CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-123

MEDICAL REVIEW

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANTI-INFLAMMATORY, ANALGESIC, AND OPHTHALMIC DRUG PRODUCTS
HFD-550, 9201 Corporate Blvd, Rockville MD 20850 Tel:(301)827-2040

REVIEW AND EVALUATION OF CLINICAL DATA

Application Information

NDA #: 21-123
Sponsor: The R.W. Johnson Pharmaceutical Research Institute.

Drug Name

Generic Name: Tramadol Hydrochloride (37.5 mg) /Acetaminophen Tablets (325 mg);
Trade Name:

Drug Categorization

Pharmacological Class: Centrally Acting Synthetic Analgesic/Non-Steroidal Anti-inflammatory

Proposed Indication: [redacted] Acute [redacted] pain.

NDA Classification: 3 S

Dosage Forms: 37.5 mg tramadol hydrochloride/325 mg acetaminophen tablets

Route: Oral

Reviewer Information

Clinical Reviewer: Chang Q. Lee, MD, M.S.H.A., Dr.PH /S/ 6/6/2000

Peer Medical reviewer: Karen Midthun, MD, Division Director /S/ 6/6/00

Original Receipt Date: August 31, 1999

Completion Date: April 30, 2000

SECTION 1.0 MATERIAL UTILIZED IN REVIEW

NDA Hard Copy of Clinical Data, Item 8, consists of 203 bound volumes:

Overall NDA Volume of 380	Item/ Volume	NDA Item
1	1/1	Index
2	2/1	Draft Labels/Labeling
3-9	3/1-7	Overall Application Summary
49	8/1 (Note: all references to Item 8 are representative of Item 8/10)	Clinical Data Section: Reviewers Guide, Alphabetical List of Investigators, List of INDs/NDAs, Background Overview of Clinical Investigations
50	8/2	Summary Presentation of Single-Dose Efficacy Data
51-61	8/3-13	Clinical Pharmacology
62-156	8/14	Individual Study Reports Protocol CA
157	8/109	Commercial Marketing & Foreign Actions
157-160	8/109-112	ISE
161-165	8/113-117	ISS
166	8/118	Drug Abuse & Overdose Benefits/Risks
167-227	8/119	Comprehensive ULTRAM® (tramadol HCl tablets) Abuse Liability Review & Update:
228 - 249	8/154	Comprehensive ULTRAM® (tramadol HCl tablets) Safety Review and Update:
250-251	8/176-177	References for Item 8
252	11/1	Tabulations (Index provides cross reference to Item 8 Trial Reports)
253 - 380	12/1	CRFs

- Electronic Data: Three CD-ROM disks were submitted as a review aid to this NDA, including Item 8/10: Clinical and Statistical Data (All text in Microsoft® Word 97 and/or PDF format (except the tramadol comprehensive abuse and safety updates) and for each clinical efficacy study SAS datasets in Transport Format.

A four-month safety update on NDA 21-123 was submitted on December 10, 1999. It consists of a written submission of 37 individual volumes, and an electronic review aid (CD-ROM Volume 4). The safety reporting period extends from April 12, 1999 to October 15, 1999.

SECTION 2.0 BACKGROUND

Tramadol hydrochloride is a centrally acting synthetic analgesic originally developed by [redacted] It is not derived from natural sources, nor is it chemically related to opiates. Through a licensing agreement with [redacted] has developed tramadol in the United States. As of March 3, 1995, the use of ULTRAM® (tramadol hydrochloride) has been approved in the United States for the management of [redacted] pain (NDA 20-281). Tramadol is also marketed as an analgesic outside of the United States by [redacted] or its other licensing partners.

Although tramadol's mode of action is not completely understood, it appears from animal tests that at least two complementary mechanisms may contribute to its antinociceptive effect: 1) binding of parent and its mono-*O*-desmethyl metabolite (M1) to μ-opioid receptors, and 2) weak inhibition of uptake or norepinephrine and serotonin. An examination of the pharmacokinetic and pharmacodynamic profile of tramadol reveals peak activity in 2 to 3 hours with a prolonged analgesic effect, suggesting that its combination with a rapid-onset, short-acting analgesic agent may provide substantial benefit to patients over either component alone.

Acetaminophen (APAP) was chosen as the second component of a fixed-dose combination with tramadol by RWJPRI. APAP is a weak inhibitor of prostaglandin biosynthesis, and has a rapid-onset and is short acting (peak analgesic activity in 0.5 - hours). Non-opioid analgesics such as APAP, aspirin, and nonsteroidal anti-inflammatory drugs (NSAIDs) are often used in alleviating pain of low-to-moderate intensity, whereas the opioid analgesics are typically used to relieve more severe pain.

The combination product (37.5 mg tramadol hydrochloride /325 mg acetaminophen tablet) combines two centrally acting analgesics, tramadol and APAP.

SECTION 2.1 INDICATION

The proposed indication for TRAM/APAP (Combination of Tramadol with Acetaminophen) is:

"INDICATED FOR THE MANAGEMENT OF [redacted] ACUTE [redacted] PAIN."

The sponsor also proposes other potential claims under "Clinical Studies" section:

- *"The onset of pain relief after TRAM/APAP was faster than tramadol alone and the duration of pain relief was significantly longer for TRAM/APAP than for tramadol or acetaminophen alone."*
- *"Tramadol/acetaminophen demonstrates comparable analgesic effectiveness to acetaminophen/Codeine and ibuprofen in the treatment of [redacted] pain."*

SECTION 2.2 RELATED IND'S AND NDA'S

Data cited in this review was conducted under the following IND or NDAs:

TABLE 1. LIST OF INDs AND NDAs

IND/NDA#	Drug Substance	Sponsor	Date Filed to FDA
[redacted]	tramadol hydrochloride/ acetaminophen combination product	The R.W. Johnson Pharmaceutical Research Institute	15 March 1996
	[redacted]	The R.W. Johnson Pharmaceutical Research Institute	25 October 1985
		The R.W. Johnson Pharmaceutical Research Institute	Filed 28 August 1992; Approved 3 March 1995

*One of the studies provided in this NDA 21-123 submission (TRAMAP-ANAG-007) was originally filed and conducted under [redacted] In an IND Annual Report dated 18 March 1999, Serial No. 245, it was noted that any further information for this study would be provided in [redacted] Tramadol Acetaminophen Combination Product. Two additional studies provided in this NDA 21-123 submission, CA and CB, were conducted under [redacted] Abbreviated final study reports for both studies were submitted to [redacted] on 15 March 1996, Serial No. 000. Revised final study reports for both studies were submitted to [redacted] on 21 May 1998, Serial No. 045, with a cross reference to [redacted] Serial No. 230.

SECTION 2.3 ADMINISTRATIVE HISTORY

The sponsor opened the IND [redacted] on March 15, 1996 to expand the clinical development program for tramadol. It was hoped that tramadol when administered as a fixed-dose combination would have the potential benefits of a reduction in the required dose of each active component and presumably an improved safety profile. Acetaminophen (APAP) was chosen as the second component of a fixed-dose combination with tramadol. The rationale is that APAP is a rapid-onset and short-acting analgesic agent while tramadol has a delayed onset and a prolonged effect.

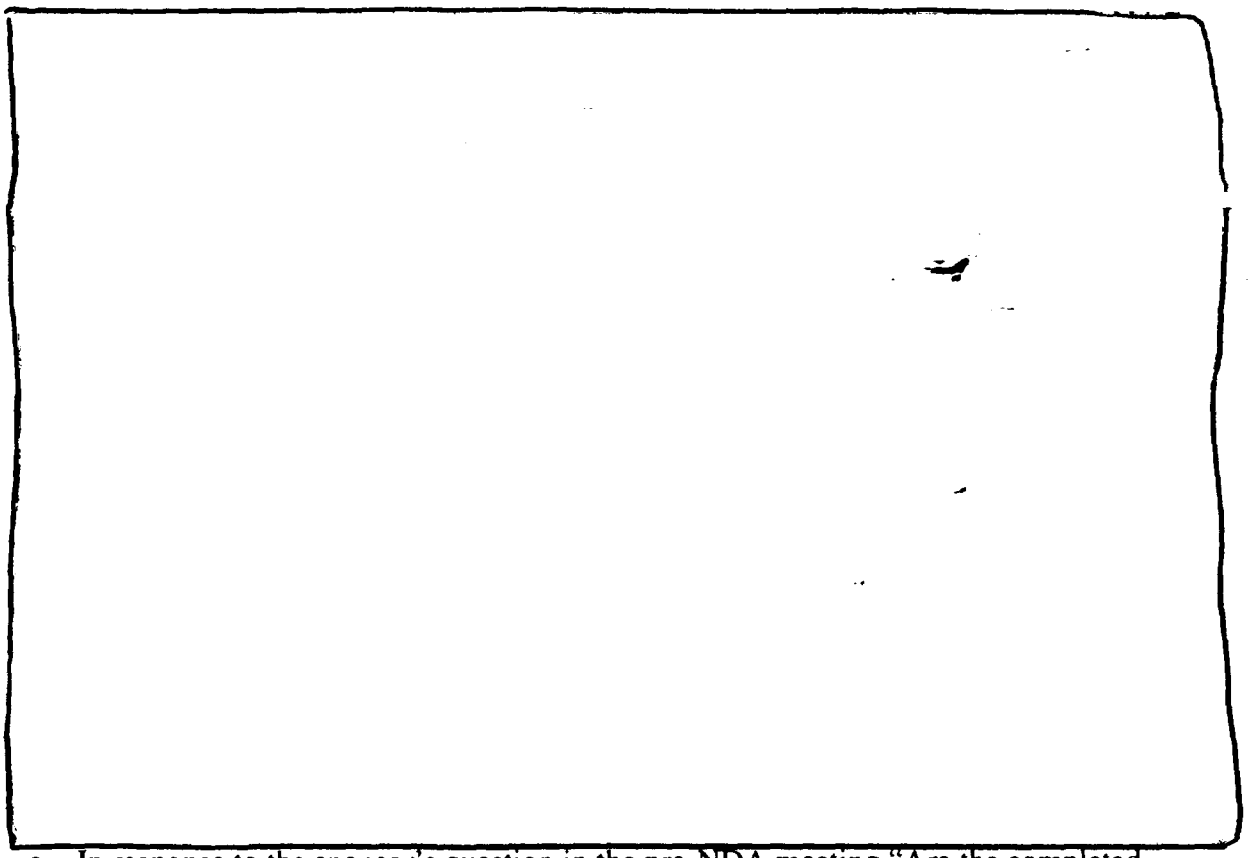
The initial pilot studies (Protocols CA and CB) and a dose-ranging trial (Protocol TRAMAP-ANAG-007) used different combinations of Tramadol/APAP (100/500 mg, 25/50 mg, 50/650 mg, and 25/650 mg). The sponsor finally selected the proposed

commercial formulation of Tramadol/APAP (37.5 mg tramadol plus 325 mg APAP). This fixed-dose combination was used in subsequent clinical trials.

- FDA had several discussions with the sponsor concerning the development program for the fixed-dose Tramadol/APAP combination during the approximate three-year period spanning from the pre-IND meeting on November 28, 1995 to the pre-NDA meeting on December 7, 1998. FDA Guidelines for the Clinical Evaluation of Analgesic Drugs (December, 1992) and the Agency's policy concerning fixed-dose combination prescription drugs [21 CFR 300.50(a)] were provided to the sponsor. These guidelines require that the analgesic effect of a combination product be statistically superior to the individual effects of each component administered alone. This requirement ensures that a combination analgesic product, such as Tramadol/APAP, offers an incremental therapeutic benefit over each of its components.

The summary of these discussions on the design of clinical trials are provided below:

- Based upon input from FDA, the original proposed active control for the single-dose dental pain trials (APAP with codeine) was changed to ibuprofen 400 mg. [11/28/95].
- The sponsor altered the proposed analysis plan for the single-dose efficacy and safety trials based upon discussions with FDA. Specifically, subject ratings of pain relief and pain intensity differences were collected at each observation timepoint (including one hour post-dose); the trials were also designed to collect information on the onset and duration of pain relief and the time to remedication. In addition, the primary efficacy analyses were expanded to include three summary efficacy endpoints: total pain relief (TOTPAR), sum of pain intensity differences (SPID), and sum of pain relief + pain intensity differences (SPRID). [11/28/95]
- A four-point scale would be used to assess pain intensity difference and a five-point scale would be used to evaluate pain relief, based upon FDA's extensive experience with these scales. [11/28/95]
- The post-dose evaluation periods for some of the efficacy and safety trials were of different lengths (i.e., six- versus eight-hours), provided the periods selected were amenable to dosing intervals. [11/28/95]
- The sponsor would provide a separate volume containing summaries of key efficacy endpoints for each single-dose trial that used the proposed Tramadol/APAP commercial formulation. Following a request by FDA to analyze efficacy data from these single-dose trials using a baseline or worst observation carried forward method, RWJPRI agreed to provide a reanalysis of key efficacy data in Protocols TRAMAP-ANAG-002, 003, 004, 005, 010, 012, and 013 using a baseline observation carried forward approach. (12/7/98)



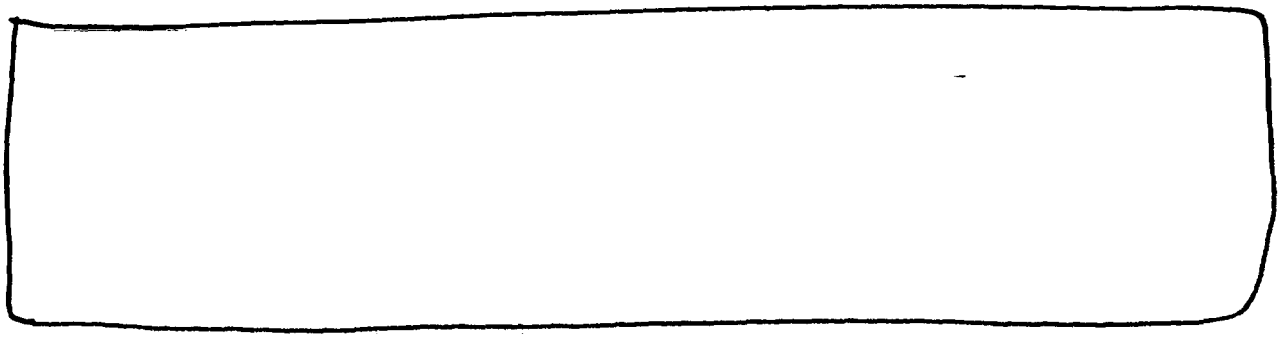
- In response to the sponsor's question in the pre-NDA meeting "Are the completed clinical studies adequate to demonstrate safety and efficacy of tramadol HCl/APAP in support of the NDA for this combination product?" the Agency stated that it could not speak to their adequacy and the approvable indication specifically without reviewing the data, and the clinical program seemed to provide a fileable package. [12/07/98 and 2/19/99]

This NDA 21-123 for the tramadol HCL/APAP was received on 9-01-1999.

SECTION 2.4 PROPOSED DIRECTIONS FOR USE

The directions for use in the proposed labeling are provided below:

DOSAGE AND ADMINISTRATION



[redacted]

SECTION 2.5 FOREIGN MARKETING

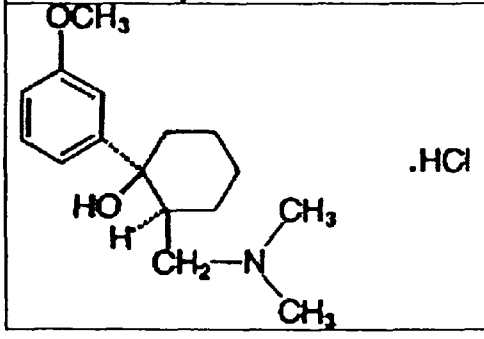
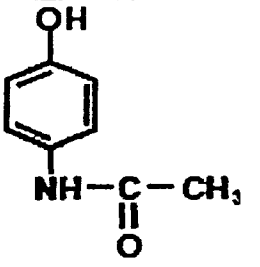
Tramadol HCL/APAP has not been marketed in any country. However, the drug substance, tramadol hydrochloride, a component of this combination product is marketed globally in various dosage forms such as capsules, drops, prolonged-release tablets, solution for injection, suppositories, soluble tablets, and tablets. Tramadol was first approved for marketing in Germany in 1973 and has since been approved for marketing in many European Union (EU) and non-EU countries. It is available in oral, injectable and suppository formulations sold in over 90 countries. Non-U.S. market exposure is estimated to be about [redacted] patients.

Acetaminophen was classified as a Category I Active ingredient (generally recognized as safe and effective) when the proposed rule establishing a monograph for OTC Internal Analgesics published in the Federal Register (FR Vol. 42, No. 131, page 35382) on Friday, July 8, 1977. Acetaminophen has been marketed in OTC dosage form in the United States for 40 years and is in wide use.

SECTION 3.0 CHEMISTRY

Compound Names: tramadol hydrochloride and acetaminophen
Chemical Names: The chemical name for tramadol hydrochloride is (±)cis-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride.

The chemical name for acetaminophen is N-acetyl-*p*-aminophenol.
The structural formula for each compound is:

Tramadol Hydrochloride	Acetaminophen
	

The molecular weight of tramadol hydrochloride is 299.84. Tramadol hydrochloride is a white, bitter, crystalline and odorless powder.

The molecular weight of acetaminophen is 151.17. Acetaminophen occurs as a white, odorless, crystalline powder, possessing a slightly bitter taste.

Tramadol/APAP tablets contain 37.5 mg tramadol hydrochloride and 325 mg acetaminophen and are light yellow in color. Inactive ingredients in the tablet are powdered cellulose, pregelatinized starch, sodium starch glycolate, starch, purified water, magnesium stearate, OPADRY Light Yellow, and carnauba wax.

SECTION 4.0 ANIMAL PHARMACOLOGY/TOXICOLOGY

The sponsor has summarized their studies and literature on toxicology data for Tramadol/APAP in Item 3, Chapter 5. The following is a condensation of that summary.

Pharmacologically, the centrally acting analgesic tramadol hydrochloride is thought to produce its effect through a dual mechanism, agonist activity at the μ-opioid receptor and inhibition of monoamine reuptake. Acetaminophen is another centrally acting analgesic. Although the exact site and mechanism of its analgesic action is not clearly defined, acetaminophen appears to produce analgesia by elevation of the pain threshold. The potential mechanism may involve inhibition of the nitric oxide pathway mediated by a variety of neurotransmitter receptors including N-methyl-D-aspartate and Substance P.

Although acetaminophen is well-tolerated at recommended therapeutic doses, acute overdoses are known to produce liver and kidney toxicity in humans as well as in experimental animals. Acetaminophen-induced changes in the liver were first reported in rats, although it was later shown that rats were not as susceptible as mice or hamsters to these effects. Hepatic lesions associated with acetaminophen administration are generally characterized morphologically by hydropic vacuolation, centrilobular necrosis, macrophage infiltration and regenerative activity, although variability among species has been reported. For example, a single oral dose of 500 mg/kg produced toxicity that included hepatic centrilobular necrosis in dogs, whereas 120 mg/kg produced more diffuse liver changes in cats.

The nonclinical safety profile of the Tramadol/APAP combination was evaluated in single and multiple-dose studies in rats and dogs. Eight nonclinical toxicity studies were completed on this analgesic combination that consisted of: three acute toxicity studies - two conducted in rats and one in dogs, four 4-week and 3-month multiple-dose toxicity studies in rats and dogs (two per species), and one developmental toxicity study in rats. no carcinogenicity or mutagenicity studies were done using the Tramadol/APAP combination product.

Single-Dose Toxicity Studies

When administered via gavage to rats and dogs, the Tramadol/APAP combination produced clinical signs similar to those produced by tramadol or APAP individually. There is no evidence that the acute toxicity of either drug is enhanced by coadministration.

Repeated-Dose Toxicity Studies
Observations made during multiple-dose toxicity studies of Tramadol/APAP were consistent with the known toxicity of the individual components. However in the dog at the highest dosage tested, a species-specific pharmacokinetic interaction was demonstrated resulting in initially elevated plasma APAP levels and initially more severe hepatotoxicity for APAP when administered in combination with tramadol as compared to that observed with administration of APAP alone; the interaction was not observed following multiple-dose administration. This interaction was determined by the sponsor to be species-specific and with little clinical significance.

Developmental Toxicity Study
No teratogenic effects were observed in a developmental toxicity study with the combination of Tramadol/APAP. Embryo-fetal toxicity in the presence of maternal toxicity was indicated by lower fetal weights and increased supernumerary ribs at only the highest dose level of combination.

SECTION 5.0 DESCRIPTION OF CLINICAL DATA SOURCES

The clinical development program to evaluate the efficacy and safety of the Tramadol/APAP in the management of [redacted] pain included a total of 19 clinical studies, all but one of which were conducted by the sponsor. Data from these 19 studies are included in this NDA. Information from 17 of the 19 trials are included in the efficacy review. [redacted] Protocol TRAMAP-ANAG-011 is a single-dose trial in a dental pain model that had data integrity problems and was terminated early (the Division and DSI were notified of this discontinuation); an abbreviated report is provided in the NDA.

- Seven controlled, single-dose, double-blind trials in dental pain (Protocols TRAMAP-ANAG-002, 003, 010, 012, and 013), including a dose-ranging trial (Protocol TRAMAP-ANAG-007) that was sponsored by [redacted] and an aborted trial (Protocol TRAMAP-ANAG-011).
- Two controlled, single-dose, double-blind trials in surgical pain (Protocols TRAMAP-ANAG-004 and 005).
- Two single-dose pilot studies in dental (Protocol CA) or surgical (Protocol CB) pain.

- Four clinical pharmacokinetic studies in healthy volunteers (Protocols TRAM-PHI-001, TRAMAP-PHI-001, TRAMAP-PHI-002, and TRAMAP-PHI-003).

SECTION 5.1 STUDY TYPE AND DESIGN/PATIENT ENUMERATION

The primary development program can be classified based on the two study types: single-dose trials and multiple-dose trials. The single-dose trials consisted of two different study models: dental pain and surgical pain. Multiple-dose trials, including double-blind trials and open-label extension safety studies, were conducted in patients pain.

Table 2: Number of Subjects Participating in Trials with Tramadol/APAP

Subject Population	Total Enrolled and Randomized	Total Randomized and Treated with TRAM/APAP
Subjects with Acute	3,783[a]	1,302
Single-Dose Trials	*2,775*	*634*
Pivotal Dental Pain[b]	1,200	240
Supportive Dental Pain[c]	1,015	253
Supportive Surgical Pain[d]	560	141
Healthy Volunteers[g]	92	87
TOTAL SUBJECTS	**3,875**	**1,389**

[b] TRAMAP-ANAG-010, 012, and 013.
[c] TRAMAP-ANAG-002, 003, 007, and CA.
[d] TRAMAP-ANAG-004, 005, and CB.

[g] TRAM-PHI-001, TRAMAP-PHI-001, TRAMAP-PHI-002, TRAMAP-PHI-003. Three of these studies (TRAMAP-PHI-001, PHI-002 and PHI-003) were crossover in design; five subjects discontinued prematurely before receiving Tramadol/APAP.
Data Source: Based on the Sponsor's Table 2 in ISE, page 25.

This review will focus on 7 single-dose studies and 3 multiple-dose studies for efficacy, and 2 long-term studies and all relevant data for safety.

5.1.1 Development Program in Single-Dose Trials

TRAM/APAP tablets were studied in 634 patients in seven of the completed single-dose trials (TRAMAP-ANAG-002, 003, 004, 005, 010, 012, and 013). Three dental pain studies of these seven trials (TRAMAP-ANAG-010, 012, and 013) are considered pivotal by the sponsor, and four (two dental and two surgical pain studies) are considered supportive (TRAMAP-ANAG-002, 003, 004, and 005).

Table 3: Safety and Efficacy Trials with Tramadol/APAP in Single-Dose

Study Type Protocol Investigator(s)	Start Date	Design	Treatment	Dose (mg)	Duration	No. of Subjects (M/F)
Pivotal Single-Dose Trial in Dental Pain						
TRAMAP-ANAG-010 T. Kiersch, D.D.S (USA)	12/8/97	Randomized, double-blind, placebo- and active-controlled, parallel group, factorial design trial in subjects with dental pain	TRAM/APAP	75/650	Single dose	38/42
			TRAM	75		25/55
			APAP	650		30/50
			PL	0		26/54
			IBU	400		32/48
TRAMAP-ANAG-012 B. Tomasetti, D.M.D. (USA)	12/15/97	Randomized, double-blind, placebo- and active-controlled, parallel group, factorial design trial in subjects with dental pain	TRAM/APAP	75/650	Single dose	41/39
			TRAM	75		27/53
			APAP	650		36/44
			PL	0		37/43
			IBU	400		38/42
TRAMAP-ANAG-013 J.R. Fricke, D.D.S. (USA)	3/20/98	Randomized, double-blind, placebo- and active-controlled, parallel group, factorial design trial in subjects with dental pain	TRAM/APAP	75/650	Single dose	28/52
			TRAM	75		33/47
			APAP	650		31/49
			PL	0		27/53
			IBU	400		28/52
Supportive Single-Dose Trials in Dental Pain						
TRAMAP-ANAG-002 D. Mehlisch, M.D., D.D.S. (USA)	4/29/96	Randomized, double-blind, placebo- and active-controlled, parallel group, factorial design trial in subjects with dental pain	TRAM/APAP	75/650	Single dose	27/23
			TRAM	75		20/30
			APAP	650		28/22
			PL	0		16/34
			IBU	400		20/30
TRAMAP-ANAG-003 S.E. Christensen, D.D.S. (USA)	5/7/96	Randomized, double-blind, placebo- and active-controlled, parallel group, factorial design trial in subjects with dental pain	TRAM/APAP	75/650	Single dose	22/28
			TRAM	75		29/21
			APAP	650		30/20
			PL	0		20/30
			IBU	400		29/21
Supportive Single-Dose Trials in Surgical Pain						
TRAMAP-ANAG-004 A. Sunshine, M.D. (USA)	9/5/96	Randomized, double-blind, placebo-controlled, parallel group, factorial design trial in female subjects with gynecologic surgical pain	TRAM/APAP	112.5/975	Single dose	0/51
			TRAM	112.5		0/49
			APAP	975		0/50
			PL	0		0/50
TRAMAP-ANAG-005 L.S. Black, M.D. (USA)	6/13/96	Randomized, double-blind, placebo-controlled, parallel group, factorial design trial in subjects with orthopedic surgical pain	TRAM/APAP	112.5/975	Single dose	29/21
			TRAM	112.5		31/19
			APAP	975		28/22
			PL	0		28/22

KEY: US = United States; USA = United States of America; TRAM/APAP = tramadol + acetaminophen; TRAM = tramadol; APAP = acetaminophen; PL = placebo; IBU = ibuprofen; COD = codeine; M = male; F = female

Data Source: Based on Sponsor's Table 7-2 in Item 3, Chapter 7, page 13-15.

5.1.2 Development Program in Multiple-Dose Trials

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

Data Source: Based on Sponsor's Table 7-2 in Item 3, Chapter 7, page 13-15.

5.1.3 Development Program in Other Supportive Studies

Table 5 presents summary information on other supportive studies.

TABLE 5. Other Supportive Studies on TRAM/APAP

Study Type Protocol Investigator(s)	Start Date	Design	Treatment	Dose (mg)	Duration	No. of Subjects (M/F)
Pilot Trial						
CB	5/15/91	Randomized, double-blind,	TRAM/APAP[d]	25/500	Single	0/40
I. Zighelboim, M.D.		placebo-controlled,	TRAM	25	dose	0/40
(Venezuela)		parallel group trial in	APAP	500		0/40
		female subjects with	PL	0		0/40
		Cesarean section pain				
CA	5/4/90	Randomized, double-blind,	TRAM/APAP[a]	100/500	Single	25/28
M. Ladov, D.D.S.		placebo-controlled,	TRAM	100	dose	25/29
(USA)		parallel group trial in	APAP	500		27/28
		subjects with dental pain	PL	0		25/28
Supportive Dose-Ranging Trial						
TRAMAP-ANAG-007	5/21/96	Randomized, double-blind,	TRAM/APAP[d]	50/650	Single	18/32
T.A. Kiersch, D.D.S.		placebo-controlled,	TRAM/APAP[d]	25/650	dose	24/26
(USA)		parallel group trial in	TRAM	50		21/29
		subjects with dental pain	TRAM	25		19/31
			APAP	650		17/33
			PL	0		26/24
Supportive Single-Dose Trial in Dental Pain						
TRAMAP-ANAG-011	12/17/97	Randomized, double-blind,	TRAM/APAP	75/650	Single	16/15
N. Nemarich,		placebo- and active-	TRAM	75	dose	14/18
D.D.S (USA)		controlled, parallel group,	APAP	650		11/21
		factorial design trial in	PL	0		9/21
		subjects with dental pain	IBU	400		6/25

KEY: US = United States; USA = United States of America; TRAM/APAP = tramadol + acetaminophen; TRAM = tramadol; APAP = acetaminophen; PL = placebo; IBU = ibuprofen; COD = codeine; M = male; F = female

Data Source: Based on Sponsor's Table 7-2 in Item 3, Chapter 7, page 13-15.

SECTION 5.2. DEMOGRAPHICS

Demographics of efficacy studies are shown in Section 7.2 for each study. This section presents summaries of baseline demographics in the studies for safety analyses.

Section 5.2.1 Single-Dose, Double-Blind Dental Pain Trials

A total of 1,856 subjects was enrolled and randomized to double-blind treatment in Protocols TRAMAP-ANAG-002, 003, 010, 011, 012, and 013 and was evaluable for safety. Across the six trials, 371 subjects were randomized to receive a single, two-tablet dose of Tramadol/APAP for a total dose of tramadol 75 mg plus APAP 650 mg.
For the six trials combined, the five treatment groups were matched with respect to demographic and baseline characteristics (Table 6).

Table 6: Demographic and Baseline Characteristics: Single-Dose, Double-Blind Dental Pain Trials (Protocols TRAMAP-ANAG-002, 003, 010, 011, 012, and 013 Combined)

	TRAM/APAP (N=371)		TRAM 75 mg (N=372)		APAP 650 mg (N=372)		Ibuprofen 400 mg (N=371)		Placebo (N=370)	
Age (Years)										
N	371		372		372		371		370	
Mean (SD)	21.8	(5.25)	21.4	(4.68)	22.0	(5.70)	21.3	(5.16)	21.4	(4.57)
Median	20.0		20.0		21.0		20.0		20.0	
Range	16-46		16-41		16-53		16-48		16-42	
Sex										
Male	172	(46%)	148	(40%)	166	(45%)	153	(41%)	135	(36%)
Female	199	(54%)	224	(60%)	206	(55%)	218	(59%)	235	(64%)
Race										
White	304	(82%)	304	(82%)	287	(77%)	311	(84%)	305	(82%)
Black	12	(3%)	12	(3%)	14	(4%)	14	(4%)	10	(3%)
Other	55	(15%)	56	(15%)	71	(19%)	46	(12%)	55	(15%)
Weight (kg)										
Mean (SD)	71.3	(15.74)	69.4	(14.21)	70.5	(16.06)	69.3	(14.81)	68.4	(13.81)
Median	68.0		66.0		68.0		66.0		67.0	
Range	37-159		44-109		40-140		35-116		44-119	
Height (cm)										
Mean (SD)	172.2	(10.22)	170.9	(9.58)	171.1	(10.27)	170.9	(9.78)	171.0	(9.89)
Median	173.0		170.0		170.0		170.0		170.0	
Range	140-198		147-201		132-196		152-198		140-198	
Baseline Pain										
Moderate	255	(69%)	265	(71%)	262	(70%)	259	(70%)	269	(73%)
Severe	116	(31%)	107	(29%)	110	(30%)	112	(30%)	101	(27%)

Data Source: Based on Sponsor's Table 4b in ISS, page 71.

Section 5.2.2. Single-Dose, Double-Blind Surgical Pain Trials

A total of 200 subjects each was enrolled and randomized to double-blind treatment in Protocols TRAMAP-ANAG-004 and 005 and was evaluable for safety. Across both trials, 101 of the 400 enrolled subjects were randomized to receive a single, three-tablet dose of Tramadol/APAP for a total dose of tramadol 112.5 mg plus APAP 975 mg. The remaining subjects were randomized to receive a single dose of tramadol 112.5 mg, APAP 975 mg, or placebo.

While in the two trials combined, the four treatment groups were generally matched with respect to demographic and baseline characteristics (Table 7), due to differences in the populations evaluated in each trial (gynecological surgical pain in TRAMAP-ANAG-004 versus orthopedic surgical pain in TRAMAP-ANAG-005), demographic and baseline characteristics differed between trials.

Table 7: Demographic and Baseline Characteristics:
Single-Dose, Double-Blind Surgical Pain Trials
(Protocols TRAMAP-ANAG-004 and TRAMAP-ANAG-005 Combined)

	TRAM/APAP (N=101)		TRAM 112 mg (N=99)		APAP 975 mg (N=100)		Placebo (N=100)	
Age (Years)								
N	101		99		100		100	
Mean (SD)	35.7	(13.70)	37.0	(15.19)	34.1	(13.24)	36.9	(15.44)
Median	34.0		34.0		30.5		32.5	
Range	18-78		19-83		18-70		18-83	
Sex								
Male	29	(29%)	31	(31%)	28	(28%)	28	(28%)
Female	72	(71%)	68	(69%)	72	(72%)	72	(72%)
Race								
White	38	(38%)	43	(43%)	42	(42%)	46	(46%)
Black	6	(6%)	1	(1%)	3	(3%)	2	(2%)
Other	57	(56%)	55	(56%)	55	(55%)	52	(52%)
Weight (kg)								
Mean (SD)	79.2	(17.65)	81.4	(19.31)	78.3	(18.82)	78.3	(19.73)
Median	79.0		80.0		76.0		75.0	
Range	43-132		47-140		42-132		45-164	
Height (cm)								
Mean (SD)	166.6	(9.90)	168.4	(10.62)	166.2	(10.01)	166.3	(11.78)
Median	165.0		168.0		163.0		163.0	
Range	147-193		152-196		150-193		122-193	
Baseline Pain								
Moderate	53	(52%)	44	(44%)	44	(44%)	48	(48%)
Severe	48	(48%)	54	(55%)	56	(56%)	52	(52%)
Missing	0		1	(1%)	0		0	

Data Source: Based on Sponsor's Table 4C in ISS, page 72

Section 5.2.3 Double-Blind Phase of Multiple-Dose, Long-Term Pain Trials

A total of 1,008 subjects in the three long-term pain trials included in this analysis group were randomized to double-blind therapy.

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

Table 10: Demographic and Baseline Characteristics: Primary Single-Dose and Multiple-Dose Pain Trials Combined (Tramadol/APAP-Exposed Subjects In Protocols TRAMAP-ANAG-002, 003, 004, 005, [redacted] 010, 011, 012, 013 [redacted] Combined)

	TRAM/APAP (N=1,909)	
Age (Years)		
N	1,909	
Mean (SD)	50.0	(19.04)
Median	53.0	
Range	16.0 - 91.0	
Sex		
Male	780	(41%)
Female	1,129	(59%)
Race		
White	1,602	(84%)
Black	122	(6%)
Other	185	(10%)
Weight (kg)		
N	1,901[a]	
Mean (SD)	80.6	(18.55)
Median	79.0	
Range	37.0 - 173.0	
Baseline Pain[b]		
None	1	(<1%)
Mild	103	(5%)
Moderate	1,014	(53%)
Severe	432	(23%)
Missing	359	(19%)

[redacted]

Data Source: Based on Sponsor's Table 4e in ISS, page 75

SECTION 5.3 EXTENT OF EXPOSURE

See Section 8.3.1 of this review.

SECTION 6.0 HUMAN PHARMACOKINETICS

Four clinical pharmacokinetic trials were conducted in healthy subjects with the Tramadol/APAP combination, which were designed to: 1) evaluate the dosage performance of the Tramadol/APAP tablet formulation (Protocol TRAM-PHI-001); 2) evaluate the influence of food on the bioavailability of the combination (Protocol TRAMAP-PHI-003); and 3) assess the pharmacokinetics of the combination following single-dose (Protocol TRAMAP-PHI-002) and multiple-dose (Protocol TRAMAP-PHI-001) oral administration. [redacted]

Section 6.1 Pharmacokinetic Profile of Tramadol

Tramadol is rapidly and almost completely absorbed after oral administration. Peak plasma concentrations of tramadol and its active metabolite, M1, occur at two and three hours, respectively, after oral administration in healthy adults. Oral administration with food does not affect the rate or extent of absorption relative to the fasted state. The mean absolute bioavailability of 100 mg tramadol oral dose after single administration is about 70% indicating some first-pass metabolism, and increases to approximately 90% after multiple dose administration. The binding of tramadol to human plasma proteins is approximately 20%. The major metabolic pathways appear to be N- and O- demethylation and glucuronidation or sulfation in the liver. Tramadol is extensively metabolized by a number of pathways, including CYP2D6 and CYP3A4, as well as by conjugation of parent and metabolites.

Renal excretion is the primary route of elimination of tramadol; 30% of a single oral dose was excreted in the urine as unchanged tramadol.

Section 6.2 Pharmacokinetic Profile of Acetaminophen

Acetaminophen is rapidly and almost completely absorbed after oral administration. The concentration in plasma reaches a peak in about 30 minutes after therapeutic doses. Acetaminophen is primarily metabolized in the liver by first-order kinetics and involves three principal separate pathways: a) conjugation with glucuronide; b) conjugation with sulfate, and; c) oxidation via the cytochrome, P450-dependent, mixed-function oxidase enzyme pathway to form a reactive intermediate metabolite, which conjugates with glutathione and is then further metabolized to form cysteine and mercapturic acid conjugates. The principal cytochrome P450 isoenzyme involved appears to be CYP2E1, with CYP1A2 and CYP3A4 additional pathways.

In adults, the majority of acetaminophen is conjugated with glucuronic acid and, to a lesser extent, with sulfate. These glucuronide-, sulfate-, and glutathione-derived metabolites lack biologic activity. In premature infants, newborns, and young infants, the sulfate conjugate predominates. Acetaminophen is eliminated from the body primarily by formation of glucuronide and sulfate conjugates in a dose-dependent manner.

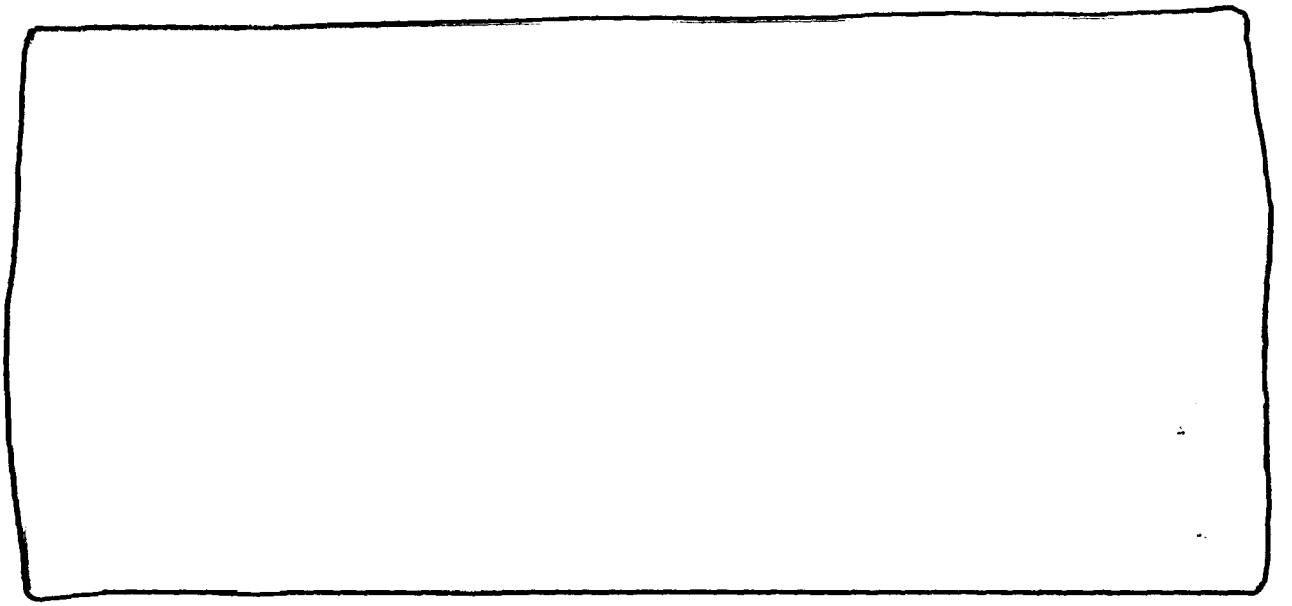
The oral bioavailability of 500 mg APAP is about 70%. Food has no effect on the extent of absorption of APAP.

Section 6.3 Pharmacokinetic Evaluations with Tramadol/APAP

In comparison with historical data, the bioavailability of a single oral dose of one combination tablet containing 37.5 mg tramadol with 325 mg APAP following a 10-hour overnight fast did not appreciably differ from the bioavailability of either component given as an oral solution, although, the rate of absorption was somewhat slower with the

tablet formulation compared to an oral solution. Moreover, a high-fat breakfast did not appreciably alter the bioavailability of either drug relative to administration under 10-hour overnight fasted condition; the absorption was somewhat delayed under fed conditions. The pharmacokinetics of tramadol, M1, or APAP were not significantly altered when the two drugs were given in combination as a single dose to healthy subjects.

Multiple dose pharmacokinetics of the (+) and (-) enantiomers of tramadol and M1 and APAP were evaluated in healthy subjects following seven days of multiple dosing of 10 combination tablets daily in four divided doses given every six hours. The steady-state pharmacokinetics of APAP in combination with tramadol were the same as when APAP was given alone. There was very little accumulation of APAP at steady-state. The steady-state tramadol and M1 plasma concentrations were reached in three days following multiple-dose oral administration of Tramadol/APAP tablets with a two-day gradual dose titration. Lower steady-state plasma concentrations of the (+) and (-) enantiomers of tramadol and M1 were found following treatment with the combination tablet relative to treatment with tramadol alone.



SECTION 7.0 EFFICACY FINDINGS

SECTION 7.1 Overview of Efficacy

This NDA submission contains three "adequate, well-controlled" studies: pivotal single-dose, dental pain trials: TRAMAP-ANAG-010, 012, and 013 for the to-be-marketed TRAM/APAP tablets. The sponsor also submits two supportive single-dose, double-blind, surgical pain trials (Protocols TRAMAP-ANAG-004, and 005) to support the acute pain indication. Doses used in the surgical pain studies were higher than the dose in the dental pain studies. The sensitivity of dental pain model was confirmed by the statistical

superiority of ibuprofen 400 mg over placebo. Ibuprofen was not included as an active control in the two single-dose, surgical pain trials. All single dose studies were designed to test the analgesic effect of the TRAM/APAP combination product to be statistically superior to the individual effects of each component administered alone.

Each of these trials above used the Tramadol/APAP fixed-dose combination tablet (37.5 mg tramadol plus 325 mg APAP) proposed for marketing. There were three additional single-dose, double-blind studies that evaluated the effectiveness of a tramadol plus APAP combination in the treatment of acute pain (CA, CB, and TRAMAP-ANAG-007). In these studies however, Tramadol/APAP was not administered as a fixed-dose combination tablet formulation. Therefore, these studies are not reviewed here.

This review section includes summary of studies (7 single dose studies and 3 multiple-dose studies) pertinent to efficacy, and focuses on the following efficacy aspects:

- Component contribution
- Acute use: the estimates of onset time for both the two- and three-tablet doses
- Duration of effect – the remedication time
- Dosing recommendations, including individual dose, total daily dose and dosing schedule
- Duration of use or chronic use
- Dose-response: No dose-response study was submitted in this NDA although there was a pilot, dose-ranging (i.e., 25 and 50 mg) study to determine amount of tramadol in the combination product.

Efficacy Assessment: The primary analgesic efficacy endpoints in the single dose studies included pain intensity (PI) measured on a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe), and pain relief (PR) as compared to baseline pain level on a 5-point scale (0 = none, 1 = a little, 2 = some, 3 = a lot, or 4 = complete). Those scales were recorded at 30 minutes, one hour, and then hourly for up to eight hours. Time to remedication was recorded. There was a direct (i.e., stopwatch) measurement of time to onset of pain relief in the three pivotal dental pain trials.

Major Analysis: Pain intensity was converted to difference from baseline (PID). PRID was computed as the sum of PID and PR. In its reports the sponsor did analyses using last observation carried forward (LOCF) extrapolation. At FDA's request, the sponsor performed analyses using baseline pain score carried forward (BOCF) after a subject took rescue medication or was prematurely discontinued from the trial for the three pivotal single-dose dental pain trials. Using the BOCF methodology, missing observations for

subjects who remained in the trial were filled in by linear interpolation using the scores immediately preceding and immediately following the missing observation.

- As outlined above, a total of 10 completed single-dose trials and one aborted single-dose trial were conducted. Seven of the completed single-dose trials were conducted using the fixed-dose combination proposed for commercial use and therefore provide the best evidence concerning the efficacy of the Tramadol/APAP combination. Three of these seven trials are considered pivotal, and four are considered supportive as outlined in Table 11.

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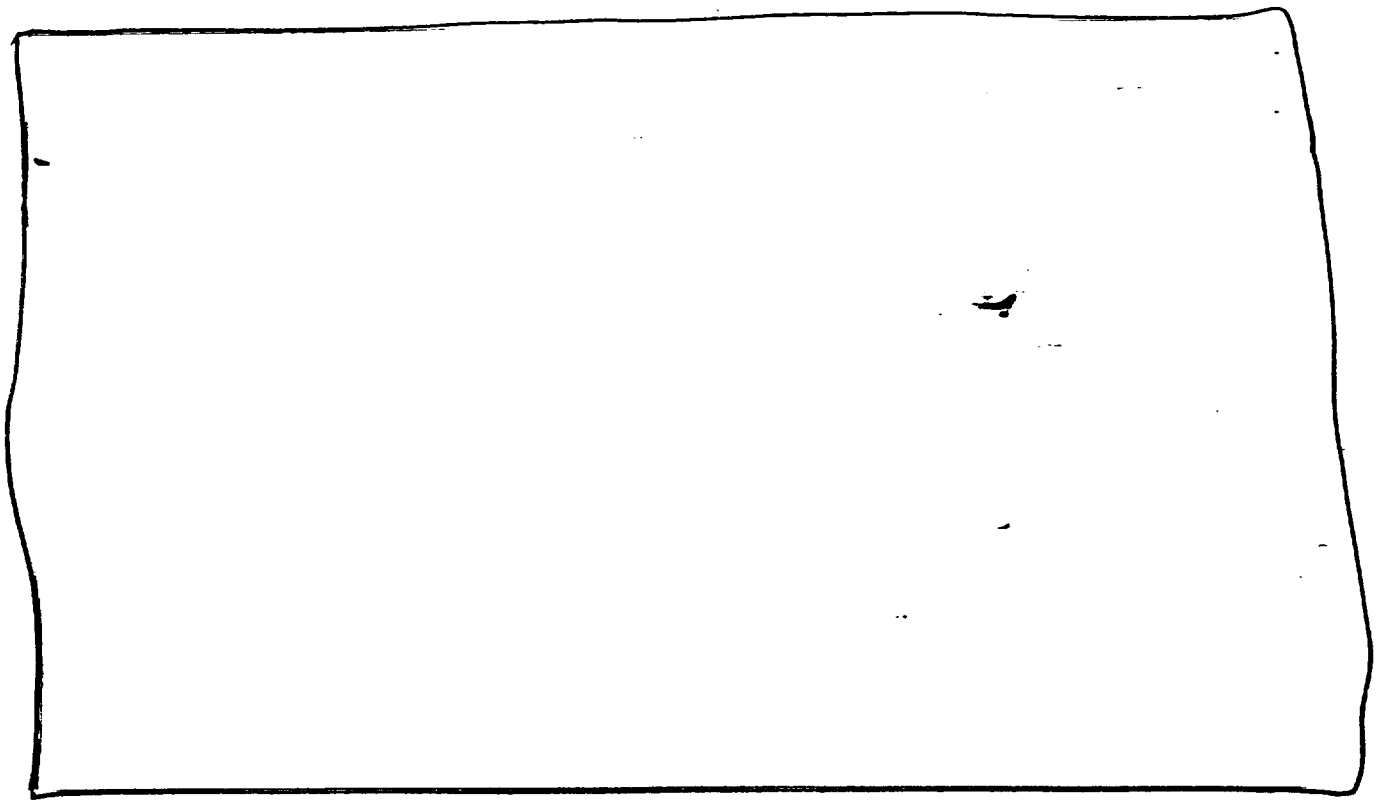
Table 11: Single-Dose Efficacy and Safety Trials with Tramadol/APAP Combination (37.5 mg tramadol with APAP 325 mg)

Protocol	Pain Model	Treatment	Dose (mg)	No. of Subjects (M/F)
Pivotal Single-Dose Trials				
TRAMAP-ANAG-010	Dental	TRAM/APAP	75/650	38/42
		TRAM	75	25/55
		APAP	650	30/50
		PL	0	26/54
		IBU	400	32/48
TRAMAP-ANAG-012	Dental	TRAM/APAP	75/650	41/39
		TRAM	75	27/53
		APAP	650	36/44
		PL	0	37/43
		IBU	400	38/42
TRAMAP-ANAG-013	Dental	TRAM/APAP	75/650	28/52
		TRAM	75	33/47
		APAP	650	31/49
		PL	0	27/53
		IBU	400	28/52
Supportive Single-Dose Trials				
TRAMAP-ANAG-002	Dental	TRAM/APAP	75/650	27/23
		TRAM	75	20/30
		APAP	650	28/22
		PL	0	16/34
		IBU	400	20/30
TRAMAP-ANAG-003	Dental	TRAM/APAP	75/650	22/28
		TRAM	75	29/21
		APAP	650	30/20
		PL	0	20/30
		IBU	400	29/21
TRAMAP-ANAG-004	Gynecologic surgical pain	TRAM/APAP	112.5/975	0/51
		TRAM	112.5	0/49
		APAP	975	0/50
		PL	0	0/50
TRAMAP-ANAG-005	Orthopedic surgical pain	TRAM/APAP	112.5/975	29/21
		TRAM	112.5	31/19
		APAP	975	28/22
		PL	0	28/22

KEY: TRAM/APAP = tramadol + acetaminophen; TRAM = tramadol; APAP = acetaminophen; PL = placebo; IBU = ibuprofen; M = male; F = female.
Data Source: Based on Sponsor's Table 1 in Item 8/Volume 1/page 65

As indicated above, three trials investigated the efficacy and/or safety of Tramadol/APAP after repeated oral administration to patients with [redacted] pain. These studies are outlined in Table 12.



SECTION 7.2 SUMMARY OF STUDIES PERTINENT TO EFFICACY

SECTION 7.2.1 TRAMAP-ANAG-010, 012, AND 013

The three pivotal double-blind, single-dose trials using a dental pain model were conducted at different sites base upon the identical protocol. Therefore, they are reviewed together in this section.

SECTION 7.2.1.1. Protocol Synopsis

Title: **EVALUATION OF THE EFFICACY AND SAFETY OF TRAMADOL/APAP IN ORAL SURGICAL PAIN**

Objectives:

This study will evaluate the safety and efficacy of Tramadol/APAP (Tramadol 37.5 mg with Acetaminophen 325 mg) in subjects with pain from oral surgical procedures involving extraction of two or more impacted third molars requiring bone removal. If only two impacted third molars are extracted, they must be ipsilateral.

Investigators/Location:

- **TRAMAP-ANAG-010:** Theodore Kiersch, D.D.S. (PI) - Cranial Pain Research, Tucson, AZ; USA
- **TRAMAP-ANAG-012:** Boyd Tomasetti, D.M.D. (PI) - SCIREX Corp., Littleton, CO; USA
- **TRAMAP-ANAG-013:** James R. Fricke, D.D.S. (PI) - PPD Pharmaco Inc., Austin, Texas; USA

Population:

The sponsor planned to enroll up to 400 subjects (80 per treatment group) in each study.

Subjects were eligible for enrollment in the study if they meet all of the following key inclusion criteria:

Table 13: Key Inclusion Criteria

- 16 years of age or older, and if female, postmenopausal or surgically rendered incapable of having children, or not pregnant and using acceptable birth control methods with a normal menstrual pattern within three months prior to entry.
- Moderate or severe pain (score of at least 5 on VAS) as a result of an oral surgical procedure. The procedure must involve extraction of two or more impacted third molars requiring bone removal. If only two impacted third molars are extracted, they must be ipsilateral and require bone removal.
- Weigh less than 243 pounds (110 kilograms).
- Sufficiently alert to understand and communicate intelligibly with the study observer.
- Good physical health.

Major exclusion criteria were presented in Table 14.

Table 14: Key Exclusion Criteria

- Received an experimental drug or used an experimental medical device within 30 days prior to screening.
- Received any analgesic medication other than short-acting pre-operative or intraoperative anesthetic agents within 12 hours before taking trial medication. Subjects who received any analgesic medication other than the single dose of study drug immediately after the oral surgical procedure was completed were also excluded.
- Received a long-acting nonsteroidal antiinflammatory drug (NSAID) within three days prior to dosing.
- History of seizures or drug or alcohol abuse within six months.
- Received monoamine oxidase inhibitors, tricyclic antidepressants, neuroleptics, or other drugs that reduce the seizure threshold within four weeks of study entry.
- Evidence of renal or hepatic dysfunction, or peptic ulcer disease.
- Received selective serotonin reuptake inhibitors (SSRIs) (e.g., paroxetine, fluoxetine), diet pills (including fenfluramine, phentermine, etc.), or methylphenidate (Ritalin®) within four weeks of study entry.
- Sensitive or allergic to tramadol, APAP, ibuprofen or other NSAIDs, or aspirin.
- At risk in terms of precautions, warnings, and contraindications in the package insert for ULTRAM® tramadol hydrochloride, Tylenol® acetaminophen, or ibuprofen.
- Previous participation in this trial.

Study Design:

This was a randomized, double-blind, placebo- and active-controlled, parallel-group factorial design trial conducted at a single site.

Subjects were to be randomly assigned to one of five treatment groups:

- Combination treatment: Two tablets of Tramadol/APAP (37.5 mg and 325 mg) and two capsules of placebo:
- Component – Tramadol: Two capsules of ULTRAM 37.5 mg and two tablets of placebo
- Component – acetaminophen: Two capsules of acetaminophen 325 mg and two tablets of placebo
- Active control: Two capsules of ibuprofen 200 mg and two tablets of placebo:
- Placebo group: Two tablets of placebo and two capsules of placebo

There were two phases to this trial.

Screening Phase: Subjects were evaluated based upon inclusion/exclusion criteria for entry into the study during the screening phase. Patients were to undergo pregnancy test.

Double-Blind Phase: Qualified subjects were randomized in equal numbers to a single dose of Tramadol/APAP, ULTRAM 75 mg, acetaminophen 650 mg, ibuprofen 400 mg, or placebo. Randomization was stratified on baseline pain severity. Subjects with moderate baseline pain were assigned the lowest available subject number in ascending sequence. Subjects with severe baseline pain were assigned the highest available subject number in descending sequence.

The subject received the single dose of medication, consisting of two tablets and two capsules, when the subject complained of moderate or severe pain (a score of at least 5 on the VAS) as a result of an oral surgical procedure. The baseline pain was recorded. Subsequently, the subject evaluated current pain and relief from starting pain at 30 minutes, 1, 2, 3, 4, 5, 6, 7, and 8 hours after receiving the dose of study medication. At time zero the subject will activate the stopwatches.

Ice packs may be used after surgery and prior to dosing. Ice packs may be used for a maximum of ten minutes after dosing. Ice packs were not used again until after the subject had experienced both perceptible and meaningful pain relief (i.e., both stopwatches have been clicked). Upon onset of perceptible pain relief, the subject stopped the first watch. Upon onset of meaningful pain relief, the subject stopped the second watch.

At any time during the eight-hour observation period, the subject may choose to receive a supplemental analgesic medication. The subject was encouraged (but not required) to wait at least two hours after dosing before taking supplemental pain medication, if there was no analgesic response to the study medication. The subject was encouraged (but not required) to wait until the pain level has returned to the baseline assessment before taking

supplemental pain medication, if there was any analgesic response to the study medication. A final assessment of current pain and relief from starting pain were made and recorded prior to a subject's taking the supplemental analgesic medication.

Pain and relief assessments stopped after the subject took the supplemental analgesic medication. At the end of the eight-hour observation period or at the time of taking the supplemental analgesic medication, whichever occurred first, the subject made an overall assessment of the study medication, selected from the scale: excellent, very good, good, fair, poor.

For the purpose of this study, physical signs or symptoms (e.g., dry sockets, ecchymosis, edema, infection, paresthesia, pain) that were expected to be a direct consequence of the surgical procedure were not recorded as adverse events on the case report form but were noted in the source document.

Postdosing adverse events were monitored for the eight-hour observation period, even if supplemental analgesic medication was taken.

A subject was considered as having completed the study

- if the subject had completed the eight-hour observation period without use of supplemental analgesic medication; or
- if the subject had had no analgesic response to the study medication *and* had completed at least two hours of the observation period without use of supplemental analgesic medication; or
- if the subject had had an analgesic response to the study medication *and* had completed at least two hours of the observation period *and* had waited until the pain intensity has returned to the same as at baseline before taking supplemental analgesic medication.

Subjects who were withdrawn for any reason prior to completing the observation period as described above were considered not to have completed.

Section 7.2.1.2 Efficacy and Statistical Analysis

Analgesic efficacy measurements included pain intensity, pain relief, use of supplemental analgesic medication, time to onset of pain relief and overall assessment.

Efficacy assessments included the total pain relief (TOTPAR), sum of pain intensity difference (SPID), pain intensity difference (PID) at each observation point, pain relief (PAR) at each observation point, overall assessment of the medication, rate of remedication and time to remedication. Time to perceptible and time to meaningful pain relief were also measured.

PLANNED ANALYSES

The objective of the efficacy analysis was to demonstrate the eight-hour analgesic superiority of Tramadol/APAP to either of its components alone and to placebo.

Evaluation of relative efficacy between treatments included comparisons of pain intensity difference from baseline (PID) and pain relief (PAR) at each observation point. The analysis of variance technique along with the Least Significant Difference procedure was utilized to compare the PIDs and PARs at each observation point. The last observation carried forward methodology (LOCF) was used by the sponsor for any missing observations during the trial and for the observation points after the subject takes supplemental analgesic medication, or discontinues the trial prematurely. The BOCF methodology requested by FDA was performed. The PID and PR scores for TRAM/APAP groups obtained from applying LOCF in the three pivotal dental trials were smaller than those obtained from BOCF methodology in most cases. Therefore, efficacy results in this review are reported based on LOCF.

The time to remedication with supplemental analgesic medication was analyzed using the Kaplan-Meier estimate to compute the failure distribution function. The distribution functions were compared among treatment arms using the log-rank test. Subjects who completed eight hours of assessment or withdrew from the trial without receiving remedication were censored at the last assessment point.

The time to onset of perceptible and meaningful relief were analyzed jointly as bivariate survival times using the Wei, Lin, Weissfeld (WLW) marginal distribution method. Univariate log-rank tests were performed for the two times separately to determine whether the time to onset of perceptible pain relief, time to onset of meaningful pain relief, or both differed significantly between the two treatment groups being compared. The above analysis is different from that planned in the protocol. In the protocol, the times to onset of perceptible and meaningful pain relief were to be estimated by the Kaplan-Meier method and the distribution functions were to be compared using the Wilcoxon text.

Determination of Sample Size

The sponsor suggested that subjects with severe baseline pain in two pilot studies had an average TOTPAR of 17 in the Tramadol/APAP group and 13 in the acetaminophen group, with a standard deviation of 8.3 and 9.9, respectively. A sample size of 80 subjects per treatment group would provide 80% power (at α=0.05 level) to detect a between-group difference in the TOTPAR of about 4 units, assuming a standard deviation of 9 units.

Section 7.2.1.3. Protocol Amendment

TRAMAP-ANAG-010: There were two amendments added to the protocol. The first amendment (dated December 19, 1997) was added to the protocol after 18 subjects entered the trial. This amendment redefined the allowed surgical procedures to include

only oral surgical procedures involving extraction of two or more impacted third molars requiring bone removal rather than at least two impacted mandibular third molars. In addition, this amendment specified that if only two 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 to the protocol after 273 subjects were enrolled and provided further clarification of the number of molar extractions that required bone removal.

TRAMAP-ANAG-012:

There was one amendment added to the protocol after 16 subjects entered the trial. This amendment (dated December 24, 1997) was the identical to the first amendment described in the study ANAG-010 above.

TRAMAP-ANAG-013:

There was one amendment added to the protocol after 320 subjects entered the trial. This amendment (dated June 19, 1998) was the identical to the first amendment described in the study ANAG-010 above.

Section 7.2.1.4 Conduct of Study

Patient Distribution and Disposition:

Of the 1,197 subjects evaluable for efficacy in the pivotal single-dose, double-blind dental trials, 892 (75%) completed their respective trial as planned (Table 15). Of the 305 subjects who were withdrawn from the trial prematurely, most (n=299; 98%) were considered to have withdrawn because they did not complete at least the two-hour evaluation before remedicating or because they took a supplemental analgesic medication before their pain intensity had returned to the baseline level. Approximately 40% of these subjects were assigned to the placebo group. Two subjects chose to withdraw (one each in the Tramadol/APAP and tramadol 75 mg groups) and four subjects withdrew due to adverse events (one in the tramadol 75 mg group, two in the ibuprofen 400 mg group, and one in the placebo group). The three subjects not included in the efficacy analyses withdrew after completing the baseline pain assessment but before receiving any study medication.

The pattern of the study completion/withdrawal across the three studies was similar (not shown in the table).

Table 15: Study Completion/Withdrawal Information:
Combined Pivotal Single-Dose Dental Trials
(Protocols TRAMAP-ANAG-010, 012, and 013)

	TRAM/ APAP	TRAM 75 mg	APAP 650 mg	Ibuprofen 400 mg	Placebo	Total
Total Evaluable Subjects	**240**	**238**	**240**	**240**	**239**	**1,197**
Subjects Who Completed	211 (88%)	157 (66%)	211 (88%)	195 (81%)	118 (49%)	892 (75%)
No rescue analgesic[a]	73 (35%)	45 (29%)	34 (16%)	89 (46%)	17 (14%)	258 (29%)
Took rescue analgesic[a]	138 (65%)	112 (71%)	177 (84%)	106 (54%)	101 (86%)	634 (71%)
Subjects Who Withdrew	29 (12%)	81 (34%)	29 (12%)	45 (19%)	121 (51%)	305 (25%)
Adverse event[b]	0	1 (1%)	0	2 (4%)	1 (1%)	4 (1%)
Subject choice[b]	1 (3%)	1 (1%)	0	0	0	2 (1%)
Took rescue analgesic [b]	28 (97%)	79 (98%)	29 (100%)	43 (96%)	120 (99%)	299 (98%)

[a] Percentages based on number of subjects who completed.
[b] Percentages based on number of subjects who withdrew.
Data Source: Based on Sponsor's Table 6 in ISE: Page 59

Protocol Deviations

TRAMAP-ANAG-010:

The sponsor granted fifty-four exceptions to the inclusion criteria specified in the protocol. The most common exceptions were granted for subjects who only had one molar requiring bone removal rather than two (n=30) and for female subjects who did not maintain a normal menstrual pattern for three months prior to study entry (n=15), primarily because of the use of Depo-Provera. All 15 of these latter subjects had a negative urine pregnancy test on the day of dosing. Three additional subjects were granted exceptions although they did not meet the weight and history of seizure criteria.

The remaining five protocol exceptions were granted for removal of the wrong type of molar (n=2), history of seizure at an early age (n=2), and body weight >243 lbs. (n=1).

TRAMAP-ANAG-012:

Subject 12028 in the TRAM/APAP group was enrolled under the original protocol that required the removal of at least two impacted mandibular third molars. This subject had two maxillary and one mandibular third molar removed.

Twenty-four protocol exceptions were granted by the sponsor for female subjects who did not maintain a normal menstrual pattern for three months prior to study entry.

TRAMAP-ANAG-013:

Subject 13092 in the TRAM/APAP group was receiving an amphetamine (Adderall) for attention deficit disorder.

Subject 13200 in the TRAM/APAP group was medicated with another analgesic that contained acetaminophen (Vicodin) after being given study medication.

Subject 13378 in the tramadol 75 mg group had reported one seizure at the age of two and therefore should not have been enrolled in the study.

Subject 13141 in the placebo group had bone removal for only one third molar.

Sixteen protocol exceptions were granted by the sponsor for female subjects who did not maintain a normal menstrual pattern for three months prior to study entry.

Demographic and Baseline Characteristics

Table 16 summarizes, by treatment group, the demographic and baseline characteristics for 1,197 of the 1,200 enrolled subjects who were evaluable for efficacy analyses across the three pivotal single-dose dental trials. Demographic and baseline characteristics were comparable across the five treatment groups.

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Table 16: Demographic and Baseline Characteristics:
Combined Pivotal Single-Dose Dental Trials
(Protocols TRAMAP-ANAG-010, 012, and 013)

	TRAM/APAP (N=240)	TRAM 75 mg (N=238)	APAP 650 mg (N=240)	Ibuprofen 400 mg (N=240)	Placebo (N=239)	Total (N=1,197)
Sex						
Male	107 (45%)	85 (36%)	97 (40%)	98 (41%)	89 (37%)	476 (40%)
Female	133 (55%)	153 (64%)	143 (60%)	142 (59%)	150 (63%)	721 (60%)
Race						
White	195 (81%)	196 (82%)	184 (77%)	200 (83%)	196 (82%)	971 (81%)
Black	8 (3%)	7 (3%)	6 (3%)	9 (4%)	4 (2%)	34 (3%)
Asian	3 (1%)	1 (<1%)	4 (2%)	6 (3%)	6 (3%)	20 (2%)
Other	34 (14%)	34 (14%)	46 (19%)	25 (10%)	33 (14%)	172 (14%)
Age (yrs)						
Mean (SD)	21.8 (5.59)	21.2 (4.72)	22.1 (5.55)	20.9 (4.67)	21.2 (4.57)	21.4 (5.05)
Median	20.0	20.0	21.0	20.0	20.0	20.0
Range	16.0 - 46.0	16.0 - 41.0	16.0 - 46.0	16.0 - 41.0	16.0 - 42.0	16.0 - 46.0
Weight (kg)						
Mean (SD)	70.2 (13.37)	68.6 (14.29)	69.9 (15.25)	69.4 (14.65)	68.6 (13.61)	69.3 (14.24)
Median	68.0	66.0	68.0	68.0	67.0	68.0
Range	42.0 - 107.0	44.0 -- 109.0	40.0 - 110.0	35.0 - 116.0	44.0 - 110.0	35.0 - 116.0
Height (cm)						
Mean (SD)	172.0 (10.00)	170.1 (9.50)	170.9 (10.31)	170.5 (9.35)	171.1 (10.13)	170.9 (9.87)
Median	173.0	170.0	170.0	170.0	170.0	170.0
Range	140.0 - 196.0	147.0 - 201.0	142.0 - 196.0	152.0 - 198.0	145.0 - 198.0	140.0 - 201.0
Baseline Pain						
Moderate	165 (69%)	162 (68%)	164 (68%)	164 (68%)	163 (68%)	818 (68%)
Severe	75 (31%)	76 (32%)	76 (32%)	76 (32%)	76 (32%)	379 (32%)
No. Molars Removed						
2	39 (16%)	33 (14%)	31 (13%)	26 (11%)	31 (13%)	160 (13%)
3	31 (13%)	29 (12%)	27 (11%)	33 (14%)	25 (10%)	145 (12%)
4	170 (71%)	176 (74%)	182 (76%)	181 (75%)	183 (77%)	892 (75%)
Bone Removal						
Moderate	38 (16%)	32 (13%)	38 (16%)	29 (12%)	36 (15%)	173 (14%)
Substantial	202 (84%)	206 (87%)	202 (84%)	211 (88%)	203 (85%)	1024 (86%)

Data Source: Based on Sponsor's Table 5 in ISE, Page 58

Sixty percent of the evaluable subjects enrolled in these pivotal trials were female, most (81%) were White, and all ranged in age from 16 to 46 years (average age of 21.4 years). All subjects were required to have moderate or severe pain before administering study medication; 818 (68%) of subjects reported having moderate pain at baseline. Most of the oral surgical procedures involved removal of four impacted third molars. Eighty-six percent of the procedures involved substantial bone removal.

Section 7.2.1.6 Sponsor's Efficacy Results

Primary Efficacy Evaluations: Combined Scores (PRID) of Hourly Pain Intensity Differences and Pain Relief Assessments

The combined scores (PRID) of hourly mean pain relief and pain intensity differences (extrapolated with missing observations imputed using the LOCF methodology) are shown graphically for Protocols TRAMAP-ANAG-010, 012, and 013 in Figures 1-3, and Table 16-18. A summary table for statistical comparison of pain scores over time is presented in Table 19. More extensive individual result summaries (i.e., PR and PID) are provided in Appendix A.

Tramadol/APAP statistically separated from placebo by the 30-minute evaluation and remained statistically superior for the remainder of the eight-hour observation interval for all three pain assessment scores in all three pivotal trials.

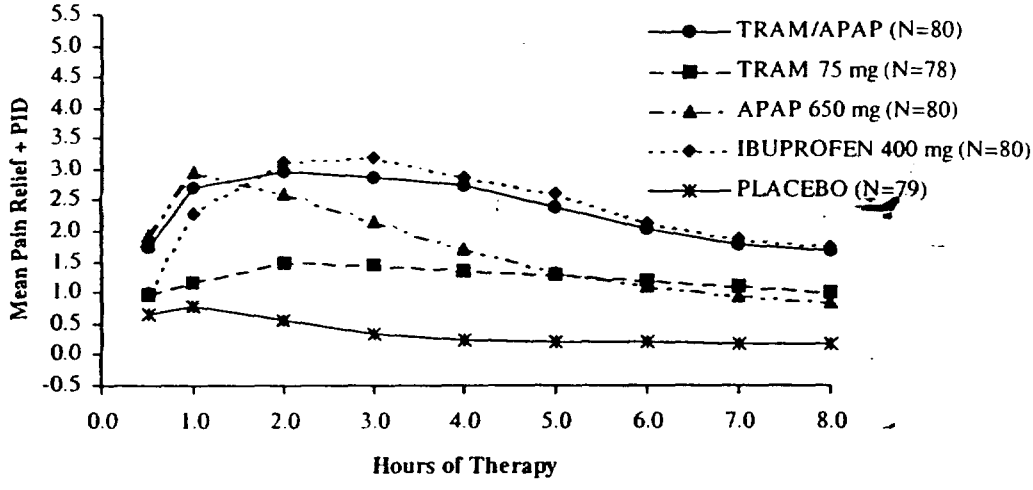
Tramadol/APAP statistically separated from tramadol 75 mg by the 30-minute evaluation and remained statistically superior for the remainder of the eight-hour observation interval for PRID in two pivotal trials, and statistically superior between 30-minute and 4-hour observation in TRAMAP-ANAG-013. The pattern of results for PR and PID generally paralleled those discussed here for PRID.

In general, the statistical superiority of Tramadol/APAP over APAP 650 mg for PRID was demonstrated at the latter observation intervals. Tramadol/APAP statistically separated from APAP 650 mg by Hour 3 (TRAMAP-ANAG-010) or Hour 4 (TRAMAP-ANAG-012) and remained statistically superior for the remainder of the eight-hour observation interval. In TRAMAP-ANAG-013, Tramadol/APAP was statistically superior to APAP 650 mg at Hours 2 and 3 and again at Hour 5, 7 and 8. The pattern of results for PR and PID generally paralleled those discussed here for PRID.

Mean PAR and PID scores in the APAP 650 mg group were generally statistically superior to those in the placebo group throughout the entire observation period with few exceptions in all three pivotal trials.

The statistical superiority of tramadol 75 mg over placebo for PRID was more limited to some of the latter observation intervals: Hours 2 through 8 in TRAMAP-ANAG-010; Hour 3 and Hours 7 through 8 in TRAMAP-ANAG-012. Hours 5- 8 in TRAMAP-ANAG-013.

Figure 1: Mean Pain Relief Plus Pain Intensity Difference (PRID) Scores Over Time (Extrapolated)
(Subjects Evaluable for Efficacy; Protocol TRAMAP-ANAG-010)



Data source: The sponsor's study report (TRAMAP-ANAP-010) in Item 8, page 27

Table 16: Mean Pain Relief Plus Pain Intensity Difference (PRID) Scores[a] Over Time (Extrapolated)
(Subjects Evaluable for Efficacy; Protocol TRAMAP-ANAG-010)

	Hours								
Treatment	0.50	1	2	3	4	5	6	7	8
TRAM/APAP	1.8 (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	1.0 (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	1.9 (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
Ibuprofen 400 mg	1.0 (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	0.6 (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

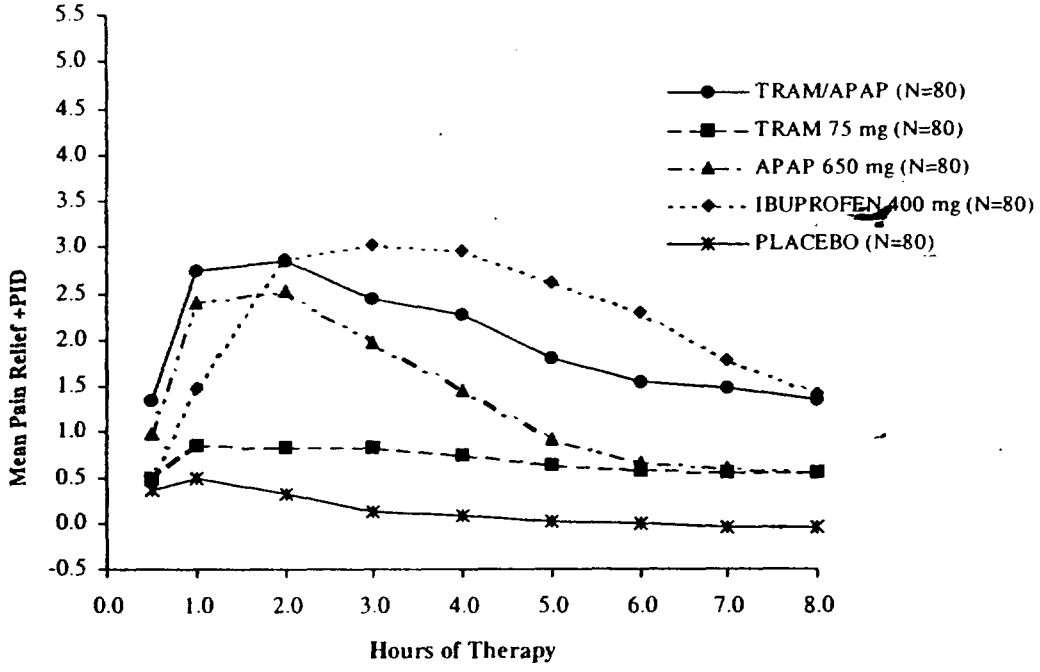
[a] Treatment means with a common letter (i.e., A,B,C,D) are not significantly different by Fisher's LSD at a level of 0.05. For each treatment group mean (SD), the number of subjects remaining in the trial is displayed at each time point.

[b] Statistically significant difference among all treatment groups at $p \leq 0.05$, F-test.

PRID rating scale -1 (pain relief of 0 and -1 PID) to 7 (complete relief of 4 and 3 PID score)

Data source: The sponsor's study report (TRAMAP-ANAP-010) in Item 8, page 27

Figure 2: Mean Pain Relief Plus Pain Intensity Difference (PRID) Scores Over Time (Extrapolated)
(Subjects Evaluable for Efficacy; Protocol TRAMAP-ANAG-012)



Data source: The sponsor's study report (TRAMAP-ANAP-012) in Item 8, page 28

Table 17: Mean Pain Relief Plus Pain Intensity Difference (PRID) Scores[a] Over Time (Extrapolated)
(Subjects Evaluable for Efficacy; Protocol TRAMAP-ANAG-012)

	Hours															
Treatment	0.5		1		2		3		4		5		6		7		8	
TRAM/APAP	1.4	(1.51)	2.8	(1.98)	2.9	(2.34)	2.5	(2.39)	2.3	(2.34)	1.8	(2.33)	1.5	(2.22)	1.5	(2.20)	1.4	(2.16)
		A		A		A		AB		B		B		B		A		A
		80		80		77		57		49		46		37		32		30
TRAM 75 mg	0.5	(0.95)	0.9	(1.49)	0.8	(1.83)	0.8	(1.99)	0.7	(2.07)	0.7	(2.02)	0.6	(2.00)	0.6	(2.01)	0.6	(2.01)
		B		C		B		C		D		CD		CD		B		B
		80		80		64		32		24		20		17		15		14
APAP 650 mg	1.0	(1.40)	2.4	(1.82)	2.5	(2.12)	2.0	(2.19)	1.5	(2.12)	0.9	(1.87)	0.7	(1.57)	0.6	(1.59)	0.6	(1.55)
		A		A		A		B		C		C		C		B		B
		80		80		78		57		45		36		23		19		15
Ibuprofen 400 mg	0.5	(1.18)	1.5	(1.92)	2.9	(2.45)	3.0	(2.48)	3.0	(2.52)	2.6	(2.48)	2.3	(2.43)	1.8	(2.27)	1.4	(2.04)
		B		B		A		A		A		A		A		A		A
		80		78		69		58		56		54		50		44		38
Placebo	0.4	(0.93)	0.5	(1.27)	0.3	(1.50)	0.1	(1.40)	0.1	(1.54)	0.0	(1.38)	-0.0	(1.35)	-0.1	(1.22)	-0.1	(1.22)
		B		C		B		D		D		D		D		C		C
		80		80		62		22		13		8		7		7		7
P-Value[b]	<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001	
RMS Error	1.216		1.720		2.075		2.125		2.141		2.053		1.957		1.898		1.832	

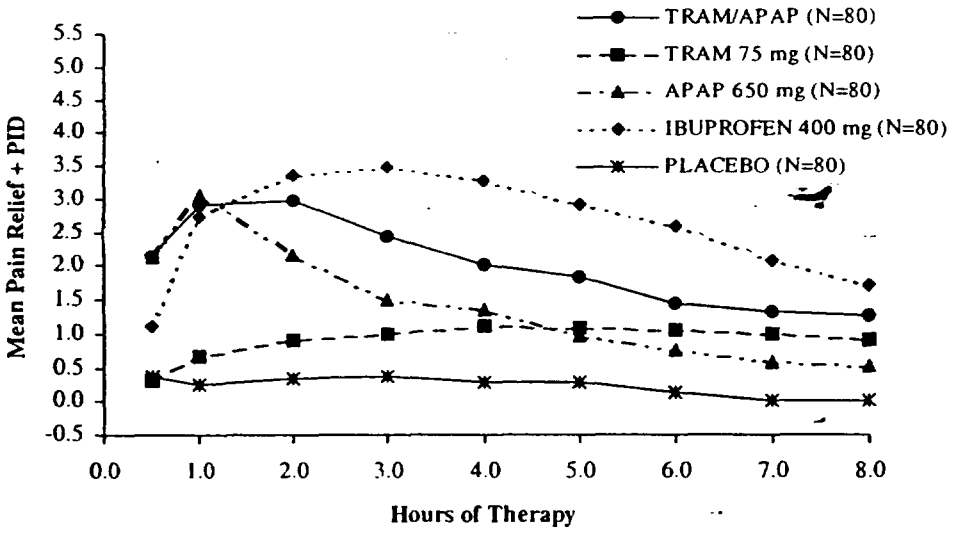
[a] Treatment means with a common letter (i.e., A,B,C,D) are not significantly different by Fisher's LSD at a level of 0.05. For each treatment group mean (SD), the number of subjects remaining in the trial is displayed at each time point.

[b] Statistically significant difference among all treatment groups at $p \leq 0.05$, F-test.

PRID rating scale -1 (pain relief of 0 and -1 PID) to 7 (complete relief of 4 and 3 PID score)

Data source: The sponsor's study report (TRAMAP-ANAP-012) in Item 8, page 28

Figure 3: Mean Pain Relief Plus Pain Intensity Difference (PRID) Scores Over Time (Extrapolated)
(Subjects Evaluable for Efficacy; Protocol TRAMAP-ANAG-013)



Data source: The sponsor's study report (TRAMAP-ANAP-013) in Item 8, page 30

Table 18: Mean Pain Relief Plus Pain Intensity Difference (PRID) Scores[a] Over Time (Extrapolated)
Subjects Evaluable for Efficacy; Protocol TRAMAP-ANAG-013)

	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	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	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
Ibuprofen	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 $p \leq 0.05$, F-test.

PRID rating scale -1 (pain relief of 0 and -1 PID) to 7 (complete relief of 4 and 3 PID score)

Data source: The sponsor's study report (TRAMAP-ANAP-013) in Item 8, page 30

Table 19: Statistical Comparison of Mean Pain Relief (PAR), Pain Intensity (PID), and Pain Relief + Pain Intensity (PRID) Scores Over Time:[a]
Pivotal Single-Dose Dental Trials
(Protocols TRAMAP-ANAG-010, 012, and 013)

Parameter/ Protocol	Statistical Separation[b]					
	TRAM/APAP			TRAM 75 mg	APAP 650 mg	Ibuprofen 400 mg
	vs. Placebo	vs. TRAM 75 mg	vs. APAP 650 mg	vs. Placebo	vs. Placebo	vs. Placebo
PAR Scores						
010	30 min - Hour 8	30 min - Hour 8	Hours 3-8	Hours 2-8	30 min - Hour 8	Hours 1-8
012	30 min - Hour 8	30 min - Hour 8	30 min; Hours 4-8	NS	30 min - Hour 5	Hours 1-8
013	30 min - Hour 8	30 min - Hour 3	Hours 2-3; Hour 5	Hours 6-8	30 min - Hour 4	30 min - Hour 8
PID Scores						
010	30 min - Hour 8	30 min - Hour 6	Hours 4-8	Hours 2-8	30 min - Hour 8	30 min - Hour 8
012	30 min - Hour 8	30 min - Hour 8	Hours 5-8	Hour 3; Hours 5-8	30 min - Hour 8	Hours 1-8
013	30 min - Hour 8	30 min - Hour 5	Hours 2-3; Hour 8	Hours 4-8	30 min - Hour 8	30 min - Hour 8
PRID Scores						
010	30 min - Hour 8	30 min - Hour 8	Hours 3-8	Hours 2-8	30 min - Hour 8	Hours 1-8
012	30 min - Hour 8	30 min - Hour 8	Hours 4-8	Hour 3; Hours 7-8	30 min - Hour 8	Hours 1-8
013	30 min - Hour 8	30 min - Hour 4	Hours 2, 3, 5, 7, 8	Hours 5-8	30 min - Hour 4	30 min - Hour -8

[a] Missing observations imputed by LOCF methodology.
[b] Treatment comparison was statistically significant by Fisher's LSD at a level of 0.05; NS = no statistical separation between treatment groups at any of the assessment intervals.
Data source: The sponsor's Table 7 in Item ISE, page 65

Times to Onset of Perceptible and Meaningful Pain Relief

The three studies include actual stopwatch times for the onset of perceptible and meaningful pain relief. The estimated onset was also analyzed to provide a comparison with other studies where the stopwatch data had not been collected, and a comparison with the time profiles calculated from the stopwatch method.

Table 20 presents the median times to onset of perceptible and meaningful pain relief in each treatment group for all three pivotal trials (the stopwatch method), while Table 21 presents the results of the statistical analyses of these data.

Table 20: Median Time (minutes) to Onset of Perceptible and Meaningful Pain Relief: Pivotal Single-Dose Dental Trials (Protocols TRAMAP-ANAG-010, 012, and 013)

Parameter/ Treatment	TRAMAP-ANAG-010	TRAMAP-ANAG-012	TRAMAP-ANAG-013
Perceptible Pain Relief			
TRAM/APAP	27.9	26.1	21.1
TRAM 75 mg	30.7	52.4	74.3
APAP 650 mg	25.4	29.8	23.5
Ibuprofen 400 mg	38.6	48.7	27.1
Placebo	43.5	---[a]	---[a]
Meaningful Pain Relief			
TRAM/APAP	103.0	59.0	54.5
TRAM 75 mg	---[a]	---[a]	---[a]
APAP 650 mg	99.8	66.6	51.8
Ibuprofen 400 mg	121.0	112.2	61.5
Placebo	---[a]	---[a]	---[a]

[a] Percentile not estimable.

- The median times to onset of meaningful pain relief or meaningful pain relief could not be estimated for these groups because more than half of the subjects in these groups did not experience meaningful pain relief or meaningful pain relief and were therefore censored and coded as 8 hours plus 1 minute, longer than all of the uncensored observations. This concentration of censored times at the right-most-portion of the Kaplan-Meier survival curves from more than half of the subjects caused the median times to be inestimable.

Data source: The sponsor's Table 9a in Item ISE, page 70

In each of the three pivotal trials, the median time to onset of perceptible pain relief following a single dose of Tramadol/APAP was less than 30 minutes. The median time to onset of meaningful pain relief with Tramadol/APAP occurred in just under one hour (54.5 and 59.0 minutes) in two of the pivotal trials (TRAMAP-ANAG-012 and 013) and in 1.7 hours (103 minutes) in the other trial (TRAMAP-ANAG-010).

The median times to onset of perceptible and meaningful pain relief following a single dose of Tramadol/APAP were comparable to those following a single dose of APAP 650 mg and earlier than those for ibuprofen 400 mg. The median time to onset of perceptible pain relief for Tramadol/APAP was also earlier than that for tramadol 75 mg.

Table 21: Analysis of Time to Onset of Perceptible and Meaningful Pain Relief:
Pivotal Single-Dose Dental Trials
(Protocols TRAMAP-ANAG-010, 012, and 013)

Parameter/ Treatment	TRAMAP-ANAG-010				TRAMAP-ANAG-012				TRAMAP-ANAG-013			
	Active vs. Placebo		TRAM/APAP vs. Other Active		Active vs. Placebo		TRAM/APAP vs. Other Active		Active vs. Placebo		TRAM/APAP vs. Other Active	
	Bivariate	Univariate	Bivariate	Univariate	Bivariate	Univariate	Bivariate	Univariate	Bivariate	Univariate	Bivariate	Univariate
Perceptible Pain Relief												
TRAM/APAP	<0.001	<0.001	---	---	<0.001	<0.001	---	---	<0.001	<0.001	--	
TRAM 75 mg	0.305	NS[a]	<0.001	0.002	0.063	NS	<0.001	<0.001	0.050[b]	0.075	<0.001	<0.001
APAP 650 mg	<0.001	<0.001	0.685	NS	<0.001	<0.001	0.428	NS	<0.001	<0.001	0.316	NS
Ibuprofen 400 mg	<0.001	0.118	0.001	<0.001	<0.001	0.003	0.003	0.001	<0.001	<0.001	0.245	NS
Meaningful Pain Relief												
TRAM/APAP	<0.001	<0.001	---	---	<0.001	<0.001	---	---	<0.001	<0.001	--	---
TRAM 75 mg	0.305	--	<0.001	<0.001	0.063	NS	<0.001	<0.001	0.050[b]	0.012	<0.001	<0.001
APAP 650 mg	<0.001	<0.001	0.685	NS	<0.001	<0.001	0.428	NS	<0.001	<0.001	0.316	NS
Ibuprofen 400 mg	<0.001	<0.001	0.001	0.382	<0.001	<0.001	0.003	0.063	<0.001	---	0.245	NS

[a] NS indicates that bivariate analysis of time to perceptible or meaningful pain relief was not significant (p>0.05) and therefore, subsequent univariate comparison was not performed.

[b] The p-value is rounded up from 0.0496, significant at the 0.05 level.

Data source: The sponsor's Table 9b in Item ISE, page 71

The estimated onset (as calculated using linear interpolation of each treatment group's mean PRID score) for each study is summarized in Table 22-24. The onset of pain relief is defined as the time required after dose administration to achieve a mean PRID rating of 1. The results show clearly that the estimated onset of pain relief is much shorter than the results measured by the stopwatch method.

Table 22: Estimated Onset
(Subjects Evaluable for Efficacy; Protocol TRAMAP-ANAG-010)

	Estimated Onset of Pain Relief (minutes)			Estimated Duration of Pain Relief (minutes)[a]		
Treatment	Mean	Lower 95% CL	Upper 95% CL	Median	Lower 95% CL	Upper 95% CL
TRAM/APAP	17.0	14.0	22.0	326.0	244.0	366.0
TRAM 75 mg	31.0	23.0	45.0	124.0	122.0	137.0
APAP 650 mg	15.0	13.0	19.0	184.0	145.0	243.0
Ibuprofen 400 mg	30.0	22.0	44.0	301.0	226.0	365.0
Placebo	46.0	33.0	78.0	122.0	109.0	123.0

[a] Based on Kaplan-Meier estimate.
Data source: The sponsor's Table 16 in the study report for ANAG-10, page 37

Table 23: Estimated Onset
(Subjects Evaluable for Efficacy; Protocol TRAMAP-ANAG-012)

	Estimated Onset of Pain Relief (minutes)			Estimated Duration of Pain Relief (minutes)[a]		
Treatment	Mean	Lower 95% CL	Upper 95% CL	Median	Lower 95% CL	Upper 95% CL
TRAM/APAP	22.0	18.0	30.0	300.5	233.0	385.0
TRAM 75 mg	62.0	43.0	109.0	122.0	122.0	129.0
APAP 650 mg	31.0	23.0	45.0	241.5	181.0	261.0
Ibuprofen 400 mg	63.0	41.0	142.0	421.0	324.0	--[b]
Placebo	86.0	54.0	211.0	104.0	84.0	122.0

[a] Based on Kaplan-Meier estimate.
[b] Not estimable because duration of pain relief was greater than the observation period.
Data source: The sponsor's Table 16 in the study report for ANAG-12, page 34

Table 24: Estimated Onset
(Subject Evaluable for Efficacy; Protocol TRAMAP-ANAG-013)

	Estimated Onset of Pain Relief (minutes)			Estimated Duration of Pain Relief (minutes)[a]		
Treatment	Mean	Lower 95% CL	Upper 95% CL	Median	Lower 95% CL	Upper 95% CL
TRAM/APAP	14.0	12.0	18.0	245.0	215.0	360.0
TRAM 75 mg	100.0	52.0	106.7	123.0	120.0	155.0
APAP 650 mg	14.0	12.0	18.0	165.0	141.0	195.0
Ibuprofen 400 mg	27.0	20.0	38.0	422.5	325.0	--[b]
Placebo	83.0	46.0	424.0	105.0	91.0	121.0

[a] Based on Kaplan-Meier estimate.
[b] Not estimable because duration of pain relief was greater than the observation period.
Data source: The sponsor's Table 17 in the study report for ANAG-13, page 37

Time-to-Remedication

Results for the analysis of time to remedication indicated a significant difference in favor of all active treatments over placebo ($p<0.001$). Median remedication times for TRAM/APAP varied from 245 minutes to 326 minutes, and they were significantly longer than those for tramadol or APAP alone.

Table 25: Selected Percentiles for Time (minutes) to Remedication (Subjects Evaluable for Efficacy; Protocol TRAMAP-ANAG-010, 012, 013)

			(Median)	
Treatment	N	25th	50th	75th
ANAG-010				
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
ANAG-012				
TRAM/APAP	80	122.0	300.5	--[a]
TRAM 75 mg	80	87.5	122.0	252.5
APAP 650 mg	80	122.0	241.5	361.5
Ibuprofen 400 mg	80	122.0	421.0	--[a]
Placebo	80	69.5	104.0	139.0
ANAG-013				
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.
Data Sources: The sponsor's Table 18, 18, and 19 p38, p36 and p39 in each individual study report, respectively.

Subgroup Analyses

The relative analgesic efficacy of the Tramadol/APAP combination to its components and to placebo was evaluated as a function of baseline pain intensity, gender, race, and body weight (separately for male and female subjects). The sponsor combined data from the three pivotal single-dose efficacy trials for these subgroup analyses.

The time course of analgesic activity for the combination relative to its components was generally similar in men and women, as indicated by hourly pain relief and pain intensity difference scores (Table 26).

Table 26: Summary Efficacy Variables for 0-8 Hour Interval by Gender: Combined Pivotal Single-Dose Trials (Protocols TRAMAP-ANAG-010, 012, and 013)

Variable	Gender	TRAM/ APAP	TRAM 75 mg	APAP 650 mg	Ibuprofen 400 mg	Placebo
Number of Subjects	Male	107	85	97	98	89
	Female	133	153	143	142	150
Mean TOTPAR (0-8 hr)	Male	11.7	7.9	9.3	15.7	3.8
	Female	12.4	6.0	8.1	12.2	3.0
Mean SPID (0-8 hr)	Male	4.3	1.9	3.4	6.9	-1.5
	Female	5.0	0.4	2.3	5.1	-1.6
Mean SPRID (0-8 hr)	Male	16.0	9.8	12.6	22.6	2.2
	Female	17.4	6.4	10.4	17.3	1.4

Data source: The sponsor's Table 12 in the study report for ANAG-13, page 37

Examination of the pattern of efficacy findings among subjects of White or Other racial origins supported the superiority of Tramadol/APAP to its components and to placebo. Among Blacks, however, separation of the combination from its components and placebo was not always apparent (data not included in the table above). The clinical relevance of this observation is unknown since fewer than 10 subjects per treatment group were Black.

It appears that baseline pain intensity and body weight had no apparent influence on the analgesic efficacy of the Tramadol/APAP combination.

Section 7.2.1.7 Reviewer's Efficacy Evaluation and Discussion

Pain Scores: Pain scores (PID, PR and PRID) can be evaluated in several ways. The plot of score vs. time together with a timepoint-by-timepoint statistical analysis show the profile of analgesia over time and convey an overall view of onset, relative magnitude of effect, and duration.

For the three pivotal dental studies, the sponsor performed required efficacy variables. The reviewer confirmed the sponsor's results regarding the statistical analyses of the pain efficacy variable data.

The analgesic efficacy of TRAM/APAP in the dental pain model was established in the three trials by the PRID and other pain score profiles. The contributions of tramadol and acetaminophen were shown in all three studies. The combination product does not increase the peak analgesic effect of tramadol or APAP. Placebo effect (peak PRID: 0.4-0.8) was small, and suggests those studies had more upside than downside sensitivity.

Onset: An analgesic for acute use should be able to separate from placebo by one hour, and earlier separation would be desirable. All three studies found statistically significant differences at 30 minutes (pain scores). Two tablets of TRAM/APAP beat placebo in all timepoints (30 min – Hour 8). The contribution of acetaminophen was seen in all three studies while tramadol 75 mg (component) was not separated from placebo until Hour 2-3. PR scores of tramadol 75 mg group in study ANA-012 were not statistically different from placebo.

Times to onset of perceptible pain relief measured by the stopwatch method were under a half hour (21 – 28 minutes) following a single dose of Tramadol/APAP. The median time to onset of meaningful pain relief with Tramadol/APAP occurred in 55 to 103 minutes. The contribution of acetaminophen was seen (statistically significant differences vs. the placebo) in all three studies.

Time-to-Remedication: Examining the times at which patients request remedication can assess duration of action. This endpoint has direct relevance to dosing interval.

The medical reviewer performed additional analyses to examine the effects by pooling data from the three studies (Table 27 and Figure 4). Table 26 shows Kaplan-Meier estimates of median times to remedication. The duration of analgesic effect of TRAM/APAP is about 5 hours with a range from 245 minutes to 326 minutes in different studies. Therefore, 4 hours (i.e., 245 minutes) may be a low remedication time estimate for TRAM/APAP. The duration of effect for placebo was the shortest among treatment groups. The results provided evidence that acetaminophen contributes to the duration of action while tramadol's contribution is limited.

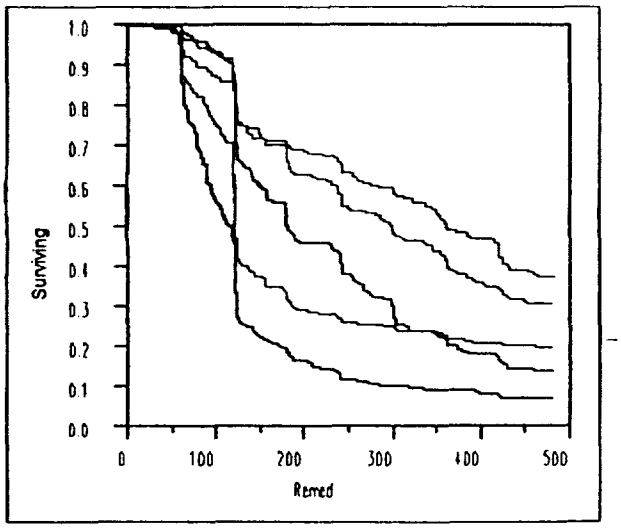
Table 27. Time-to-Remedication (in minutes)

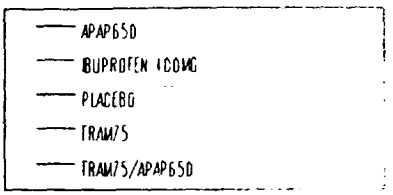
Level/Percentile	10.0%	25.0%	median	75.0%	90.0%
APAP 650 mg*	120	122	183	318.75	480
IBUPROFEN 400 mg*	80	130	362.5	480	480
PLACEBO	62	72	120	143	320
TRAM 75 mg	62	100	122	302	480
TRAM 75 / APAP 650*	121	130	302	480	480

* Statistically significant differences vs. placebo in Wilcoxon median test

The results of time-to-remedication are consistent with the findings based on TOTPAR (see Summary Section for detail), and these results suggest that the combination product may increase duration of analgesic effect over tramadol and APAP although it does not increase the peak analgesic effect of its each component.

Figure 4. Product-Limit Plot of Time-to-Remedication





Tests Between Groups

Test	Chi-Square	DF	Prob>ChiSq
Log-Rank	218.0271	4	<.0001
Wilcoxon	257.5610	4	<.0001

SECTION 7.2.2 PROTOCOLS TRAMAP-ANAG-002, 003

Two additional supportive single-dose dental trials were conducted by the sponsor at an earlier date than the three pivotal trials discussed in the previous section.

SECTION 7.2.2.1. **Protocol Summary**

Two protocols were identical, and they were very similar to the protocol for the three pivotal trials with few exceptions:

- The dental procedures performed in Study ANAG-002 and 003 were less extensive, suggesting a lower pain level in these studies compared with the pivotal trials. Only ANAG-002 involved the extraction of at least one impacted mandibular third molar requiring bone removal, and Study ANAG-003 involved the extraction of at least one impacted third molar. In contrast, the pivotal studies involved extraction of two or more impacted third molars, two of which required bone removal.
- Studies ANAG-002 and 003 did not use the stopwatch method for measuring onset of pain relief.

In brief, Studies ANAG-002 and 003 were randomized, double-blind, parallel-group, factorial design trials with active and placebo controls that evaluated the single-dose analgesic efficacy and safety of the combination tramadol 75 mg with APAP 650 mg (TRAM/APAP) in subjects with pain following oral surgical procedures. TRAM/APAP was compared to each of its components, tramadol 75 mg and APAP 650 mg. An active control, ibuprofen 400 mg, was used to determine the sensitivity of the clinical endpoints. Fifty subjects were randomized to each of the five treatment groups in each study.

Other protocol information, including inclusion/exclusion criteria, was described in details in the previous section for the three pivotal trials.

Section 7.2.2.2. Protocol Amendments:

Study ANAG-002:

One amendment was made to the protocol before any subjects entered the trial; this amendment (dated March 11, 1996) revised the minimum age for study eligibility from 18 years to 16 years.

The amendment to the protocol (prior to study drug initiation) modified the statistical analysis to be performed by specifying that all randomized subjects who received study drug and had any subsequent evaluation would be included in the efficacy analysis. Additionally, the amendment specified the Least Significant Difference (LSD) procedure as the method for analysis of variance timepoint comparisons of mean scores of PAR and PID, and PAR plus PID (PRID) at each observation point.

Based on Amendment 1 of the protocol, statistical analysis of time to remedication was modified to state that time in the trial was to be censored at the time of the last observation for subjects who completed the trial without remedicating and for subjects who withdrew from the trial without remedicating. For subjects who took rescue medication the actual remedication time was included in the analysis.

Study ANAG-003:

There was one amendment to the protocol. This amendment (dated March 12, 1996) revised the minimum age for study eligibility from 18 years to 16 years and modified the statistical procedures to be used in analyzing efficacy data described in the ANAG-002 above.

Section 7.2.2.3 Conduct of Study

Protocol Deviations

ANAG-002: Subject 1132, a 27-year-old man with a history of drug abuse, was enrolled in this trial as an exception to the protocol exclusion criterion regarding history of drug abuse. The subject had been drug-free for five years and, therefore, was approved for trial participation by the RWJPRI medical monitor.

ANAG-003: There were no clinically important protocol deviations noted during this study.

Patient Distribution/Disposition:

A total of 250 subjects each were enrolled and randomized to double-blind treatment in Protocols TRAMAP-ANAG-002 and 003. All but one subject completed the trial ANAG-

002 as planned. Subject 1152, a 33-year-old man in the placebo group, left the study site after completing his half-hour efficacy assessments and was lost to follow-up.

All but four subjects completed the trial ANAG-003. Three subjects (1222 in the TRAM/APAP group, 1195 in the tramadol 75 mg group, and 1240 in the ibuprofen 400 mg group) were withdrawn prematurely as a result of an adverse event. Subjects 1222 and 1195 completed only the 30-minute evaluation while subject 1240 completed only the baseline evaluation. The fourth subject (1043) in the placebo group chose to withdraw after completing the one-hour evaluation.

Patient disposition is tabulated in Table 28.

Table 28: Study Completion/Withdrawal Information: Supportive Single-Dose, Dental Trials (Protocols TRAMAP-ANAG-002 and 003)

	Protocol	TRAM/ APAP	TRAM 75 mg	APAP 650 mg	Ibuprofen 400 mg	Placebo
Total Subjects	002	50	50	50	50	50
	003	50	50	50	50	50
Subjects Who Completed	002	50	50	50	50	49
	003	49	49	50	49	49
Subjects Who Withdrew	002	0	0	0	0	1
	003	1	1	0	1	1
Subject choice	002 + 003	0	0	0	0	1
Adverse event	002 + 003	1	1	0	1	0
Lost to follow-up	002 + 003	0	0	0	0	1

Data source: The sponsor's Table 14 in ISE, Page 84

Demographics:

Demographic information is listed in Table 29 and 30. In each trial, the five treatment groups were generally well-matched with respect to demographic and baseline characteristics. The percentage of subjects in each group who were male ranged from 32% to 56% (overall, 44%) in TRAMAP-ANAG-002 and from 40% to 60% in TRAMAP-ANAG-003 (overall, 52%). Most subjects enrolled in the two trials were White (70% and 96%, respectively), and the average age of subjects was 23.9 years (range, 16-48 years) in TRAMAP-ANAG-002 and was 18.8 years (range, 16-33 years) in TRAMAP-ANAG-003. All subjects were required to have moderate or severe pain before administering study medication; the percentage of subjects who reported their baseline pain as moderate in severity was 81% in TRAMAP-ANAG-002 and 67% in TRAMAP-ANAG-003.

Section 7.2.2.4 Sponsor's Efficacy Results:

Efficacy results were generally similar for the two supportive single-dose, dental pain trials, showing that Tramadol/APAP provided analgesic efficacy that was statistically superior to placebo and tramadol 75 mg, but was not statistically superior to APAP 650 mg. In these trials, the efficacy of tramadol 75 mg was not statistically different from that of placebo, while comparisons generally statistically favored APAP 650 mg over placebo.

Figure 5: Mean PRID Scores Over Time (Extrapolated)
(All Randomized Subjects; Protocol TRAMAP-ANAG-002)

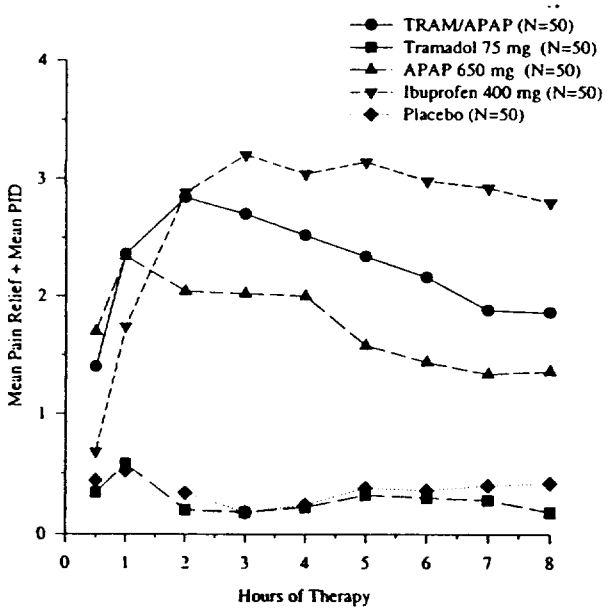


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Table 29: Mean PRID Scores[a] Over Time (Extrapolated)
(All Randomized Subjects; Protocol TRAMAP-ANAG-002)

	Hours								
Treatment	0.50	1	2	3	4	5	6	7	8
TRAM/APAP	1.4 (1.63)	2.4 (1.80)	2.8 (2.18)	2.7 (2.35)	2.5 (2.52)	2.3 (2.54)	2.2 (2.64)	1.9 (2.44)	1.9 (2.51)
	A	A	AB	AB	AB	AB	AB	B	B
	50	50	45	41	34	27	26	22	19
Tramadol 75 mg	0.3 (1.30)	0.6 (1.63)	0.2 (1.43)	0.2 (1.44)	0.2 (1.52)	0.3 (1.75)	0.3 (1.72)	0.3 (1.64)	0.2 (1.44)
	B	B	C	C	C	C	C	C	C
	50	50	27	9	7	7	7	7	7
APAP 650 mg	1.7 (1.93)	2.3 (1.90)	2.0 (2.41)	2.0 (2.51)	2.0 (2.60)	1.6 (2.45)	1.4 (2.36)	1.3 (2.42)	1.4 (2.46)
	A	A	B	B	B	B	B	B	B
	50	50	44	29	26	24	19	18	16
Ibuprofen 400 mg	0.7 (1.35)	1.7 (2.05)	2.9 (2.42)	3.2 (2.60)	3.0 (2.66)	3.1 (2.74)	3.0 (2.69)	2.9 (2.69)	2.8 (2.66)
	B	A	A	A	A	A	A	A	A
	50	50	39	34	33	31	30	29	28
Placebo	0.4 (1.05)	0.5 (1.40)	0.3 (1.55)	0.2 (1.48)	0.2 (1.61)	0.4 (1.93)	0.4 (1.88)	0.4 (1.98)	0.4 (2.01)
	B	B	C	C	C	C	C	C	C
	50	49	22	13	9	8	8	8	8
P-Value[b]	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
RMS Error	1.483	1.772	2.042	2.136	2.237	2.312	2.291	2.266	2.26

[a] PRID represents pain relief plus pain intensity difference. Treatment means with a common letter 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 timepoint.
[b] Statistically significant difference among all treatment groups at $p \leq 0.05$, F-test.

Data Source: The sponsor's Table 11 in the study report (ANAG-002), page 23

Figure 6: Mean PRID Scores Over Time (Extrapolated)
(Subjects Evaluable for Efficacy; Protocol TRAMAP-ANAG-003)

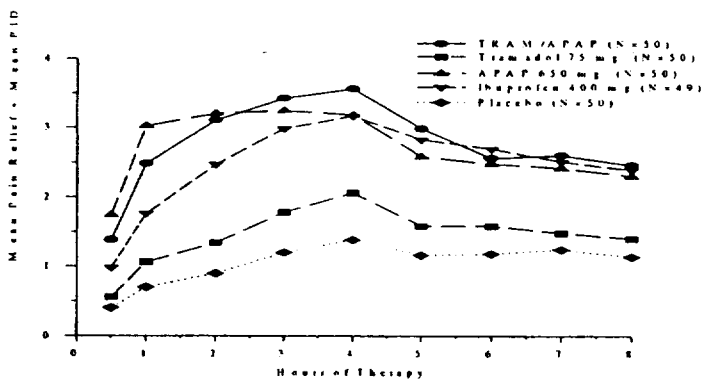

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Table 30: Mean PRID Scores[a] Over Time (Extrapolated)
(Subjects Evaluable for Efficacy; Protocol TRAMAP-ANAG-003)

	Hours								
Treatment	0.50	1	2	3	4	5	6	7	8
TRAM/APAP	1.38 (1.78)	2.48 (1.83)	3.10 (1.92)	3.42 (1.93)	3.56 (1.99)	2.98 (2.04)	2.56 (1.98)	2.60 (2.17)	2.46 (2.07)
	AB	A	A	A	A	A	A	A	A
	50	49	49	41	39	39	36	31	29
TRAM 75 mg	0.56 (1.21)	1.06 (1.73)	1.34 (2.12)	1.78 (2.47)	2.06 (2.65)	1.58 (2.34)	1.58 (2.42)	1.48 (2.46)	1.40 (2.44)
	CD	C	B	B	B	B	B	B	B
	50	49	37	26	26	26	25	23	21
APAP 650 mg	1.74 (1.55)	3.02 (1.36)	3.20 (2.03)	3.24 (2.00)	3.18 (1.96)	2.58 (2.07)	2.48 (2.18)	2.42 (2.13)	2.30 (2.15)
	A	A	A	A	A	A	A	A	A
	50	50	49	44	41	40	36	31	28
Ibuprofen 400 mg	0.98 (1.15)	1.76 (1.79)	2.47 (2.13)	2.98 (2.31)	3.16 (2.41)	2.82 (2.34)	2.69 (2.29)	2.51 (2.24)	2.39 (2.28)
	BC	B	A	A	A	A	A	A	A
	49	49	39	34	34	34	32	32	31
Placebo	0.40 (1.26)	0.70 (1.54)	0.90 (1.83)	1.20 (2.14)	1.38 (2.35)	1.16 (2.24)	1.18 (2.26)	1.24 (2.34)	1.14 (2.26)
	D	C	B	B	B	B	B	B	B
	50	50	33	20	19	19	18	18	17
P-Value[b]	0.000	0.000	0.000	0.000	0.000	0.000	0.001	0.004	0.005
RMS Error	1.412	1.659	2.011	2.177	2.286	2.210	2.229	2.271	2.244

[a] PRID represents pain relief plus pain intensity difference. 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 timepoint.

[b] Statistically significant difference among all treatment groups at $p \leq 0.05$, F-test

Data Source: The sponsor's Table 11 in the study report (ANAG-002), page 24

Estimates of the onset of pain relief in the supportive dental pain trials followed a pattern similar to that in the pivotal trials. In both supportive trials, the onset of pain relief for the combination Tramadol/APAP product (21 and 22 minutes in TRAMAP-ANAG-002 and 003, respectively) was similar to that for APAP 650 mg alone (18 and 17 minutes, respectively) and faster than that for tramadol 75 mg alone (88 and 54 minutes, respectively).

As noted for the pivotal single-dose trials, the median time to remedication provides an estimate of the duration of pain relief provided by each of the study treatments. In TRAMAP-ANAG-002, the median time to remedication in the Tramadol/APAP group (320.5 minutes, or 5.3 hours) was significantly longer than that for tramadol 75 mg (88 minutes, or 1.5 hours) ($p<0.001$) and numerically longer than that for APAP 650 mg (242.5 minutes, or 4.1 hours). The median time to remedication could not be calculated for the Tramadol/APAP and APAP 650 mg groups in TRAMAP-ANAG-003 since at least half of the subjects in these groups did not remedicate. Compared to the pivotal trials, a smaller proportion of subjects in all groups required rescue medication at some time during the trials.

Table 31: Number of Subjects Who Took Rescue Medication at Each Hour
(All Randomized Subjects; Protocol TRAMAP-ANAG-002 and 003)

	Cumulative Number of Subjects Remedicating at Each Hour[a]								
Treatment	1	2	3	4	5	6	7	8	Total (%) Not Remedicating
ANAG-002									
TRAM/APAP (N = 50)	0 (0)	6 (6)	11 (5)	19 (8)	24 (5)	28 (4)	29 (1)	31 (2)	19 (38)
Tramadol 75 mg (N = 50)	0 (0)	30 (30)	42 (12)	43 (1)	43 (0)	43 (0)	43 (0)	43 (0)	7 (14)
APAP 650 mg (N = 50)	0 (0)	16 (16)	22 (6)	24 (2)	26 (2)	32 (6)	33 (1)	34 (1)	16 (32)
Ibuprofen 400 mg (N = 50)	0 (0)	13 (13)	17 (4)	18 (1)	19 (1)	20 (1)	21 (1)	22 (1)	28 (56)
Placebo (N = 50)	1 (1)	32 (31)	39 (7)	41 (2)	41 (0)	41 (0)	41 (0)	41 (0)	8[b] (16)
ANAG-003									
TRAM/APAP (N=50)	0 (0)	6 (6)	10 (4)	10 (0)	12 (2)	16 (4)	19 (3)	22 (3)	28 (56%)
TRAM 75 mg (N=50)	11 (11)	21 (10)	23 (2)	23 (0)	23 (0)	26 (3)	28 (2)	28 (0)	22 (44%)
APAP 650 mg (N=50)	1 (1)	6 (5)	8 (2)	10 (2)	13 (3)	17 (4)	22 (5)	25 (3)	25 (50%)
Ibuprofen 400 mg (N=49)	10 (10)	15 (5)	15 (0)	15 (0)	17 (2)	17 (0)	17 (0)	19 (2)	30 (61%)
Placebo (N=50)	17 (17)	29 (12)	30 (1)	30 (0)	31 (1)	31 (0)	31 (0)	32 (1)	18 (36%)

[a] Total number of subjects remedicating during the specified interval is noted in parenthesis.
[b] Does not include subject 1152 who prematurely withdrew from the trial without remedicating

Data Sources: The sponsor's Table 13 in the individual study report page 25-26

Section 7.2.2.5 Reviewer's Efficacy Evaluation and Discussion:

For the two supportive dental studies, the sponsor performed required efficacy variables. The reviewer confirmed the sponsor's conclusions regarding the statistical analyses of the pain efficacy variable data.

Contribution of Components: The analgesic efficacy of TRAM/APAP was better than placebo in the two dental trials by the PRID and other pain score profiles. However, the contributions of tramadol and acetaminophen were not established in the studies. The analgesic effect of TRAM/APAP couldn't be statistically separated from acetaminophen in both trials. The failure to show the separation may have been a consequence of low pain level resulting from less extensive dental procedures performed in the studies (see the key inclusion criteria in the protocol summary). Acetaminophen may be an adequate analgesic agent under this condition. Therefore, it is difficult for TRAM/APAP to show a difference.

Onset: The stopwatch method was not used in the studies. Estimates of the onset of pain relief followed a pattern similar to that in the pivotal trials.

Time-to-Remedication: There was a great variation of estimated duration of pain relief (i.e., a marker of time-to-remedication) in the two studies. The duration of analgesic effect of TRAM/APAP was 240 minutes (lower 95%CL estimate) in study ANAG-002 comparing to 380 minutes in study ANAG-003 (the lower 95%CL estimate is used for the comparison because median time in ANAG-003 was not estimated). An even greater variation of the estimate was seen in acetaminophen effect: 124 min (ANAG-002) vs. 385 min (ANAG-003), which indicates a problem in the study model sensitivity.

Section 7.2.3 Study TRAMAP-ANAG-004 and TRAMAP-ANAG-005

Two randomized, double-blind, placebo-controlled, parallel group, factorial design trials were conducted in subjects with pain from a gynecologic surgical procedure (TRAMAP-ANAG-004) or from an orthopedic surgical procedure (TRAMAP-ANAG-005). In both trials, subjects were confined to the study clinic for the duration of the eight-hour observation period. The efficacy evaluations in these two surgical pain trials were similar to those mentioned above for the single-dose, dental pain trials, TRAMAP-ANAG-002 and 003.

There were two major differences in their designs when compared to the dental pain trials:

1. A higher dose of Tramadol/APAP combination (tramadol 112.5 mg with APAP 975 mg was used in the post-surgical trials vs. tramadol 75 mg with APAP 650 mg in the dental trials). The sponsor believed that a higher dose of tramadol was required to effectively manage pain after a surgical procedure as compared to a dental pain model.
2. There was no active-control arm such as ibuprofen in the dental trials to measure study model sensitivity.

In addition, all subjects in TRAMAP-ANAG-004 were female.

Section 7.2.3.1 Protocol Summary

Objectives: The primary objectives of the randomized, double-blind, parallel-group, factorial design trials with placebo control were to evaluate the efficacy and safety of the combination tramadol 112.5 mg (TRAM) with acetaminophen (APAP) 975 mg in subjects experiencing pain from a gynecologic surgical procedure or from an orthopedic surgical procedure and to demonstrate the contribution of each component to the analgesic effect of the combination.

INVESTIGATOR:
Study TRAMAP-ANAG-004: Abraham Sunshine, M.D. - Hospital Municipal de San Juan, Rio Piedras, Puerto Rico
TRAMAP-ANAG-005: L. Suzanne Black, M.D. - SCIREX Corp.-TX, Austin, TX; USA

Study Design:

They were randomized, double-blind, placebo-controlled, parallel-group, factorial design trials that evaluated the single-dose analgesic efficacy and safety of the combination tramadol 112.5 mg with APAP 975 mg (TRAM/APAP) in subjects with pain from gynecologic surgical procedures or from an orthopedic surgical procedure. TRAM/APAP was compared to each of its components, tramadol 112.5 mg and APAP 975 mg. Subjects who experienced moderate or severe pain following a gynecologic surgical procedure

(ANAG-004) or from an orthopedic surgical procedure (ANAG-005) were eligible for trial participation. Qualified subjects were randomized in equal numbers to a single dose of TRAM/APAP, tramadol 112.5 mg, APAP 975 mg, or placebo. Following the recording of baseline pain intensity and administration of study medication, subjects evaluated current pain and relief from starting pain at 30 minutes, and 1, 2, 3, 4, 5, 6, 7, and 8 hours. Each subject 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 subject 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 subject took a supplemental analgesic. At the end of the eight-hour observation period or at the time supplemental analgesic was taken, whichever occurred first, the subject provided an overall assessment of the trial medication.

Section 7.2.3.2 Efficacy and Statistical Analysis:

Efficacy: Pain relief (PAR) and pain intensity difference (PID), the difference between current pain and baseline pain assessment, were averaged for each timepoint and summarized by treatment group. Additionally, pain relief + PID= (PRID) was averaged for each observation timepoint and summarized by treatment group. Additional efficacy variables included the number (%) of subjects using supplemental analgesics at each timepoint, onset of analgesia, duration of analgesia, and subject's overall assessment of trial medication.

A one-way analysis of variance was used to analyze hourly pain relief, PID and PRID scores. The last observation carried forward method was used for missing observations and for observation points after a subject took rescue medication. Time to remedication was analyzed by using the Kaplan-Meier estimate to compute the failure distribution function. The distribution functions were compared using the log-rank test. Time of onset of pain relief was calculated by linear interpolation of each treatment group's mean PRID score and was defined as the time at which the PRID score for a given group reached 1 as calculated by linear interpolation. Duration of pain relief was defined as the earliest time when half of the subjects in a treatment group remedicated. The 95% confidence limits for the mean time to onset and duration of pain relief were calculated.

Inclusion/Exclusion Criteria

Study ANAG-004:

Key inclusion criteria for entry into this trial are presented in Table 31.

Table 31: Key Inclusion Criteria
(Protocol TRAMAP-ANAG-004)

- Females 18 years of age or older who are not pregnant or not nursing within 48 hours after medication.
- Moderate or severe pain as a result of a major abdominal gynecologic surgical procedure other than laparoscopy.
- Able to take oral medication.
- Sufficiently alert to understand and communicate intelligibly with the study observer.
- Good physical health.

Data Sources: The sponsor's Table 1 in the individual study report page 6.

Key criteria for exclusion from this trial are presented in Table 32.

Table 32: Key Exclusion Criteria
(Protocol TRAMAP-ANAG-004)

- Received an experimental drug or used an experimental medical device within 30 days prior to screening.
- Received any oral or topical analgesic medication (either centrally or peripherally acting) within three hours prior to administering trial medication or injectable or transdermal analgesic within two hours before taking trial medication.
- Gynecologic surgery due to malignancy.
- Required concomitant use of sedatives, other than those used during surgery.
- History of seizures or narcotic or alcohol abuse.
- Currently taking monoamine oxidase inhibitors, tricyclic antidepressants, neuroleptics, or other drugs that reduce the seizure threshold.
- Sensitive or allergic to tramadol, APAP, or opiates.
- At risk in terms of precautions, warnings, and contraindications in the package insert for ULTRAM® tramadol hydrochloride.
- Previous participation in this study.

Data Sources: The sponsor's Table 2 in the individual study report page 6.

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Study ANAG-005:

Key inclusion criteria for entry into this trial are presented in Table 33 .

Table 33: Key Inclusion Criteria
(Protocol TRAMAP-ANAG-005)

- 18 years of age or older, and, if female, postmenopausal or surgically rendered incapable of having children, or not pregnant or nursing and using acceptable birth-control methods.
- Moderate or severe pain as a result of an orthopedic surgical procedure.
- Able to take oral medication.
- Sufficiently alert to understand and communicate intelligibly with the study observer.
- Good physical health.

Data Sources: The sponsor's Table 1 in the individual study report page 5.

Key criteria for exclusion from this trial are presented in Table 34.

Table 34: Key Exclusion Criteria
(Protocol TRAMAP-ANAG-005)

- Received an experimental drug or used an experimental medical device within 30 days prior to screening.
- Received any oral or topical analgesic medication (either centrally or peripherally acting) within three hours prior to administering trial medication or injectable or transdermal analgesic within two hours before taking trial medication.
- Required concomitant use of sedatives, other than those used during surgery.
- History of seizures or narcotic or alcohol abuse.
- Currently taking monoamine oxidase inhibitors, tricyclic antidepressants, neuroleptics, or other drugs that reduce the seizure threshold.
- Sensitive or allergic to tramadol, APAP, or opiates.
- At risk in terms of precautions, warnings, and contraindications in the package insert for ULTRAM® tramadol hydrochloride.
- Previous participation in this study.

Data Sources: The sponsor's Table 2 in the individual study report page 6.

Section 7.2.3.3 Protocol Amendments

Study ANAG-004:

There was one amendment added to the protocol before any subjects entered the trial. This amendment (dated February 29, 1996) expanded the allowed surgical procedures to include any major abdominal gynecologic surgical procedure other than laparoscopy.

Study ANAG-005:

There were no amendments to the protocol.

Section 7.2.3.4. Conduct of Study

Protocol Deviations

Study ANAG-004: Subject 1016 in the tramadol 112.5 mg treatment group took Percocet 10 minutes before trial medication was administered;

Study ANAG-005: After completion of the trial it was discovered that the investigator had been incorrectly informed that subjects who received a supplemental analgesic were to be monitored for only one hour after administration of the concomitant analgesic. The potential therefore exists for under-reporting of those adverse events occurring during the period of time after the one-hour following the supplemental analgesic administration and prior to the completion of the eight-hour interval. All adverse events that were persisting at the time of supplemental analgesic administration were followed to resolution.

Patient Distribution/Disposition

A total of 200 subjects each were enrolled and randomized to double-blind treatment in Protocols TRAMAP-ANAG-004 and 005.

All randomized subjects in the two single-dose, surgical pain trials received a single dose of study medication, and all but 14 subjects completed their respective trial as planned. Seven subjects in TRAMAP-ANAG-004 (one, four, and two randomized to tramadol 112.5 mg, APAP 975 mg, and placebo, respectively), and seven in TRAMAP-ANAG-005 (two each randomized to tramadol 112.5 mg and APAP 975 mg and three randomized to placebo) withdrew prematurely (Table 35).

Table 35: Study Completion/Withdrawal Information:
Supportive Single-Dose, Surgical Pain Trials
(Protocols TRAMAP-ANAG-004 and 005)

	Protocol	TRAM/ APAP	TRAM 112.5 mg	APAP 975 mg	Placebo
Total Subjects	004	51	49	50	50
	005	50	50	50	50
Subjects Who Completed	004	51	48	46	48
	005	50	48	48	47
Subjects Who Withdrew	004	0	1	4	2
	005	0	2	2	3
Subject choice	004 + 005	0	1	1	2
Adverse event	004 + 005	0	1	2	2
Other[a]	004	0	1	3	1

[a] In TRAMAP-ANAG-004, one subject in the tramadol 112.5 mg group took Percocet 10 minutes before trial drug was administered. The remaining four subjects withdrew due to lack of efficacy.

Data Source: Based on Sponsor's Table 16 in ISE, Page 89

Demographics: Demographic information is listed in Appendix C. In each trial the four treatment groups were generally well-matched with respect to demographic and baseline characteristics.

All subjects in TRAMAP-ANAG-004 were female and Hispanic, and subjects' average age was 26.5 years (range, 18 to 49 years). Approximately 94% of the gynecologic surgical procedures performed were Cesarean sections, and the majority of subjects (84%) reported severe pain at baseline.

In TRAMAP-ANAG-005, slightly more than one-half (58%) of the subjects were male (range, 56% to 62%), most (85%) were White, and the average age was 45.4 years (range, 20 to 83 years). Approximately 80% of the orthopedic surgical procedures involved the foot or ankle, spine, or knee, and the majority of subjects (79%) reported moderate baseline pain.

Section 7.2.3.5 Sponsor's Efficacy Results

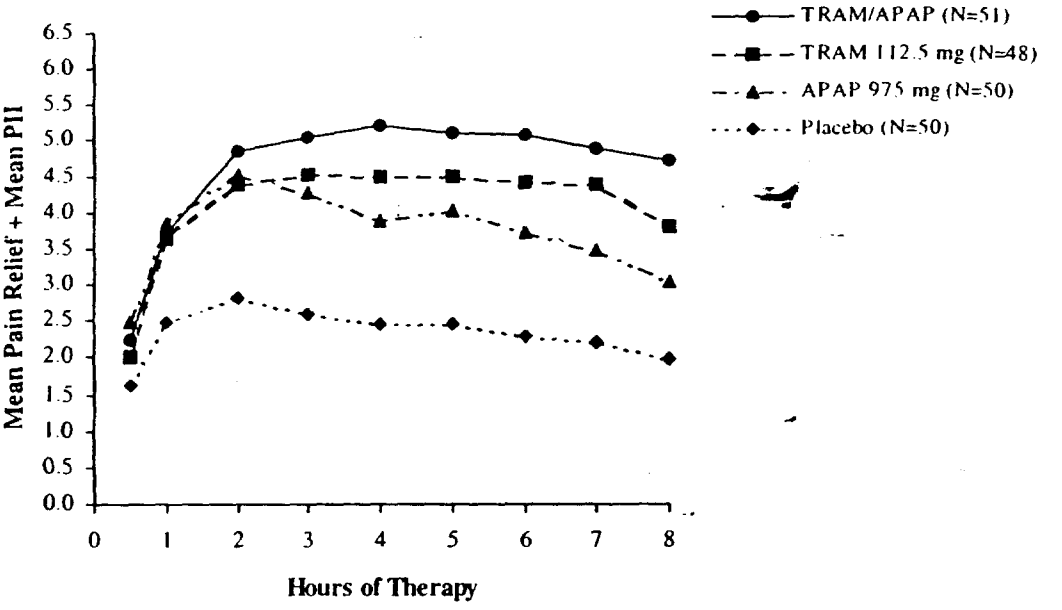
Contribution of Components and Pain Scores:

In both supportive surgical pain trials, Tramadol/APAP was significantly superior to placebo by Hour 1 when comparing pain relief, PID, and PRID scores and remained statistically superior throughout the eight-hour observation interval ($p \leq 0.05$). PRID scores are presented in Figure 6-7 and Table 36-37 below. Results on PR and PID are included in Appendix C.

For PAR and PRID, Tramadol/APAP was statistically superior to APAP 975 mg during the latter half of the observation interval (Hours 4 to 8) in TRAMAP-ANAG-004 and at Hours 5 to 8 in TRAMAP-ANAG-005.

In both trials, although the numerical scores of Tramadol/APAP over tramadol 112.5 mg were higher for each of the three hourly pain assessments (PAR, PID and PRID) statistical separation was not achieved for any of these pain assessments in either trial.

Figure 6: Mean Pain Relief Plus Pain Intensity Difference (PRID) Scores Over Time (Extrapolated)
(Subjects Evaluable for Efficacy; Protocol TRAMAP-ANAG-004)



PRID rating scale -1 (pain relief of 0 and -1 PID) to 7 (complete relief of 4 and 3 PID score)

Table 36: Mean Pain Relief Plus Pain Intensity Difference (PRID) Scores[a] Over Time (Extrapolated)
(Subjects Evaluable for Efficacy; TRAMAP-ANAG-004)

	Hours								
Treatment	1/2	1	2	3	4	5	6	7	8
TRAM/APAP	2.2 (2.04)	3.7 (2.37)	4.8 (2.14)	5.0 (2.20)	5.2 (2.26)	5.1 (2.33)	5.1 (2.34)	4.9 (2.48)	4.7 (2.49)
	AB	A	A	A	A	A	A	A	A
	51	51	51	45	44	44	44	44	41
TRAM 112.5 mg	2.0 (1.80)	3.6 (2.17)	4.4 (2.27)	4.5 (2.43)	4.5 (2.58)	4.5 (2.63)	4.4 (2.61)	4.4 (2.66)	3.8 (2.49)
	AB	A	A	A	AB	AB	AB	AB	AB
	48	48	48	43	41	40	38	37	37
APAP 975 mg	2.5 (1.75)	3.9 (2.10)	4.5 (2.11)	4.3 (2.25)	3.9 (2.29)	4.0 (2.39)	3.7 (2.42)	3.5 (2.55)	3.0 (2.42)
	A	A	A	A	B	B	B	B	B
	50	50	50	47	44	39	36	35	33
Placebo	1.6 (1.92)	2.5 (2.13)	2.8 (2.48)	2.6 (2.68)	2.4 (2.70)	2.4 (2.73)	2.3 (2.79)	2.2 (2.70)	2.0 (2.57)
	B	B	B	B	C	C	C	C	C
	50	50	50	38	31	24	21	21	19
P-Value[b]	0.132	0.006	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
RMS Error	1.880	2.195	2.254	2.397	2.464	2.524	2.541	2.599	2.494

[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 $p \leq 0.05$, F-test.

Data Source: The sponsor's Table 11 in the individual report, page 23

Figure 7: Mean PRID Scores Over Time (Extrapolated)
(All Randomized Subjects; Protocol TRAMAP-ANAG-005)

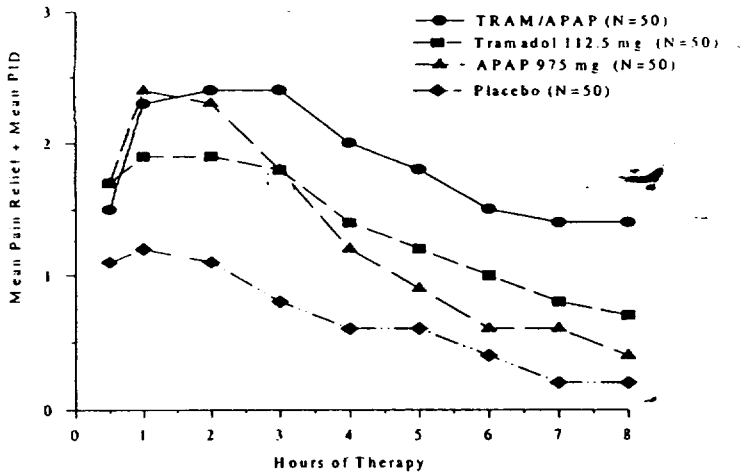


Table 37: Mean PRID Scores[a] Over Time (Extrapolated)
(All Randomized Subjects; Protocol TRAMAP-ANAG-005)

	Hours								
Treatment	0.50	1	2	3	4	5	6	7	8
TRAM/APAP	1.5 (1.68)	2.3 (2.01)	2.4 (2.15)	2.4 (2.27)	2.0 (2.28)	1.8 (2.26)	1.5 (2.22)	1.4 (2.16)	1.4 (2.22)
	A	A	A	A	A	A	A	A	A
	50	50	47	37	33	27	22	16	16
TRAM 112.5 mg	1.7 (1.47)	1.9 (1.67)	1.9 (1.89)	1.8 (2.24)	1.4 (2.26)	1.2 (2.25)	1.0 (2.11)	0.8 (1.87)	0.7 (1.78)
	A	AB	A	A	AB	AB	AB	AB	B
	50	50	46	37	27	18	15	13	8
APAP 975 mg	1.7 (1.66)	2.4 (2.00)	2.3 (2.18)	1.8 (2.14)	1.2 (1.96)	0.9 (1.85)	0.6 (1.55)	0.6 (1.63)	0.4 (1.46)
	A	A	A	A	AB	B	B	B	B
	50	49	43	36	28	21	14	9	8
Placebo	1.1 (1.53)	1.2 (1.67)	1.1 (2.01)	0.8 (1.90)	0.6 (1.87)	0.6 (1.97)	0.4 (1.66)	0.2 (1.43)	0.2 (1.42)
	A	B	B	B	B	B	B	B	B
	50	48	45	25	20	14	13	10	7
P-Value[b]	0.274	0.010	0.005	0.002	0.016	0.040	0.014	0.006	0.003
RMS Error	1.585	1.844	2.059	2.140	2.100	2.090	1.908	1.792	1.750

[a] PRID represents pain relief plus pain intensity difference. Treatment means with a common letter (i.e., A,B,C) 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 timepoint.

[b] Statistically significant difference among all treatment groups at $p \leq 0.05$, F-test.

Data Source: The sponsor's Table 11 in the individual report, page 23

The estimated onset of pain relief in all active treatment groups in the supportive surgical pain trials was faster than that observed in the supportive dental trials (Appendix C). In the two surgical pain trials, the onset of pain relief for the combination Tramadol/APAP product (13 and 19 minutes in TRAMAP-ANAG-004 and 005, respectively) was similar to that for APAP 975 mg alone (12 and 18 minutes, respectively) and tramadol 112.5 mg alone (15 and 18 minutes, respectively).

In TRAMAP-ANAG-004, the percentage of subjects who required rescue medication at some point during the eight-hour trial was comparable in the Tramadol/APAP and tramadol 112.5 mg groups (20% and 25%, respectively) and lower than that in the APAP 975 mg group (36%). In contrast, 72% of subjects in the Tramadol/APAP group in TRAMAP-ANAG-005 required rescue medication compared to 82% and 86% of subjects in the tramadol 112.5 mg and APAP 975 mg groups, respectively.

Table 38: Number of Subjects Who Took Rescue Medication at Each Hour (Subjects Evaluable for Efficacy; Protocol TRAMAP-ANAG-004 and 005)

		Cumulative Number of Subjects Remedicating at Each Hour[a]								
Treatment	N	1	2	3	4	5	6	7	8	Total (%) Not Remedicating
ANAG-004										
TRAM/APAP	51	0 (0)	5 (5)	6 (1)	7 (1)	7 (0)	7 (0)	9 (2)	10 (1)	41 (80%)
TRAM 112.5 mg	48	0 (0)	4 (4)	6 (2)	8 (2)	10 (2)	11 (1)	11 (0)	12 (1)	36 (75%)
APAP 975 mg	50	0 (0)	2 (2)	5 (3)	9 (4)	13 (4)	14 (1)	15 (1)	18 (3)	32 (64%)
Placebo	50	0 (0)	9 (9)	17 (8)	24 (7)	27 (3)	28 (1)	30 (2)	30 (0)	20 (40%)
ANAG-005										
TRAM/APAP	50	2 (2)	13 (11)	15 (2)	22 (7)	26 (4)	34 (8)	34 (0)	36 (2)	14 (28%)
TRAM 112.5 mg	50	3 (3)	10 (7)	20 (10)	28 (8)	32 (4)	34 (2)	38 (4)	41 (3)	9 (18%)
APAP 975 mg	50	2 (2)	12 (10)	18 (6)	25 (7)	35 (10)	39 (4)	40 (1)	43 (3)	7 (14%)
Placebo	50	2 (2)	21 (19)	28 (7)	31 (3)	35 (4)	37 (2)	41 (4)	42 (1)	8 (16%)

[a] Total number of subjects remedicating during the specified interval is noted in parenthesis.

Data Sources: The sponsor's Table 13 in the individual reports, page 26-27

In TRAMAP-ANAG-004, the median time to remedication was inestimable for the three active treatment groups because fewer than half of the subjects remedicated in these groups. In TRAMAP-ANAG-005, the median time to remedication in the Tramadol/APAP group (260 minutes) was longer than that in the tramadol 112.5 mg (200 minutes) and APAP 975 mg (232.5 minutes) groups, but these differences didn't reach statistical significance (Appendix C).

Section 7.2.3.6 **Reviewer's Efficacy Evaluation and Discussion**:

Contribution of Components: The analgesic efficacy of TRAM/APAP was better than placebo in the two surgical pain trials by the PRID and other pain score profiles. However, the contributions of tramadol and acetaminophen to the combination product were not established in the studies. The analgesic effect of TRAM/APAP was not significantly different from that of tramadol in either trial (with the exceptions at three