated current pain and relief from starting pain at 30 minutes, and 1, 2, 3, 4, 5, 6, 7, and 8 hours. Each patient was encouraged, but not required, to wait at least one hour before taking supplemental (rescue) pain medication if there was no analgesic response to the trial medication. Additionally, each patient was encouraged, but not required, to wait until the current pain level had returned to the baseline assessment level before taking supplemental pain medication. A final assessment of current pain and relief from starting pain was made and recorded before a patient took a supplemental analgesic. At the end of the 8-hour observation period or at the time supplemental analgesic was taken, whichever occurred first, the patient provided an overall assessment of the trial medication.

2. Patient Disposition: Patients ranged in age from 20 to 83 years (mean±sd, 45.4±13.38), and the majority (58%) were men. Eighty-five percent (169/200) of the patients were Caucasian.

8. Sponsor's Results: All 200 patients were included in the efficacy analyses. The sponsor reports that while the single, 3-tablet dose of combination TRAM 112.5/APAP 975 was statistically superior to Placebo and to APAP 975 mg, it was only numerically superior to Tramadol 112.5 mg with regard to pain relief, and pain intensity difference. The sponsor's results of this trial demonstrate superior analgesic efficacy for the TRAM/APAP combination relative to one of its components, APAP 975 mg, but not the other, Tramadol 112.5 mg.

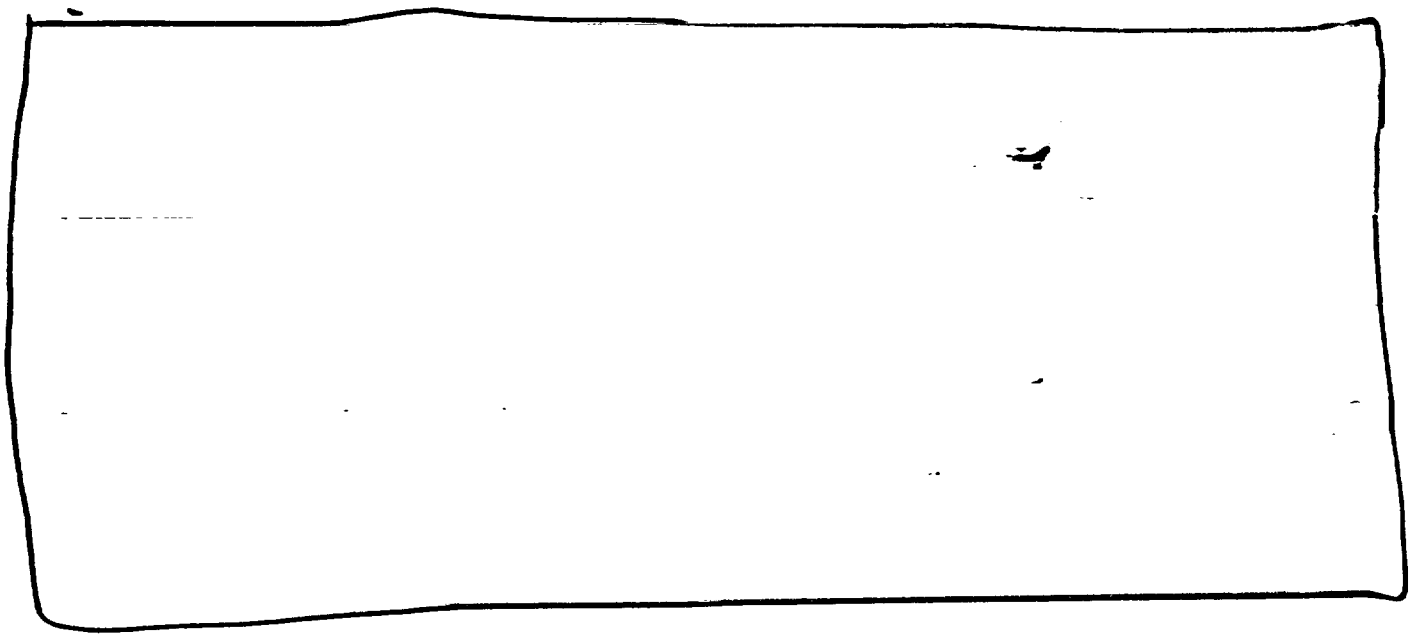
TRAM/APAP separated numerically from APAP 975 mg beginning at Hour 2 and was statistically superior during the latter half of the observation interval for pain relief (Hours 5 to 8), PRID (Hours 5 to 8), and PID (Hours 6 to 8). TRAM/APAP was significantly superior to APAP 975 mg for TOTPAR (4-8 hour and 0-8 hour) and SPID (4-8 hour) ($p \leq 0.031$).

The superiority of TRAM/APAP over Tramadol 112.5 mg alone was less consistently demonstrated in this trial compared to APAP 975 mg. For pain relief, PID, and PRID scores, TRAM/APAP numerically separated from Tramadol 112.5 mg by Hour 1 and remained numerically superior for the duration of the observation interval; however, the differences achieved statistical significance only at Hours 7 and 8 for PR and at Hour 8 for PRID. During the 4-8 hour interval, the mean TOTPAR score for TRAM/APAP was significantly superior to that for Tramadol alone (p=0.027). In addition, across the 0-8 hour observation interval, there was a trend toward significance for TRAM/APAP over Tramadol alone for TOTPAR (p=0.052). While SPID scores numerically favored TRAM/APAP over Tramadol, the differences were not statistically significant.

While the mean onset of pain relief was similar for all active treatments (18 to 19 minutes), the median duration of pain relief was numerically longer for TRAM/APAP (260.0 minutes) than for either APAP 975 mg (232.5 minutes) or Tramadol 112.5 mg (200.0 minutes). The percentage of patients remedicating also numerically favored TRAM/APAP over its components, and there was a trend in favor of TRAM/APAP over APAP 975 mg with respect to the time to remedicate (p=0.059). There were no significant differences between active treatments with regard to patients' overall assessment of trial medication.

4. Reviewer's Results: The sponsor reports that the results of this trial demonstrate superior analgesic efficacy for the single, 3-tablet dose of TRAM 112.5/APAP 975 combination relative to one of its components, APAP 975 mg, but not the other, Tramadol 112.5 mg. No further analyses were done.

2 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.



VI. Reviewer Conclusions which may be Conveyed to the Sponsor.

The following summarizes this reviewer's results on 4 selected studies investigating the indications of acute [redacted] pain in the clinical program of this NDA. This reviewer does not agree with the sponsor's conclusion regarding efficacy of the 4 selected studies assigned for evaluation.

1. Efficacy in Treatment of Acute Pain in Single Dose Studies: Approval for the treatment of acute pain requires positive findings from 2 confirmatory studies in at least 2 pain models.

This reviewer was assigned to examine 3 studies (-005, -010, -013) conducted to investigate the efficacy of TRAM/APAP in treating moderate to severe acute pain. Single dose studies -010 and -013 used a dental postsurgical pain model and Study -005 used an orthopedic postsurgical pain model.

The results of these 3 studies showed insufficient evidence to declare statistical separation between the combination product and each of its components throughout the 8-hour interval of postsurgical observation. Furthermore, these studies were fixed-dose and did not demonstrate the use of this drug product as repeat-dosing in acute pain. Therefore, based on these studies, the combination is not approvable even though it demonstrated superiority over Placebo. Active control, Ibuprofen 400 mg provided numerically greater pain relief than TRAM/APAP.

Orthopedic Surgery Study TRAMAP-ANAG-005 was conducted to evaluate the analgesic superiority and safety of single dose combination Tramadol 112.5 mg with Acetaminophen 975 mg in patients experiencing pain from a orthopedic surgical procedure to each component alone and to Placebo. The sponsor reports that while the single, 3-tablet dose of combination TRAM 112.5/APAP 975 was statistically superior to Placebo and to APAP 975 mg, it was only numerically superior to Tramadol 112.5 mg. The sponsor reports that the results of this trial demonstrate superior analgesic efficacy for the TRAM/APAP combination relative to one of its components, APAP 975 mg, but not the other, Tramadol 112.5 mg. ***[Study Review on page 21]***

Oral Surgery Studies TRAMAP-ANAG-010 and -013 were conducted to demonstrate the 8-hour analgesic superiority of single dose combination Tramadol 75 mg with Acetaminophen 650 mg to each component alone and to Placebo in patients experiencing moderate to severe pain from an oral surgical procedure. Ibuprofen 400 mg was included as an active reference control.

The DAAODP encourages the guidance of FDA's "Presentation of Efficacy Results of Single Dose Analgesics for Studies using Acute Pain Models", dated January 1997. This document explains, "single center studies require fewer number of patients per treatment group to achieve the same power as that obtained at multi-investigator studies, and statistical power calculations should be based on careful consideration for likely validity and the implications of the clinical significance of the differences to be detected. Most published parallel studies use from 30 to 50 patients per treatment group".

Larger sample sizes would allow for statistically significant differences to be achieved without clinically meaningful relevance, i.e. no clinically meaningful effect size. The guidance also states, "Comparisons of SPID and TOTPAR are generally not useful for overall comparisons of effectiveness", and instead, "Hourly pain and relief measurements may be useful within each study design".

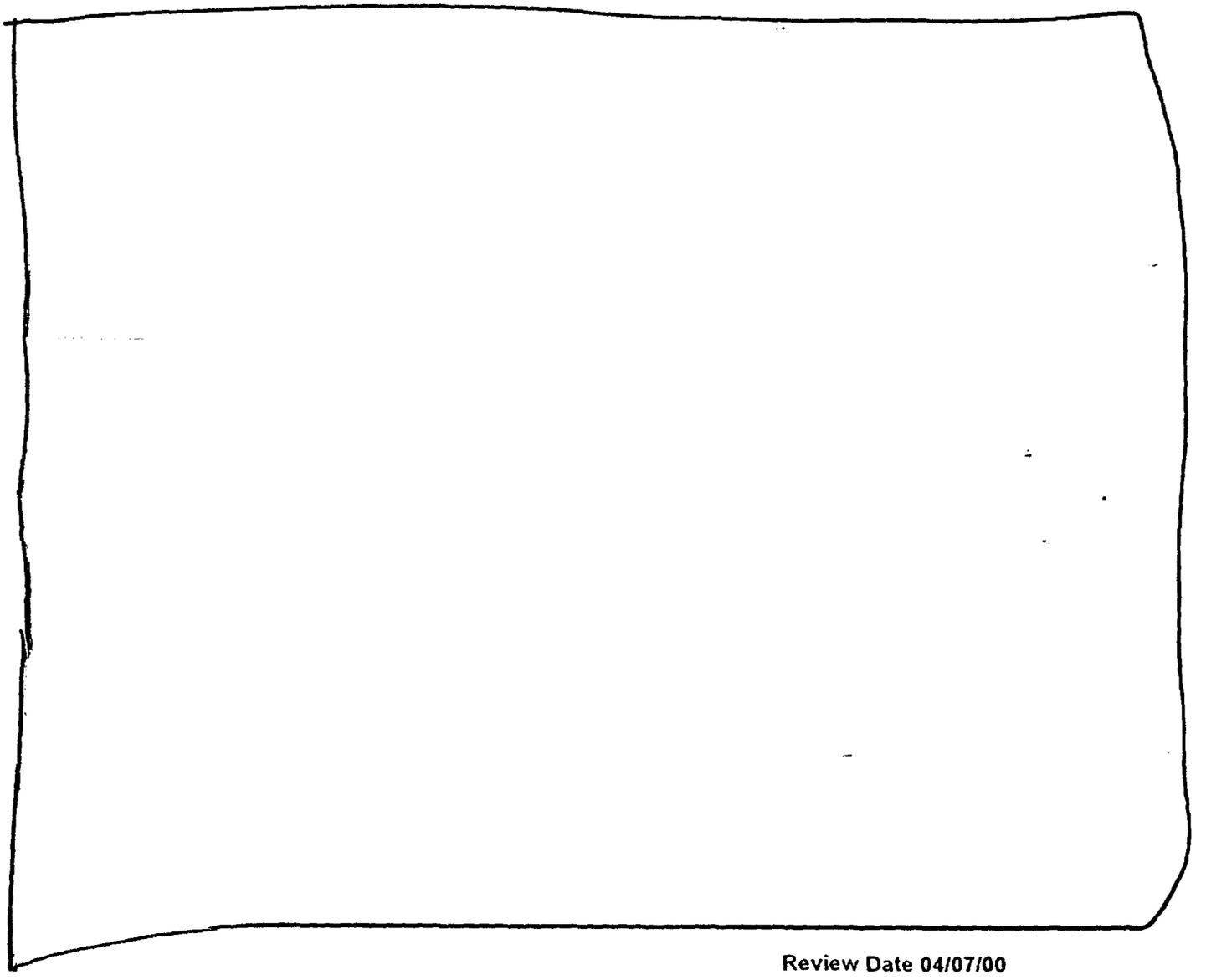
Postsurgical dental pain studies (-010 and -013) were conducted in sample sizes of 80 patients per treatment group. Although the protocols did not specifically define any particular efficacy variable(s) as primary, the sponsor increased the sample size in order to detect a between-group difference in total 8-hour pain relief (TOTPAR) of about 4 units, with an alpha level of 0.05. This equates to only a ½ unit mean difference. ***[Study Reviews on pages 2 and 13]***

Results were marginally positive. Both studies failed to show statistical separation between TRAM/APAP and each component throughout the 8-hour observation interval and demonstrated that greater efficacy can be realized from Ibuprofen 400 mg. Interpretation regarding efficacy is further complicated by the fact that after a significant number of patients completed study, the protocols were amended in order to change inclusion/exclusion criteria by redefining the allowed surgical procedure. Results on change in pain intensity from baseline, pain relief, and total pain relief scores for the 8 hours of postsurgical assessment are illustrated in the graphical and tabular summaries of these studies. ***[Attachments 1 through 5 - pages 30-34]***

The 2-sided testing used analysis of covariance with baseline pain intensity as the covariate, and an adjustment for the multiplicity of testing issues at an alpha level of 1.25%. Pairwise

comparisons for pain relief are consistent with those for pain intensity differences. Because the 95% confidence intervals for differences between TRAM/APAP and its components include zero, the component cannot be declared different from Tramadol 75 mg nor from APAP 650 mg.

With regard to change in pain intensity from that of baseline (PID) for all 8 hours of assessments, there was insufficient evidence to declare statistically significant differences between TRAM/APAP and APAP 650 mg. TRAM/APAP did separate statistically from Placebo for all time points in both studies, as did Ibuprofen 400 mg, with the exception of the 30 minute post-dose assessment. With regard to pain relief (PR) for all 8 hours, again there was insufficient evidence to determine statistically significant differences between TRAM/APAP and APAP 650 mg. And again, TRAM/APAP separated statistically from Placebo for all time points, as did Ibuprofen 400 mg, with the exception of the 30 minute post-dose assessment.



1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

/S/ 4-7-00

Lillian Patrician, MS, MBA
Mathematical Statistician

Concur: Stan Lin, PhD
cc: Orig. NDA 21-123
[redacted]
HFD-550/File/Midthun/Lee/Kong
HFD-725/File/Huque/Lin/Patrician
Chron.

STUDIES TRAMAP-ANAG -010 and -013 *Attachment 1 - Table AA*

Treatment Pairwise Comparisons in Postsurgical Dental Pain Studies

ITT using LOCF

Reviewer's Results: Time-Specific Change in Pain Intensity (PID) and Pain Relief (PR)

Measure - Study	Pairwise Comparison	Hour 0.5	Hour 1	Hour 2	Hour 3	Hour 4	Hour 5	Hour 6	Hour 7	Hour 8
Intensity Change (PID)										
PID -010	TRAM/APAP vs TRAM75	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.017	0.047	0.048
PID -013	TRAM/APAP vs TRAM75	<0.001	<0.001	<0.001	<0.001	0.015	0.021	0.170	0.111	0.074
PID -010	TRAM/APAP vs APAP650	0.958	0.327	0.278	0.086	0.007	0.004	0.018	0.018	0.018
PID -013	TRAM/APAP vs APAP650	0.604	0.675	0.024	0.027	0.135	0.036	0.110	0.038	0.034
PID -010	TRAM/APAP vs Placebo	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
PID -013	TRAM/APAP vs Placebo	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
PID -010	Ibuprofen400 vs Placebo	0.030	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
PID -013	Ibuprofen400 vs Placebo	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Pain Relief (PR)										
PR -010	TRAM/APAP vs TRAM75	0.002	<0.001	<0.001	<0.001	<0.001	<0.001	0.005	0.014	0.007
PR -013	TRAM/APAP vs TRAM75	<0.001	<0.001	<0.001	0.001	0.050	0.140	0.487	0.738	0.691
PR -010	TRAM/APAP vs APAP650	0.216	0.432	0.274	0.015	<0.001	<0.001	<0.001	0.002	0.001
PR -013	TRAM/APAP vs APAP650	0.812	0.690	0.041	0.019	0.100	0.029	0.062	0.059	0.054
PR -010	TRAM/APAP vs Placebo	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
PR -013	TRAM/APAP vs Placebo	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.003	0.004	0.006
PR -010	Ibuprofen400 vs Placebo	0.271	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
PR -013	Ibuprofen400 vs Placebo	0.018	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

The above are p-values (2-sided testing) using analysis of covariance with baseline pain intensity as the covariate.

Shaded cells represent statistically significant differences between treatment groups for post dose assessment times adjusted for the multiplicity of testing issues (at alpha level of 1.25%).

STUDIES TRAMAP-ANAG -010 and -013 *Attachment 2 - Table BB*

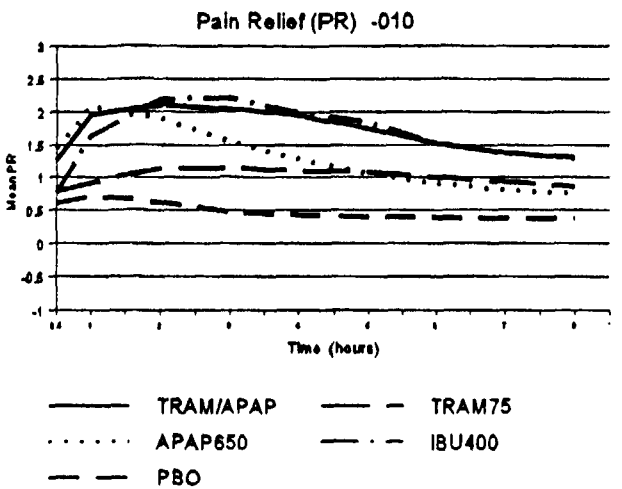
Treatment Pairwise Comparisons in Postsurgical Dental Pain Studies

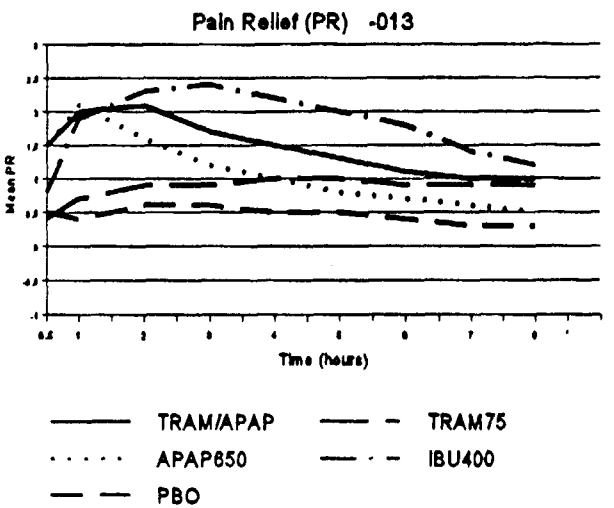
Reviewer's Results: Time-Specific Change in Pain Intensity (PID) and Pain Relief (PR) - ITT using LOCF

Pain Intensity Difference	Study - 010	Study - 013	Pain Relief	Study - 010	Study - 013
TRAM/APAP vs APAP650	95% CI [Diff]	95% CI [Diff]	TRAM/APAP vs APAP650	95% CI [Diff]	95% CI [Diff]
PID - Hour 0.5	[-0.18, 0.18] [A]	[-0.15, 0.27] [A]	PR - Hour 0.5	[-0.22, 0.16] [A]	[-0.35, 0.27] [A]
PID - Hour 1	[-0.32, 0.11] [A]	[-0.30, 0.20] [A]	PR - Hour 1	[-0.48, 0.21] [A]	[-0.45, 0.29] [A]
PID - Hour 2	[-0.12, 0.40] [A]	[0.05, 0.65]	PR - Hour 2	[-0.17, 0.59] [A]	[0.02, 0.90]
PID - Hour 3	[-0.03, 0.49] [A]	[0.04, 0.70]	PR - Hour 3	[0.10, 0.88]	[0.09, 1.03]
PID - Hour 4	[0.10, 0.61]	[-0.08, 0.60] [A]	PR - Hour 4	[0.27, 1.05]	[-0.08, 0.90] [A]
PID - Hour 5	[0.12, 0.62]	[0.02, 0.70]	PR - Hour 5	[0.31, 1.07]	[0.06, 1.02]
PID - Hour 6	[0.05, 0.54]	[-0.06, 0.58] [A]	PR - Hour 6	[0.26, 0.98]	[-0.02, 0.90] [A]
PID - Hour 7	[0.05, 0.51]	[0.02, 0.62]	PR - Hour 7	[0.22, 0.90]	[-0.02, 0.87] [A]
PID - Hour 8	[0.04, 0.49]	[0.02, 0.62]	PR - Hour 8	[0.22, 0.88]	[-0.005, 0.86] [A]
TRAM/APAP vs TRAM75	95% CI [Diff]	95% CI [Diff]	TRAM/APAP vs TRAM75	95% CI [Diff]	95% CI [Diff]
PID - Hour 0.5	[0.13, 0.49]	[0.53, 0.95]	PR - Hour 0.5	[0.44, 0.50]	[0.79, 1.41]
PID - Hour 1	[0.30, 0.72]	[0.68, 1.18]	PR - Hour 1	[0.70, 1.38]	[0.97, 1.71]
PID - Hour 2	[0.27, 0.79]	[0.56, 1.16]	PR - Hour 2	[0.59, 1.35]	[0.77, 1.66]
PID - Hour 3	[0.28, 0.80]	[0.30, 0.96]	PR - Hour 3	[0.51, 1.28]	[0.32, 1.25]
PID - Hour 4	[0.28, 0.80]	[0.08, 0.76]	PR - Hour 4	[0.46, 1.24]	[-0.01, 0.97] [A]
PID - Hour 5	[0.19, 0.69]	[0.06, 0.74]	PR - Hour 5	[0.28, 1.04]	[-0.12, 0.84] [A]
PID - Hour 6	[0.05, 0.54]	[-0.10, 0.55] [A]	PR - Hour 6	[0.16, 0.88]	[-0.30, 0.62] [A]
PID - Hour 7	[0.005, 0.47]	[-0.05, 0.55] [A]	PR - Hour 7	[0.10, 0.78]	[-0.37, 0.52] [A]
PID - Hour 8	[0.004, 0.45]	[-0.03, 0.57] [A]	PR - Hour 8	[0.12, 0.78]	[-0.35, 0.50] [A]

[A] *Confidence intervals that include zero indicate a null hypothesis of equal treatment means cannot be rejected.*

STUDIES TRAMAP-ANAG -010 and -013 ***Attachment 3 - Graph AA***
Postsurgical Dental Pain (Single Dose Studies)
Reviewer's Results
Mean Pain Relief (PR)
Intent-to-treat Population with Last Observation Carried Forward (LOCF)



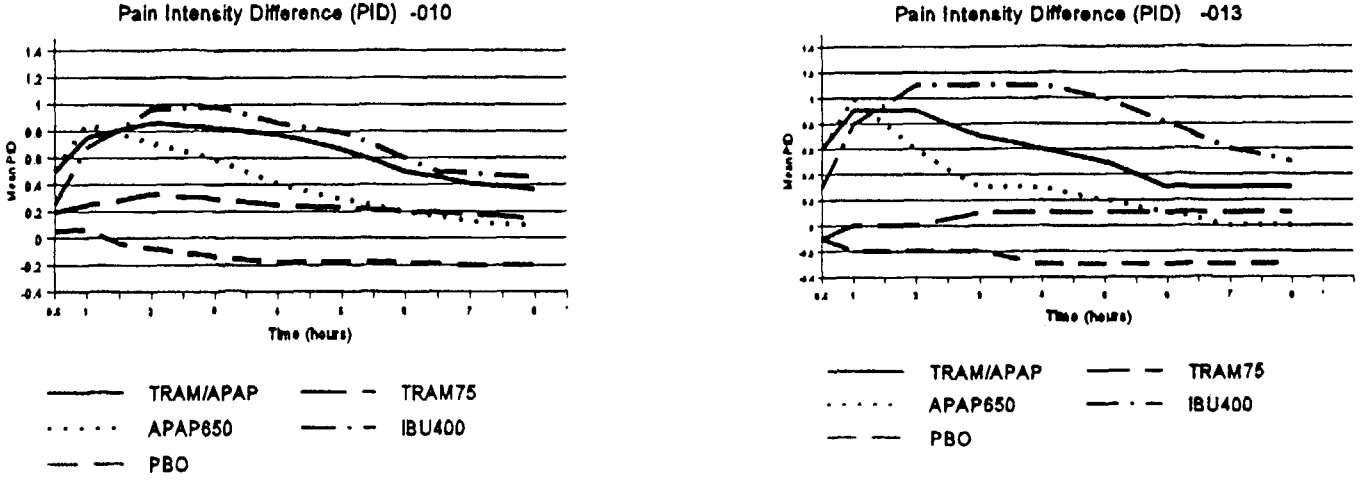


TRAM/APAP = Tramadol 75 mg / Acetaminophen 650 mg *TRAM75 = Tramadol 75 mg* *APAP650 = Acetaminophen 650 mg*
IBU400 = Ibuprofen 400 mg *PBO = Placebo*

Pain Relief (PR) Scores: 0=none; 1=little; 2=some; 3=lot; 4=complete

The above graphical representations of mean pain relief illustrate a close parallel between the TRAM75/APAP650 combination treatment and Ibuprofen 400 mg. In Study -013, there is earlier onset of action for TRAM75/APAP650 combination treatment, but overall, Ibuprofen 400 mg demonstrated greater pain relief over a longer period of time. In both studies, it appears that the APAP component in the TRAM/APAP combination treatment group contributes to the first 2 hours of pain relief while the Tramadol 75 mg then helps to sustain that relief through Hour 8. This demonstrates what the sponsor expected, i.e. combining the 2 products would provide for the rapid onset of action of APAP and the prolonged effect of Tramadol. Yet greater overall pain relief was realized in the Ibuprofen 400 mg group.

STUDIES TRAMAP-ANAG -010 and -013 ***Attachment 4 - Graph BB***
Postsurgical Dental Pain (Single Dose Studies)
Reviewer's Results
Mean Pain Intensity Difference (PID)
Intent-to-treat Population with Last Observation Carried Forward (LOCF)

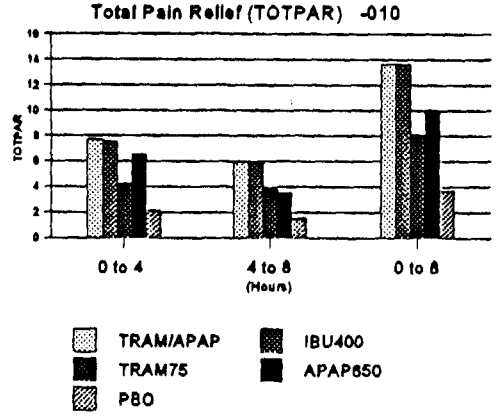


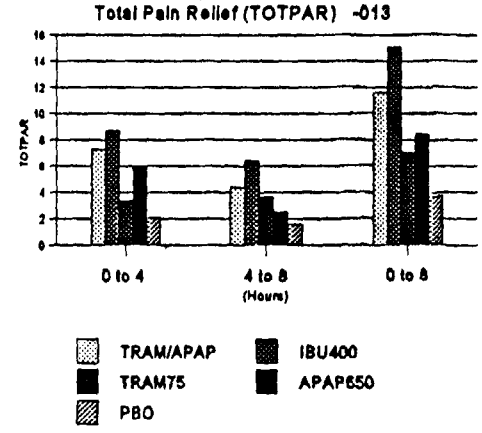
TRAM/APAP = Tramadol 75 mg / Acetaminophen 650 mg *TRAM75 = Tramadol 75 mg* *APAP650 = Acetaminophen 650 mg*
IBU400 = Ibuprofen 400 mg *PBO = Placebo*

** *Pain Intensity Difference (PID): -3 to -1 = pain increase; 0= no change; 1 to 3 =* pain decrease

The above graphical representations of mean change in pain intensity from baseline (PID) illustrate for both studies a greater mean decrease in pain intensity for the Ibuprofen 400 mg group. As is shown in the graphical representation for mean pain relief, in the TRAM/APAP combination treatment group, it appears that the APAP 650 mg component contributes to the first 2 hours of change in pain while the Tramadol 75 mg then helps to sustain that decrease through Hour 8.

STUDIES TRAMAP-ANAG -010 and -013 ***Attachment 5 - Graph CC***
Postsurgical Dental Pain (Single Dose Studies)
Reviewer's Results
Total Pain Relief (TOTPAR) at 0 to 4 hours; 4 to 8 hours; and 0 to 8 hours
Intent-to-treat Population with Last Observation Carried Forward (LOCF)





TRAM/APAP = Tramadol 75 mg / Acetaminophen 650 mg *TRAM75 = Tramadol 75 mg* *APAP650 = Acetaminophen 650 mg*
IBU400 = Ibuprofen 400 mg *PBO = Placebo*

TOTPAR Scores: *0= no pain relief; 2= little; 3= some; 4=complete*
max (0 to 4 hours) = 16 (complete relief at every evaluation)
max (0 to 8 hours) = 32 (complete relief at every evaluation)

The above graphical representation of total pain relief scores over time (TOTPAR) illustrates the overall sum of pain relief scores across the 8 hours of assessment. In Study -010, Ibuprofen 400 mg and TRAM/APAP provided comparable overall total pain relief across the 8 hours; in Study -013 Ibuprofen 400 mg was numerically greater than TRAM/APAP. Patients receiving TRAM/APAP, Ibuprofen 400 mg, and APAP 650 mg realized more total pain relief during the first 4 hours post surgery. APAP 650 mg appears to be contributing to the total pain relief during the first 4 hours of assessment, and then for the remaining 4 to 8 hours, each component (Tramadol 75 mg and APAP650 mg) appears to provide comparable total pain relief.

Secondary Statistical Review
(NDA 21-123, Ultracet Tablets)

This secondary review is written after reading the statistical review and after consultations with the medical reviewer. The statistical review disagreed with the sponsor's finding of efficacy for the combination product (Ultracet, also referred to as TRAM/APAP combination) relative to its components in all four studies reviewed. (These four studies are summarily described in the appendix 1 to this secondary review and further details are found in the statistical review.) [redacted] 010 and 013, have demonstrated superior efficacy of the combination compared to its components.

In reviewing the efficacy data, it is useful to bear in mind the rationale behind the development of the TRAM/APAP combination, namely, the combination of a rapid onset, short-acting agent (APAP) with a slower onset, longer-acting agent (tramadol). Thus it may not be entirely reasonable to expect, or to demand the combination product to be statistically superior to its components at all time points of evaluation (0.5, 1, ...8 hours), and the protocols never stipulated about this. With this in mind, the sponsor's results on the usual efficacy endpoints (PR, PID, PRID, Onset, and Duration) from these two dental pain studies can be summarized and evaluated. For the endpoints pain relief and pain intensity difference, these are summarized in Tables B-010 and B-013 (pages 7 and 15 of the statistical review, which is attached). It is clear from these summaries that the two studies consistently demonstrated the early separation of these two pain scores between the combination product and tramadol, because of the addition of the faster onset APAP in the combination product. As would be expected, no significant differences were detected between the combination product and APAP in these early measurements. It is also notable that even after the initial hours, the combination product still scored numerically (but not statistically) better in both pain relief and pain intensity difference than its two components, in both studies.

The results for PRID for the two studies are summarized in the appendix 2. Again, the statistical tests show expected pattern of results. The results on perceptible and meaningful pain relief according to the stop-watch approach are summarized and depicted in the appendix 3. Again as expected, No significant difference is evident in the onset between the combination and APAP, but the combination showed a faster onset compared to tramadol, especially in terms of the meaningful pain relief. Duration of effect usually has been measured in terms of the median time to re-medication. The results on this are shown in appendix 4. These show that the combination product has a longer duration of effect compared to its components.

In summary, this is a somewhat complicated submission involving a combination of two well-known analgesic products. Therefore, the interpretation of the study results must take into account the rationale for the combination, namely a faster onset of analgesic effect than tramadol and a longer duration of analgesic effect than APAP. The single-dose dental surgery pain studies demonstrated the superiority of the combination product

over its components in analgesic effects. This is not to conclude that the submission is approvable for its intended indication because there are deficiencies in the package, for example, lack of adequate repeat-dosing information. These deficiencies will be further discussed in the medical review and are not within the scope of this review.

/S/ 6/7/00

Stan Lin, Ph.D.

Concur: /S/ 6/7/00
Dr. Huque

cc: NDA21-123
HFD-550/Lee/Midthun
HFD-550/Div. File
HFD-725/Huque/Patrician/Lin St.
HFD-725/Div. File
HFD-550/Kong
This review has two pages of text and four appendices of tables

Appendix 1

Study	Design	Dose	N	Endpoints
005	**Orthopedic Surg Pain** DB,factorial, Single Dose Comb/Tram/Apap/Pbo	T112.5, A975 Pbo	200	PRID, PI, PR, Onset, Duration
[redacted]				
010	**Dental Pain** DB, factorial, Single Dose Comb/Tram/Apap/pbo/Ibu	T75, A650 Ibu 400	400	PRID, PID, PR, Onset, Duration
013	**Dental Pain** DB, factorial, Single Dose Comb/Tram/Apap/pbo/Ibu	T75, A650 Ibu 400	400	PRID, PID, PR, Onset, Duration
T=Tramadol, A=APAP, in mg. Pbo=Placebo, Ibu=Ibuprofen, A/C=Active control				

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Appendix 2

Protocol TRAMAP-ANAG-010: Mean Pain Relief Plus Pain Intensity Difference (PRID) Scores[a]

	Hours								
Treatment	0.50	1	2	3	4	5	6	7	8
TRAM/APAP	1. (1.66)	2.7 (1.75)	3.0 (1.93)	2.9 (2.11)	2.7 (2.17)	2.4 (2.10)	2.0 (2.15)	1.8 (2.07)	1.7 (1.89)
	A	AB	A	A	A	A	A	A	A
	79	80	75	59	51	47	42	30	23
TRAM 75 mg	1. (1.37)	1.2 (1.74)	1.5 (2.10)	1.4 (2.14)	1.3 (2.04)	1.3 (2.05)	1.2 (1.94)	1.1 (1.89)	1.0 (1.77)
	B	C	B	C	B	B	B	B	B
	78	78	69	30	21	18	17	14	11
APAP 650 mg	1. (1.60)	3.0 (1.69)	2.6 (2.13)	2.2 (2.11)	1.7 (1.96)	1.3 (1.80)	1.1 (1.64)	0.9 (1.47)	0.9 (1.31)
	A	A	A	B	B	B	B	B	B
	79	80	78	49	39	29	18	14	10
Ibuprof 400 mg	1. (1.45)	2.3 (2.04)	3.1 (2.27)	3.2 (2.39)	2.9 (2.45)	2.6 (2.38)	2.1 (2.15)	1.9 (2.09)	1.7 (2.04)
	B	B	A	A	A	A	A	A	A
	80	80	72	57	51	42	38	28	20
Placebo	0. (1.17)	0.8 (1.40)	0.5 (1.55)	0.3 (1.40)	0.3 (1.37)	0.2 (1.37)	0.2 (1.37)	0.2 (1.31)	0.2 (1.33)
	B	C	C	D	C	C	C	C	C
	79	79	56	19	10	6	5	5	3
P-Value[b]	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
RMS Error	1.459	1.738	2.012	2.058	2.032	1.969	1.875	1.792	1.694

[a]Treatment means with a common letter (i.e., A,B,C,D) are not significantly different by Fisher's LSD at a level of 0.05. For each treatment group mean (SD), the number of subjects remaining in the trial is displayed at each time point.
[b]Statistically significant difference among all treatment groups at p_0.05, F-test.

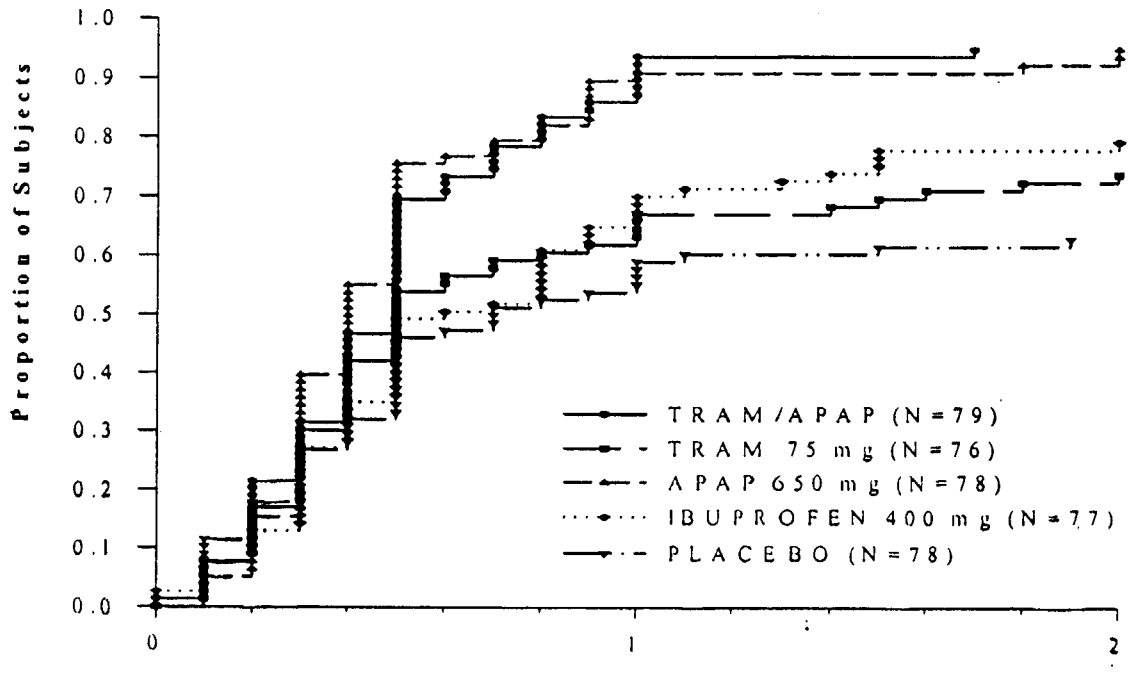
Protocol TRAMAP-ANAG-013: Mean Pain Relief Plus Pain Intensity Difference (PRID) Scores[a]

	Hours								
Treatment	0.5	1	2	3	4	5	6	7	8
TRAM/APAP	2.1 (2.02)	2.9 (2.09)	3.0 (2.47)	2.4 (2.77)	2.0 (2.78)	1.8 (2.81)	1.4 (2.61)	1.3 (2.58)	1.3 (2.62)
	80	80	78	67	51	39	35	29	25
	A	A	A	B	B	B	B	B	AB
TRAM 75 mg	0.3 (1.22)	0.7 (1.71)	0.9 (2.16)	1.0 (2.39)	1.1 (2.62)	1.1 (2.63)	1.1 (2.59)	1.0 (2.50)	0.9 (2.40)
	80	80	71	33	27	24	23	23	22
	C	B	C	CD	CD	BC	B	BC	BC
APAP 650 mg	2.1 (1.93)	3.1 (2.28)	2.2 (2.60)	1.5 (2.64)	1.3 (2.66)	1.0 (2.39)	0.8 (2.22)	0.6 (1.99)	0.5 (1.92)
	80	80	80	52	31	26	20	16	13
	A	A	B	C	BC	CD	BC	CD	CD
Ibuprof400 mg	1.1 (1.52)	2.7 (2.24)	3.4 (2.61)	3.5 (2.77)	3.3 (2.95)	2.9 (2.99)	2.6 (2.93)	2.1 (2.74)	1.7 (2.63)
	80	80	79	65	59	54	49	44	38
	B	A	A	A	A	A	A	A	A
Placebo	0.4 (1.30)	0.3 (1.35)	0.4 (1.93)	0.4 (2.11)	0.3 (2.15)	0.3 (2.19)	0.1 (1.94)	0.0 (1.82)	0.0 (1.82)
	80	80	69	25	18	14	12	10	7
	C	B	C	D	D	D	C	D	D
p-Value[b]	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
RMS Error	1.631	1.967	2.368	2.551	2.644	2.617	2.482	2.352	2.303

[a]Treatment means with a common letter (i.e., A,B,C,D) are not significantly different by Fisher's LSD at a level of 0.05. For each treatment group mean (SD), the number of subjects remaining in the trial is displayed at each time point.
[b]Statistically significant difference among all treatment groups at p≤0.05, F-test.

Appendix 3.1: Last Observation Carried Forward (Continued)
(Protocol TRAMAP-ANAG-010)

TIME TO ONSET OF PERCEPTIBLE PAIN RELIEF



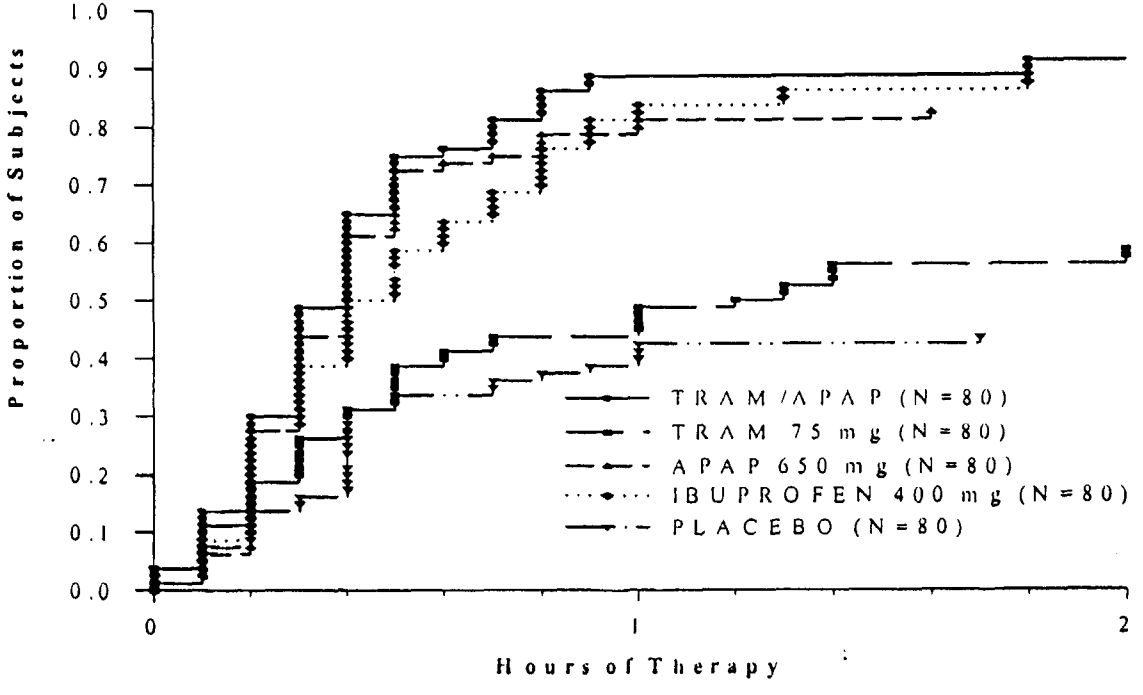
TIME TO ONSET OF PERCEPTIBLE PAIN RELIEF

		Selected Percentiles (in minutes)				
Treatment	N	25%	50% (median)	Lower 95% CL	Upper 95% CL*	75%
TRAM/APAP	79	18.5	27.9	24.9	31.1	40.2
TRAM	76	16.2	30.7	24.9	56.5	.
APAP	78	17.1	25.4	21.0	28.6	32.1
Ibuprofen	77	19.4	38.6	30.4	50.8	91.0
Placebo	78	20.4	43.5	29.9	89.8	.

* Confidence limits for the median.

Appendix 32: Last Observation Carried Forward (Continued)
(Protocol TRAMAP-ANAG-013)

TIME TO ONSET OF PERCEPTIBLE PAIN RELIEF



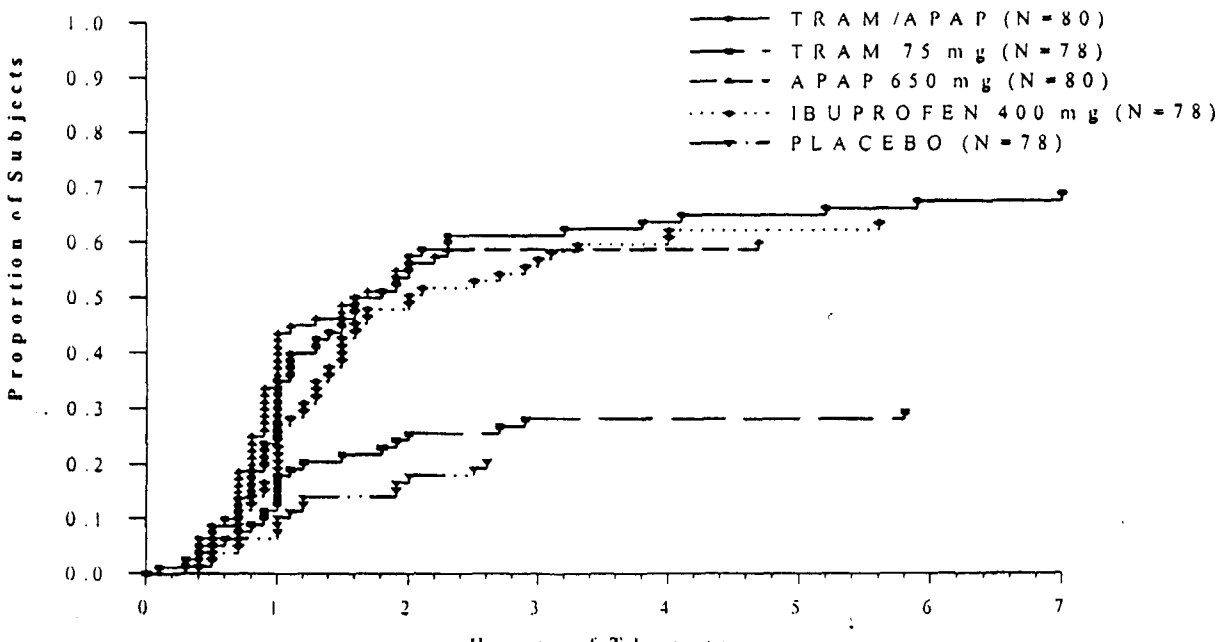
TIME TO ONSET OF PERCEPTIBLE PAIN RELIEF

		Selected Percentiles (in minutes)				
Treatment	N	25%	50% (median)	Lower 95% CL	Upper 95% CL	75%
TRAM/APAP	80	13.5	21.1	17.8	24.3	35.
TRAM	80	20.5	74.3	33.9	.	.
APAP	80	14.7	23.5	20.1	27.0	43.
Ibuprofen	80	13.8	27.1	22.2	35.9	50.
Placebo	80	24.4	.	57.3	.	.

* Confidence limits for the median.

Appendix 3.3: Last Observation Carried Forward (Continued)
(Protocol TRAMAP-ANAG-010)

TIME TO ONSET MEANINGFUL PAIN RELIEF



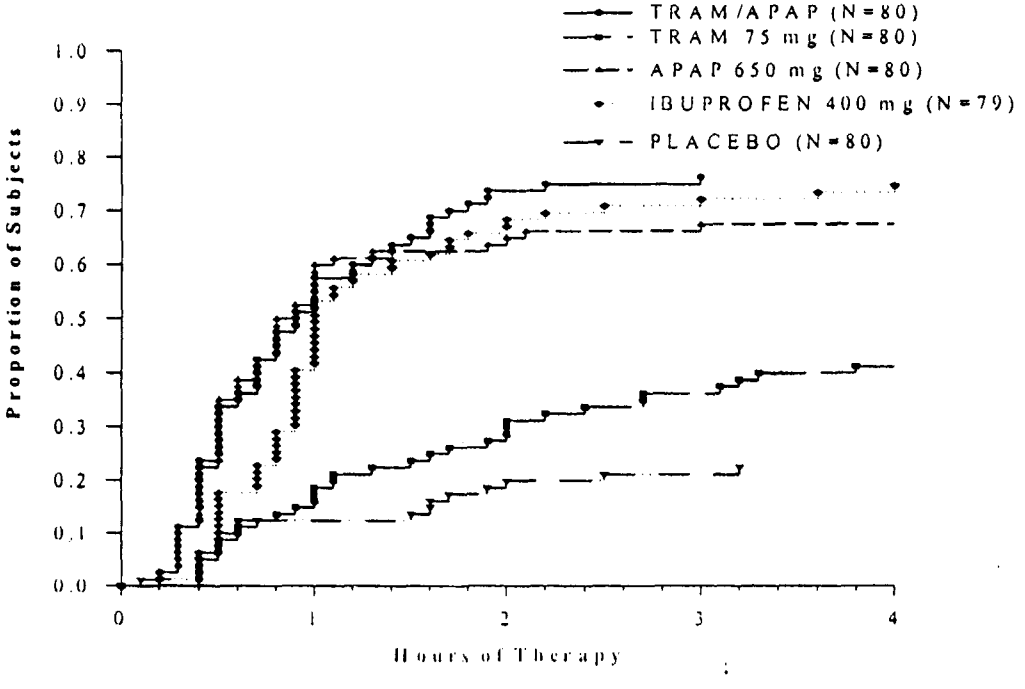
TIME TO ONSET OF MEANINGFUL PAIN RELIEF

Treatment	N	Selected Percentiles (in minutes) 25%	50% (median)	Lower 95% CL	Upper 95% CL	75%
TRAM/APAP	80	57.8	103.0	68.7	138.3	.
TRAM	78	121.6	.	.	.	.
APAP	80	51.4	99.8	60.0	.	.
Ibuprofen	78	61.9	121.0	90.3	241.7	.
Placebo	78	.	.	.	.	.

* Confidence limits for the median.

Appendix 3.4: Last Observation Carried Forward (Continued) (Protocol TRAMAP-ANAG-013)

TIME TO ONSET OF MEANINGFUL PAIN RELIEF



TIME TO ONSET OF MEANINGFUL PAIN RELIEF

		Selected Percentiles (in minutes)				
Treatment	N	25%	50% (median)	Lower 95% CL	Upper 95% CL	75%
TRAM/APAP	80	29.3	54.5	40.1	78.2	154.9
TRAM	80	100.6	.	197.0	.	.
APAP	80	29.3	51.8	42.5	63.5	.
Ibuprofen	79	47.0	61.5	56.4	97.4	300.0
Placebo	80	.	.	.	.	.

* Confidence limits for the median.

Appendix 4

Protocol TRAMAP-ANAG-010: Selected Percentiles for Time (minutes) to Remedication

Treatment	N	25th	50th (Median)	75th
TRAM/APAP	80	141.0	326.0	--[a]
TRAM 75 mg	78	121.0	124.0	238.0
APAP 650 mg	80	123.0	184.0	304.0
Ibuprofen 200 mg	80	126.0	301.0	460.0
Placebo	79	80.0	122.0	128.0

[a] Percentile not estimable.

Protocol TRAMAP-ANAG-010: Analysis of Time (minutes) to Remedication[a]

Treatment	N	Combination vs. Each Component[a]	Active Treatments vs. Placebo[a]
TRAM/APAP	80	--	<0.001
TRAM 75 mg	78	<0.001	0.002
APAP 650 mg	80	<0.001	<0.001
Ibuprofen 400 mg	80	--	<0.001

[a] Using Log-rank statistics for pairwise comparisons; statistically significant if p_0.05.

Protocol TRAMAP-ANAG-013: Selected Percentiles for Time (Minutes) to Remedication

Treatment	N	25th	50th (Median)	75th
TRAM/APAP	80	150.0	245.0	--[a]
TRAM	80	98.5	123.0	--[a]
APAP	80	120.0	165.0	310.0
Ibuprofen	80	182.5	422.5	--[a]
Placebo	80	78.5	105.0	159.0

[a] Percentile not estimable.

Protocol TRAMAP-ANAG-013: Analysis of Time (Minutes) to Remedication[a]

Treatment	N	Combination vs. Each Component	Active Treatments vs. Placebo
TRAM/APAP	80	--	<0.001
TRAM	80	0.012	0.001
APAP	80	0.003	<0.001
Ibuprofen	80	--	<0.001

[a] Using Log-rank statistics for pairwise comparisons; statistically significant if p≤0.05.