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APPLICATION NUMBER: NDA 20716

MEDICAL REVIEW(S)

Vicoprofen Tablets
(Ibuprofen 200 mg/Hydrocodone Bitartrate 7.5 mg Tablets)

NDA #20-716

Medical Officer Review

Submission Date:	4/25/96
Received Date:	4/26/96
Review Date:	1/27/97, Revised 3/31/97
Drug Name:	Vicoprofen Tablets
Generic Name:	Ibuprofen, Hydrocodone Bitartrate
Applicant:	Knoll Pharmaceutical Co. 199 Cherry Hill Road Parsippany, New Jersey 07054 (201) 426-2600
Pharmacologic Category:	Non-steroidal Anti-inflammatory, Opioid Analgesic
Proposed Indication:	Management of moderate to severe pain
Dosage Form and Route:	Oral tablet, ibuprofen 200 mg with hydrocodone bitartrate 7.5 mg
Submission Type:	Original NDA

John E. Hyde 3-31-97

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Medical Officer

Orig NDA # 20-716
HFD-550/Div File
HFD-550/PM/LoBianco
HFD-550/Pharm/Weir
HFD-550/Chem/Yaciw
HFD-550/Biopharm/Bashaw
HFD-725/Statistics/Stein
HFD-550/MO/JHyde

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Vicoprofen Executive Summary

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Significant Issues

- If approved, this would be the first analgesic combination of an opioid with a modern "true" NSAID (i.e., other than acetaminophen or aspirin).

- The applicant requested a general pain indication. Since the product contains an NSAID and does not have established efficacy in a chronic condition, it is recommended that the product be for short-term use.

- It is difficult for formulate a well-supported dosing recommendation based on the NDA studies, and there is inadequate safety support for the highest dose proposed. If approved, a Phase 4 requirement is recommended to

- A special DSI investigation is underway involving a major investigator in Study 04, the study that provides the NDA's core clinical safety data. The applicant should be asked to re-analyze that study with the suspect data removed.

Highlights

- The key clinical studies consisted of several single-dose pain trials, and a one-month chronic pain study.

- The contribution of the ibuprofen and the hydrocodone components were demonstrated with replication in single-dose surgical pain trials. The studies included only females. Vicoprofen and the control drugs were similar, but not bioequivalent, in the rate of absorption of the drug components.

- There was only one single-dose dose-response trial, and it found no difference between one and two tablets. The one-month study showed greater efficacy, but also greater toxicity, using two-tablet doses compared to one-table doses. The reviewer has reservations about interpretation of some of the results of the one-month study.

- The duration of effect differed markedly between the Puerto Rican and the non-Puerto Rican single-dose studies. In non-Puerto Rican trials the median time to remedication for V 200/7.5 was 3 hours (which may be an underestimate); for V 400/7.5 it was 4 to 6 hours (using extrapolation from supporting studies).

- The safety profile was about what might be expected from such an NSAID/opioid combination. With a two-tablet dose in chronic use, the opioid effects appeared to dominate.

- The medical officer found the NDA approvable, pending restriction of the indication to short term use, modification of the dosing, incorporation of current NSAID class labeling, and some other labeling revisions, but the DSI investigation will need to be resolved.

- The pharmacology reviewer found the NDA approvable pending some labeling revisions.

- The biopharmaceutics reviewer found the NDA approvable pending a tightening of the *in vitro* dissolution specification.

- The chemistry reviewer found the NDA approvable pending resolution of several deficiencies.

- The tradename "Vicoprofen" was rejected by the nomenclature committee, but the division decided to accept it in response to commitments made by the applicant.

- The product should be a schedule III controlled substance, as proposed by the applicant.

Vicoprofen Background and Overview
NDA #20-716

MEDICAL OFFICER REVIEW

HYDROCODONE AND IBUPROFEN

Hydrocodone bitartrate (often referred to briefly as simply hydrocodone) is a narcotic with antitussive and analgesic properties. As an analgesic it is about 6 to 8 times as potent as codeine. A ratio of 6 has been adopted for the FDA hydrocodone Substitution Policy for suitability petitions (see Appendix B, page A3). Hydrocodone is felt to have a greater addiction potential than codeine and it may produce more sedation. For analgesia, the recommended dose (from MEDEX drug evaluation) is 5 to 10 mg po Q6H with a recommended daily maximum of 40 mg. Peak serum levels usually occur in about one hour and peak analgesia in about 2 hours. It is metabolized in the liver to active metabolites, and its half-life is about 4 hours. The primary adverse effects are dizziness, drowsiness, nausea and constipation. Respiratory depression may occur with larger than recommended doses.

Hydrocodone is not usually used alone, however. Most of the marketed products are a combination of hydrocodone with aspirin or acetaminophen. The contribution of components to the hydrocodone/acetaminophen combination was shown in the early eighties. According to recommended dosing for the combination products, the usual dose of the hydrocodone component is 5 to 10 mg, usually given every 4 to 6 hours, with a daily maximum of about 40 mg. The hydrocodone substitution policy, as a derivative of the codeine dosing limits, set the dosing limits for hydrocodone at 10 mg for an individual dose, and 60 mg for the daily dose.

Ibuprofen is a widely used NSAID having analgesic, anti-inflammatory and antipyretic activity. As an OTC analgesic, the recommended dosing is 200 mg Q4-6H, with 400 mg if needed. The maximum daily OTC dose is 1200 mg. The ceiling analgesic effect is achieved with a 400 mg dose, and the prescription dose for mild to moderate pain is 400 mg Q4-6 hours. The maximum daily dose for any prescription indication is 3200 mg. The most common adverse events are nausea, epigastric pain, heartburn, dizziness and rash. Rare but serious adverse events associated with NSAID's are GI ulceration, bleeding or perforation.

If this application is approved it would be the first narcotic combination analgesic using a modern "true" NSAID (i.e., other than acetaminophen or aspirin). This is something of a challenge, since ibuprofen is quite effective as an analgesic, and opioids tend to perform less well in one of the staples of analgesic research, the dental pain model. Most of the applicant's studies

used the post-operative pain model.

NDA FINDINGS

Clinical

Component Contribution: Substantial evidence for the contribution of hydrocodone to analgesic effect was provided by Studies 09 and 23 (although they used different doses), and substantial evidence for the contribution of ibuprofen was provided by Studies 23 and 29 (although at different doses). It is noted that only females participated in these studies. In one of the two principal studies to include males, Study 13, Vicoprofen did numerically better than the components, but there were no statistically significant differences between active treatments.

Acute Use: The estimates of onset time for both the one- and two-tablet doses (V 200/7.5 and V 400/15) were all less than 30 minutes, and most of the confidence limits were as well. However, both of the estimates for V 200/7.5, and 2 of the 4 estimates for V 400/15, came from studies that had relatively short placebo onset times of only 16 or 17 minutes.

V 400/15 provided substantial evidence of separating from placebo at one hour (on PRID) in 3 of the 4 principal studies in which it was used (09, 13 and 29). V200/7.5 showed separation at one hour in only one (Study 23) of the two studies in which it was used. As supporting information, two tablets of the alternate combination, V 400/10, beat placebo on PRID at one hour in 3 of 4 studies.

Dose-Response: This application failed to show a dose response in single dose studies. One trial (Study 21) used both V 400/15 and V200/7.5, and both performed very similarly. The study unfortunately had a large placebo response, and probably lacked adequate upside sensitivity to show separation of doses.

Dose response was also investigated in the one-month trial (Study 04). The results showed more analgesic efficacy with the higher dose, as well as greater toxicity. There were some problems with that study: There was a small, but statistically significant difference in weights, which may have contributed to the small but statistically significant difference in response. Also, the trial recommended TID to QID dosing. In light of the results of single dose studies, that may have been too long a dosing interval. It is not clear whether doubling the dose provided stronger analgesia or merely

longer duration of analgesia. The way in which analgesic effect was ascertained made it impossible to shed light on that distinction.

Duration of affect: The Puerto Rican single-dose studies consistently showed a much longer remedication time than did the other studies. This phenomenon has been seen with other applications as well. This reviewer feels that dosing interval recommendations should be based on information from the non-Puerto Rican studies. The time to remedication with one tablet was 3 hours in the one non-Puerto Rican study that used it. However, that study had short remedication times for all arms, so 3 hours may reflect the low end of performance for a single tablet.

The V400/15 dose had a remedication time to 4 to 5 hours in three non-Puerto Rican studies. Studies of the V 400/10 combination found remedication times up to 6 hours. If one assumes that V 400/15 would have lasted at least as long as V 400/10, one could augment the estimate to the range of 4 to 6 hours.

Dosing Recommendations: This is one of the most difficult parts of the application. Several issues are involved:

Individual Dose: The applicant proposed using up to two tablets. There are several reasons why the reviewer finds that not to be supported. First, single-dose studies did not show a dose-response (although the possibility is not refuted). Second, such a dose would exceed the Substitution Policy Memo upper limit of 10 mg for a single dose of hydrocodone bitartrate. Third, the one-month safety Study 04 used the two-tablet dose in only 153 patients, less than the 300 that are usually required. Fourth, in Study 04 there was significantly greater toxicity with the two-tablet dose, although it is not clear if the individual or the total daily dose was the problem.

Total daily dose: Study 04 used one or two tablets at dosing of TID to QID. The higher dose arm had 153 patients. Thus the total daily dose at that exposure level has insufficient safety data. The lower dose can be considered adequately supported since there were over 300 patients at that dose or above. Since patients took between 3 and 4 doses per day, one could consider stretching the supported daily dose to 4 tablets per day.

Dosing schedule: From the non-Puerto Rican single-dose studies, dosing every 4 to 6 hours is suggested. This is consistent with other hydrocodone and ibuprofen products. One interpretation of Study 04 is that the dosing interval of 6 to 8 hours may have been too long. Although a regimen of one tablet every 4 to 6 hours, up to 6 per day, might seem reasonable, the safety support for that total daily dose is inadequate. Even 5 tablets per day, which would allow dosing Q4H while awake, is shy of having adequate safety support. On the other hand, four tablets per day may not provide the best results that could be obtained with this product.

Duration of use: This product contains an NSAID. Because of the cumulative risk of significant GI bleeding with prolonged use, the division has a concern about indefinite use of NSAID's if efficacy for use in chronic conditions (such as OA or RA) has not been established. Prolonged use of opioids has problems as well. The efficacy studies were done in post-operative pain. Treatment of acute, transient conditions seems to be the most appropriate use for this product. The indications should include a limitation on the duration of use.

Pharmacology

In acute oral toxicity studies in rats and mice, the toxicity was dose-related and appeared to be due primarily to the ibuprofen component. In 90-day repeat-dose studies in rats, the toxicity also appeared to be primarily due to the ibuprofen component.

The pharmacologist recommended in inclusion of the following wording under a section on Carcinogenicity, mutagenicity and impairment of fertility:

> "The carcinogenic and mutagenic potential of Vicoprofen has not been investigated. The ability of Vicoprofen to impair fertility has not been assessed."

The pharmacologist also recommended that, in the pregnancy section, the information on individual components be replaced by information specific to Vicoprofen.

The final recommendation was approvable, pending labeling changes.

Biopharmaceutics

The biopharmaceutics reviewer found that the ibuprofen and hydrocodone did not interfere with each other's absorption or pharmacokinetics. There was no gender difference in PK. The clinical product was bioequivalent to the market image.

The recommendation was approvable, pending revision of *in vitro* dissolution specifications.

Chemistry

The chemist's review found sixteen deficiencies, but recommended the application be approvable, pending their resolution. The stability data supported only an 18 month expiration date. Some minor changes were

recommended concerning storage instructions and in the How Supplied section. The dissolution specification was unsatisfactory.

Nomenclature

The trade name "Vicoprofen" was rejected by the nomenclature committee because it ended in "-profen," which a stem for the generic names of several anti-inflammatory (ibuprofen, ketoprofen, flurbiprofen, fenoprofen). In the submission of 9/19/96, the applicant cited precedents for using generic stems in trade names. In the submission dated 10/3/96, the applicant provided commitments that the applicant would not object to the use of the stem "-profen" in other trade names or USAN generic names.

Control Status

Hydrocodone bitartrate and combination products containing it are schedule III controlled substances. DACCAD (HFD-170) was consulted regarding abuse liability and scheduling recommendations. In a response dated 7/12/96, the consult division recommended putting the product in schedule III, and recommended some modifications in the WARNING section of the labeling.

Scientific Investigations

DSI investigated single-dose studies 09, 23, 29, and 0103, and found them acceptable. Study 04 was a one-month repeated dose study in 469 patients at 31 sites. The largest contributor (Dansak, 90 patients) was audited and found acceptable. However, DSI became aware of irregularities in certain other studies of one of the investigators (Fiddes) who contributed 36 of the patients to Study 04. DSI issued a Distant Early Warning Notice regarding Dr. Fiddes on 9/27/96, and additional investigations are underway. The status of data from Study 04 is uncertain, pending completion of special investigations by DSI. A final action should await the outcome. The site contributing the second largest number of patients (Serfer, Hollywood, 43 patients) was inspected and found to be acceptable.

It is not clear if the disqualification of Dr. Fiddes would be fatal to the application. He contributed about 8% of the patients in Study 04, so the safety database might be deemed acceptable if analyzed with Dr. Fiddes' data excluded (however, adverse events reported from his site should not be disregarded).

Vicoprofen Single-Dose Analgesia Trials
NDA #20-716

MEDICAL OFFICER REVIEW

INTRODUCTION:
The applicant provided 10 single-dose efficacy trials in a variety of surgical pain models. Half of these (Studies 09, 13, 21, 23 and 29) had a design capable of providing substantial evidence for efficacy. The other half (Studies 0101, 0102, 0103, 0104, and 12) used a product variant with a different ratio of components, and therefore were only capable of providing supporting data.

An eleventh trial, Study 22, was a smaller PK/PD study in dental surgery pain. It used the proposed formulation, but used an ibuprofen suspension, rather than a tablet, as the ibuprofen control. The applicant reported on the study in the PK section of the NDA, but did not include it among the efficacy studies and did not provide the same reports and analyses as for the other efficacy studies. This reviewer has included study 22 in this section, but the study is omitted from some tables for which data are not available.

The applicant's study designations all had the prefix "VP-." The prefix has been omitted in this presentation. The collection of the four non-principal design studies 0101, 0102, 0103, and 0104 are referred to by the applicant as "Protocol VP-01." They are treated as separate studies for this review, since they were at different sites, used difference types of surgical patients, and each was large enough to stand alone.

The basic study characteristics are set out in Table 1 (page 12). The studies all used standard single-dose analgesia study protocols, and they were quite similar in design. These studies are therefore presented as a group, rather than presented as individual study reviews. The common features are described below:

Basic Design: Upon emergence of pain ranked as moderate or severe, patients were randomized to one of the treatment arms, were given a single dose of study medication, and pain data were recorded for the subsequent several hours. Randomization was stratified based on baseline pain. Concomitant analgesics were not allowed, but rescue analgesic was given on request, after which pain ratings were no longer recorded.

Treatments: Possible treatments consisted of the following: one or two tablets of ibuprofen 200 mg, one or two tablets of hydrocodone bitartrate 7.5 mg, one or two tablets of Vicoprofen (200 mg ibuprofen with 7.5 mg hydrocodone bitartrate), or placebo. Study 12 and the 01 studies (0101, 0102, 0103, 0104) used two tablets of an alternate Vicoprofen product containing

mg of ibuprofen but only ng of hydrocodone bitartrate. All the studies used 2 or 3 active treatments, but only Studies 13, 23 and 29 had full factorial designs. Only Study 21 used two different doses of Vicoprofen. Study 12 did not include a placebo. Study 22 used 400 mg of an ibuprofen suspension instead of tablets.

Table 1: Study Characteristics
Vicoprofen Single-Dose Pain Studies

							Distribution by Treatment							
Study ID	Pain Model	Investigator (Site)	Hours	No. of Sites	% Female	Total N	V 400 / 15	V 400 / 10	I 400	H 15	V 200 / 7.5	I 200	H 7.5	PL
9	Cesarean, Abd Gyn Surg	Sunshine (Puerto Rico)	6	1	100	120	40		40					39*
13	Ortho Surg	Honig (New York, NY)	8	1	49	199	50		50	49				50
21	Cesarean, Gyn Surg	Sunshine (Puerto Rico)	8	1	100	180	60				60			60
22	Dental (PK/PD)	Cooper (Washington)	8	1	50	72	18		18**	18				18
23	Abd & Pelvic Gyn Surg, Misc	Wideman (Birmingham)	8	1	100	240					59	60	61	60
29	Abd & Pelvic Gyn Surg, Cesarean	Wideman (Birmingham)	8	1	100	201	50		50	50				51
0101	Abd Gyn, Cesarean, Ortho Surg	Jain (New Orleans)	6	1	86	120		40	40					40
0102	Abd & Pelvic Gyn Surg	Sunshine (Puerto Rico)	6	1	100	120		40	40					40
0103	Abd Gyn, Cesarean, Ortho, GU	Wideman (Birmingham)	6	1	98	120		40	40					40
0104	Ortho Surg	Kantor (New York, NY)	6	1	48	120		40	40					40
12	Back Surg	VanWagoner (Murray, VT)	6	1	36	45		15	15			15		
						1537	218	175	315	117	119	75	61	399

* One additional subject in this group was randomized but had no efficacy data.
** This study (22) used ibuprofen suspension rather than tablets

Demographics: Demographic data are presented in Table 2 on page 13. In general, the preponderance of pain models was gynecological surgery, and the study population was mostly young or middle-aged women. A few specific items deserve comment:

Data on race were not collected for Studies 9, 12 or the 01 series. Three studies (9, 21, and 0102) were done in Puerto Rico. The only one of these that

collected race data was Study 21, and all participants in that study were "non-Caucasian" (meaning Hispanic). Study 9 was done at the same site as Study 21 but at a different time. It would be reasonable to presume the population was similar.

The only principal-design study to include a substantial fraction of elderly was Study 13. The 01 series also included about 10% elderly. Studies 9, 23, 21 and 29 included only females.

Table 2: Demographics
Vicoprofen Single-Dose Pain Studies

Study ID	Investigator (Site) Model	Treatment	Total N	Female	Non-Caucasian	Age ≥ 65
9	Sunshine (Puerto Rico) C/S, Gyn Surg	V 400/15	40	40 (100%)	N/A	0 (0%)
		I 400	40	40 (100%)	N/A	0 (0%)
		PL	40	40 (100%)	N/A	0 (0%)
13	Honig (New York, NY) Ortho Surg	V 400/15	50	23 (46%)	17 (34%)	22 (44%)
		I 400	50	24 (48%)	18 (36%)	21 (42%)
		H 15	49	23 (47%)	23 (47%)	20 (41%)
		PL	50	27 (54%)	25 (50%)	20 (40%)
21	Sunshine (Puerto Rico) C/S, Gyn Surg	V 400/15	60	60 (100%)	60 (100%)	0 (0%)
		V 200/7.5	60	60 (100%)	60 (100%)	0 (0%)
		PL	60	60 (100%)	60 (100%)	0 (0%)
22	Cooper (Washington DC) Dental PK/PD	V 400/15	18	10 (56%)	7 (39%)	0 (0%)
		I 400	18	7 (39%)	7 (39%)	0 (0%)
		H 15	18	9 (50%)	7 (39%)	0 (0%)
		PL	18	10 (56%)	6 (33%)	0 (0%)
23	Wideman (Birmingham) Gyn Surg	V 200/7.5	59	59 (100%)	9 (15%)	2 (3%)
		I 200	60	60 (100%)	17 (28%)	0 (0%)
		H 7.5	61	61 (100%)	16 (26%)	1 (2%)
		PL	60	60 (100%)	11 (18%)	1 (2%)
29	Wideman (Birmingham) Gyn Surg, C/S	V 400/15	50	50 (100%)	11 (22%)	0 (0%)
		I 400	50	50 (100%)	11 (22%)	0 (0%)
		H 15	50	50 (100%)	12 (24%)	2 (4%)
		PL	51	51 (100%)	6 (12%)	0 (0%)
VP-01	(Composite of 4 Sites) Gyn, C/S, Ortho	V 400/10	160	133 (83%)	N/A	14 (9%)
		I 400	160	133 (83%)	N/A	13 (8%)
		PL	160	133 (83%)	N/A	13 (8%)
12	VanWagoner (Murray, VT) Back Surg	V 400/10	15	6 (40%)	N/A	0 (0%)
		I 400	15	7 (47%)	N/A	2 (13%)
		I 200	15	3 (20%)	N/A	1 (7%)
		Totals:	1537	1209 (79%)	N/A	132 (9%)

V xx/yy = Vicoprofen: xx mg ibuprofen + yy mg hydrocodone
H xx = Hydrocodone xx mg, I xx = Ibuprofen xx mg, PL = Placebo

Efficacy Assessment: The primary ascertainment of efficacy used pain intensity measured on a 4-point scale (0=none, 1=mild, 2=moderate, 3=severe), and pain relief (PR) measured on a 5=point scale (0=none, 1=a little, 2=moderate, 3=a lot, 4=complete). The schedule differed depending on duration of observation: In studies using 6 hours of observation, pain assessments were made at 30 minutes and hourly for 1 through 6 hours. In studies with 8 hours of observation, assessments were made every 20 minutes to 2 hours, at 2 1/2 hours, and hourly from 3 through 8 hours. Time to remedication was recorded, usually even if it occurred after the pain assessment period. There was no direct (i.e., stopwatch) measurement of time to onset of pain relief.

Analysis: Pain intensity was converted to difference from baseline (PID). PRID was computed as the sum of PID and PR. In its reports the applicant did standard analyses using last observation carried forward (LOCF) extrapolation. At FDA's request, the applicant interpolated values for 30 minutes for those studies that made observations at 20 and 40 minutes, performed analyses using worst observation carried forward (WOCF) extrapolation, and prepared charts of PID, PR and PRID together with tables of timepoint-by-timepoint comparisons using Fisher's protected LSD.

Protocol Violations, Irregularities:

In Study 09, one patent in the placebo arm had no efficacy data.

For Study 13, an interim analysis was done at the halfway point. Two patients in study 13 were enrolled twice: patient #40 got Vicoprofen and then got hydrocodone a year later as patient #101; patient #351 got placebo and then got hydrocodone 2 1/2 months later as patient #123. Patient #64 requested remedication but later declined--this was counted as a remedication. Patient #331 dropped out before receiving medication.

In Study 21, patient #14 had severe baseline pain but was randomized in the moderate group due to unavailability of severe group study medication. Patient #308 had moderate baseline pain intensity but was randomized to the severe group by mistake.

In Study 23, the study medication for #001 was dropped and lost, so the patient was entered as #002. The container for #153 had the wrong number of tablets, so the patient was entered as #154.

Safety: (See also separate Integrated Safety Review, page 57.) No deaths or serious adverse events were reported in any of these studies, and only two of the studies had events recorded as severe for active treatments. The events recorded as severe for Vicoprofen were two cases of somnolence and one case of vomiting. The predominant adverse event reported for Vicoprofen was somnolence.

Efficacy Results

Pain Scores: Pain scores (pain intensity difference, or PID, pain relief, or PR, and their sum, PRID) can be evaluated several ways. The plot of score vs. time together with a timepoint-by-timepoint statistical analysis shows the profile of analgesia over time and conveys an overall view of onset, relative magnitude of effect, and duration. Usually the differences between treatments are consistent enough that one can make comparative statements with confidence, although there is a subjective element. A sum of scores, or AUC based on scores, provides a single simple object of analysis, but does not distinguish between magnitude and duration of analgesia, and it can be influence by the method used for extrapolation. A 3-hour (or, sometimes, halfway point) sum of scores also does not show the time profile, but provides a single value that is less dependent on duration and extrapolation method.

Most of the time, all methods point to the same conclusions. Table 3 (page 16) shows this reviewer's assessment of the results for pain scores for the single-dose studies. Those cases for which there might be some question about the assessment are indicated by the addition of a question mark (?). In those few borderline cases this reviewer has relied on the PR sum (TOTPAR) for half the study interval in making the final call. The statistically significant differences indicated in the table are in concurrence with those found in the FDA Statistician's Review.

The full PRID profiles provided by the applicant are reproduced on pages 26 through 36. More extensive individual study result summaries are provided in Appendix C (pp. A4 -- A57).

By this analysis, the analgesic efficacy of Vicoprofen was established in each trial in which it was used. The contribution of ibuprofen was shown in studies 23 and 29, and the contribution of hydrocodone was shown in studies 9 and 23. Support for the contribution of hydrocodone also comes from study 0103, which used a slightly different combination ratio.

It is noteworthy that Study 21 had a particularly large placebo effect (peak PRID was 3.18). Studies 23 and 29 also had moderate placebo effects with peak PRID's of 2.3 and 2.14, respectively. The large placebo effect in Study 21 suggests the study had more downside than upside sensitivity. The failure to show any dose-response in that study may have been a consequence of that feature.

Table 3: Pain Score Results
Vicoprofen Single-Dose Pain Studies

Study ID	Pain Scores: Statistical Comparisons								
	V 400 / 15	V 400 / 10	I 400	H 15	V 200 / 7.5	I 200	H 7.5	Active Comparisons	Comments
9	+		+					V 400/15 > I 400	Clear separation between all doses, early & sustained.
13	+		+?	+					V numerically better first few hrs, V sep from PL by 40 min, others not until 80 min
21	+				+				V400/15 and V200/7.5 were similar. Big placebo effect. No sep. from PL until 2 hrs.
22	+		+	-					I 400 numerically > V400/15@ .33-4 hrs, H 15 similar to PL
23					+	-	-	V200/7.5 > I 200 V200/7.5 > H 7.5	Median time to remedication was <= 3 hrs. in all arms
29	+		+	-				V 400/15 > H 15 I 400 > H 15	I 400 not > PL until 100 min. V not > I ?
0101		+	-?						V 400/10 not > PL until 2 hrs (V not > I, and I not > P by 4 hr. TOTPAR)
0102		+	+						V 400/10 & I 400 similar. Both beat PL by 1 hr.
0103		+	+					V 400/10 > I 400	
0104		+	+						
12		*	*			*			V 400/10 numerically worse than I 400 and I 200 at 2 hrs. and beyond

+ = statistically different from placebo.
- = not statistically different from placebo.
* = no placebo for comparision.
? = analysis-dependent result (see text).

V xx/yy = Vicoprofen: xx mg Ibuprofen + yy mg hydrocodone
H xx = Hydrocodone xx mg, I xx = Ibuprofen xx mg, PL = Placebo

Onset: An analgesic for acute use should be able to separate from placebo by one hour. While earlier separation would of course be desirable, placebo response usually makes that difficult to achieve in practice; only Study 9 found statistically significant differences at 30 minutes. Table 4 (page 17) shows the statistical results for PRID comparisons at one hour; by that time separation was starting to occur. Two tablets of Vicoprofen (V 400/15) beat placebo at one hour in 3 of the 4 studies in which it was used. A single tablet (V 200/7.5) beat placebo at one hour in 1 of 2 studies. A contribution of hydrocodone at one hour was seen in three studies: 09, 23 and 29. The ibuprofen contribution at one hour was seen only in Study 29, but not in Study 23, which did show an ibuprofen contribution overall.

Table 4: PRID Results at 1 Hour
Vicoprofen Single-Dose Pain Studies

Study ID	Investigator (Site)	Total N	Statistical Comparisons for PRID at 1 Hour							
			V 400 / 15	V 400 / 10	I 400	H 15	V 200 / 7.5	I 200	H 7.5	Active Comparisons
9	Sunshine (Puerto Rico)	119	+		+					V 400/15 > I 400
13	Honig (New York, NY)	199	+		-	-				
21	Sunshine (Puerto Rico)	180	-				-			
23	Wideman (Birmingham)	240					+	-	-	V200/7.5 > I 200
29	Wideman (Birmingham)	201	+		-	-				V 400/15 > I 400 V 400/15 > H 15
0101	Jain (New Orleans)	120		-	-					
0102	Sunshine (Puerto Rico)	120		+	+					
0103	Wideman (Birmingham)	120		+	-					
0104	Kantor (New York, NY)	120		+	+					
12	VanWagoner (Murray, VT)	45		*	*			*		

+ = statistically different from placebo.
- = not statistically different from placebo.
* = no placebo for comparision.

V xx/yy = Vicoprofen: xx mg Ibuprofen + yy mg hydrocodone
H xx = Hydrocodone xx mg, I xx = Ibuprofen xx mg, PL = Placebo

Table 5 shows estimated times to onset of effect. This is calculated using linear extrapolation between 0 and the 30-minute PRID to estimate the time at which the mean PRID would be 1.0. All the estimates in principal studies for Vicoprofen are under a half hour, and most of the upper limits of confidence intervals are as well. Study 09 was the only one in which statistically significant differences were found; it showed a contribution of hydrocodone to onset. It should be noted that in Studies 21, 23 and 29, the strong placebo effect produced short onset time estimates for the placebo, so the short onset times for Vicoprofen in those studies may not accurately reflect a true drug effect.

Table 5: Onset Times
Vicoprofen Single-Dose Pain Studies

Study ID	Investigator (Site)	Hours	Total N	Onset Times in Minutes (95% C.I.) Estimated via LS mean PRID at 30 minutes							
				V 400 / 15	V 400 / 10	I 400	H 15	V 200 / 7.5	I 200	H 7.5	PL
9	Sunshine (Puerto Rico)	6	119	12* (10-16)		19* (14-28)					39* (24-99)
13	Honig (New York, NY)	8	199	26 (20-39)		37 (27-61)	34 (26-51)				48 (34-81)
21	Sunshine (Puerto Rico)	8	180	13 (11-16)				17 (14-21)			16 (13-20)
23	Wideman (Birmingham)	8	240					13 (11-16)	18 (14-23)	18 (14-25)	16 (12-20)
29	Wideman (Birmingham)	8	201	14 (12-19)		17 (14-24)	16 (13-22)				17 (13-23)
0101	Jain (New Orleans)	6			20 (16-28)	36 (25-64)					29 (21-45)
0102	Sunshine (Puerto Rico)	6			21 (15-32)	28 (20-46)					41 (28-81)
0103	Wideman (Birmingham)	6			18 (13-29)	21 (15-39)					20 (14-34)
0104	Kantor (New York, NY)	6			23 (16-37)	23 (16-39)					48 (30-116)
12	VanWagoner (Murray, VT)	6	45		22 (14-63)	18 (11-45)			21 (14-48)		

* In Study 9, all differences in onset times were statistically significant.
(No other study had statistically significant differences in onset times.)

V xx/yy = Vicoprofen: xx mg ibuprofen + yy mg hydrocodone
H xx = Hydrocodone xx mg, I xx = Ibuprofen xx mg, PL = Placebo

Time to Remedication: Duration of action can be assessed by examining the times at which patients request remedication. This endpoint has direct relevance to dosing interval, and can be obtained without imputation (at least through the end of the observation period). Table 6 shows Kaplan-Meier estimates of median times to remedication, and Table 7 (page 20) shows results of statistical comparisons based on logrank tests.

Table 6: Time to Remedication
Vicoprofen Single-Dose Pain Studies

Study ID	Investigator (Site)	Hours	Total N	Median Time to Remedication (Hrs.)							
				V 400 / 15	V 400 / 10	I 400	H 15	V 200 / 7.5	I 200	H 7.5	PL
9	Sunshine (Puerto Rico)	6	119	11.6		11.4					2.3
13	Honig (New York, NY)	8	199	4.0		3.5	2.8				2.0
21	Sunshine (Puerto Rico)	8	180	10.5				10.5			3.0
23	Wideman (Birmingham)	8	240					3.0	1.3	1.7	1.3
29	Wideman (Birmingham)	8	201	5.0		3.7	2.0				1.7
0101	Jain (New Orleans)	6	120		4.2	2.8					2.4
0102	Sunshine (Puerto Rico)	6	120		10.5	12.3					2.0
0103	Wideman (Birmingham)	6	120		6.5	3.9					2.3
0104	Kantor (New York, NY)	6	120		6.1	6.1					2.2
12	VanWagoner (Murray, VT)	6	45		2.1	2.0			2.0		

V xx/yy = Vicoprofen: xx mg ibuprofen + yy mg hydrocodone
H xx = Hydrocodone xx mg, I xx = Ibuprofen xx mg, PL = Placebo

Median remedication times appear to vary widely in Table 6, but closer inspection shows that the longer durations (i.e., 10 hours or more) are all seen in the Puerto Rican studies (09, 21, and 0102). This reviewer has previously noted analgesic trials from Central and South America showing relatively long duration of action. Whether due to a regional phenotype or a cultural attitude toward analgesics, the experience from such studies has been at odds with the usual North American experience.

Looking at both the V 400/15 and V 400/10 results from non-Puerto Rican trials only, the results suggest a median duration of action of 4 to 6 hours (if

one allows extrapolation from V 400/10 on the assumption that V 400/15 should last at least as long). The only study to look at the dose response, Study 21, was a Puerto Rican study with late remedication times that were the same for both doses. Only one non-Puerto Rican study (23) used V 200/7.5. The remedication time was 3 hours, but remedication times in that study tended to be short: the placebo time was the shortest of any study. Thus, 3 hours may be a low for remedication time estimate for V 200/7.5.

Table 7: Remedication Time Comparisons
Vicoprofen Single-Dose Pain Studies

Study ID	Hours	Total N	Time to Remedication: Statistical Comparisons							
			V 400 / 15	V 400 / 10	I 400	H 15	V 200 / 7.5	I 200	H 7.5	Active Comparisons
9	6	119	+		+					
13	8	199	+		+	+				
21	8	180	+				+			
23	8	240					+	-	-	V 200/7.5 > H 7.5
29	8	201	+		+	-				V 400/15 > I 400 > H 15
0101	6	120		+	+					
0102	6	120		+	+					
0103	6	120		+	+					
0104	6	120		+	+					
12	6	45		*	*			*		

+ = statistically different from placebo.
- = not statistically different from placebo.
* = no placebo for comparision.

V xx/yy = Vicoprofen: xx mg ibuprofen + yy mg hydrocodone
H xx = Hydrocodone xx mg, I xx = Ibuprofen xx mg, PL = Placebo

The statistical comparisons in Table 7 show that one or two tablets work longer than placebo. The only treatments that failed to outlast placebo were the two low doses of the components (I 200 and H 7.5), and one of the high dose components (H 15). Study 23 provided evidence that ibuprofen contributes to the duration of action, and Study 29 provided evidence that both components do.

Correlation with Pharmacokinetics Information: Rapid absorption is an important attribute for an acute analgesic. A formulation with more rapid absorption may even perform uniformly better than one with the same extent of absorption but slower rate. A suggestion of this was seen in the numerical superiority of the ibuprofen suspension over Vicoprofen in PK/PD Study 22.

It can be informative to interpret the single-dose results in light of bioavailability parameters. Table 8 correlated the lots used for the key pain studies with the lots studied in PK studies.

PK Study 27 showed that Vicoprofen tended to have slower ibuprofen absorption than the ibuprofen tablets. Thus the superiority of V over I in Pain Study 23 is solid evidence for a hydrocodone contribution.

However, the superior rate of absorption of hydrocodone from the Vicoprofen tables in PK Study 22 detracts from the evidence for the ibuprofen contribution in Pain Studies 23, and 29, since part of the difference might be attributed to the better rate of absorption of hydrocodone.

The better rate of absorption of ibuprofen from Vicoprofen, seen in PK Study 02, detracts from the supporting evidence for the hydrocodone contribution in Pain Study 0103.

PK data for the Vicoprofen lot used in Pain Study 09 do not appear to be available. However, PK Study 02 suggested the ibuprofen bioavailability from the ibuprofen control was less than ideal, raising concern about the significance of the apparent hydrocodone contribution in Pain Study 09.

Table 8: PK/Efficacy Correlation
for Key Vicoprofen Single-Dose Studies

Pain Study	Vicoprofen Lot #	Ibuprofen Lot #	Hydrocodone Lot #	Efficacy Result
09	55-0189	29-0186	–	V>I
23	55-0392	29-0291	128-0191	V>I, V>H
29	55-0392	29-0291	128-0191	V>H
0103	H46-226	29-0186		V 400/10 > I
PK Study				Pertinent PK Result
02	H46-226	29-0186	(5 mg)	V-ibu Cmax ~ 1.15 x I-ibu Cmax
22	55-0329	(susp)	128-0191	V-hyd Cmax ~ 1.27 x H-hyd Cmax V-hyd AUC8 ~ 1.13 x H-hyd AUC8
27	55-0392	29-0291	(5 mg)	V-ibu Cmax ~ 0.91 x I-ibu Cmax

PK values are from Biopharmaceutics Review (differs for applicant for study 22)

Effect of age, race and gender on efficacy: The evidence for the contribution of components comes only from studies of non-geriatric females, and Caucasians predominated in all but one of those studies. Only Study 13 entered a substantial number of males. Vicoprofen tended to do better for the males than females in that study in terms of pain relief and duration. The PK Study 22 also included males, but the study was small, and the applicant did not provide gender analysis for that study.

Race data were not collected for Study 09, but it would be reasonable to presume the population was Hispanic. The applicant analyzed Caucasians vs. "non-Caucasians" (which included Hispanics). There was a tendency for non-Caucasians to have higher, and more variable, average PR scores. Both groups showed similar trends regarding the relative performance of Vicoprofen and its components. As noted above, the duration of analgesia was notably longer in the Puerto Rican Studies.

Only Study 13 had a substantial proportion of elderly (age≥65). That study did not find differences between active treatments overall. Vicoprofen tended to do worse than its components for the elderly, but better than its components for the non-elderly.

Details are reported in the applicant's Integrated Summary of Efficacy (section 7.4.6.1, vol. 1.38, pp. 334-337, and Tables 7.33-7.38 on pp. 382-387).

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DISCUSSION and CONCLUSIONS:

Component Contribution

This application meets the minimum clinical efficacy requirement for an analgesic combination. Substantial evidence for the contribution of hydrocodone to analgesic effect was provided by Studies 09 and 23 (although they used different doses), and substantial evidence for the contribution of ibuprofen was provided by Studies 23 and 29 (also at different doses). It is noted that only females participated in these studies. In one of the two principal studies to include males, Study 13, Vicoprofen did numerically better that the components, but there were no statistically significant differences between active treatments. In the other, Study 22, Vicoprofen did numerically better than hydrocodone, but worse than an ibuprofen suspension. Study 0103 used a different ratio of components, but at least provides support that addition of hydrocodone can augment the efficacy of ibuprofen.

The Analgesic Guidelines require only that component contribution be demonstrated in one analgesic model. In this case the postoperative pain model was used. Opioids generally do not perform as well as NSAID's in the dental pain model, and it well might have been more difficult to show the hydrocodone contribution if that model had been used. To the point, Study 22 found hydrocodone not much different from placebo. It is helpful that the contribution of both components was shown in the same model: an application showing a hydrocodone contribution in surgical models, and an ibuprofen contribution only in dental models, would have been more challenging to interpret.

It is noteworthy that in two studies, 09 and 0103, the efficacy of the ceiling analgesic dose of ibuprofen (400 mg) was exceeded by a combination of ibuprofen and hydrocodone.

Data from the PK studies detract somewhat from the clinical evidence: for several of the studies better rate of absorption of one component compared to control could have contributed toward the apparent effect of the other component. Absent any division or agency requirement for bioequivalence of test articles used in demonstrating component contribution, this reviewer makes the judgment that clinical difference observed outstripped the effects that would reasonably be expected from the relatively minor differences in bioavailability. However, the lots used for Study 09 have not been compared for ibuprofen bioavailability. It would be desirable to be assured at least of comparable ibuprofen dissolution of the test and control drugs.

The findings for the elderly in Study 13 are bothersome. While the study suggests Vicoprofen might be no better, or even worse, than its components in the elderly, the data are too sparse to be conclusive. Some reassurance

might be found in the one-month study (Study 04), where the results for the elderly were consistent with those for the non-elderly.

Acute Use

The estimates of onset time for both the one- and two-tablet doses (V 200/7.5 and V 400/15) were all less than 30 minutes, as were most of the confidence limits. However, both of these estimates for V 200/7.5, and 2 of the 4 estimates for V 400/15, came from studies that had placebo onset times of only 16 or 17 minutes.

V 400/15 provided substantial evidence of separating from placebo by one hour (on PRID) in 3 studies (09, 13 and 29) of the 4 principal ones in which it was used. V200/7.5 showed separation in only one (Study 23) of the two in which it was used. As supporting information, the alternate combination, V 400/10, beat placebo on PRID at one hour in 3 of 4 studies.

Dose Response

Only Study 21 compared one- and two-tablet doses (200/7.5 vs. 400/15) head-to-head, and no difference was seen. The study had a large placebo response, suggesting poor upside sensitivity. Thus the study does not provide much evidence against a dose response, either, and the question of whether there is a dose response remains open.

The applicant provided an argument using a cross-study analysis of Studies 23 and 29 (which had the same site and investigator) to make the case for a dose response. However, such a comparison cannot be considered as substantial evidence.

Dosing Interval

The Puerto Rican studies showed especially long remedication times compared to the other studies, and are not considered by this reviewer to be relevant for estimating doing interval for the bulk of the (i.e., North American) U.S. population.

For V 200/7.5, the remedication time in the only non-Puerto Rican study was 3 hours. That study had particularly short remedication times, so that 3 hours may be an underestimate.

For V 400/15 the remedication times were 4 to 5 hours in non-Puerto Rican studies, or up to 6 hours based on extrapolation from the V 400/10 results.

RECOMMENDATIONS:

The application has passed the basic efficacy hurdle of showing the contribution of the components, and the drug product is approvable from the clinical standpoint, provided safety is acceptable and adequate instructions for dosing can be determined. However, the applicant should be asked to provide some assurance that the dissolution rates of ibuprofen from the active and control drugs in Study 09 were reasonably comparable.

The onset of action is sufficiently rapid that the product can be considered suitable for acute pain.

The need for a two-tablet dose instead of a one-tablet dose is not established by these studies, and it should not be recommended unless other evidence can be found to support it.

The dosing interval suggested by these studies is somewhere in the range of 3 to 6 hours, but the results of repeat-dose studies, and knowledge of the components, should be taken into account in formulating the dosing interval recommendations.

With regard to efficacy, there is no need for the labeling to make distinctions on the basis of age, race or gender.

See also Overall Conclusions (page 77) for further discussion and refinement of recommendations.

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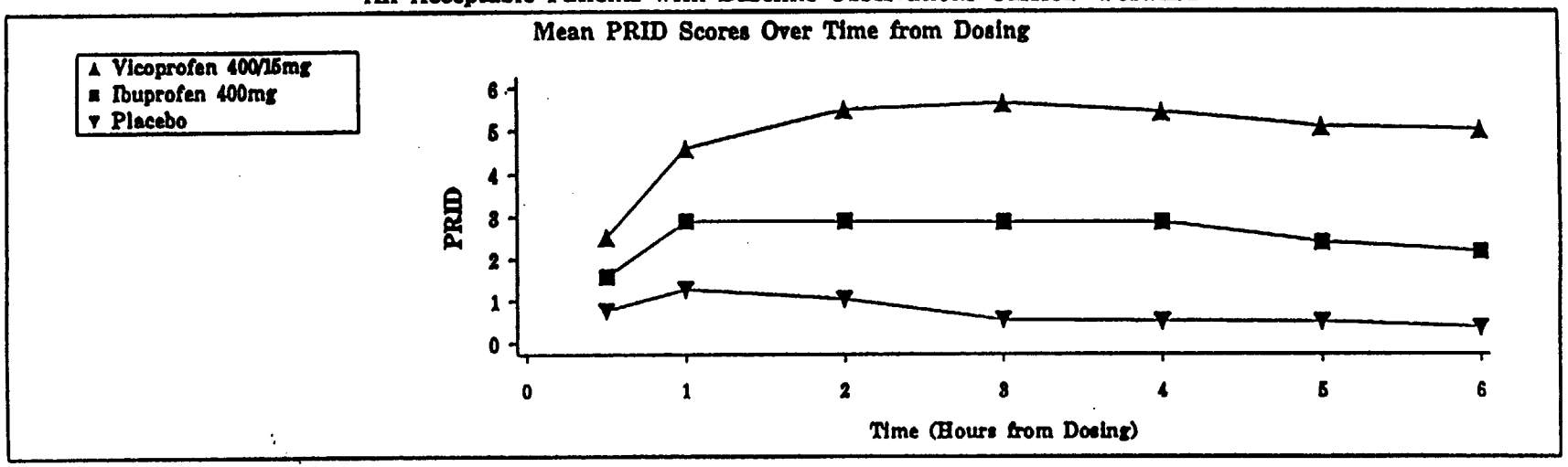
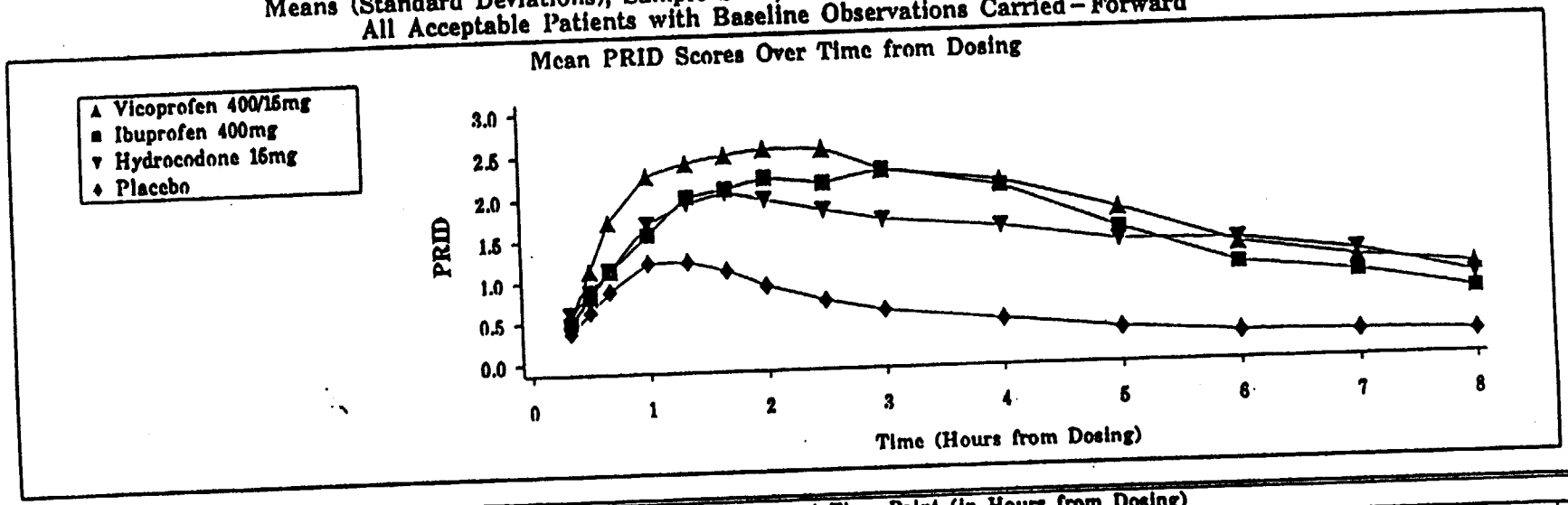
FIGURE 3
VP-09-0901 PRID Scores
Means (Standard Deviations), Sample Sizes, and Fisher's Protected LSD Comparisons
All Acceptable Patients with Baseline Observations Carried-Forward



Treatment	Assessment Time Point (in Hours from Dosing)													
	0.5		1		2		3		4		5		6	
Vicoprofen 400/15mg (n=40)(e)	2.63 [40](a)	(1.87) A(d)	4.60 [40]	(1.48) A	5.50 [40]	(1.24) A	5.65 [40]	(1.08) A	5.45 [40]	(1.13) A	5.10 [40]	(1.28) A	5.03 [40]	(1.23) A
Ibuprofen 400mg (n=40)	1.58 [40]	(1.60) B	2.90 [40]	(1.77) B	2.90 [29]	(2.12) B	2.88 [34]	(2.05) B	2.88 [30]	(1.98) B	2.40 [30]	(1.84) B	2.18 [30]	(1.72) B
Placebo (n=39)	0.77 [39]	(1.44) C	1.28 [39]	(1.76) C	1.05 [25]	(1.59) C	0.54 [20]	(1.39) C	0.51 [12]	(1.35) C	0.49 [7]	(1.32) C	0.36 [7]	(1.01) C
Treatment P-Value(b)	<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001	
Trt*Baseline P-Value(c)	0.618		0.129		0.189		0.758		0.742		0.280		0.617	
RMS Error(b)	1.653		1.659		1.674		1.558		1.531		1.494		1.341	

(a) Represents the number of subjects evaluating efficacy at that time point (i.e. number of active subjects).
(b) Model: PRID $= \mu + Trt(i) + Baseline(j) + Error$
(c) Model: PRID $= \mu + Trt(i) + Baseline(j) + Trt*Baseline(ij) + Error$
(d) Protected LSD based on Model LSMEANS. Same letters indicate non-significant treatment differences. Different letters indicate the overall treatment p-value from ANOVA $<= 0.05$.
(e) Represents the number of subjects analyzed for efficacy based on extrapolated data.

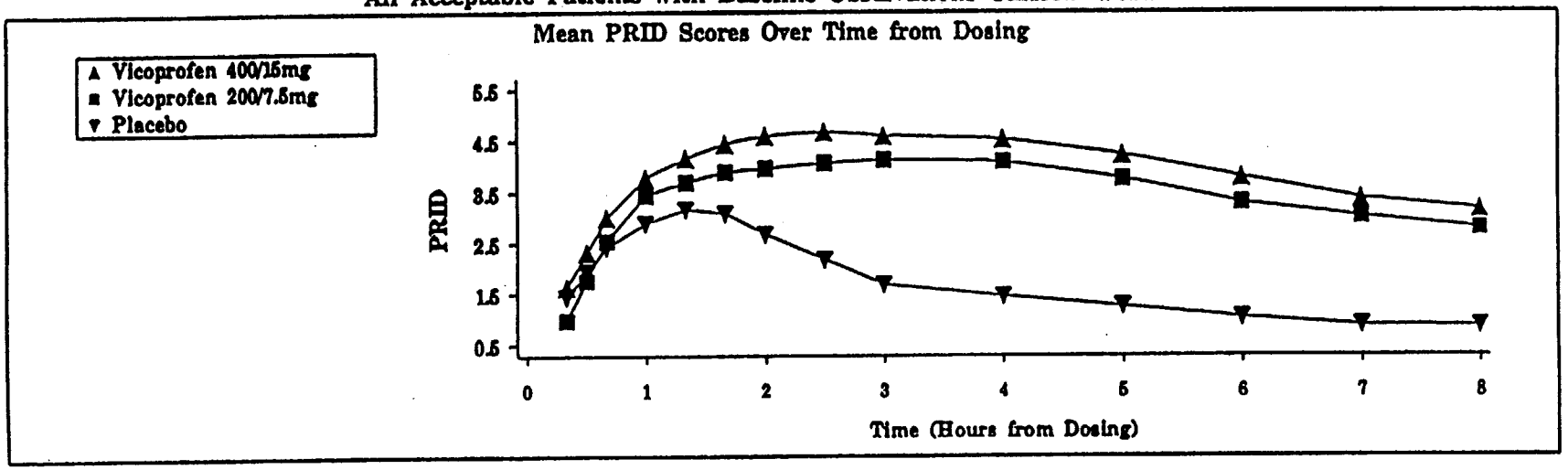
FIGURE 3
VP-13-1301 PRID Scores
Means (Standard Deviations), Sample Sizes, and Fisher's Protected LSD Comparisons
All Acceptable Patients with Baseline Observations Carried-Forward



Treatment	Assessment Time Point (in Hours from Dosing)													
	0.33	0.5	0.67	1	1.33	1.67	2	2.5	3	4	5	6	7	8
Vicoprofen 400/15mg (n=50)(e)	0.56 (1.13) [50](a)A(d)	1.14 (1.31) [50] A	1.72 (1.85) [50] A	2.26 (2.07) [50] A	2.40 (2.17) [45] A	2.48 (2.23) [39] A	2.54 (2.48) [37] A	2.52 (2.55) [32] A	2.26 (2.58) [29] A	2.10 (2.64) [27] A	1.74 (2.38) [23] A	1.28 (2.13) [18] A	1.08 (2.03) [13] A	0.96 (1.97) [13] A
Ibuprofen 400mg (n=50)	0.50 (1.05) [50] A	0.81 (1.13) [50] A	1.12 (1.61) [50] AB	1.56 (1.68) [50] AB	2.00 (1.98) [44] A	2.08 (2.05) [38] A	2.20 (2.19) [36] A	2.12 (2.26) [32] A	2.26 (2.42) [29] A	2.04 (2.54) [26] A	1.50 (2.33) [21] A	1.04 (2.06) [17] A	0.90 (1.87) [12] A	0.66 (1.69) [10] A
Hydrocodone 15mg (n=49)	0.61 (0.91) [49] A	0.88 (1.02) [49] A	1.14 (1.34) [49] AB	1.69 (1.65) [49] AB	1.92 (1.69) [45] AB	2.04 (1.88) [39] A	1.94 (2.05) [38] A	1.80 (2.11) [30] A	1.67 (2.18) [25] A	1.55 (2.16) [21] A	1.35 (2.05) [19] A	1.33 (2.02) [19] A	1.16 (1.93) [17] A	0.84 (1.84) [11] A
Placebo (n=50)	0.38 (0.85) [50] A	0.63 (0.92) [50] A	0.88 (1.35) [50] B	1.22 (1.69) [50] B	1.22 (1.73) [35] B	1.10 (1.69) [27] B	0.90 (1.49) [26] B	0.70 (1.52) [20] B	0.56 (1.45) [14] B	0.42 (1.11) [10] B	0.28 (0.97) [7] B	0.20 (0.81) [3] B	0.18 (0.72) [3] B	0.14 (0.[illegible]) [3] A
Treatment P-Value(b)	0.672	0.142	0.045	0.033	0.021	0.005	<0.001	<0.001	<0.001	<0.001	0.002	0.008	0.020	0.063
Trt*Baseline P-Value(c)	0.206	0.222	0.425	0.351	0.409	0.413	0.415	0.385	0.530	0.812	0.779	0.870	0.593	0.894
RMS Error(b)	0.991	1.104	1.527	1.775	1.903	1.974	2.067	2.143	2.202	2.202	2.014	1.838	1.723	1.619

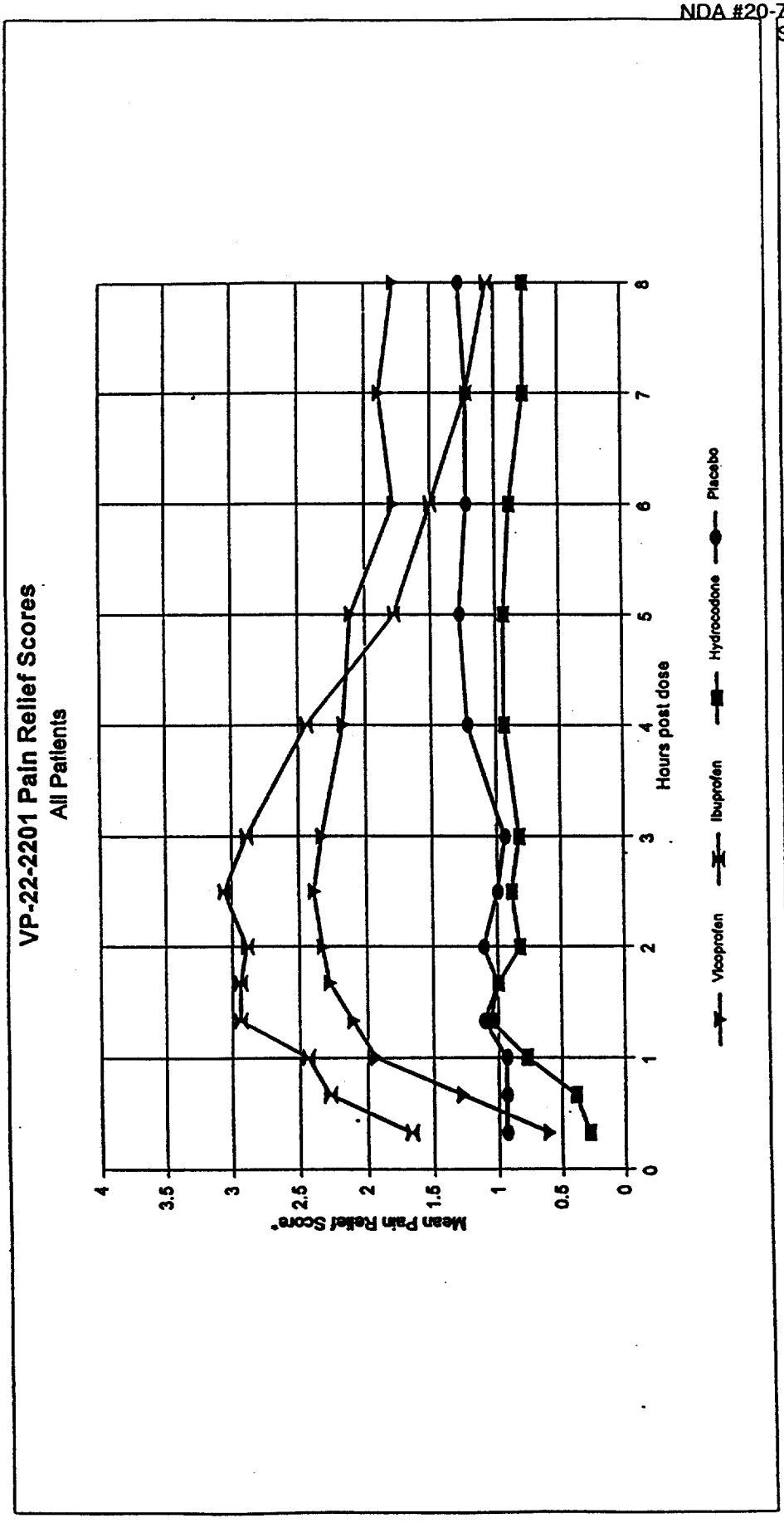
(a) Represents the number of subjects evaluating efficacy at that time point (i.e. number of active subjects).
(b) Model: PRID = μ + Trt(i) + Baseline(j) + Error
(c) Model: PRID = μ + Trt(i) + Baseline(j) + Trt*Baseline(ij) + Error
(d) Protected LSD based on Model LSMEANS. Sam letters indicate non-significant treatment differences. Different letters indicate the overall treatment p-value from ANOVA <= 0.05.
(e) Represents the number of subjects analyzed for efficacy based on extrapolated data.

FIGURE 3
VP-21-2101 PRID Scores
Means (Standard Deviations), Sample Sizes, and Fisher's Protected LSD Comparisons
All Acceptable Patients with Baseline Observations Carried-Forward



Treatment	Assessment Time Point (in Hours from Dosing)													
	0.33	0.5	0.67	1	1.33	1.67	2	2.5	3	4	5	6	7	8
Vicoprofen 400/15mg (n=60)(e)	1.65 (1.79) [60](a)A(d)	2.53 (1.86) [60] A	3.02 (2.22) [60] A	3.80 (2.24) [60] A	4.17 (2.37) [57] A	4.45 (2.48) [51] A	4.60 (2.51) [50] A	4.68 (2.56) [49] A	4.60 (2.61) [49] A	4.53 (2.58) [47] A	4.23 (2.51) [47] A	3.80 (2.39) [47] A	3.38 (2.37) [46] A	3.18 (2.35) [45] A
Vicoprofen 200/7.5mg (n=60)	0.98 (1.27) [60] A	1.77 (1.86) [60] A	2.55 (1.84) [60] A	3.45 (2.09) [60] A	3.70 (2.16) [59] A	3.90 (2.19) [53] AB	3.97 (2.27) [51] A	4.07 (2.36) [51] A	4.13 (2.35) [49] A	4.10 (2.43) [49] A	3.77 (2.27) [48] A	3.30 (2.09) [48] A	3.03 (2.11) [47] A	2.80 (2.05) [44] A
Placebo (n=60)	1.45 (1.72) [60] A	1.94 (1.72) [60] A	2.43 (1.99) [60] A	2.90 (2.17) [60] A	3.18 (2.29) [53] A	3.10 (2.33) [50] B	2.68 (2.33) [48] B	2.18 (2.34) [44] B	1.68 (2.27) [39] B	1.45 (2.24) [26] B	1.25 (1.94) [21] B	1.03 (1.74) [20] B	0.87 (1.49) [18] B	0.85 (1.47) [16] B
Treatment P-Value(b)	0.071	0.164	0.249	0.076	0.064	0.007	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Trt*Baseline P-Value(c)	0.069	0.086	0.193	0.240	0.320	0.733	0.814	0.891	0.801	0.865	0.945	0.726	0.999	0.960
RMS Error(b)	1.615	1.664	2.019	2.174	2.280	2.341	2.374	2.427	2.418	2.424	2.245	2.082	2.014	1.983

(a) Represents the number of subjects evaluating efficacy at that time point (i.e. number of active subjects).
(b) Model: PRID $= \mu + Trt(i) + Baseline(j) + Error$
(c) Model: PRID $= \mu + Trt(i) + Baseline(j) + Trt*Baseline(ij) + Error$
(d) Protected LSD based on Model LSMEANS. Sam letters indicate non-significant treatment differences. Different letters indicate the overall treatment p-value from ANOVA <= 0.05.
(e) Represents the number of subjects analyzed for efficacy based on extrapolated data.



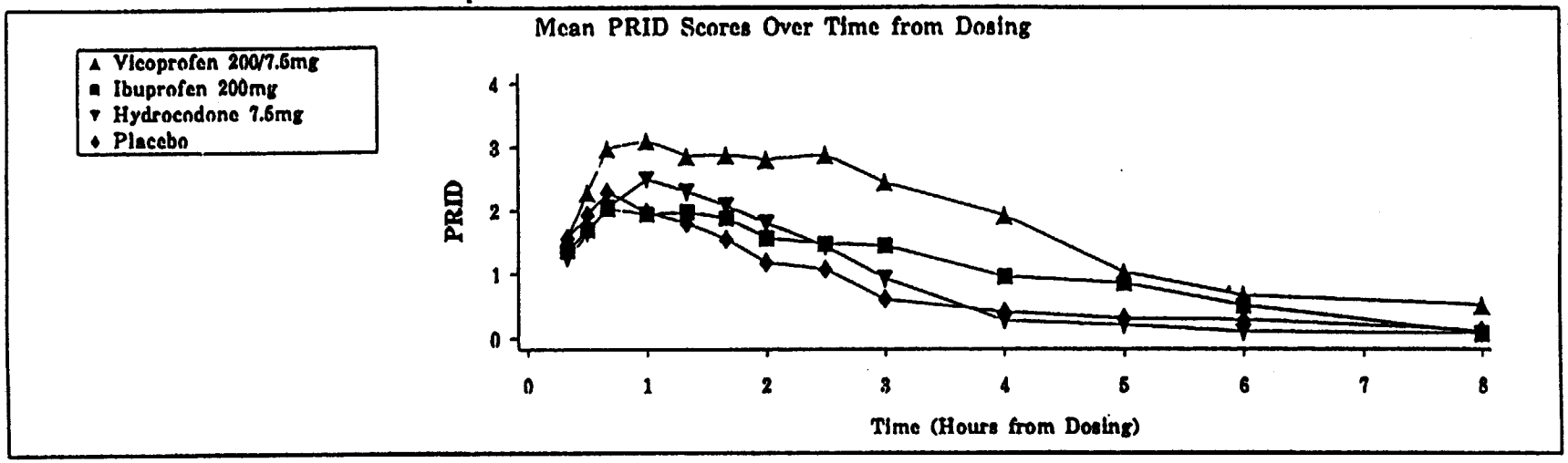
	Hours post dose																													
	0.33		0.67		1		1.33		1.67		2		2.5		3		4		5		6		7		8	
Vicoprofen (400/15 mg)	*mean sd	0.61	(0.61)	1.28	(1.07)	1.84	(1.35)	2.11	(1.57)	2.28	(1.80)	2.33	(1.81)	2.39	(1.81)	2.33	(1.57)	2.17	(1.54)	2.11	(1.64)	1.78	(1.59)	1.89	(1.53)	1.78	(1.59)
	n	18		18		18	X	18	X	18	X	18	X	18	X	15	X	13	X	13		12		11		11	
Ibuprofen (400 mg)	*mean sd	1.67	(0.67)	2.28	(1.13)	2.44	(1.16)	2.94	(1.00)	2.94	(1.06)	2.89	(1.06)	3.06	(1.39)	2.89	(1.41)	2.44	(1.25)	1.78	(1.56)	1.50	(1.62)	1.22	(1.56)	1.06	(1.39)
	n	18	X	18	X	18	X	18	X	18	X	18	X	18	X	17	X	16	X	16		13		11		8	
Hydrocodone (15mg)	*mean sd	0.28	(0.83)	0.39	(0.85)	0.78	(1.11)	1.06	(1.30)	1.00	(1.26)	0.83	(1.29)	0.89	(1.32)	0.83	(1.25)	0.94	(1.51)	0.94	(1.51)	0.89	(1.41)	0.78	(1.31)	0.78	(1.31)
	n	18		18		18		18		14		10		7		6		7		6		6		6		6	
Placebo	*mean sd	0.94	(1.26)	0.94	(1.21)	0.94	(1.06)	1.11	(1.23)	1.00	(1.18)	1.00	(1.26)	1.00	(1.14)	0.94	(1.06)	1.22	(1.31)	1.28	(1.48)	1.22	(1.52)	1.22	(1.52)	1.28	(1.39)
	n	18		18		18		18		14		11		11		11		10		10		9		8		8	
	p-value	<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		0.005		0.121		0.333		0.175		0.240	

Mean AUC-PR Scores	0-4 hr	0-8hr
Vicoprofen	7.51 X	15.23 X
Ibuprofen	8.88 X	18.71 X
Hydrocodone	2.85	8.30
Placebo	3.72	8.63
p-value	<0.001	0.007

Sample sizes (n) represent number of patients remaining at each evaluation time point. However, mean values and comparisons are based on all patients, with values extrapolated after remedication.

*Xe significantly different from placebo (p<=0.05)

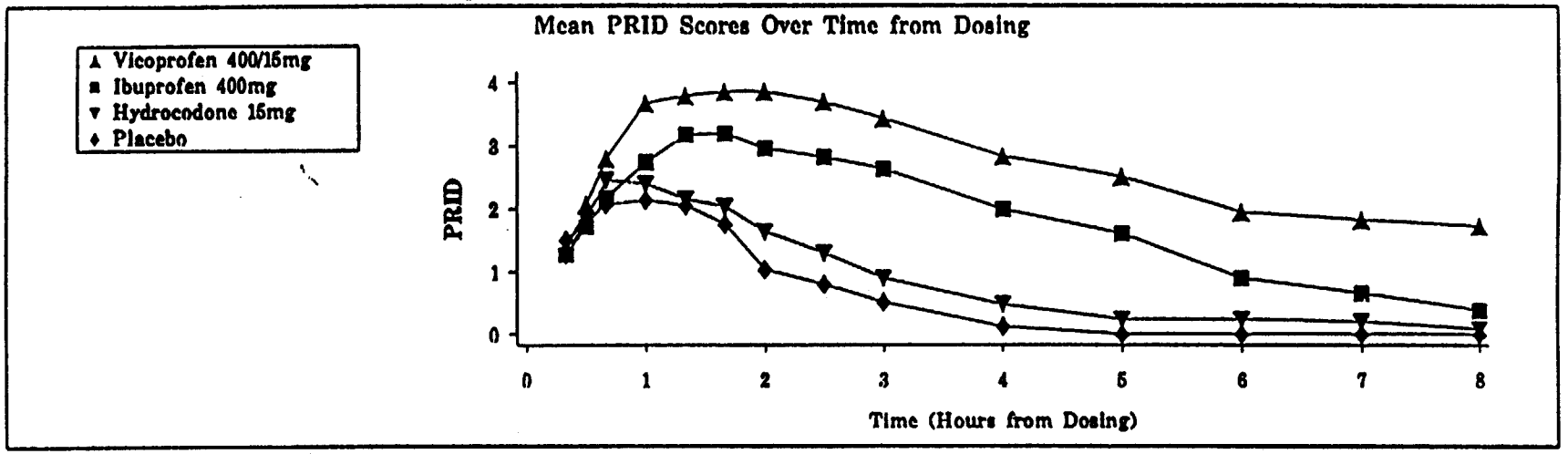
FIGURE 3
VP-23-2301 PRID Scores
Means (Standard Deviations), Sample Sizes, and Fisher's Protected LSD Comparisons
All Acceptable Patients with Baseline Observations Carried-Forward



Treatment	Assessment Time Point (In Hours from Dosing)													
	0.33	0.5	0.67	1	1.33	1.67	2	2.5	3	4	5	6	8	
Vicoprofen 200/7.5mg (n=59)(e)	1.59 (1.66) [59](a)A(d)	2.29 (1.69) [59] A	2.98 (2.11) [59] A	3.10 (2.40) [59] A	2.86 (2.66) [41] A	2.88 (2.75) [34] A	2.80 (2.74) [33] A	2.88 (2.79) [32] A	2.44 (2.71) [32] A	1.92 (2.58) [26] A	1.03 (2.08) [22] A	0.66 (1.72) [14] A	0.51 (1.59) [8] A	
Ibuprofen 200mg (n=60)	1.38 (1.71) [60] A	1.71 (1.64) [60] A	2.03 (1.83) [60] B	1.95 (2.32) [60] B	1.98 (2.35) [33] A	1.88 (2.43) [28] B	1.67 (2.34) [25] B	1.48 (2.35) [21] B	1.45 (2.32) [19] B	0.95 (2.13) [18] B	0.85 (2.00) [11] AB	0.50 (1.58) [11] A	0.07 (0.55) [5] B	
Hydrocodone 7.5mg (n=61)	1.25 (1.73) [61] A	1.65 (1.76) [61] A	2.05 (2.16) [61] B	2.49 (2.45) [61] AB	2.30 (2.44) [38] A	2.08 (2.44) [34] AB	1.80 (2.48) [30] B	1.44 (2.36) [24] B	0.93 (1.90) [21] BC	0.26 (1.20) [13] C	0.20 (0.85) [6] C	0.10 (0.54) [3] A	0.07 (0.51) [1] B	
Placebo (n=60)	1.58 (1.67) [60] A	1.94 (1.83) [60] A	2.30 (2.21) [60] AB	1.98 (2.41) [60] B	1.80 (2.38) [32] A	1.55 (2.35) [26] B	1.18 (2.23) [23] B	1.07 (2.05) [15] B	0.60 (1.48) [14] C	0.40 (1.24) [9] BC	0.30 (1.08) [6] BC	0.28 (1.08) [4] A	0.12 (0.6 [3] B	
Treatment P-Value(b)	0.623	0.176	0.046	0.031	0.097	0.029	0.003	<0.001	<0.001	<0.001	0.009	0.099	0.027	
Trt*Baseline P-Value(c)	0.254	0.160	0.162	0.047	0.074	0.101	0.055	0.067	0.277	0.027	0.500	0.540	0.630	
RMS Error(b)	1.696	1.736	2.084	2.404	2.463	2.494	2.448	2.395	2.160	1.879	1.697	1.311	0.933	

(a) Represents the number of subjects evaluating efficacy at that time point (i.e. number of active subjects).
(b) Model: PRID = μ + Trt(i) + Baseline(j) + Error
(c) Model: PRID = μ + Trt(i) + Baseline(j) + Trt*Baseline(ij) + Error
(d) Protected LSD based on Model LSMEANS. Sam letters indicate non-significant treatment differences. Different letters indicate the overall treatment p-value from ANOVA <= 0.05.
(e) Represents the number of subjects analyzed for efficacy based on extrapolated data.

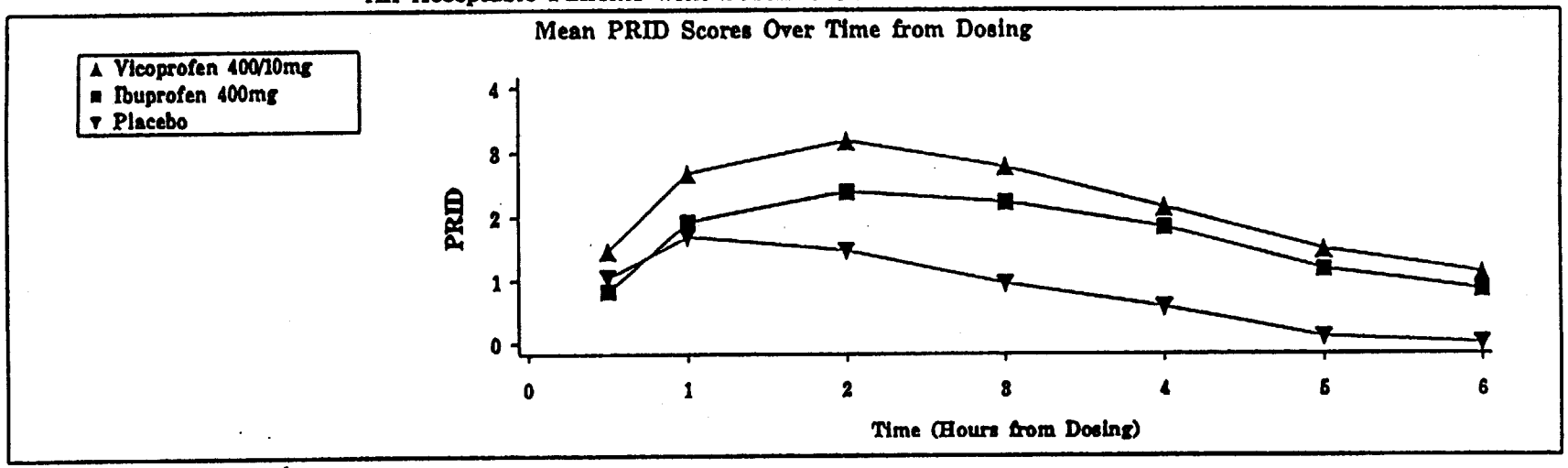
FIGURE 3
VP-29-2901 PRID Scores
Means (Standard Deviations), Sample Sizes, and Fisher's Protected LSD Comparisons
All Acceptable Patients with Baseline Observations Carried-Forward



Treatment	Assessment Time Point (in Hours from Dosing)															
	0.33	0.5	0.67	1	1.33	1.67	2	2.5	3	4	5	6	7	8
Vicoprofen 400/15mg (n=50)(e)	1.36 (1.59) [50](a)(d)	2.08 (1.77) [50] A	2.80 (2.26) [50] A	3.68 (2.43) [50] A	3.80 (2.51) [39] A	3.86 (2.72) [39] A	3.86 (2.77) [37] A	3.70 (2.82) [36] A	3.44 (2.76) [33] A	2.84 (2.67) [32] A	2.52 (2.70) [28] A	1.96 (2.66) [23] A	1.84 (2.61) [19] A	1.74 (2.61) [18] A
Ibuprofen 400mg (n=50)	1.28 (1.55) [50] A	1.73 (1.63) [50] A	2.18 (1.95) [50] A	2.74 (2.38) [50] B	3.18 (2.65) [35] A	3.20 (2.73) [33] A	2.96 (2.88) [33] A	2.82 (2.90) [29] A	2.64 (2.86) [27] A	2.00 (2.76) [26] B	1.62 (2.58) [19] B	0.90 (2.10) [15] B	0.66 (1.83) [8] B	0.38 (1.46) [7] B
Hydrocodone 15mg (n=50)	1.26 (1.58) [50] A	1.86 (1.75) [50] A	2.46 (2.26) [50] A	2.40 (2.24) [50] B	2.16 (2.33) [33] B	2.04 (2.28) [28] B	1.64 (2.19) [27] B	1.30 (2.06) [21] B	0.90 (1.94) [18] B	0.48 (1.49) [11] C	0.24 (1.20) [6] C	0.24 (1.19) [2] BC	0.20 (1.01) [2] BC	0.08 (0.57) [2] B
Placebo (n=51)	1.51 (1.74) [51] A	1.79 (1.75) [51] A	2.08 (1.97) [51] A	2.14 (2.27) [51] B	2.06 (2.28) [31] B	1.76 (2.28) [27] B	1.04 (1.90) [23] B	0.80 (1.64) [14] B	0.51 (1.49) [13] B	0.12 (0.59) [7] C	0.00 (0.00) [2] C	0.00 (0.00) [0] C	0.00 (0.00) [0] C	0.00 (0.00) [0] B
Treatment P-Value(b)	0.851	0.747	0.316	0.007	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Trt*Baseline P-Value(c)	0.766	0.899	0.957	0.692	0.426	0.280	0.225	0.148	0.029	0.017	0.034	0.191	0.285	0.739
RMS Error(b)	1.600	1.718	2.116	2.337	2.454	2.512	2.471	2.418	2.333	2.081	1.960	1.795	1.669	1.620

a) Represents the number of subjects evaluating efficacy at that time point (i.e. number of active subjects).
b) Model: PRID = μ + Trt(i) + Baseline(j) + Error
c) Model: PRID = μ + Trt(i) + Baseline(j) + Trt*Baseline(ij) + Error
d) Protected LSD based on Model LSMEANS. Sam letters indicate non-significant treatment differences. Different letters indicate the overall treatment p-value from ANOVA <= 0.05.
e) Represents the number of subjects analyzed for efficacy based on extrapolated data.

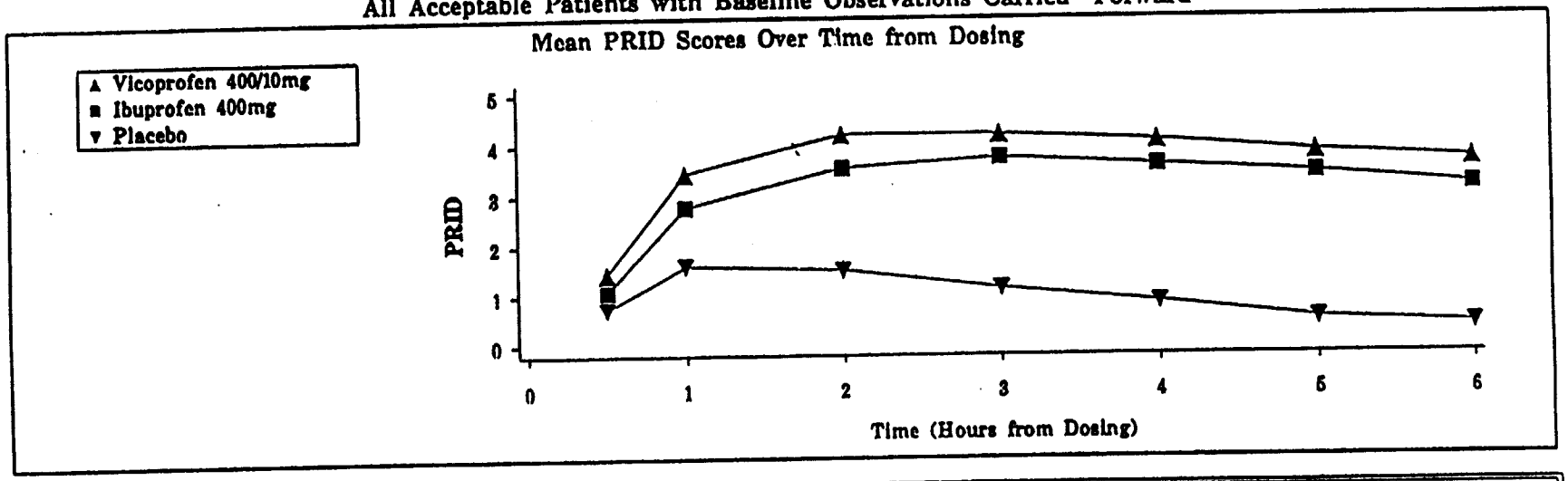
FIGURE 3
VP-01-0101 PRID Scores
Means (Standard Deviations), Sample Sizes, and Fisher's Protected LSD Comparisons
All Acceptable Patients with Baseline Observations Carried-Forward



Treatment	Assessment Time Point (in Hours from Dosing)													
	0.5		1		2		3		4		5		6	
Vicoprofen 400/10mg (n=40)(a)	1.48 (1.30) [40](a) A(d)		2.68 (2.03) [40] A		2.18 (2.54) [34] A		2.78 (2.60) [26] A		2.15 (2.38) [24] A		1.50 (2.23) [16] A		1.13 (1.95) [12] A	
Ibuprofen 400mg (n=40)	0.83 (1.11) [40] A		1.93 (2.02) [40] A		2.40 (2.50) [30] AB		2.23 (2.75) [20] A		1.85 (2.54) [17] A		1.18 (2.11) [15] A		0.85 (1.90) [9] A	
Placebo (n=40)	1.05 (1.18) [40] A		1.70 (1.65) [40] A		1.48 (1.80) [28] B		0.95 (1.66) [14] B		0.58 (1.45) [10] B		0.10 (0.38) [5] B		0.00 (0.00) [1] B	
Treatment P-Value(b)	0.061		0.061		0.006		0.003		0.004		0.002		0.005	
Trt*Baseline P-Value(c)	0.187		0.231		0.358		0.215		0.179		0.105		0.154	
RMS Error(b)	1.200		1.914		2.312		2.378		2.177		1.793		1.679	

(a) Represents the number of subjects evaluating efficacy at that time point (i.e. number of active subjects).
(b) Model: PRID $= \mu + Trt(i) + Baseline(j) + Error$
(c) Model: PRID $= \mu + Trt(i) + Baseline(j) + Trt*Baseline(ij) + Error$
(d) Protected LSD based on Model LSMEANS. Same letters indicate non-significant treatment differences. Different letters indicate the overall treatment p-value from ANOVA $<= 0.05$.
(e) Represents the number of subjects analyzed for efficacy based on extrapolated data.

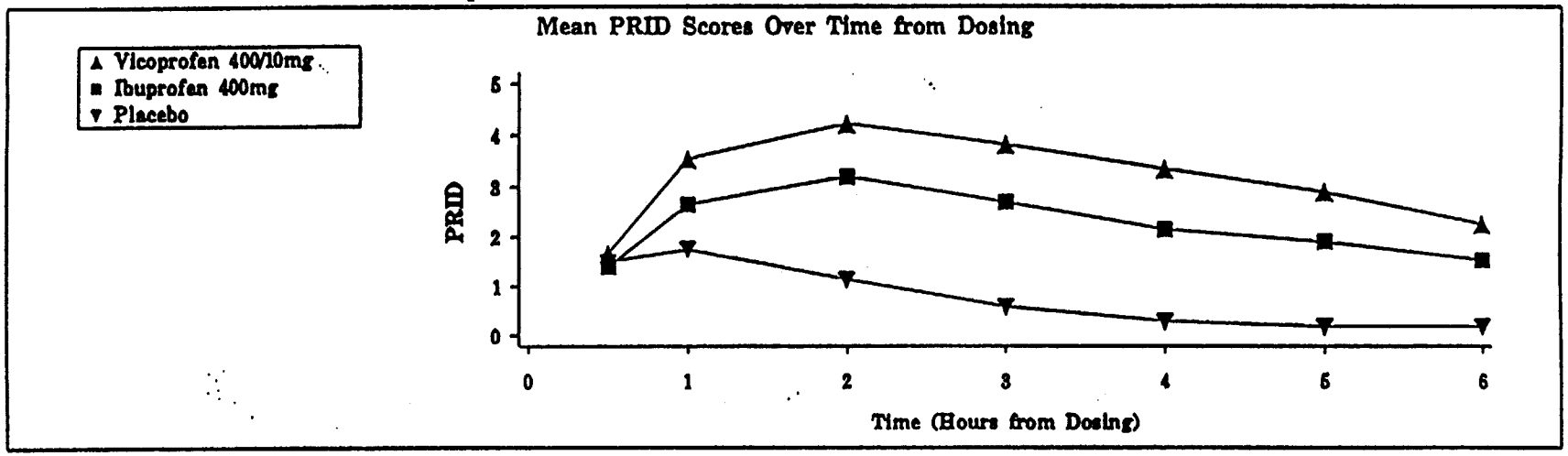
FIGURE 3
VP-01-0102 PRID Scores
Means (Standard Deviations), Sample Sizes, and Fisher's Protected LSD Comparisons
All Acceptable Patients with Baseline Observations Carried-Forward



Treatment	Assessment Time Point (in Hours from Dosing)													
	0.5		1		2		3		4		5		6	
Vicoprofen 400/10mg (n=40)(e)	1.45 [40](a)	(1.60) A(d)	3.45 [40]	(2.11) A	4.20 [36]	(2.47) A	4.20 [33]	(2.28) A	4.08 [32]	(2.59) A	3.85 [29]	(2.69) A	3.70 [28]	(2.74) A
Ibuprofen 400mg (n=40)	1.08 [40]	(1.33) A	2.78 [40]	(2.21) A	3.55 [34]	(2.30) A	3.75 [30]	(2.50) A	3.60 [28]	(2.71) A	3.43 [27]	(2.66) A	3.18 [26]	(2.55) A
Placebo (n=40)	0.72 [40]	(1.11) A	1.60 [40]	(1.81) B	1.50 [20]	(1.95) B	1.13 [15]	(1.90) B	0.85 [13]	(1.85) B	0.50 [8]	(1.43) B	0.38 [7]	(1.37) B
Treatment P-Value(b)	0.059		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001	
Trt*Baseline P-Value(c)	0.104		0.146		0.117		0.094		0.385		0.439		0.564	
RMS Error(b)	1.345		2.028		2.252		2.245		2.420		2.347		2.311	

(a) Represents the number of subjects evaluating efficacy at that time point (i.e. number of active subjects).
(b) Model: PRID = μ + Trt(i) + Baseline(j) + Error
(c) Model: PRID = μ + Trt(i) + Baseline(j) + Trt*Baseline(ij) + Error
(d) Protected LSD based on Model LSMEANS. Same letters indicate non-significant treatment differences. Different letters indicate the overall treatment p-value from ANOVA <= 0.05.
(e) Represents the number of subjects analyzed for efficacy based on extrapolated data.

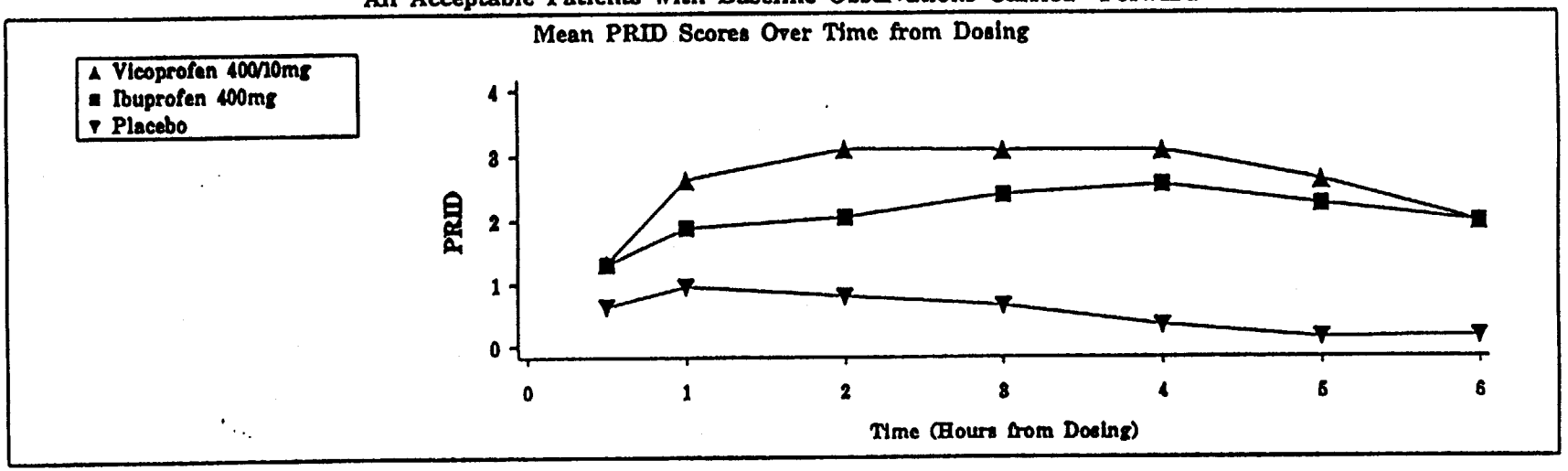
FIGURE 3
VP-01-0103 PRID Scores
Means (Standard Deviations), Sample Sizes, and Fisher's Protected LSD Comparisons
All Acceptable Patients with Baseline Observations Carried-Forward



Treatment	Assessment Time Point (in Hours from Dosing)													
	0.5		1		2		3		4		5		6	
Vicoprofen 400/10mg (n=40)(a)	1.68 [40](a)	(2.02) A(d)	2.55 [40]	(2.35) A	4.23 [34]	(2.60) A	3.83 [21]	(2.62) A	3.35 [28]	(2.61) A	2.90 [27]	(2.75) A	2.25 [23]	(2.61) A
Ibuprofen 400mg (n=40)	1.40 [40]	(1.98) A	2.65 [40]	(2.13) AB	3.20 [30]	(2.71) A	2.70 [25]	(2.80) B	2.15 [21]	(2.66) B	1.90 [17]	(2.58) B	1.53 [14]	(2.44) A
Placebo (n=40)	1.50 [40]	(1.96) A	1.75 [40]	(1.94) B	1.13 [27]	(1.84) B	0.58 [14]	(1.30) C	0.28 [7]	(0.93) C	0.18 [3]	(0.84) C	0.18 [2]	(0.84) B
Treatment P-Value(b)	0.821		0.001		<0.001		<0.001		<0.001		<0.001		<0.001	
Trt*Baseline P-Value(c)	0.121		0.424		0.808		0.938		0.904		0.937		0.794	
RMS Error(b)	1.979		2.120		2.381		2.343		2.224		2.222		2.126	

(a) Represents the number of subjects evaluating efficacy at that time point (i.e. number of active subjects).
(b) Model: PRID $= \mu + Trt(i) + Baseline(j) + Error$
(c) Model: PRID $= \mu + Trt(i) + Baseline(j) + Trt*Baseline(ij) + Error$
(d) Protected LSD based on Model LSMEANS. Same letters indicate non-significant treatment differences. Different letters indicate the overall treatment p-value from ANOVA <= 0.05.
(e) Represents the number of subjects analyzed for efficacy based on extrapolated data.

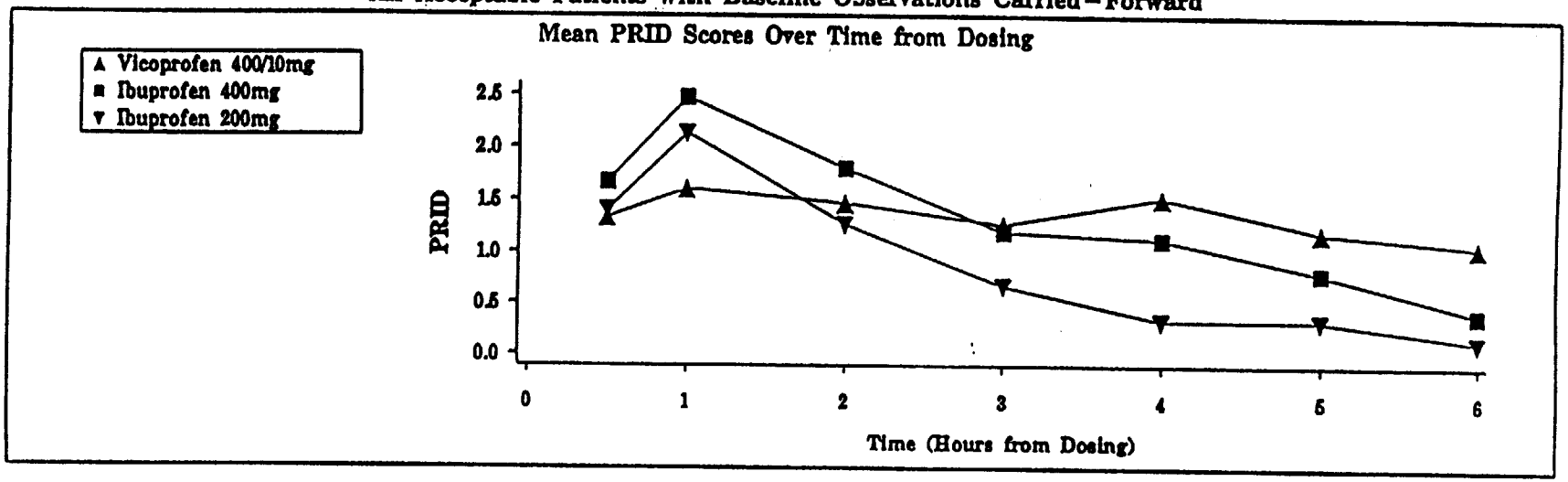
FIGURE 3
VP-01-0104 PRID Scores
Means (Standard Deviations), Sample Sizes, and Fisher's Protected LSD Comparisons
All Acceptable Patients with Baseline Observations Carried-Forward



Treatment	Assessment Time Point (in Hours from Dosing)													
	0.5		1		2		3		4		5		6	
Vicoprofen 400/10mg (n=40)(e)	1.83 [40](a)	(1.59) A(d)	2.63 [40]	(2.39) A	3.10 [33]	(2.50) A	3.08 [30]	(2.43) A	2.96 [27]	(2.69) A	2.63 [26]	(2.78) A	1.98 [21]	(2.63) A
Ibuprofen 400mg (n=40)	1.30 [40]	(1.68) A	1.88 [39]	(1.84) A	2.05 [33]	(2.11) B	2.40 [27]	(2.51) A	2.55 [25]	(2.62) A	2.25 [24]	(2.64) A	1.98 [21]	(2.54) A
Placebo (n=40)	0.63 [40]	(1.15) A	0.95 [40]	(1.60) B	0.80 [27]	(1.74) C	0.65 [15]	(1.39) B	0.33 [11]	(1.10) B	0.13 [7]	(0.72) B	0.15 [4]	(0.66) B
Treatment P-Value(b)	0.064		0.001		<0.001		<0.001		<0.001		<0.001		<0.001	
Trt*Baseline P-Value(c)	0.329		0.655		0.432		0.522		0.575		0.747		0.824	
RMS Error(b)	1.496		1.976		2.144		2.174		2.257		2.258		2.147	

(a) Represents the number of subjects evaluating efficacy at that time point (i.e. number of active subjects).
(b) Model: PRID = μ + Trt(i) + Baseline(j) + Error
(c) Model: PRID = μ + Trt(i) + Baseline(j) + Trt*Baseline(ij) + Error
(d) Protected LSD based on Model LSMEANS. Same letters indicate non-significant treatment differences. Different letters indicate the overall treatment p-value from ANOVA <= 0.05.
(e) Represents the number of subjects analyzed for efficacy based on extrapolated data.

FIGURE 3
VP-12-1201 PRID Scores
Means (Standard Deviations), Sample Sizes, and Fisher's Protected LSD Comparisons
All Acceptable Patients with Baseline Observations Carried-Forward



Treatment	Assessment Time Point (In Hours from Dosing)											
	0.5		1		2		3		4		5		6	
Vicoprofen 400/10mg (n=15)(e)	1.53 [15](a)	(1.54) A(d)	1.60 [15]	(1.45) A	1.47 [9]	(1.92) A	1.27 [7]	(1.83) A	1.53 [6]	(2.07) A	1.20 [5]	(2.06) A	1.07 [4]	(1.87) A
Ibuprofen 400mg (n=15)	1.67 [15]	(1.80) A	2.47 [15]	(2.13) A	1.80 [10]	(2.24) A	1.20 [6]	(1.97) A	1.13 [5]	(1.85) A	0.80 [5]	(1.52) A	0.40 [3]	(1.12) A
Ibuprofen 200mg (n=15)	1.40 [15]	(1.40) A	2.13 [15]	(1.68) A	1.27 [10]	(1.79) A	0.67 [4]	(1.40) A	0.33 [2]	(1.29) A	0.33 [1]	(1.29) A	0.13 [1]	(0.52) A
Treatment P-Value(b)	0.875		0.531		0.797		0.593		0.188		0.400		0.162	
Trt*Baseline P-Value(c)	0.272		0.103		0.032		0.342		0.238		0.102		0.552	
RMS Error(b)	1.608		1.788		2.015		1.769		1.786		1.680		1.308	

(a) Represents the number of subjects evaluating efficacy at that time point (i.e. number of active subjects).
(b) Model: PRID $= \mu + Trt(i) + Baseline(j) + Error$
(c) Model: PRID $= \mu + Trt(i) + Baseline(j) + Trt*Baseline(ij) + Error$
(d) Protected LSD based on Model LSMEANS. Same letters indicate non-significant treatment differences. Different letters indicate the overall treatment p-value from ANOVA $<= 0.05$.
(e) Represents the number of subjects analyzed for efficacy based on extrapolated data.

Vicoprofen Repeated-Dose Analgesia Trials
NDA #20-716

MEDICAL OFFICER REVIEW

NOTICE: After this review was essentially complete, it was learned that one of the major investigators in Study 04, Dr. Fiddes at Whittier, CA (site 0439), was the subject of a DSI early warning notice. There is reason to believe that part of the data on which this review was based may be unreliable. As of the date of this review, Dr. Fiddes' data for this study have not been audited. The conclusions and recommendations based on Study 04 are tentative pending the outcome of a special DSI investigation.

INTRODUCTION:

The applicant provided four repeated-dose efficacy trials in a variety of surgical pain models. Two of these studies (04 and 14) used the proposed drug product, but Study 14 was truncated with a small number of patients entered, so Study 04 is the major repeated-dose study. The other two studies (07 and 08) used an alternate product with a different ratio of components, and they were relatively short, so they provide only supporting data.

The applicant's study designations all had the prefix "VP-." The prefix has been omitted in this review.

The basic study characteristics are set out in Table 9 on page 38. Except for Study 04, they were short-term studies of up to 5 days. These shorter studies all used a dosing interval of 4 to 6 hours. Study 04, in contrast to the others, was a one-month chronic pain study. The dosing regimen was TID to QID, essentially equivalent to 6 to 8 hour dosing.

Demographic data are presented in Table 10 on page 38. Unlike the single-dose studies, there is a more even distribution of gender. Study 04 has a respectable complement of elderly. Race data were not available for the studies using the alternate formulation.

Because of their limited contribution, Studies 07, 08 and 14 are reviewed rather briefly in the following pages. Study 04 is reviewed last in greater depth.

Table 9: Study Characteristics
Vicoprofen Repeated-Dose Pain Studies

Study ID	Pain Model	Investigator (Site)	No. of Sites	Days of Treatment	Dosing Interval (hours)	Total N	Distribution by Treatment				
							V 400 / 15	V 400 / 10	V 200 / 7.5	APAP + CO	APAP + Oxy
4	Chronic Pain	Multiple (31) (U.S.)	31	30	6-8	469	153		156	160	
14	Postop	Beaver (Washington, DC)	1	5	4-6	26	13*				13*
7	Postop	Multiple (4) (U.S.)	4	5	4-6	133		64		69	
8	Burn Pain (Hospitalized)	Heimback (Seattle)	1	5	4-6	55		28		27	
					Totals:	683	166	92	156	256	13

* In Study 14 patients could take 1 or 2 tables per dose. As most took 2 tablets at each dose, subjects are tabulated under the 2-tablet dose.

V xx/yy = Vicoprofen: xx mg ibuprofen + yy mg hydrocodone bitartrate
APAP+CO = Acetaminophen 600 mg + Codeine Phosphate 60 mg
APAP+Oxy = Acetaminophen 650 mg + Oxycodone HCl 10 mg

Table 10: Basic Demographics
Vicoprofen Repeated-Dose Pain Studies

Study ID	Investigator Model	Treatment	Total N	Female	Non-Caucasian	Age ≥ 65
4	Multiple (31) Chronic Pain	V 400/15	153	91 (59%)	39 (25%)	39 (25%)
		V 200/7.5	156	77 (49%)	38 (24%)	35 (22%)
		APAP+CO	160	87 (54%)	27 (17%)	32 (20%)
14	Beaver Post-op	V 400/15*	13	4 (31%)	3 (23%)	2 (15%)
		APAP+Oxy*	13	6 (46%)	3 (23%)	1 (8%)
7	Multiple (4) Post-op	V 400/10	64	56 (88%)	N/A	8 (13%)
		APAP+CO	69	59 (86%)	N/A	14 (20%)
8	Heimbach Burn Pain	V 400/10	28	5 (18%)	N/A	2 (7%)
		APAP+CO	27	2 (7%)	N/A	1 (4%)
		Totals:	683	387 (57%)	N/A	134 (20%)

* In Study 14 patients could take 1 or 2 tables per dose. As most took 2 tablets at each dose, subjects are tabulated under the 2-tablet dose.

V xx/yy = Vicoprofen: xx mg ibuprofen + yy mg hydrocodone
APAP+CO = Acetaminophen 600 mg + Codeine Phosphate 60 mg
APAP+Oxy = Acetaminophen 650 mg + Oxycodone HCl 10 mg

Study 07 (4 Sites)
Five-Day, Repeated-Dose, Surgical Pain (alternate formulation)

This was a randomized, double-blind, parallel, active-control study of post-operative pain at four study sites. Three of the sites, Jain (New Orleans), Wideman (Birmingham), and Kantor (New York City) also participated in single-dose Study 01; and could accept follow-on patients from that study. The fourth site, Homesley (Winston-Salem) was not part of any other Vicoprofen study, and that site contributed just over half of the total study patients.

Treatment: Study treatments were either two tablets of an alternate Vicoprofen formulation consisting of ibuprofen mg with hydrocodone mg (V 400/10), or two tablets of an active control consisting of APAP 300 mg with codeine phosphate 30 mg (A/CO). Patients were to take <u>two</u> tablets as needed, no more often than every 4 to 6 hours, for up to 5 days. Randomization was stratified on baseline severity.

Assessment: Parameters measured included pain intensity (PI) before medication, minimum PI after last dose, global assessment, and rescue medication usage.

Results: A total of 133 patients was entered: 64 in the V 400/10 arm, 69 in the A/CO arm. There were no differences in age, sex, weight, type of surgery or baseline pain. There were no significant differences in pain scores, globals or rescue usage. However there were significantly fewer drop-outs for lack of efficacy (DOLE's) in the V 400/10 arm (8 vs. 20). Average doses/day (mean ± S.D.) for V 400/10 was 1.9 ± .7 on day 1 and 2.4 ± 1.2 on day 2. Most of the patients were discharged from the hospital and discontinued from the study after day 3.

Safety: There were 6 drop-outs for adverse events (DOAE's) in the V 400/10 arm, and 5 in the A/CO arm. There were no serious adverse events (AE's). The more common AE's were nausea and somnolence. Nine AE's were severe: 7 were in the A/CO arm, while V the 400/10 arm had one case each of severe nausea and severe somnolence.

Study 08 (Heimbach)
Five-Day, Repeated-Dose, Acute Burn Pain (alternate formulation)

This was a randomized, double-blind, parallel, active-control study of acute burn pain in inpatients at one study site in Seattle.

Treatment: Study drugs were either an alternate Vicoprofen formulation consisting of ibuprofen mg with hydrocodone mg (V 400/10), or the active control consisting of APAP 300 mg with codeine phosphate 30 mg (A/CO). Patients were to take two tablets as needed, no more often than every 4 to 6 hours, for up to 5 days.

Assessment: Parameters measured included pain intensity (PI) before medication, minimum PI after last dose, global assessment, number of doses used, rescue medication usage.

Results: A total of 55 patients was entered: 28 in the V 400/10 arm, 27 in the A/CO arm. There were no differences in age, sex, weight, burn cause, surface area burned, severity of burn, or baseline pain.

The V 400/10 arm had lower minimum PI scores on day 1 (0.83 vs. 1.25, p=.031), but no other differences were seen in PI or PI differences.

The mean doses/day for V 400/10 was 2.3 on day 1, but then it ranged between 5.3 and 5.8 doses/day for days 2 through 4. Mean dosing in the A/CO arm was very similar.

Safety: There were no serious adverse events. The predominant complaint was nausea. Four adverse events were severe: there was one case of severe nausea in the A/CO arm, while the V 400/10 arm had two cases of severe nausea and one case of severe nausea and vomiting.

Study 14 (Beaver)
Five-Day, Repeated-Dose, Surgical Pain (proposed formulation)

This was a randomized, double-blind, parallel, active-control study of acute postoperative pain at one study site by Beaver (Washington, DC). The study was stopped early after discussions with FDA about a revised design.

Treatment: Study drugs were either Vicoprofen (V), or an active control consisting of APAP 325 mg with oxycodone hydrochloride 5 mg (A/Oxy). Patients were to take one or two tablets as needed, no more often than every 4 to 6 hours, for up to 5 days.

Assessment: Parameters measured included pain intensity (PI) before medication, maximum pain relief (PR) in the four hours following the dose, global assessment, number of doses used daily, rescue medication usage, duration of treatment.

Results: A total of 26 patients was entered: 13 in the V arm, 13 in the A/Oxy arm. Some summary values are given in the table below:

	V (N=13)	A/Oxy (N=13)
Mean of Max PR 0-4 h after dose (0-4 scale)	2.9	3.0
Mean of PI before each dose (0-3 scale)	1.9	2.0
Mean duration of treatment (days)	3.7	4.4
# Patients reporting AE	4	2
# Patients using rescue medication	6	2
Mean daily rescue doses	.30	.50
DOLE	1	0
DOAE	2	0

In the V arm the mean number of doses per day taken on day 1 was 2.2, and on day 2 it was 2.6. The corresponding mean numbers of tablets per day were 4.3 and 4.6, so patients usually took two tablets for each dose.

Safety: There were no serious or severe adverse events. Mild nausea was the predominant complaint.

Study 04 (31 Sites)
One-Month, Repeated-Dose, Chronic Pain (proposed formulation)

Basic Design:
This was a randomized, double-blind, three-arm, active-control trial of two doses of Vicoprofen, vs. APAP with codeine, given for up to one month for chronic pain.

Study Population:
Males and females 18 years or older with a chronic painful condition requiring daily treatment with an opioid/NSAID combination.

Exclusions:
Hypersensitivity to hydrocodone, ibuprofen or any NSAID; past or present ulcer disease, or dependence on anti-ulcer medication; positive baseline Hemoccult; depressed respiratory function; significant cardiovascular, metabolic, renal, hepatic, urinary, CNS, or hematological disease; significant infectious disease; acute abdominal condition; pregnancy or breast-feeding; females of childbearing potential not using medically recognized contraception; alcohol or drug abuse; current or recent investigational drug use; rheumatoid arthritis or medication-dependent osteoarthritis.

Treatment:
Subjects were randomized to one of three treatment arms:

Vicoprofen 200/7.5
Vicoprofen 400/15
APAP with codeine 600/60.

The medication was packaged in blister packs of 30 doses for a week's supply, and was distributed at each of four weekly visits. The doses consisted of two identical-appearing tablets. For the V 200/7.5 arm, one of the tablets was placebo.

Patients were instructed to take both tablets simultaneously with water. The recommended dose was TID; the maximum dosing was every 6 to 8 hours, not to exceed 8 tablets per 24 hours. The dosing interval was to be adjusted by the patient based on need; use of the lowest daily dose was encouraged. Dosing was without regard to meals.

Concomitant medication could include "analgesic adjuvants" such as antidepressants. Occasional use of bedtime sedatives was permitted. The following were excluded: antipsychotics, other sedatives or hypnotics, steroids, methotrexate, gold, penicillamine, hydroxychloroquine, pyrazolon derivatives, H2 blockers, misoprostol, omeprasole, sucralfate.

Use of rescue analgesia was permitted, but limited to one dose between doses of study medication, with a maximum of two doses in 24 hours.

Long-acting opioids, long-acting NSAID's, and PCA were excluded as supplemental analgesia. Use of alcohol during the study was discouraged.

Efficacy Assessment:
Patients were given diaries and asked to record pain relief once daily on a 5-point categorical scale (0=poor to 4=complete). At the end of each week, patient and investigator together made a global assessment on a 5-point scale (1=poor to 5=excellent). The diaries were also used to record daily study drug use, daily supplemental drug use, and adverse events. Data were obtained by interviewing the patient if the diaries were incomplete.

Statistical issues:
The study was randomized with blocks for each center. No interim analysis was planned or done. The protocol listed the primary measures for efficacy as: weekly global scores, daily doses of study medication required, daily supplemental analgesia required, and daily pain relief scores.

Demographics:
The investigators and study sites that contributed patients are listed in Table 11 on page 44. Although there were 40 candidate sites, only 31 actually contributed patients. The largest three centers were Dansak in Birmingham, AL (site 0431), with 90 patients, Serfer in Hollywood, FL (site 0433), with 44 patients, and Fiddes in Whittier, CA (site 0439), with 36 patients. Four other investigators contributed 21 to 30 patients each, nine contributed 11 to 20 patients each, and 15 investigators contributed 1 to 10 patients each.

Demographic data for the 469 included patients are shown in Table 12 on page 45. Although 471 patients were randomized, two withdrew without taking study medication or providing efficacy data, so they have been excluded by the applicant.

There is a statistically borderline difference in mean age, but the differences were less than 10% of mean age. The difference in weights is statistically significant with greatest mean weight in the V 200/7.5 arm. The biggest difference in means is less than 8%. The mean weights may be in part of reflection of the proportion of females in each arm.

Just under half of the patients had back pain as their primary cause of pain. Arthritis was the primary cause of pain in about a third of patients overall. Only about 11% of patients had anything other than a musculo-skeletal primary cause of pain.

Table 11: Study Sites
Vicoprofen Study 04

Site No.	Investigator	Location	Entered	Excluded	D/C	Completed
0401	Harris	Whittier, CA	25		7	18
0402	Levine	Detroit, MI	7		1	6
0403	Herron	Chicago, IL	11		2	9
0404	Soler	Seffner, FL	10		5	5
0406	Marbury	Orlando, FL	20		6	14
0409	Appelrouth	Atlanta, GA	10		5	5
0411	Irick	Indianapolis, IN	11		3	8
0412	Kliman	Boston, MA	3		1	2
0413	Rauck	Winston-Salem, NC	17		6	11
0414	Sinclair	Encinitas, CA	7		3	4
0417	Shashidhar	Tampa, FL	7		2	5
0420	Crews & Gregg	Cincinnati, OH	1		0	1
0421	Caldwell	Daytona Beach, FL	6		2	4
0424	Honig	New York, NY	6		3	3
0425	Gilderman	Pembroke Pines, FL	3		1	2
0426	Graham	Altamonte Springs, FL	11		4	7
0427	Smucker	Columbus, OH	10		3	7
0429	Pinson	Nashville, TN	1		1	0
0430	Unnoppet	Birmingham, AL	24		6	18
0431	Dansak	Mobile, AL	90	1	25	64
0432	Goldberg	Passaic, NJ	16		3	13
0433	Serfer	Hollywood, FL	44	1	18	25
0434	Levy	Hartford, CT	12		0	12
0435	Littlejohn	Winston-Salem, NC	9		3	6
0437	Ruff	San Antonio, TX	10		4	6
0438	Scott	Lake Jackson, TX	6		2	4
0439	Fiddes	Whittier, CA	36		9	27
0440	Rhoades	Modesto, CA	13		2	11
0442	Cohen	Dallas, TX	10		3	7
0443	Billerbeck	Fair Oaks, CA	22		6	16
0444	Chappel	Kissimmee, FL	13		0	13
		Totals:	471	2	136	333

Table 12: Demographics
Vicoprofen Study 04

	V 400/15 (N=153)	V 200/7.5 (N=156)	A/CO (N=160)	p-value
Age:				
mean ± SD	53 ± 15	51 ± 16	49 ± 16	.061
range	21 - 89	20 - 88	21 - 85	
Percent ≥ 65 years	25%	22%	20%	
Gender:				
Percent female	60%	49%	54%	.203
Weight (lb.):				
mean ± SD	179 ± 48	192 ± 43	181 ± 38	.021*
range	77 - 360	101 - 345	99-279	
Race:				
White	75%	76%	83%	
Black	19%	17%	11%	.170
Hispanic	5%	8%	6%	
Other	1%	0%	0%	
Primary Pain Cause:				
Arthritis	35%	31%	26%	
Back	45%	45%	47%	
Other Musc-Skel	9%	16%	16%	
Cancer	1%	1%	3%	
Diabetic. Neuropathy	1%	1%	1%	.614
Postherpetic	1%	1%	1%	
Other Neuro	5%	3%	6%	
Other	3%	3%	1%	
Prior Medication:				
Analgesic & CNS	28%	17%	20%	
Only Analgesic	70%	81%	73%	
Only CNS	1%	1%	1%	
Neither	2%	1%	6%	

Patient Disposition:
The disposition of study patients is shown in Table 13 on page 46. While the majority completed the study, over a quarter of patients did not. The predominant reason was adverse events, but lack of efficacy was cited in the V 200/7.5 and A/CO arms. There were statistically significant differences between arms for adverse-event and lack-of-efficacy dropouts. In particular, V 400/15 had more DOAE's than V 200/7.5 and fewer DOLE's than A/CO. These finding suggest V 400/15 produced more of a drug effect, both in terms of efficacy and safety.

Table 13: Patient Disposition
Vicoprofen Study 04

	V 400/15 (N=153)	V 200/7.5 (N=156)	A/CO (N=160)	p-value
Completed	105 (69%)	118 (76%)	110 (69%)	.295
Discontinued:	48 (31%)	38 (24%)	50 (31%)	
Adverse Event	40 (26%)	23 (15%)	29 (18%)	.035* [1]
Lack of Efficacy	2 (1%)	8 (5%)	12 (8%)	.033* [2]
Intercurrent Medical	1 (1%)	1 (1%)	1 (1%)	
Lost to F/U	1 (1%)	2 (1%)	1 (1%)	
Lack of Compliance	1 (1%)	1 (1%)	4 (3%)	
Entry Criteria Unmet	0	1 (1%)	0	
Other	3 (2%)	2 (1%)	3 (2%)	

1 p=.013 for paired comparison of V 400/15 vs. V 2007.5
2 p=.008 for paired comparison of V 400/15 vs. A/CO

Protocol Violations, Irregularities:
Two patients (0431-030 and 0433-015) were dispensed study drug, but subsequently withdrew from the study without taking any medication; they returned all the dispensed drug. One gave no explanation. The other withdrew because he wanted to donate blood. Neither patient provided any efficacy or follow-up data, and neither reported adverse events. The applicant excluded these two patients from all safety and efficacy analyses.

Four patients were lost to follow-up during the study. Patient 0430-020 was lost after the first dose was dispensed; he was included in baseline analyses and in the denominator for safety analyses. Patient 0433-041 was lost and provided no data after visit 2 (i.e., after one week). Patients 0403-006 and 0433-010 provided no data after visit 3 (i.e., after two weeks).

Two patients (0430-005 and 0443-021) lost their medication cards and diaries during week 3, although the second one reported he had taken all the medication. Medication use for these patients was imputed using available data together with average use in the first two weeks. No other data were imputed for them.

There was a dispensing error in which a medication card for patient 0438-002 was given to patient 0438-001. Both were discontinued early.

Study appendix M (vol. 33, p. 229-238) lists deviations from inclusion/exclusion criteria. Some summary tabulations are provided in Table 14 below:

Table 14: Protocol Violations
Vicoprofen Study 04

Protocol Violation	Number of Patients
Entry Criteria Violations:	
Not taking regular daily opioids	24
Hypersensitivity to component	5
Significant organ system disease	43 (instances)
Drug abuse history	5
Baseline labs > 7 days before entry	40
Significant lab abnormality	17
Concomitant Medication Violations:	
Used sedative/hypnotic	22
Used steroids	5
Used H-2 blocker	9
Used antipsychotic	1
Used long acting NSAID	3
Treatment Regimen Violations:	
Exceeded 2 rescue in 24 hours	52
Exceeded 4 doses/day	160
Follow-up Violations:	
Missed physical exam	14
Missed lab evaluation	32

Organ system disease is listed only as instances, since a single patient could produce the violation for more than one reason. Many of the labs more than 7 days before entry were done at 8 days. The many violations of treatment regimen were not really under investigator control, and may reflect on the suitability of the protocol regimen. Unfortunately, the applicant did not tabulate violations by treatment arm.

Efficacy Results:
The applicant's figures and tables for the four primary analyses are reproduced on pages 49 through 52. The results are described below:

Average weekly pain relief: This was obtained by computing for each patient the weekly average pain relief. Then that single value for each patient was used compute the arm mean (i.e., the patient is the unit of observation, not each daily score). The values are graphed and tabulated on page 49. The averages are all within a half point of 2 (moderate relief), but there were statistically significant differences between the arms at each week: the V 400/15 arm was rated as providing better relief than the other two arms for the first three weeks, and it beat A/CO in the fourth week as well. The high dose of Vicoprofen was .35 to .36 points better than the lower dose in the first three weeks, .24 points better in the last week.

Global evaluation: This assessment of overall effectiveness was done weekly with the patient and investigator together. The means presented in the graph and table on page 50 are the averages of the weekly values. In that table, results are reported by visit instead of week: visit 2 corresponds to the end of week 1, visit 3 to the end of week 2, etc. The mean global scores were generally in the range of 2 to 3 (fair to good effectiveness). There were statistically significant differences between arms for all four weeks: The V 400/15 arm was ranked higher than the other two for weeks 1, 2 and 4, and V 400/15 also beat A/CO in week 3. The difference between the two Vicoprofen doses was between .20 and .34 points.

Daily Study Drug Use: As with weekly pain relief, the reported value is the mean of individual patient averages for each week. Mean study drug use is graphed and tabulated on page 51. Average use overall was about TID in the first week, but it rose slightly for subsequent weeks to between TID and QID on average. Week 1 was the only interval that showed a statistically significant difference between arms in study drug use: the V400/15 arm used about .3 fewer doses per day than the other two arms.

Daily Supplemental (Rescue) Medication Use: Again, the reported value is the mean of individual patient averages for each week. The applicant's mean supplemental drug usage graph and table are on page 52. The use of a scale from 0 to 1 makes rather small differences visually impressive. With one exception, rescue medication use did not average more than a half dose a day (effectively, once every other day). The only statistically significant difference was in the first week, in which the V 400/15 arm used fewer rescue doses than the other two arms.

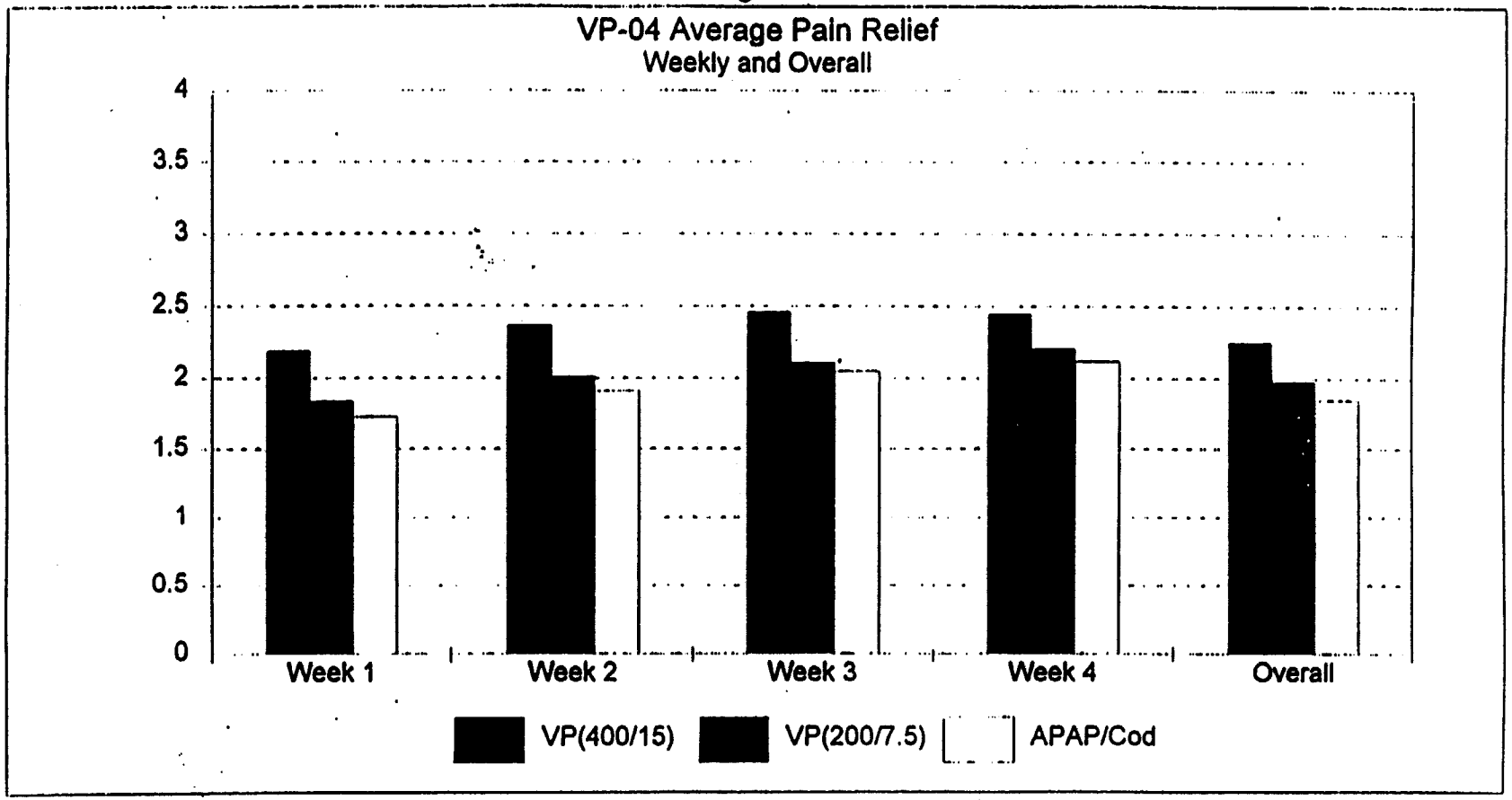
Effect of age, race and gender on efficacy: Weekly mean global efficacy scores tended to be similar for the elderly (age ≥ 65) and non-elderly. Except for week 4, the trend in relative performance, A/CO < V200/7.5 < V 400/15, was consistent in both groups.

Males and females were fairly consistent in their global efficacy scores and relative performance trend between arms.

Global efficacy score averages were generally similar in the Vicoprofen arms for Caucasians and Others. However, A/CO tended to score lower than the Vicoprofen arms for the Caucasians but higher than the Vicoprofen arms for the Others.

Details are reported in the applicant's Integrated Summary of Efficacy (section 7.4.6.2, vol. 1.38, pp. 337-338, and Tables 7.39-7.44 on pp. 388-402).

Figure 2

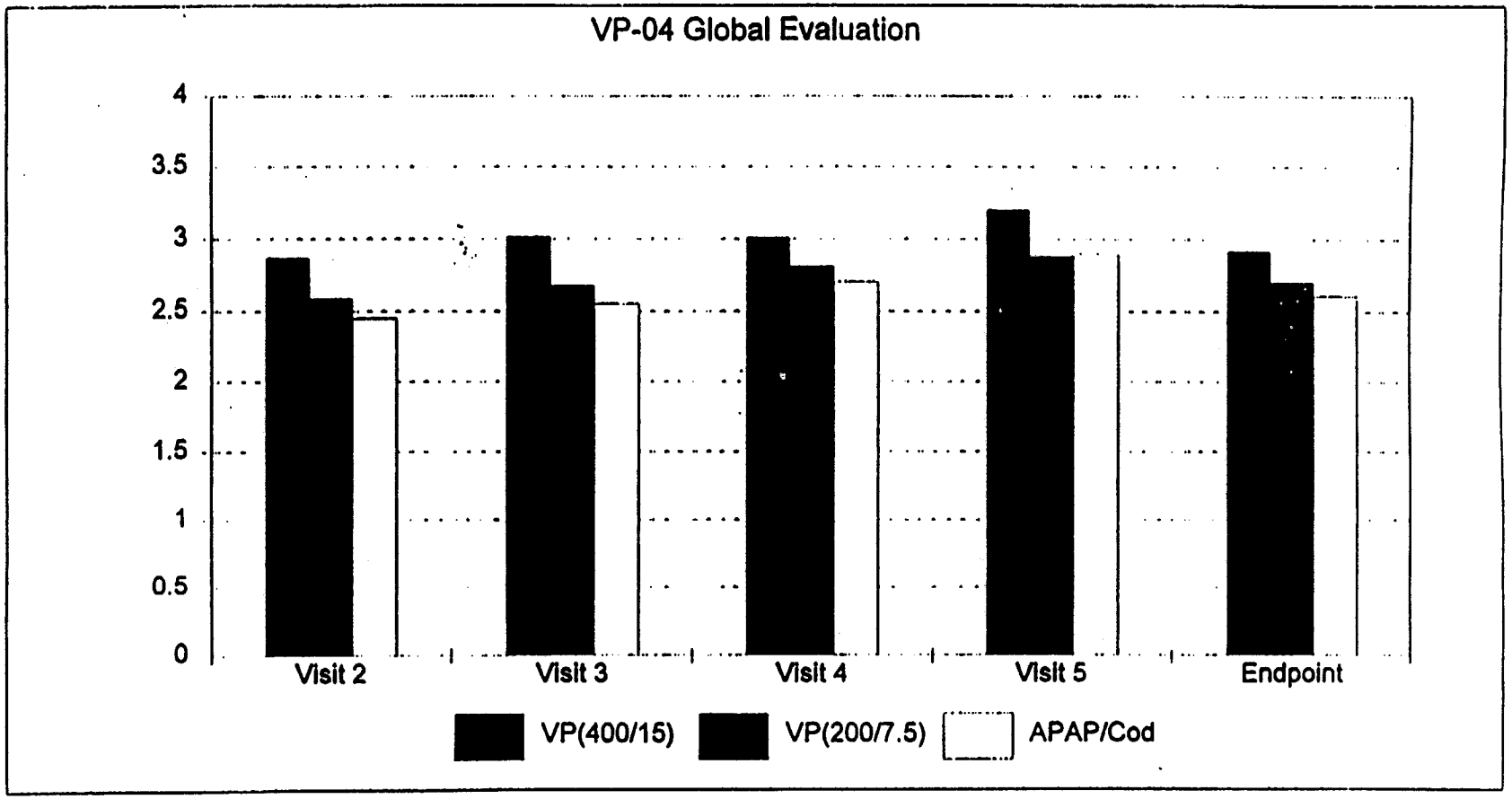


			Week 1		Week 2		Week 3		Week 4		Overall	
Vicoprofen	*mean	sd	2.19	(0.95)	2.37	(0.86)	2.46	(0.79)	2.45	(0.90)	2.25	(0.89)
(400/15 mg)	n	sig	151	A	120	A	115	A	110	A	151	A
Vicoprofen	*mean	sd	1.84	(0.93)	2.01	(0.93)	2.11	(0.96)	2.21	(0.86)	1.98	(0.87)
(200/7.5 mg)	n	sig	154	B	137	B	131	B	122	AB	154	B
Acetaminophen/Codeine	*mean	sd	1.73	(1.04)	1.91	(0.98)	2.05	(0.95)	2.12	(0.99)	1.85	(0.96)
(600/60 mg)	n	sig	157	B	137	B	125	B	115	B	157	B
Treatment p-value				<0.001		<0.001		0.002		0.019		<0.001

Sample sizes (n) represent number of patients remaining at each evaluation time point.

*Means labeled with different letters are significantly different (p<=0.05), but means sharing a letter are not significantly different.

Figure 9

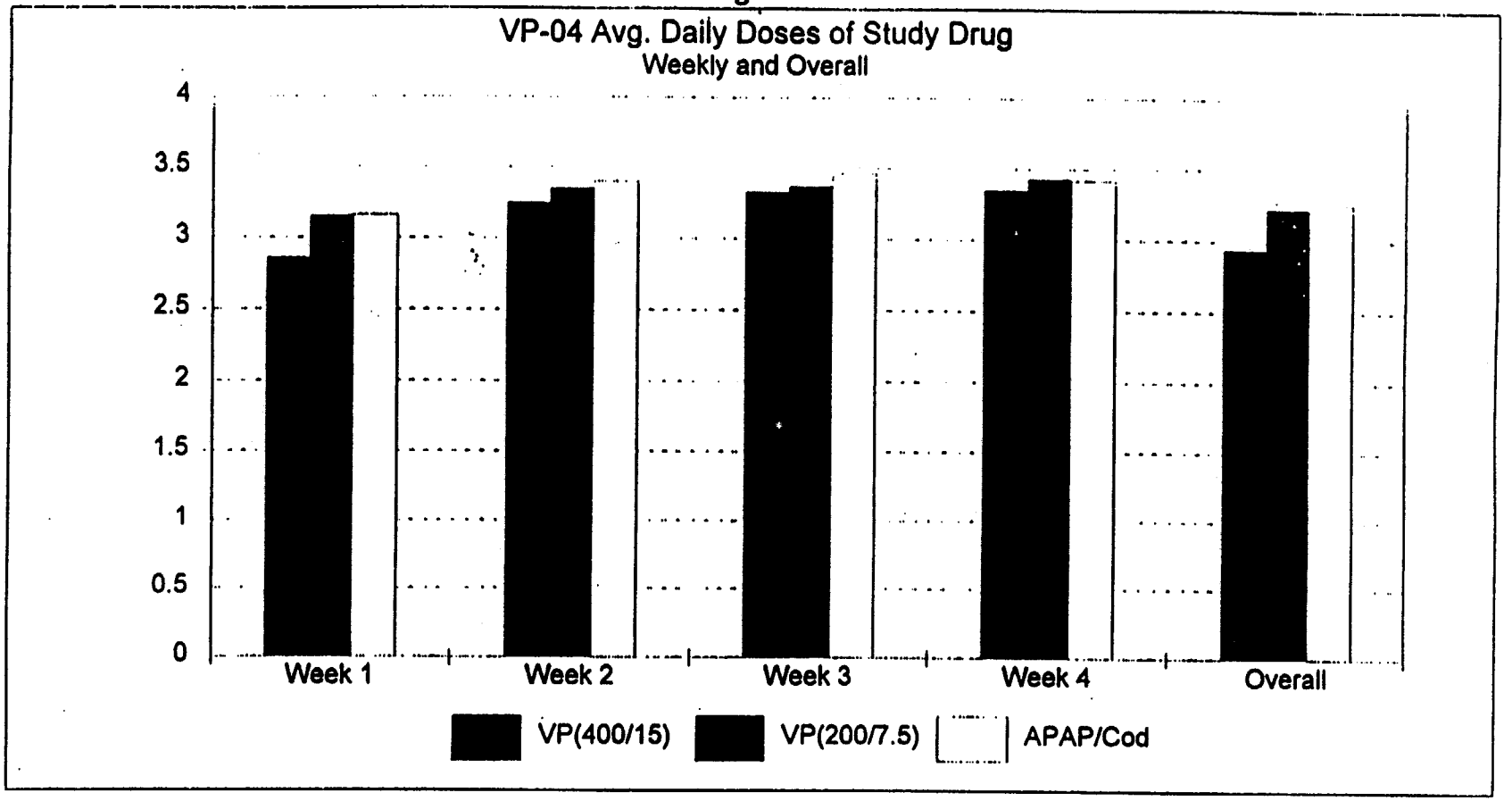


			Visit 2		Visit 3		Visit 4		Visit 5		Endpoint	
Vicoprofen (400/15 mg)	*mean	sd	2.87	(1.10)	3.02	(0.91)	3.01	(0.86)	3.20	(0.92)	2.92	(1.10)
	n	sig	149	A	119	A	113	A	108	A	149	A
Vicoprofen (200/7.5 mg)	*mean	sd	2.59	(0.96)	2.68	(0.99)	2.81	(0.99)	2.88	(1.00)	2.70	(1.06)
	n	sig	153	B	136	B	123	AB	119	B	154	AB
Acetaminophen/Codeine (600/60 mg)	*mean	sd	2.45	(1.03)	2.55	(0.94)	2.70	(0.95)	2.90	(1.03)	2.61	(1.10)
	n	sig	155	B	132	B	122	B	110	B	155	B
Treatment p-value				0.001		< 0.001		0.038		0.026		0.043

Sample sizes (n) represent number of patients remaining at each evaluation time point.

*Means labeled with different letters are significantly different (p<=0.05), but means sharing a letter are not significantly different.

Figure 3

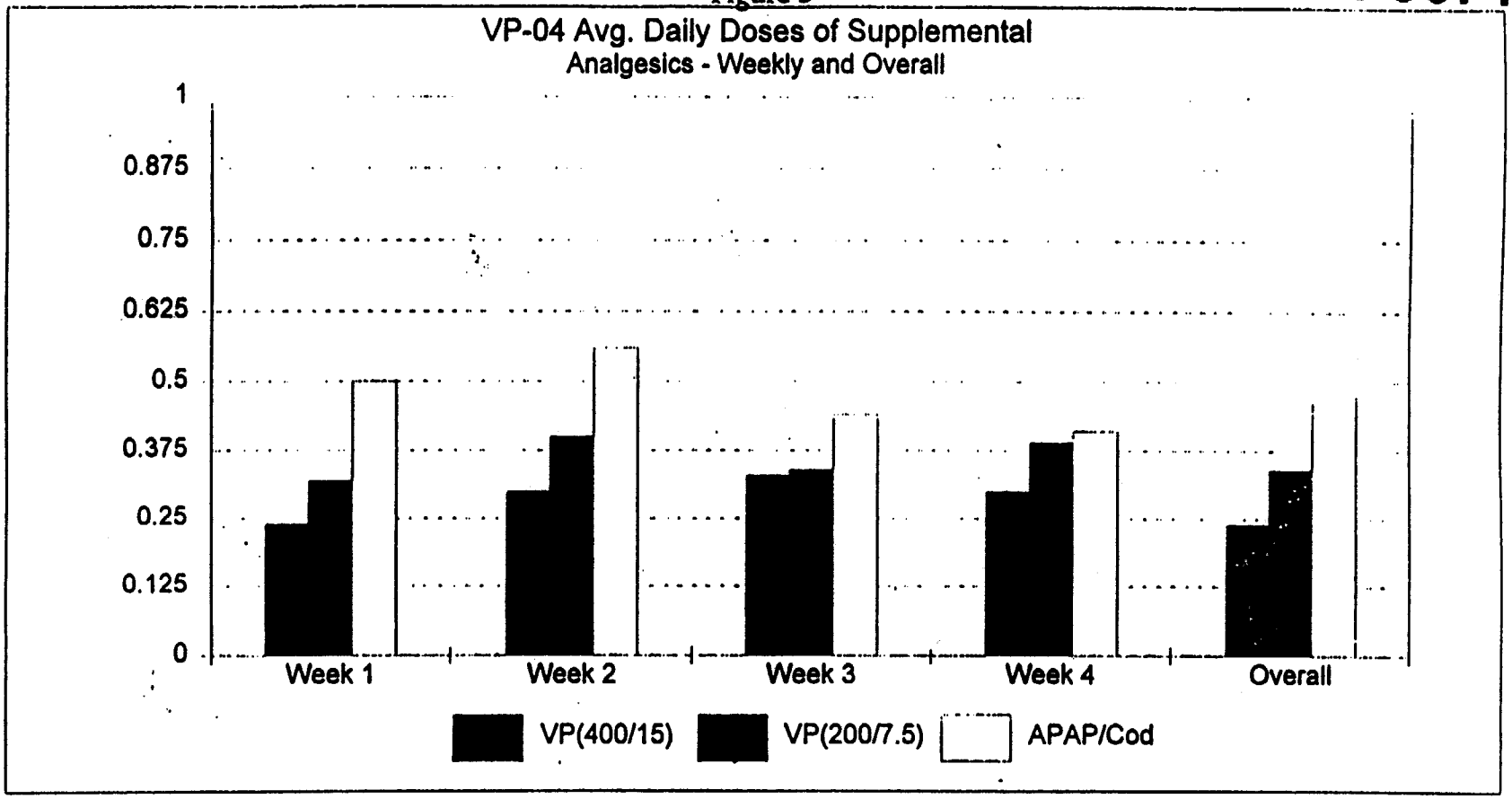


			Week 1		Week 2		Week 3		Week 4		Overall	
Vicoprofen	*mean	sd	2.86	(0.99)	3.25	(0.92)	3.33	(0.86)	3.35	(0.88)	2.94	(0.99)
(400/15 mg)	n	sig	153	A	122	A	115	A	112	A	153	A
Vicoprofen	*mean	sd	3.15	(0.80)	3.35	(0.79)	3.37	(0.85)	3.43	(0.80)	3.23	(0.76)
(200/7.5 mg)	n	sig	155	B	138	A	131	A	122	A	155	B
Acetaminophen/Codeine	*mean	sd	3.16	(0.80)	3.40	(0.80)	3.46	(0.76)	3.42	(0.81)	3.26	(0.75)
(600/60 mg)	n	sig	160	B	138	A	125	A	116	A	160	B
Treatment p-value				0.018		0.422		0.572		0.899		0.029

Sample sizes (n) represent number of patients remaining at each evaluation time point.

*Means labeled with different letters are significantly different ($p<=0.05$), but means sharing a letter are not significantly different.

Figure 5



			Week 1		Week 2		Week 3		Week 4		Overall	
Vicoprofen	*mean	sd	0.24	(0.61)	0.30	(0.61)	0.33	(0.70)	0.30	(0.80)	0.24	(0.49)
(400/15 mg)	n	sig	153	A	122	A	115	A	112	A	153	A
Vicoprofen	*mean	sd	0.32	(0.55)	0.40	(0.73)	0.34	(0.66)	0.39	(0.76)	0.34	(0.58)
(200/7.5 mg)	n	sig	155	B	138	A	131	A	122	A	155	B
Acetaminophen/Codeine	*mean	sd	0.50	(1.06)	0.56	(1.01)	0.44	(0.86)	0.41	(0.88)	0.49	(0.85)
(600/60 mg)	n	sig	160	B	138	A	125	A	116	A	160	B
Treatment p-value				0.014		0.082		0.542		0.165		0.019

Sample sizes (n) represent number of patients remaining at each evaluation time point.

*Means labeled with different letters are significantly different (p<=0.05), but means sharing a letter are not significantly different.

Safety Results:
(See also separate Integrated Safety Review, page 57.)
There were no deaths in the study, but there were four serious adverse events leading to hospitalization. Two were in the V 400/15 arm, and there was one in each of the other two arms:

Patient 0413-009 in the V 400/15 arm was a 30 y.o. female with a history of asthma, bronchitis, morphine allergy and multiple other medical problems. She was hospitalized on day 20 for exacerbation of asthma following exposure to drywall dust. She had taken 3 doses of study medication that day. The blind was broken when her condition worsened. The hospital physician determined she had a history of aspirin allergy, and she was discontinued from the study. Causality assessment was not provided.

Patient 0431-042 in the V 400/15 arm was a 41 y.o. female with chronic back pain and arachnoiditis. She was hospitalized on day 21 for exacerbation of back pain after attempting to lift a vacuum cleaner. She was discontinued from the study. The event resolved in 11 days. Causality assessment was not provided.

Patient 0402-005 in the V 200/7.5 arm was a 34 y.o. male with chronic back pain. He was hospitalized on day 11 for severe anxiety attack. The event resolved in one day. Study drug was interrupted, but he was not discontinued from the study. The investigator felt the event was not related to study drug.

Patient 0431-083 in the A/CO arm was a 53 y.o. male with OA, chronic back pain, depression, insomnia and hypothyroidism. He was hospitalized on day 22 for exacerbation of back pain when his daughter fell on his back. He was discontinued from the study. The event resolved in 27 days. Causality assessment was not provided.

Except for the anxiety attack, there is an identifiable precipitating event for the adverse events. It is possible, with the history of opioid and aspirin allergy, that Vicoprofen may have had contributory role in the asthma case.

Table 15 on page 54 compares adverse event rates for the body systems and COSTART terms for terms with an overall rate of at least 3%. Nominal p-values are provided for comparison of individual COSTART terms.

Table 15: Comparison of Common (≥3% Overall) AE's
Vicoprofen Study 04

	V 400/15 (N=153)	V 200/7.5 (N=156)	A/CO (N=160)	Nominal p-value
Any Adverse Event	83%	80%	81%	.723
Body as a Whole	31%	40%	34%	
Asthenia	3.9%	5.1%	6.3%	.646
Headache	19%	27%	18%	.111
Pain Abd	2.0%	3.8%	5.6%	.241
Cardiovascular	6.5%	4.5%	3.8%	
Vasodilation	3.9%	2.6%	2.5%	.709
Digestive	53%	50%	55%	
Constipation	20%	22%	24%	.595
Diarrhea	**2.0%**	**3.2%**	**10.6%**	**.001**
Dry mouth	3.9%	5.8%	6.3%	.628
Dyspepsia	**3.3%**	**12.0%**	**14.0%**	**.003**
Flatulance	1.3%	4.5%	5.0%	.169
Nausea	**36%**	**21%**	**23%**	**.005**
Vomitting	**13.0%**	**5.1%**	**8.8%**	**.050**
Metabolic	7.8%	4.5%	5.6%	
Edema	7.2%	4.5%	5.0%	.545
Nervous	56%	42%	43%	
Dizziness	**31%**	**14%**	**16%**	**.001**
Insomnia	9.8%	6.4%	5.0%	.235
Nervousness	5.2%	4.5%	3.1%	.645
Somnolence	29%	22%	23%	.320
Respiratory	10.5%	9.6%	8.8%	
Rhinitis	3.3%	2.6%	3.1%	.928
Skin & Appendages	29%	11%	11%	
Pruritus	**18.0%**	**8.3%**	**7.5%**	**.004**
Sweating	**10.5%**	**3.2%**	**1.3%**	**.001**
Special Senses	7.2%	3.8%	3.8%	
Urogenital	5.2%	3.8%	2.5%	

The findings concerning pruritus, sweating, nausea, vomiting, and dizziness would be consistent with higher peak opioid level in the V 400/15 arm. However, vasodilation and somnolence were not markedly higher in the V 400/15 arm. Constipation was about the same across arms.

As noted above, the V 400/15 arm had a higher rate of discontinuation for adverse events. The main AE's associated with the discontinuations were nausea and dizziness (for details see Table 19 on page 62 in the Integrated Safety Review).

DISCUSSION & CONCLUSIONS:

Since studies 07 and 08 used an alternate formulation with less hydrocodone, these studies cannot provide direct safety evidence for the proposed product. But they can be construed as supporting single and total daily doses of the proposed product that provide an amount of hydrocodone that does not exceed the amount provided in those two studies. In a general way, those studies do suggest that some combination of ibuprofen and hydrocodone can be a feasible alternative to an APAP/codeine combination.

It is interesting to contrast the burn pain study (Study 08) with the two surgical pain studies. All three started with an average of about two doses on the first day. However, the burn patients increased dosing to between 5 and 6 doses/day, while usage did not increase in surgical patients. One explanation might be that there was sustained pain in the burn patients vs. subsiding pain in the surgical patients. Usage pattern in burn patients after the first day (viz., 5 to 6 doses/day) may be the best indication of what dosing is required to cover significant pain.

In Study 04, the use of V 400/15 according to the protocol dosing schedule provided greater analgesic efficacy than V 200/7.5, but it also produced more DOAE's and greater opioid side effects. However, the greater mean weight in the low-dose arm could have diminished the drug effect, leading to an overestimate of the difference in effect between doses.

It is not clear whether the better efficacy result for the higher dose of Vicoprofen in Study 04 represents a greater analgesic effect, or merely longer duration of effect. The recommended dosing interval (TID) was long compared to the remedication times seen in single-dose and compared to what was used at "steady state" in the burn patients. This suggests that the dosing interval may have been inadequate for many patients. Study 04 did not separately rate best analgesia or trough analgesia in relation to dosing, as did the other repeated-dose studies. This makes it difficult to interpret just how the higher dose produced its better analgesic result. If the high dose truly provided greater relief of pain, one might have seen higher peak effect rates for the high dose. If the higher dose only extended the effect, then peak ratings would have been similar to the lower dose, but trough ratings would have been better. It is possible that the same daily dose allowed in the high dose arm (1200 mg ibuprofen/45 mg hydrocodone) given as smaller more frequent doses, i.e., as V 200/7.5 every 4 hours, could have provided equivalent analgesia but with lower peak concentrations and less toxicity.

In Study 04 the adverse event profile of the high Vicoprofen dose was more suggestive of an opioid than the profile at the lower dose.

RECOMMENDATIONS:

These studies provide sufficient safety support (at least 300 patients exposed for about a month) for the dose used in the low-dose arm of Study 04, viz., a dose of one tablet, and a maximum dose of 3 to 4 tablets per day. The two-tablet dose was used chronically in fewer than 200 patients and produced greater toxicity, albeit slightly better efficacy. The two-table single dose should not be recommended.

While a regimen of one tablet every 4 to 6 hours might be expected to work well, it is partly speculation. The applicant should be asked to make a Phase 4 commitment to test this dosing, or others, to provide a better foundation for repeated-use dosing instructions.

These studies do not provide substantial evidence for efficacy in any of the usual NSAID chronic pain indications. Therefore, the indication should reflect the product's appropriateness only for short-term use.

The applicant should provide a re-analysis of efficacy data from Study 04 with Dr. Fiddes' data removed, and including a tabulation of protocol violations by treatment group.

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