Vicoprofen Appendicies

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Appendix A: Contents of Submission Volumes

	Vicoprofen Jackets Index, NDA #20-716	
Subm. Date	Vol. No.	Description
4-25-96	1	Contents, Annotated Labeling, Summary
4-25-96	2 -	Chemistry
4-25-96	4	Labeling
4-25-96	5	Toxicology Summary
4-25-96	9	Human PK Summary
4-25-96	9 -	VP-30 (PK- wet vs. dry granulation)
4-25-96	12 -	VP-27 (PK-bioavialability)
4-25-96	15 -	VP-02 (PK-component interaction)
4-25-96	16 -	VP-22 (PK/PD Dental Pain)
4-25-96	18	Clinical Contents
4-25-96	18	VP-09 SD Postop
4-25-96	19	VP-29 SD Postop
4-25-96	20	VP-23 SD Postop
4-25-96	21	VP-21 SD Postop
4-25-96	22 -	VP-13 SD Postop
4-25-96	24 -	VP-01 SD Postop (VP-0101, VP-0102, VP-0103, VP-0104)
4-25-96	26	VP-12 SD Back Surgery
4-25-96	27	VP-14 Repeated-Dose Postop
4-25-96	27 -	VP-07 Repeated-Dose Postop
4-25-96	29	VP-08 Repeated-Dose Burn Pain
4-25-96	30 -	VP-04 Repeated-Dose Chronic Pain
4-25-96	38	Ongoing Studies: VP-28, VP-09-0902, VP-26-2601
4-25-96	38	Integreated Efficacy Summary
4-25-96	39	Integrated Safety Summary
4-25-96	39	Drug Abuse
4-25-96	40	Safety Update
4-25-96	40 -	Statistical
4-25-96	62	CR Tabulations Contents
4-25-96	62 -	CR Tabulations VP-01, VP-02, VP-04
4-25-96	67	CR Tabulations VP-07, VP-08, VP-09
4-25-96	68	CR Tabulations VP-12, VP-13, VP-14, VP-21
4-25-96	69	CR Tabulations VP-22, VP-23, VP-27
4-25-96	70	CR Tabulations VP-29, VP-30
4-25-96	71	CRF Section Contents
4-25-96	71	CRF VP-27, VP-04
4-25-96	72-75	CRF VP-04,
4-25-96	75	CRF VP-07, VP-08, VP-14
9-19-96	4.1	MedWatch Tabulations for Hydrocodone & Ibuprofen

MEMORANDUM FOR THE RECORD

March 13, 1987

Acetaminophen (APAP) and codeine combination products are currently approved in the following strengths and dosages

APAP/codeine	Dosage
325 or 300 mg - 7.5 mg	1 or 2 every 4 hours
325 or 300 mg - 15 mg	
325 or 300 mg - 30 mg	
325 or 300 mg - 60 mg	
325 mg - 45 mg	1 every 4 hours
650 mg - 30 mg	1 every 4 hours
	1 every 4 hours

Acetaminophen and Hydrocodone Bitartrate (HCB) in combination is currently approved in the following strength and dose

APAP	HCB	
500 mg	5 mg	1 every 6 hours or 1 every 4 hours, may increase to 2 every 6 hours (max. of 8 in 24 hours)

Principles of Substitution*

1. For purposes of substitution, the potency ratio of codeine to HCB is 6:1.

2. The maximum currently approved single dose of codeine is 60 mg; therefore the maximum approvable single dose of HCB is 10 mg.

3. Since the currently approved maximum total daily dose of codeine is 360 mg (60mg every 4 hours = 6x60 mg), and based on the 6:1 ratio the maximum total daily dose of HCB may not exceed 60 mg.

4. Direct substitutions of HCB at the above ratio may be made for approved strengths of codeine.

Codeine	HCB
15 mg	2.5 mg
30 mg	5 mg
45 mg	7.5 mg
60 mg	10 mg

5. The total maximum daily dose of APAP may not exceed 4000 mg and a single dose may not exceed 1000 mg.

6. Dosing schedules for solid oral dosage forms should read either:

   1 tablet every 4-6 hours not to exceed _x_ dosage units a day

   or

   1 or 2 tablets every 4-6 hours not to exceed _x_ a day

Dosing schedules should be selected based on the limitations of APAP and HCB set forth above.

7. HCB is not approved for use in children therefore no HCB product can be approved for pediatric indications without additional studies.

8. Liquid forms of APAP/HCB may be approvable if they are targeted towards adults and if they conform to the APAP/HCB dosage limits and recommendations cited above.

9. Based on the above recommendations it is clear that there are listed APAP/codeine and/or APAP/HCB products that may be referred to in ANDA suitability petitions for the proposed products mentioned on the attached page. In addition, if additional solid oral dosage forms or liquid dosage forms of APAP/HCB conform to the above recommendations that are requested based on an approved APAP/coedine or APAP/HCB they would also be found ANDA suitable. Where petitions are submitted that are <u>not</u> direct substitutions of HCB for codeine or where other changes are requested, these petitions will need to be considered individually..

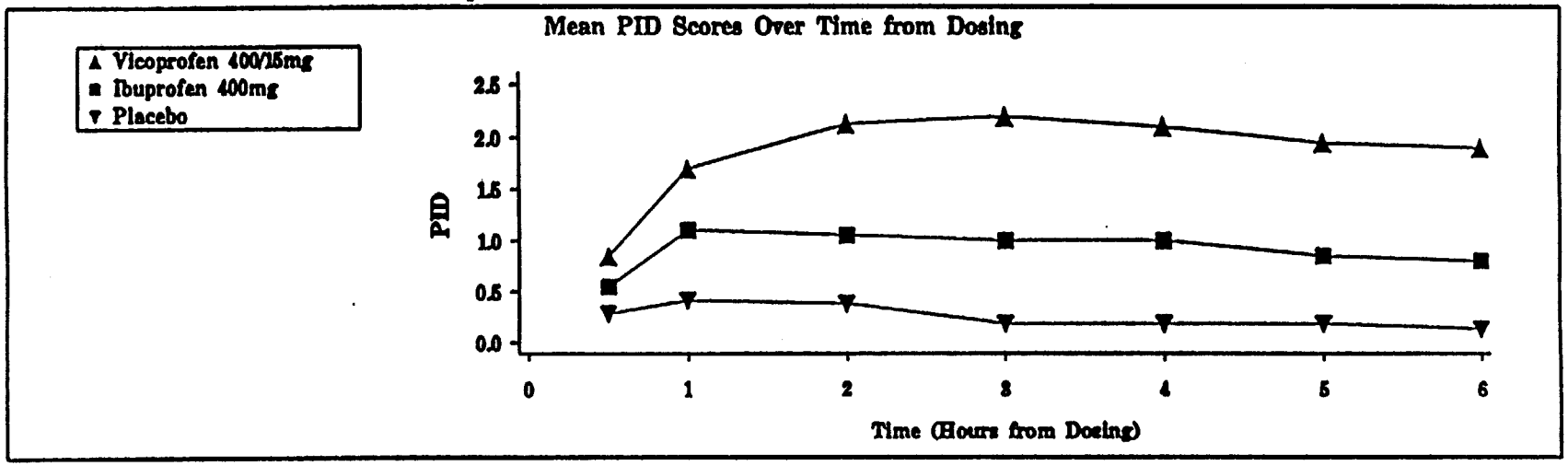
Concur:

Paul Leber, M.D. — 3/13/87 date

Robert Temple, M.D. — 3/13/87 date

* See enclosed 3/10/87 memorandum from Dr. Temple to Mr. Morrison

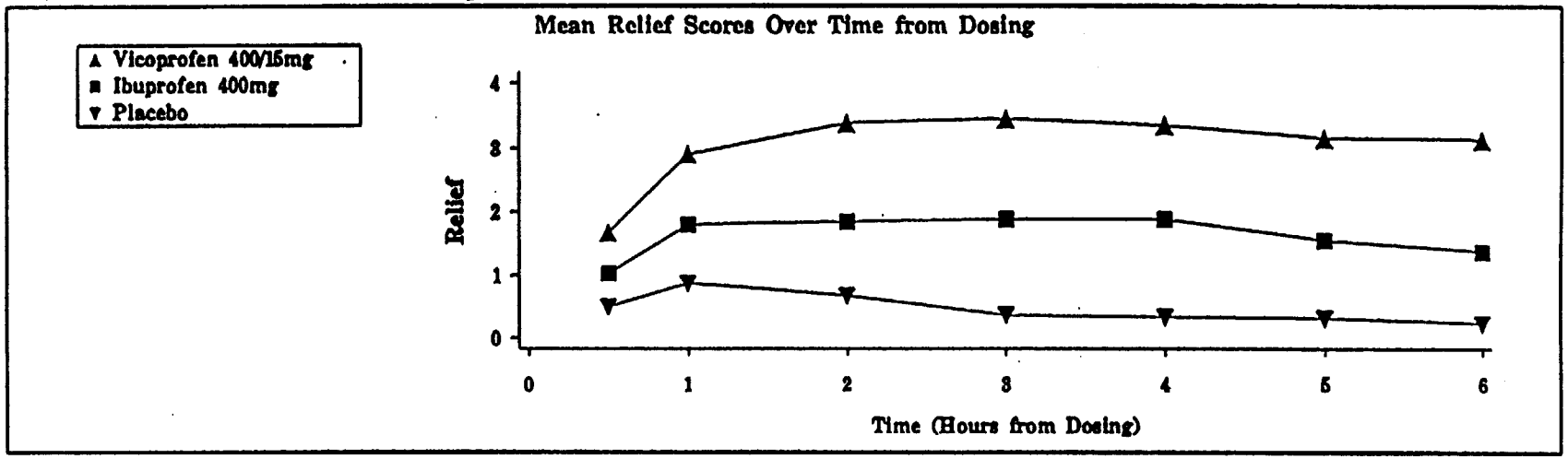
FIGURE 1
VP-09-0901 PID Scores
Means (Standard Deviations), Sample Sizes, and Fisher's Protected LSD Comparisons
All Acceptable Patients with Baseline Observations Carried-Forward



Treatment	Assessment Time Point (in Hours from Dosing)													
	0.5		1		2		3		4		5		6	
Vicoprofen 400/15mg (n=40)(e)	0.85 [40](a)	(0.70) A(d)	1.70 [40]	(0.72) A	2.13 [40]	(0.69) A	2.20 [40]	(0.61) A	2.10 [40]	(0.63) A	1.95 [40]	(0.64) A	1.90 [40]	(0.67) A
Ibuprofen 400mg (n=40)	0.55 [40]	(0.60) B	1.10 [40]	(0.74) B	1.05 [39]	(0.88) B	1.00 [34]	(0.85) B	1.00 [30]	(0.78) B	0.85 [30]	(0.74) B	0.80 [30]	(0.69) B
Placebo (n=39)	0.28 [39]	(0.56) B	0.41 [39]	(0.79) C	0.38 [25]	(0.63) C	0.18 [20]	(0.56) C	0.18 [12]	(0.51) C	0.18 [7]	(0.51) C	0.13 [7]	(0.41) C
Treatment P-Value(b)	<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001	
Trt*Baseline P-Value(c)	0.914		0.332		0.205		0.343		0.198		0.105		0.071	
RMS Error(b)	0.614		0.693		0.693		0.646		0.626		0.601		0.557	

(a) Represents the number of subjects evaluating efficacy at that time point (i.e. number of active subjects).
(b) Model: PID $= \mu + Trt(i) + Baseline(j) + Error$
(c) Model: PID $= \mu + Trt(i) + Baseline(j) + Trt*Baseline(ij) + Error$
(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.

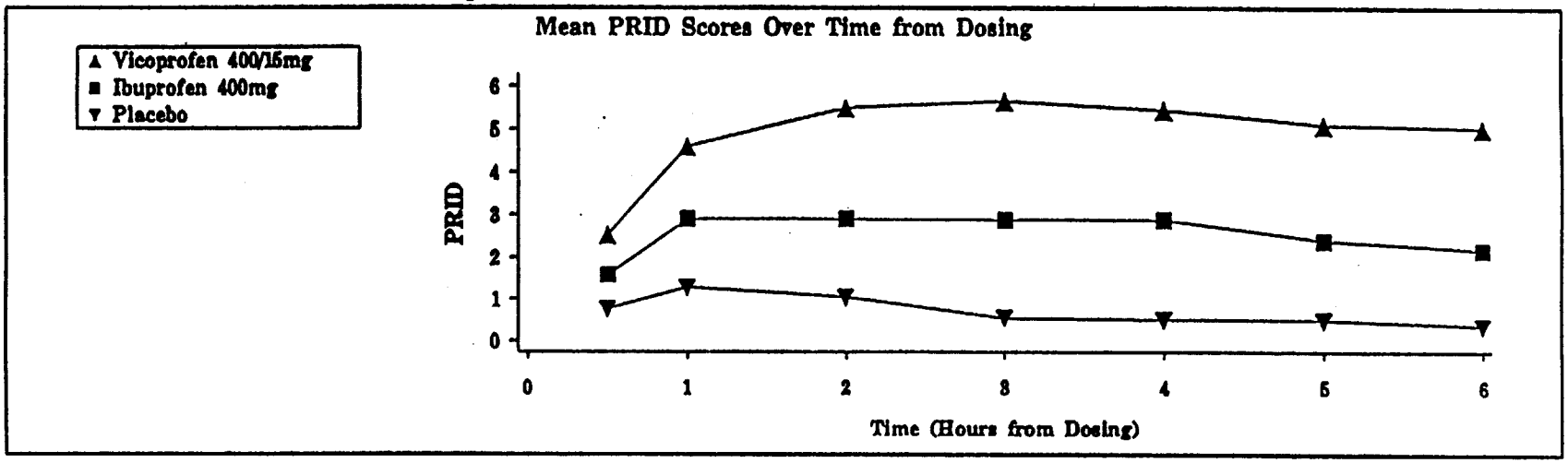
FIGURE 2
VP-09-0901 Pain Relief Scores
Means (Standard Deviations), Sample Sizes, and Fisher's Protected LSD Comparisons
All Acceptable Patients with Baseline Observations Carried-Forward



Treatment	Assessment Time Point (in Hours from Dosing)													
	0.5		1		2		3		4		5		6	
Vicoprofen 400/15mg (n=40)(d)	1.68 [40](a)	(1.23) A(c)	2.90 [40]	(0.84) A	3.38 [40]	(0.63) A	3.45 [40]	(0.55) A	3.35 [40]	(0.58) A	3.15 [40]	(0.74) A	3.13 [40]	(0.65) A
Ibuprofen 400mg (n=40)	1.03 [40]	(1.05) B	1.80 [40]	(1.09) B	1.85 [39]	(1.29) B	1.88 [34]	(1.26) B	1.88 [30]	(1.24) B	1.55 [30]	(1.15) B	1.38 [30]	(1.10) B
Placebo (n=39)	0.49 [39]	(0.91) C	0.87 [39]	(1.06) C	0.67 [25]	(1.01) C	0.36 [20]	(0.87) C	0.33 [12]	(0.87) C	0.31 [7]	(0.83) C	0.23 [7]	(0.63) C
Treatment P-Value(b)	<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001	
RMS Error(b)	1.073		1.002		1.013		0.943		0.938		0.925		0.824	

(a) Represents the number of subjects evaluating efficacy at that time point (i.e. number of active subjects).
(b) Model: REL $= \mu + Trt(i) + Error$
(c) 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.
(d) Represents the number of subjects analyzed for efficacy based on extrapolated data.

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

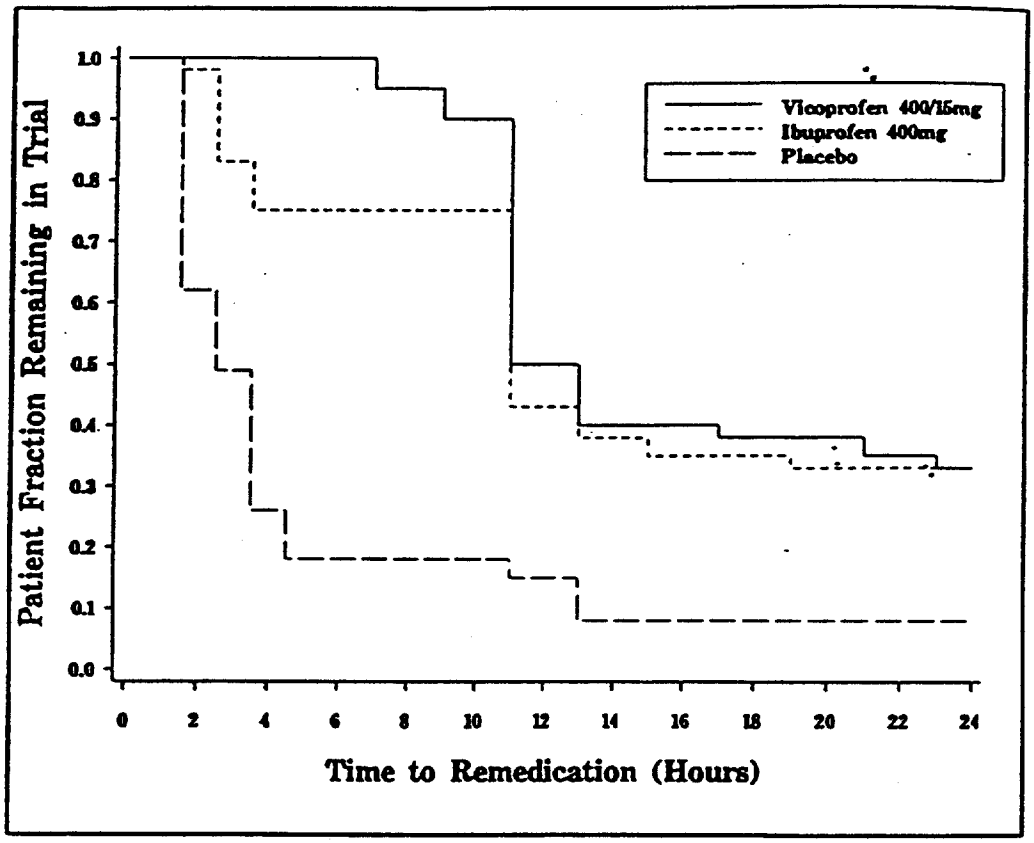


Treatment	Assessment Time Point (in Hours from Dosing)													
	0.5		1		2		3		4		5		6	
Vicoprofen 400/15mg (n=40)(e)	2.53 (1.87) [40](a) A(d)		4.60 (1.48) [40] A		5.50 (1.24) [40] A		5.65 (1.08) [40] A		5.45 (1.13) [40] A		5.10 (1.28) [40] A		5.03 (1.23) [40] A	
Ibuprofen 400mg (n=40)	1.58 (1.60) [40] B		2.90 (1.77) [40] B		2.90 (2.12) [39] B		2.88 (2.05) [34] B		2.88 (1.96) [30] B		2.40 (1.84) [30] B		2.18 (1.72) [30] B	
Placebo (n=39)	0.77 (1.44) [39] C		1.28 (1.76) [39] C		1.05 (1.59) [25] C		0.54 (1.39) [20] C		0.51 (1.35) [12] C		0.49 (1.32) [7] C		0.36 (1.01) [7] 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		0.139		0.758		0.742		0.280		0.617	
RMS Error(b)	1.653		1.659		1.674		1.658		1.631		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 4

Product Limit Plot of Time-to-Remedication
(All Evaluable Subjects)



Treatment	Calculated Time-to-Remedication	
	Median Time [1] (decimal hours)	95%-CI [2] (decimal hours)
Vicoprofen 400/15mg	11.58 A [3]	10.75 - 23.67
Ibuprofen 400mg	11.42 A	10.58 - 19.08
Placebo	2.27 B	1.58 - 3.00

[1] Kaplan-Meier estimate (see Miller, Survival Analysis, page 75)

[2] Method of Simon & Lee, Cancer Treat Rep 66:37-42, 1982

[3] Logrank test applied as in Fisher's PLSD.

Date: 27FEB96
Time: 16:09

Knoll Pharmaceuticals
Protocol #: VP-09

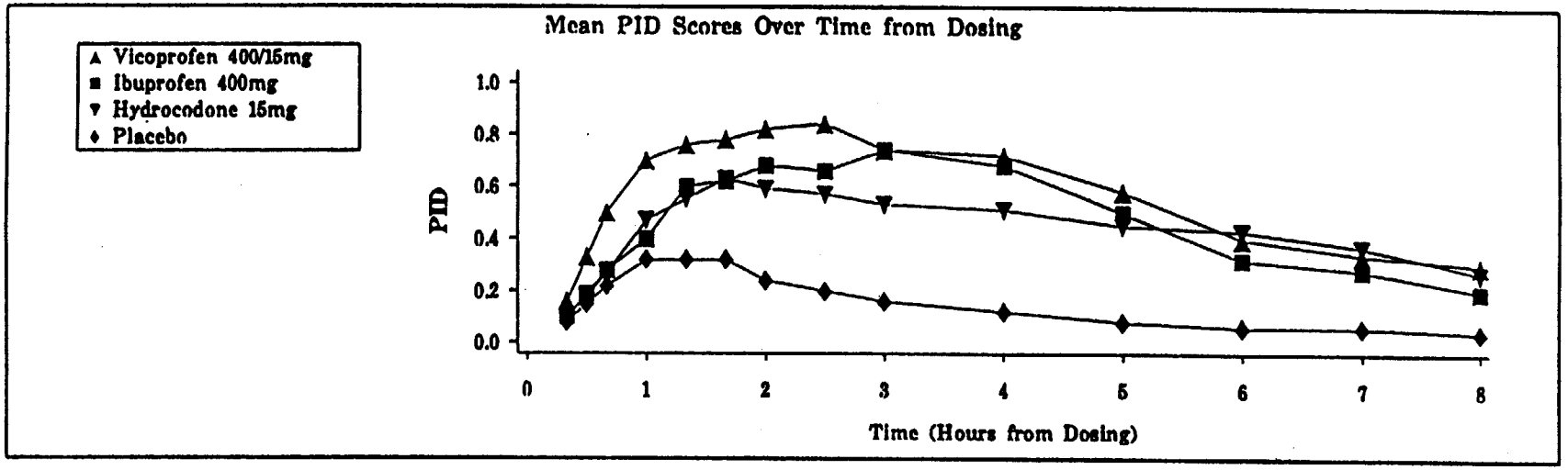
Table 1

Estimated Onset of Pain Relief (on-PR)

Treatment	PRID at 30 min			Estimated on-PR	
	Mean	SD	N	Time in min	95%-CI in min
Vicoprofen 400/15mg	2.53	1.87	40	11.9 A (1)	9.6 - 15.6
Ibuprofen 400mg	1.58	1.60	40	19.0 B	14.4 - 28.2
Placebo	0.77	1.44	39	39.0 C	24.3 - 99.3

Note: Onset = 30/PRID30 (Combined pain relief and pain intensity difference scores at 30 minutes).
(1) Separation based on 30 minute PRID LSmeans.

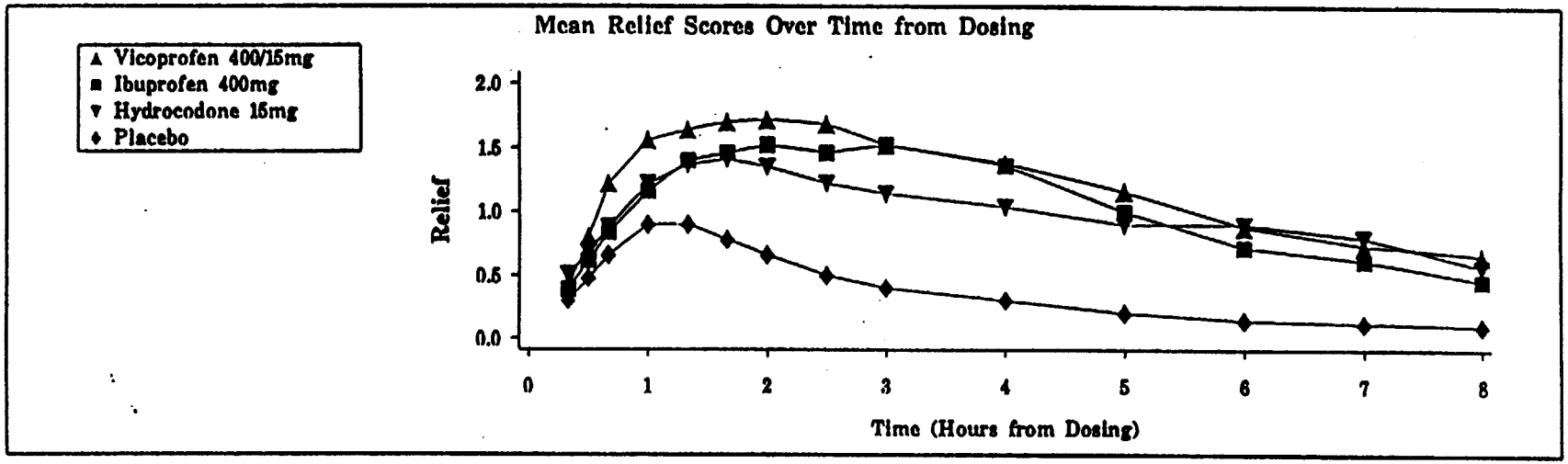
FIGURE 1
VP-13-1301 PID Scores
Means (Standard Deviations), Sample Sizes, and Fisher's Protected LSD Comparisons
All Acceptable Patients with Baseline Observations Carried-Forward



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)	0.16 (0.42) [50](a)A(d)	0.33 (0.50) [50] A	0.50 (0.71) [50] A	0.70 (0.79) [50] A	0.76 (0.85) [45] A	0.78 (0.89) [39] A	0.82 (0.98) [37] A	0.84 (0.98) [32] A	0.74 (0.96) [29] A	0.72 (0.97) [27] A	0.58 (0.86) [23] A	0.40 (0.76) [18] A	0.34 (0.69) [13] A	0.30 (0.68) [13] A
Ibuprofen 400mg (n=60)	0.10 (0.42) [50] A	0.19 (0.45) [50] A	0.28 (0.57) [50] A	0.40 (0.67) [50] B	0.60 (0.76) [44] A	0.62 (0.78) [38] A	0.68 (0.84) [36] A	0.66 (0.80) [32] A	0.74 (0.85) [29] A	0.68 (0.91) [26] A	0.50 (0.84) [21] A	0.32 (0.74) [17] A	0.28 (0.61) [12] AB	0.20 (0.53) [10] A
Hydrocodone 15mg (n=49)	0.10 (0.31) [49] A	0.18 (0.33) [49] A	0.27 (0.45) [49] A	0.47 (0.62) [49] AB	0.55 (0.61) [45] AB	0.63 (0.76) [39] A	0.59 (0.81) [38] A	0.57 (0.79) [30] A	0.53 (0.79) [25] A	0.51 (0.79) [21] A	0.45 (0.77) [19] A	0.43 (0.74) [19] A	0.37 (0.70) [17] A	0.27 (0.64) [11] A
Placebo (n=60)	0.08 (0.27) [50] A	0.15 (0.32) [50] A	0.22 (0.51) [50] A	0.32 (0.65) [50] B	0.32 (0.59) [35] B	0.32 (0.55) [27] B	0.24 (0.43) [26] B	0.20 (0.45) [20] B	0.16 (0.42) [14] B	0.12 (0.33) [10] B	0.08 (0.27) [7] B	0.06 (0.24) [3] B	0.06 (0.24) [3] B	0.04 (0.20) [3] A
Treatment P-Value(b)	0.713	0.127	0.062	0.033	0.019	0.019	0.002	<0.001	<0.001	<0.001	0.003	0.020	0.040	0.087
Trt*Baseline P-Value(c)	0.208	0.098	0.162	0.141	0.103	0.068	0.048	0.048	0.170	0.476	0.406	0.579	0.389	0.926
RMS Error(b)	0.360	0.404	0.559	0.671	0.696	0.740	0.766	0.765	0.774	0.788	0.716	0.649	0.588	0.541

a) Represents the number of subjects evaluating efficacy at that time point (i.e. number of active subjects).
b) Model: PID = μ + Trt(i) + Baseline(j) + Error
c) Model: PID = 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.

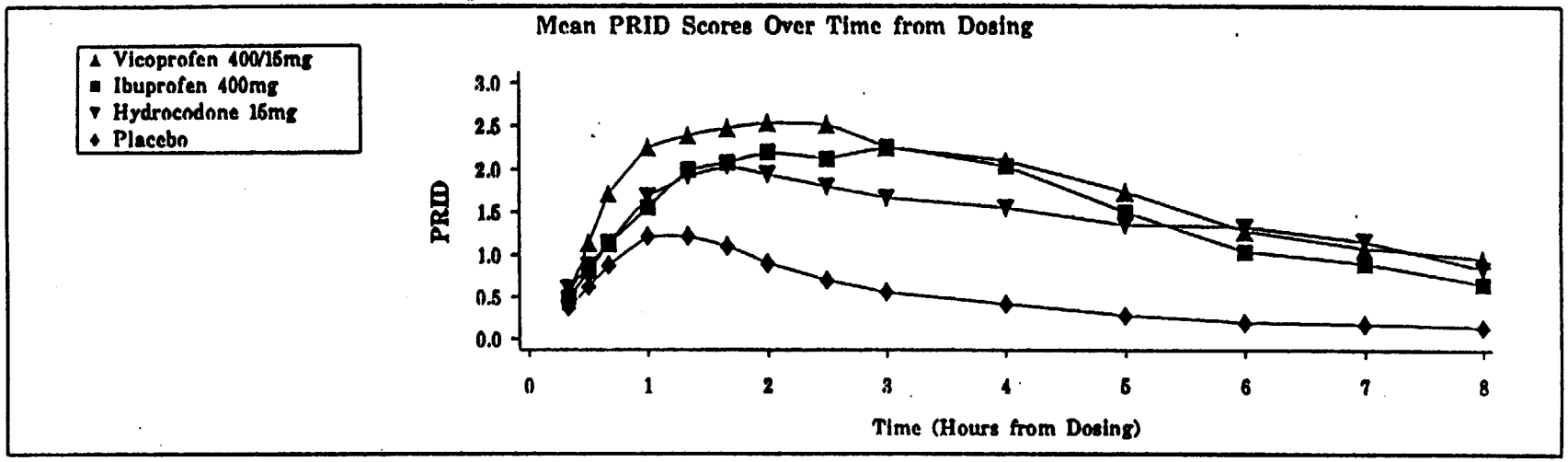
FIGURE 2
VP-13-1301 Pain Relief Scores
Means (Standard Deviations), Sample Sizes, and Fisher's Protected LSD Comparisons
All Acceptable Patients with Baseline Observations Carried-Forward



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)(d)	0.40 (0.76) [50](a)A(c)	0.81 (0.85) [50] A	1.22 (1.20) [50] A	1.56 (1.33) [50] A	1.64 (1.38) [45] A	1.70 (1.40) [39] A	1.72 (1.57) [37] A	1.68 (1.63) [32] A	1.52 (1.66) [29] A	1.38 (1.70) [27] A	1.16 (1.56) [23] A	0.88 (1.41) [18] A	0.74 (1.37) [13] A	0.66 (1.[illegible]) [13] A
Ibuprofen 400mg (n=50)	0.40 (0.70) [50] A	0.62 (0.72) [50] A	0.84 (1.00) [50] A	1.16 (1.08) [50] AB	1.40 (1.28) [44] A	1.46 (1.33) [38] A	1.52 (1.40) [36] A	1.46 (1.50) [32] A	1.52 (1.61) [29] A	1.36 (1.66) [26] A	1.00 (1.53) [21] A	0.72 (1.36) [17] A	0.62 (1.28) [12] A	0.46 (1.[illegible]) [10] A
Hydrocodone 15mg (n=49)	0.51 (0.68) [49] A	0.69 (0.74) [49] A	0.88 (0.95) [49] A	1.22 (1.09) [49] AB	1.37 (1.13) [45] AB	1.41 (1.17) [39] A	1.35 (1.28) [38] A	1.22 (1.37) [30] A	1.14 (1.44) [25] A	1.04 (1.41) [21] A	0.90 (1.33) [19] A	0.90 (1.33) [19] A	0.80 (1.27) [17] A	0.57 (1.[illegible]) [11] A
Placebo (n=50)	0.30 (0.61) [50] A	0.48 (0.63) [50] A	0.66 (0.89) [50] A	0.90 (1.09) [50] B	0.90 (1.18) [35] B	0.78 (1.17) [27] B	0.66 (1.08) [26] B	0.50 (1.07) [20] B	0.40 (1.03) [14] B	0.30 (0.79) [10] B	0.20 (0.70) [7] B	0.14 (0.57) [3] B	0.12 (0.48) [3] B	0.10 (0.[illegible]) [3] A
Treatment P-Value(b)	0.514	0.162	0.051	0.042	0.029	0.003	<0.001	<0.001	<0.001	<0.001	0.002	0.006	0.016	0.058
RMS Error(b)	0.690	0.743	1.017	1.150	1.247	1.272	1.345	1.411	1.455	1.439	1.323	1.215	1.156	1.091

) Represents the number of subjects evaluating efficacy at that time point (i.e. number of active subjects).
) Model: REL = μ + Trt(I) + Error
) 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.
.) 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

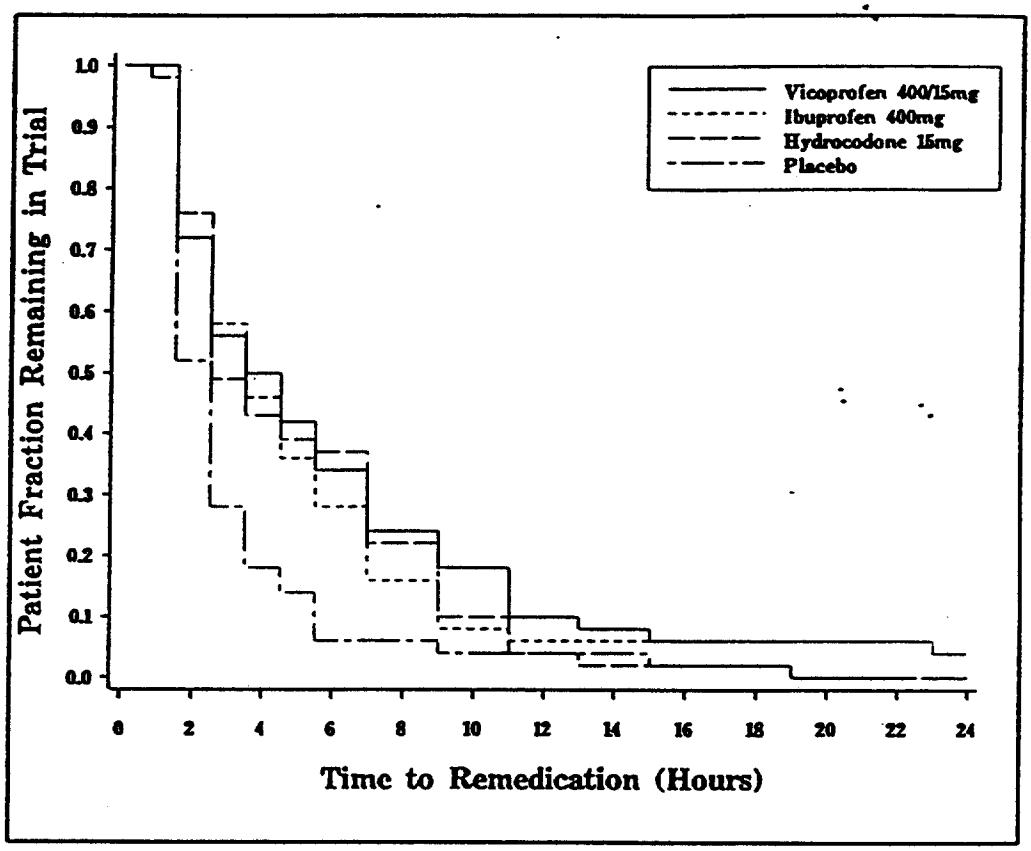


Treatment	Assessment Time Point (in Hours from Dosing)													
	0.33	0.5	0.67	1	1.33	1.67	2	2.5	3	4	5	6	7	8
Vicoprofen 400/15mg (n=50)(e)	0.56 (1.13) [50](a)A(d)	1.14 (1.31) [50] A	1.72 (1.85) [50] A	2.26 (2.07) [50] A	2.40 (2.17) [45] A	2.48 (2.23) [39] A	2.54 (2.48) [37] A	2.52 (2.55) [32] A	2.26 (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 (1.91) [13] A
Ibuprofen 400mg (n=50)	0.50 (1.05) [50] A	0.81 (1.13) [50] A	1.12 (1.51) [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) [46] 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 (0.51) [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. 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 4

Product Limit Plot of Time-to-Remedication (All Evaluable Subjects)



Treatment	Calculated Time-to-Remedication	
	Median Time [1] (decimal hours)	95%-CI [2] (decimal hours)
Vicoprofen 400/15mg	3.96 A [3]	2.50 – 5.00
Ibuprofen 400mg	3.54 A	2.50 – 4.75
Hydrocodone 15mg	2.75 A	2.00 – 6.00
Placebo	2.00 B	1.33 – 2.33

[1] Kaplan-Meier estimate (see Miller, Survival Analysis, page 75)

[2] Method of Simon & Lee, Cancer Treat Rep 66:37-42, 1982

[3] Logrank test applied as in Fisher's PLSD.

Date: 29APR96
Time: 13:53

Knoll Pharmaceuticals
Protocol #: VP-13

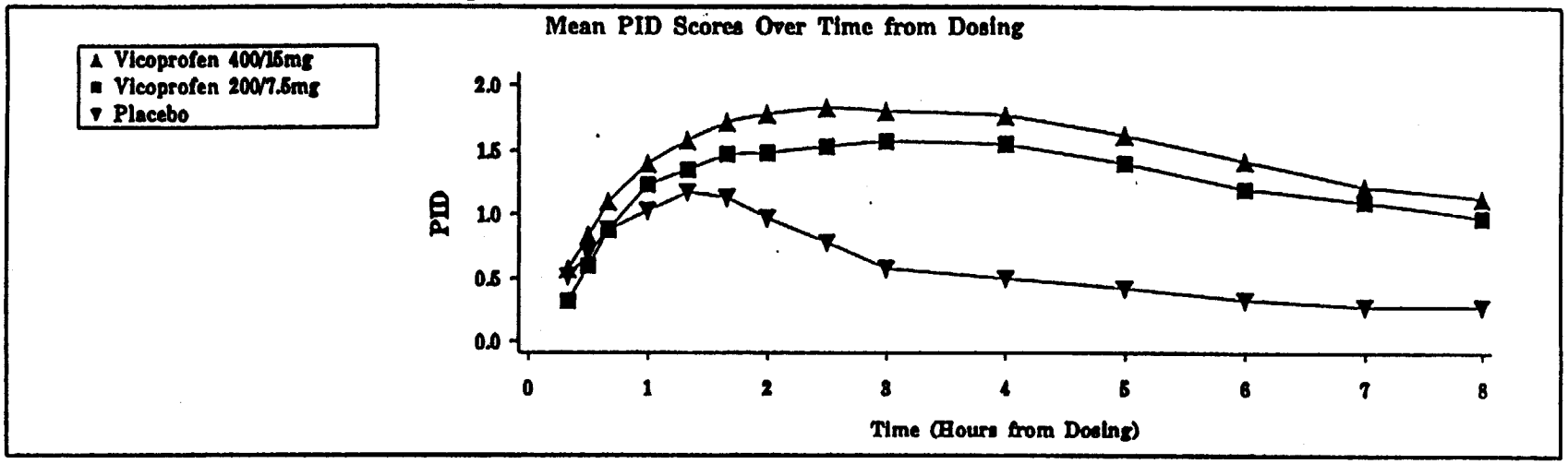
Table 1

Estimated Onset of Pain Relief (on-PR)

Treatment	PRID at 30 min			Estimated on-PR	
	Mean	SD	N	Time in min	95%-CI in min
Vicoprofen 400/15mg	1.14	1.31	50	26.3 A (1)	19.8 - 39.1
Ibuprofen 400mg	0.81	1.13	50	37.0 A	26.5 - 61.3
Hydrocodone 15mg	0.88	1.02	49	34.2 A	25.6 - 51.4
Placebo	0.63	0.92	50	47.6 A	33.7 - 81.4

Note: Onset = 30/PRID30 (Combined pain relief and pain intensity difference scores at 30 minutes).
(1) Separation based on 30 minute PRID LSmeans.

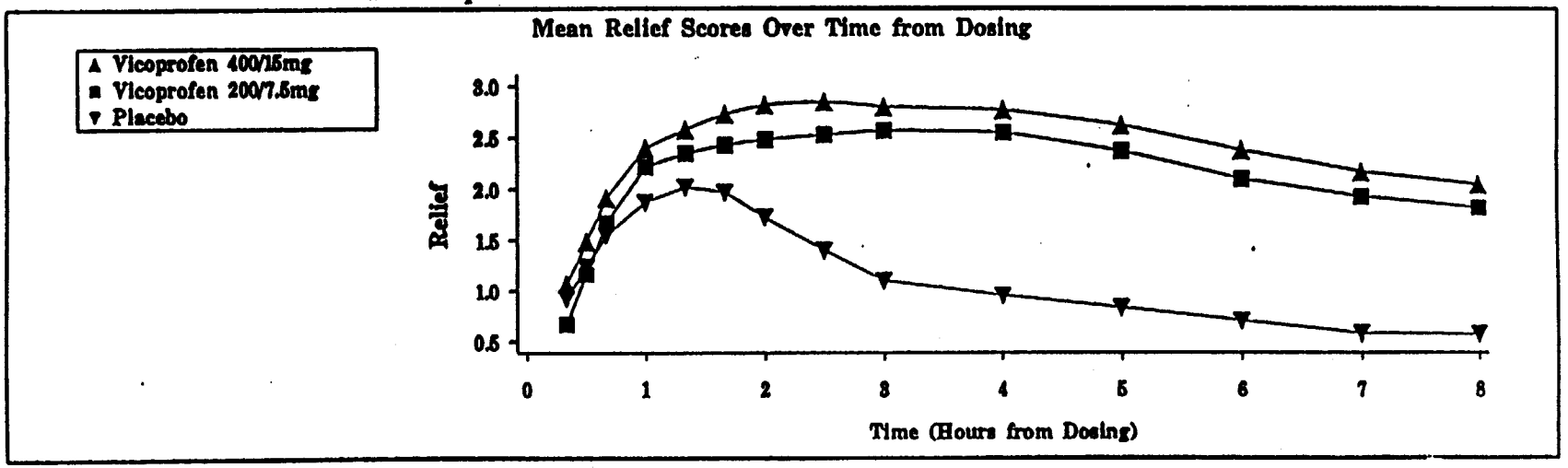
FIGURE 1
VP-21-2101 PID Scores
Means (Standard Deviations), Sample Sizes, and Fisher's Protected LSD Comparisons
All Acceptable Patients with Baseline Observations Carried-Forward



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)	0.58 (0.67) [60](a)A(d)	0.84 (0.72) [60] A	1.10 (0.90) [60] A	1.40 (0.94) [60] A	1.58 (1.00) [57] A	1.72 (1.06) [51] A	1.78 (1.08) [50] A	1.83 (1.09) [49] A	1.80 (1.10) [49] A	1.77 (1.09) [47] A	1.62 (1.06) [47] A	1.42 (0.96) [47] A	1.22 (0.99) [46] A	1.13 (0.9) [45] A
Vicoprofen 200/7.5mg (n=60)	0.32 (0.54) [60] A	0.60 (0.58) [60] A	0.88 (0.80) [60] A	1.22 (0.96) [60] A	1.35 (0.95) [59] A	1.47 (0.93) [53] AB	1.48 (0.97) [51] A	1.53 (1.02) [51] A	1.57 (1.01) [49] A	1.55 (1.05) [49] A	1.40 (0.94) [48] A	1.20 (0.84) [48] A	1.10 (0.84) [47] A	0.98 (0.8) [44] A
Placebo (n=60)	0.52 (0.72) [60] A	0.70 (0.73) [60] A	0.88 (0.87) [60] A	1.03 (0.92) [60] A	1.17 (0.94) [53] A	1.13 (0.95) [50] B	0.97 (0.94) [48] B	0.78 (0.94) [44] B	0.58 (0.89) [39] B	0.50 (0.87) [26] B	0.42 (0.70) [21] B	0.33 (0.63) [20] B	0.28 (0.49) [18] B	0.28 (0.9) [16] B
Treatment P-Value(b)	0.066	0.138	0.257	0.093	0.059	0.006	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Trt*Baseline P-Value(c)	0.276	0.231	0.329	0.354	0.431	0.853	0.923	0.860	0.704	0.730	0.653	0.828	0.502	0.551
RMS Error(b)	0.646	0.664	0.828	0.916	0.953	0.969	0.986	1.008	0.997	1.001	0.911	0.829	0.802	0.782

a) Represents the number of subjects evaluating efficacy at that time point (i.e. number of active subjects).
b) Model: PID = μ + Trt(i) + Baseline(j) + Error
c) Model: PID = 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.

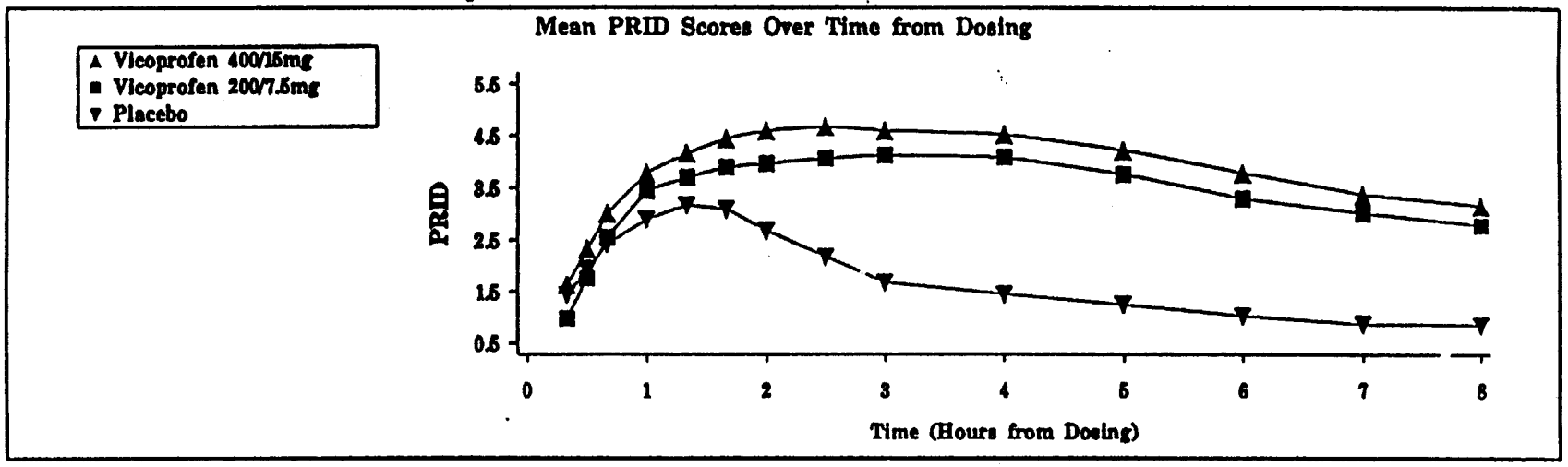
FIGURE 2
VP-21-2101 Pain Relief Scores
Means (Standard Deviations), Sample Sizes, and Fisher's Protected LSD Comparisons
All Acceptable Patients with Baseline Observations Carried-Forward



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)(d)	1.07 (1.18) [60](a)(c)	1.49 (1.19) [60] A	1.92 (1.28) [60] A	2.40 (1.36) [60] A	2.58 (1.43) [57] A	2.73 (1.47) [51] A	2.82 (1.48) [50] A	2.85 (1.52) [49] A	2.80 (1.55) [49] A	2.77 (1.53) [47] A	2.62 (1.50) [47] A	2.38 (1.46) [47] A	2.17 (1.43) [46] A	2.05 (1.43) [45] A
Vicoprofen 200/7.5mg (n=60)	0.87 (0.80) [60] A	1.17 (0.82) [60] A	1.67 (1.08) [60] A	2.22 (1.21) [60] A	2.35 (1.26) [59] A	2.43 (1.32) [53] AB	2.48 (1.36) [51] A	2.53 (1.40) [51] A	2.57 (1.39) [49] A	2.55 (1.45) [49] A	2.37 (1.38) [48] A	2.10 (1.31) [48] A	1.93 (1.33) [47] A	1.82 (1.36) [44] A
Placebo (n=60)	0.93 (1.06) [60] A	1.24 (1.04) [60] A	1.55 (1.20) [60] A	1.87 (1.31) [60] A	2.02 (1.40) [53] A	1.97 (1.43) [50] B	1.72 (1.43) [48] B	1.40 (1.44) [44] B	1.10 (1.41) [39] B	0.95 (1.40) [26] B	0.83 (1.25) [21] B	0.70 (1.14) [20] B	0.58 (1.01) [18] B	0.57 (1.00) [16] B
Treatment P-Value(b)	0.096	0.197	0.250	0.074	0.076	0.012	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
RMS Error(b)	1.022	1.030	1.228	1.292	1.364	1.407	1.422	1.452	1.453	1.464	1.383	1.311	1.268	1.269

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

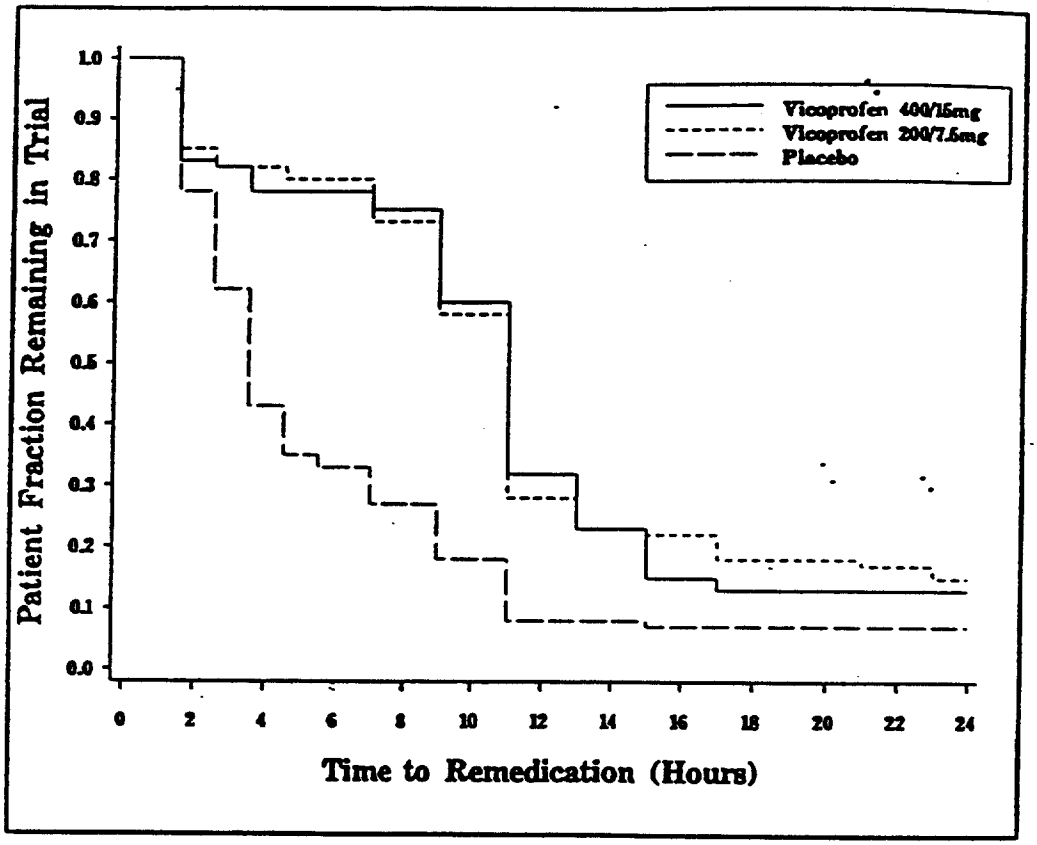


Treatment	Assessment Time Point (in Hours from Dosing)													
	0.33	0.5	0.67	1	1.33	1.67	2	2.5	3	4	5	6	7	8
Vicoprofen 400/15mg (n=60)(e)	1.65 (1.79) [60](a)A(d)	2.33 (1.86) [60] A	3.02 (2.22) [60] A	3.80 (2.24) [60] A	4.17 (2.37) [57] A	4.45 (2.48) [51] A	4.60 (2.51) [50] A	4.68 (2.56) [49] A	4.60 (2.61) [49] A	4.53 (2.58) [47] A	4.23 (2.61) [47] A	3.80 (2.39) [47] A	3.38 (2.57) [46] A	3.18 (2.15) [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	3.50 (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 (1.5) [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.

FIGURE 4

Product Limit Plot of Time-to-Remedication
(All Evaluable Subjects)



Treatment	Calculated Time-to-Remedication	
	Median Time [1] (decimal hours)	95%-CI [2] (decimal hours)
Vicoprofen 400/15mg	10.50 A [3]	9.67 - 11.25
Vicoprofen 200/7.5mg	10.54 A	9.92 - 11.33
Placebo	3.00 B	2.75 - 4.33

[1] Kaplan-Meier estimate (see Miller, Survival Analysis, page 75)

[2] Method of Simon & Lee, Cancer Treat Rep 66:37-42, 1982

[3] Logrank test applied as in Fisher's PLSD.

Date: 08MAR96
Time: 15:26

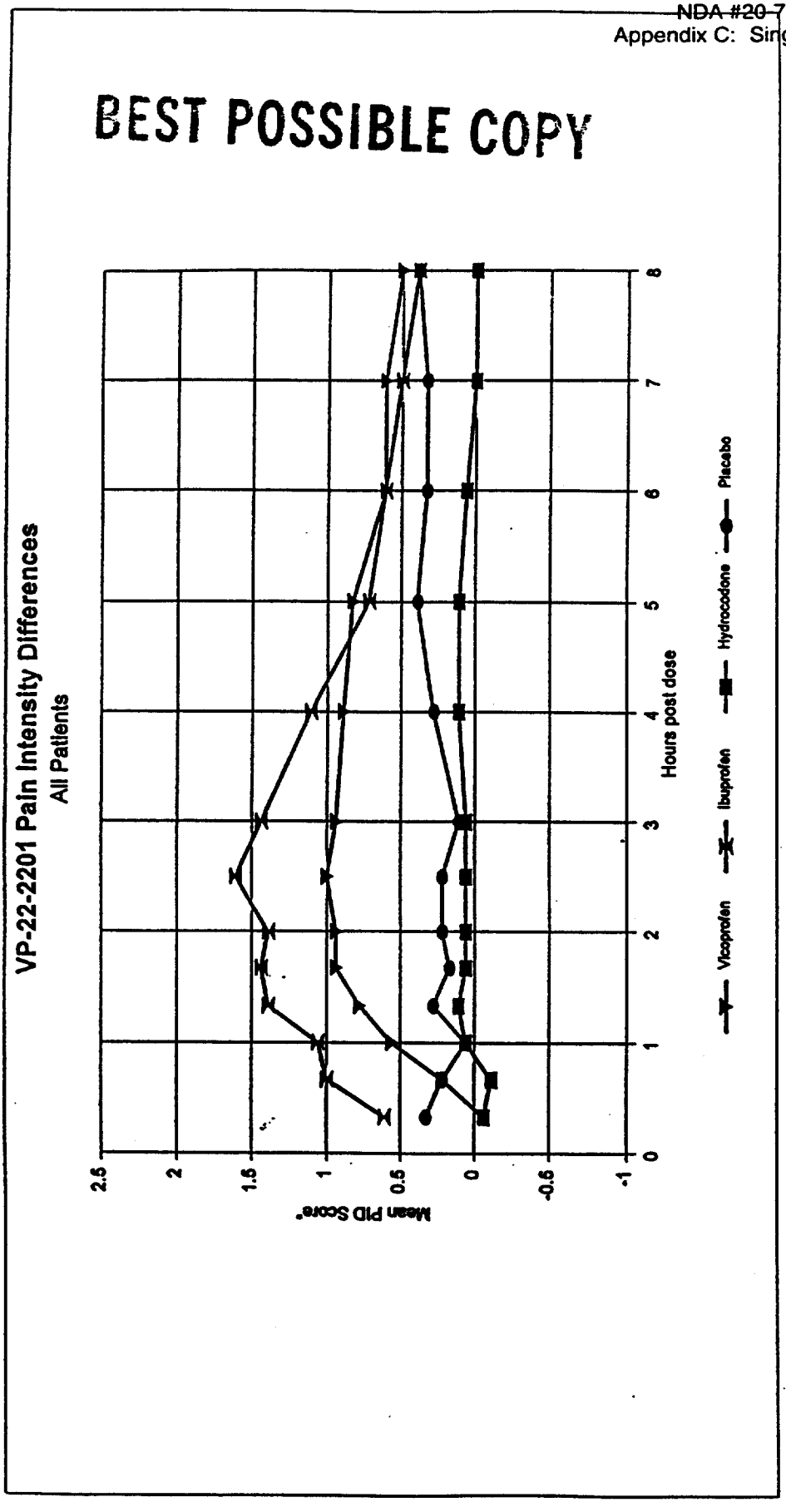
Knoll Pharmaceuticals
Protocol #: VP-21

Table 1

Estimated Onset of Pain Relief (on-PR)

Treatment	PRID at 30 min			Estimated on-PR	
	Mean	SD	N	Time in min	95%-CI in min
Vicoprofen 400/15mg	2.33	1.86	60	12.9 A (1)	10.7 - 16.2
Vicoprofen 200/7.5mg	1.77	1.36	60	17.0 A	14.2 - 21.2
Placebo	1.94	1.72	60	15.5 A	12.6 - 20.0

Note: Onset = 30/PRID30 (Combined pain relief and pain intensity difference scores at 30 minutes).
(1) Separation based on 30 minute PRID LSmeans.

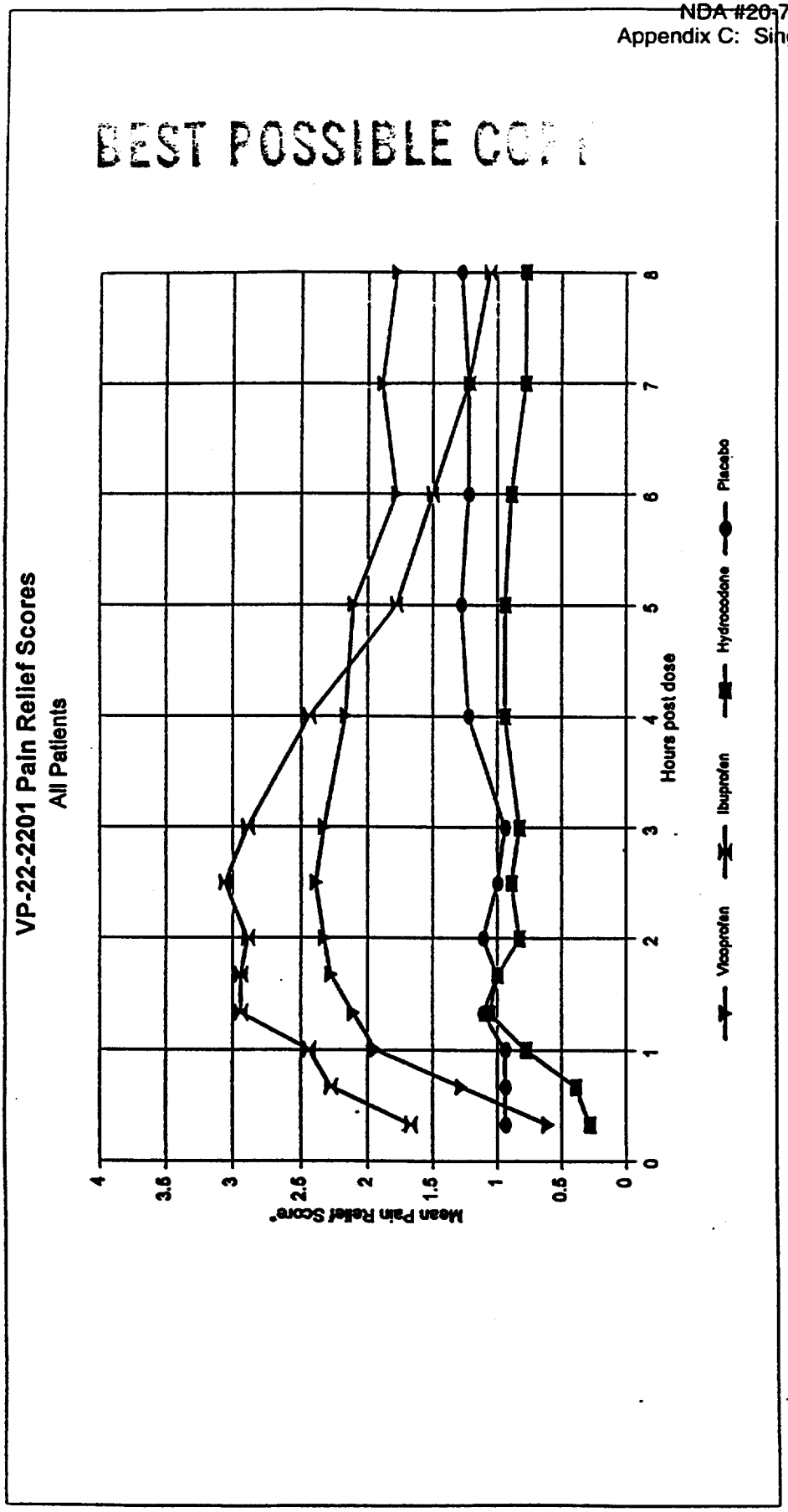


	Hours post dose																															
	0.33		0.67		1		1.33		1.67		2		2.5		3		4		5		6		7		8	
Vicoprofen (400/15 mg)	*mean sd n dh	-0.06 (0.64) 18	0.22 (0.81) 18	0.56 (0.86) 18	0.78 (1.00) 18	0.94 (1.06) 18 X	1.00 (1.08) 18 X	0.94 (1.08) 15 X	0.89 (1.13) 13	0.83 (1.20) 13	0.81 (1.14) 12	0.61 (1.04) 11	0.50 (0.92) 11
Ibuprofen (400 mg)	*mean sd n dh	0.61 (0.78) 18	1.00 (0.84) 18 X	1.06 (1.00) 18 X	1.39 (0.85) 18 X	1.44 (0.76) 18 X	1.39 (0.76) 18 X	1.61 (0.85) 18 X	1.44 (0.96) 17 X	1.11 (0.68) 16 X	0.72 (0.89) 16	0.81 (0.98) 13	0.50 (0.92) 11	0.33 (0.98) 8
Hydrocodone (15mg)	*mean sd n dh	-0.06 (0.64) 18	-0.11 (0.85) 18	0.06 (1.00) 18	0.11 (1.06) 18	0.06 (1.00) 14	0.06 (1.11) 13	0.06 (1.16) 10	0.06 (1.16) 7	0.11 (1.25) 6	0.11 (1.26) 6	0.06 (1.11) 6	0.00 (1.14) 6	0.00 (1.14) 6
Placebo	*mean sd n dh	0.33 (0.69) 18	0.22 (0.73) 18	0.06 (0.73) 18	0.28 (0.83) 18	0.17 (0.86) 18	0.22 (0.86) 14	0.22 (0.81) 11	0.11 (0.68) 11	0.28 (0.89) 10	0.39 (0.98) 10	0.33 (0.97) 9	0.33 (0.97) 8	0.39 (0.97) 8
	p-value	0.011	<0.001	0.008	<0.001	<0.001	<0.001	<0.001	<0.001	0.010	0.196	0.337	0.305	0.507

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.

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

Mean AUC-PID Scores	0-4 hr	0-8hr
Vicoprofen	2.72 X	5.36
Ibuprofen	4.85 X	7.01 X
Hydrocodone	0.15	0.34
Placebo	0.88	2.04
p-value	<0.001	0.017



	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	(0.81)	1.26	(1.07)	1.94	(1.35)	2.11	(1.57)	2.28	(1.60)	2.33	(1.61)	2.39	(1.61)	2.33	(1.87)	2.17	(1.54)	2.11	(1.64)	1.78	(1.59)	1.89	(1.53)	1.78	(1.53)		
	n, sig	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	(0.97)	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	(1.36)	1.50	(1.62)	1.22	(1.59)	1.06	(1.39)		
	n, sig	18	X	18	X	18	X	18	X	18	X	18	X	18	X	17	* X	16	X	18		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	(1.29)	0.83	(1.29)	0.89	(1.32)	0.83	(1.25)	0.94	(1.31)	0.94	(1.31)	0.89	(1.41)	0.78	(1.31)	0.78	(1.39)		
	n, sig	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	(1.16)	1.11	(1.28)	1.00	(1.14)	0.94	(1.06)	1.22	(1.31)	1.28	(1.49)	1.22	(1.52)	1.22	(1.52)	1.28	(1.52)		
	n, sig	18		18		18		18		16		14		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		0.353		0.175		0.240					

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.

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

Mean AUC-PR Scores	0-4 hr	0-8hr
Vicoprofen	7.51 X	15.23 X
Ibuprofen	9.88 X	18.71 X
Hydrocodone	2.85	6.30
Placebo	3.72	6.83
p-value	<0.001	0.007

FIGURE 7

VP-22-2201 Proportion of Patients in Study

All Patients

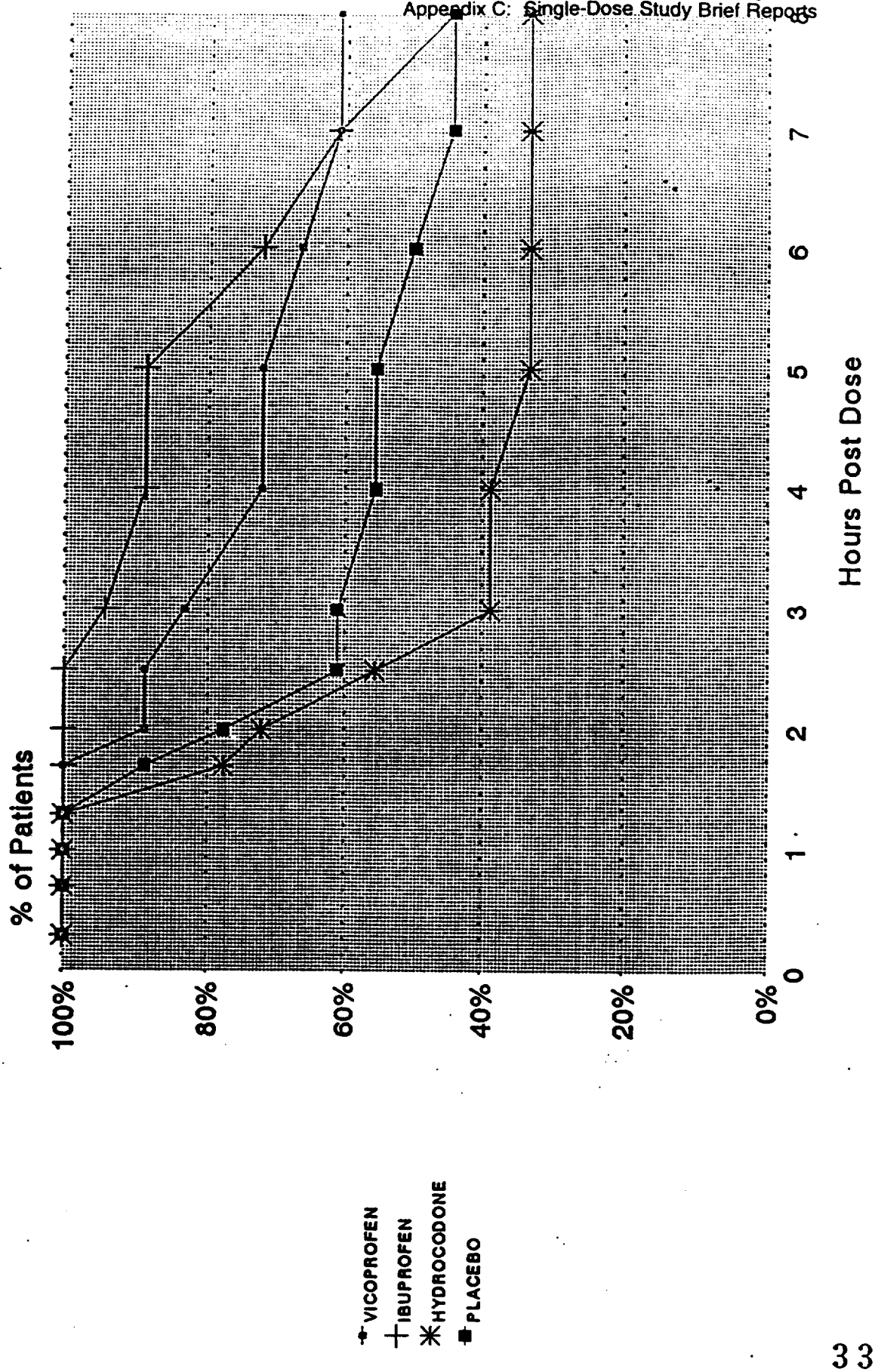
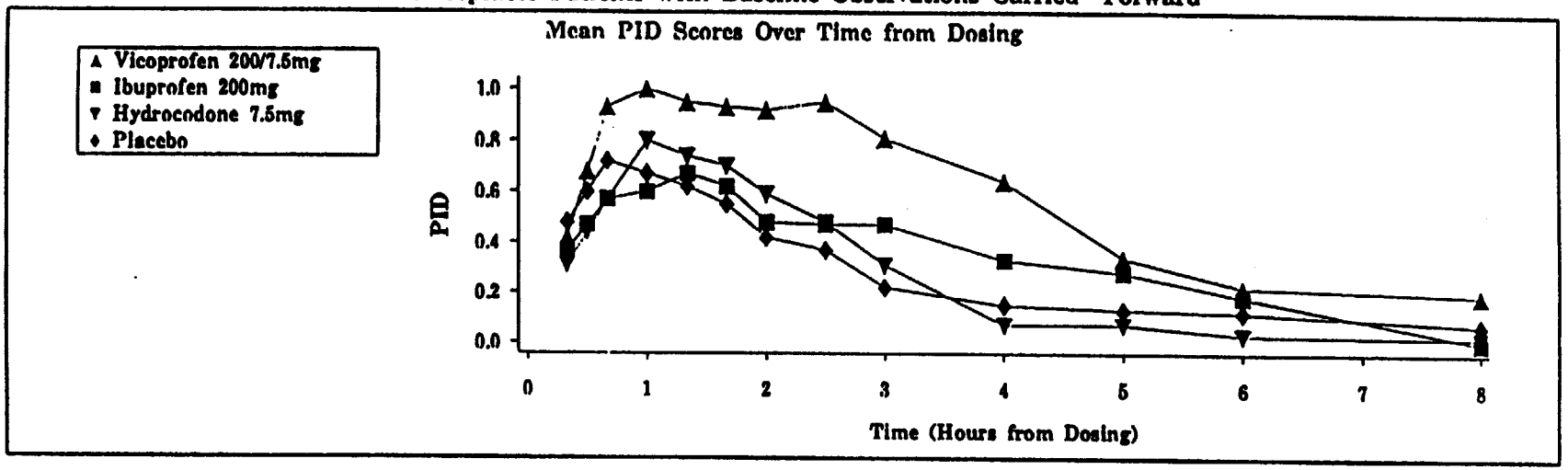


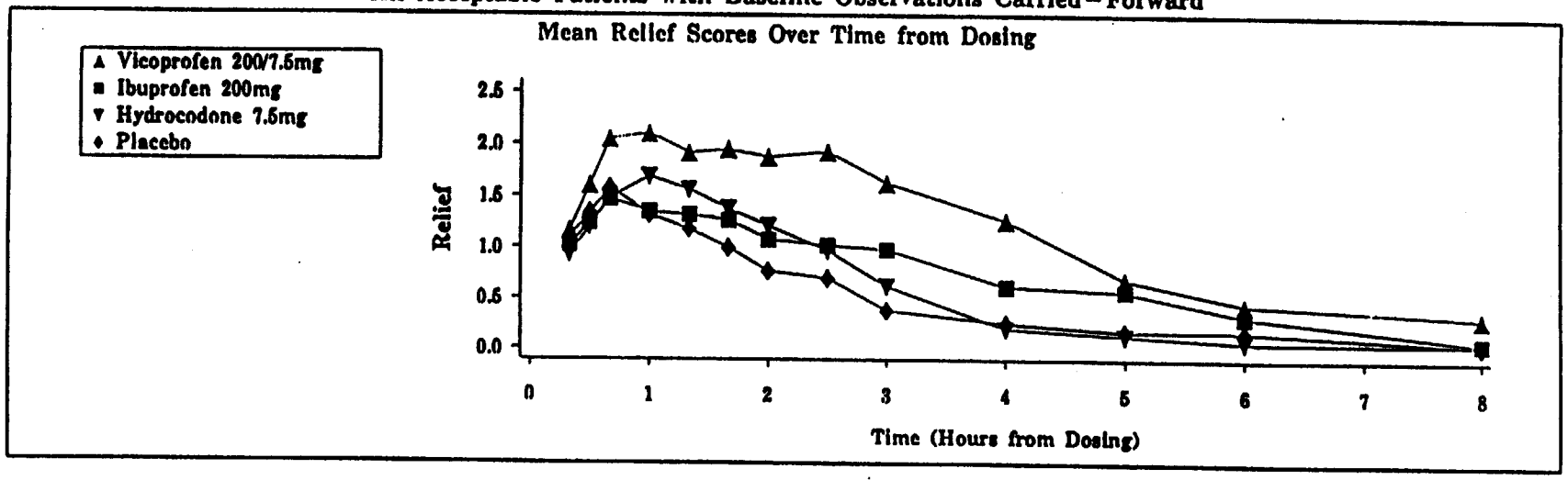
FIGURE 1
VP-23-2301 PID Scores
Means (Standard Deviations), Sample Sizes, and Fisher's Protected LSD Comparisons
All Acceptable Patients with Baseline Observations Carried-Forward



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)	0.42 (0.65) [59](a)A(d)	0.68 (0.62) [59] A	0.93 (0.76) [59] A	1.00 (0.85) [59] A	0.95 (0.94) [41] A	0.93 (0.96) [34] A	0.92 (0.93) [33] A	0.95 (0.95) [32] A	0.81 (0.94) [32] A	0.64 (0.87) [26] A	0.34 (0.71) [22] A	0.22 (0.59) [14] A	0.19 (0.5 [8] A
Ibuprofen 200mg (n=60)	0.37 (0.64) [60] A	0.47 (0.59) [60] A	0.57 (0.65) [60] B	0.60 (0.85) [60] A	0.67 (0.80) [33] A	0.62 (0.83) [28] A	0.48 (0.79) [25] B	0.47 (0.79) [21] B	0.47 (0.79) [19] B	0.33 (0.77) [18] B	0.28 (0.72) [11] A	0.18 (0.57) [11] A	0.00 (0.1 [5] B
Hydrocodone 7.5mg (n=61)	0.31 (0.59) [61] A	0.44 (0.60) [61] A	0.57 (0.76) [61] B	0.80 (0.87) [61] A	0.74 (0.83) [38] A	0.70 (0.82) [34] A	0.59 (0.84) [30] B	0.48 (0.83) [24] B	0.31 (0.67) [21] B	0.07 (0.48) [13] C	0.07 (0.31) [5] B	0.03 (0.18) [3] A	0.02 (0.1 [1] B
Placebo (n=60)	0.48 (0.65) [60] A	0.60 (0.69) [60] A	0.72 (0.85) [60] AB	0.67 (0.93) [60] A	0.62 (0.88) [32] A	0.55 (0.85) [26] A	0.42 (0.81) [23] B	0.37 (0.74) [15] B	0.22 (0.56) [14] B	0.15 (0.48) [9] BC	0.13 (0.47) [6] AB	0.12 (0.45) [4] A	0.07 (0.3 [3] AB
Treatment P-Value(b)	0.468	0.125	0.029	0.066	0.166	0.091	0.008	<0.001	<0.001	<0.001	0.032	0.143	0.020
Trt*Baseline P-Value(c)	0.216	0.165	0.222	0.049	0.073	0.074	0.049	0.052	0.304	0.068	0.522	0.700	0.655
RMS Error(b)	0.629	0.623	0.757	0.870	0.861	0.858	0.848	0.833	0.763	0.671	0.574	0.475	0.355

(a) Represents the number of subjects evaluating efficacy at that time point (i.e. number of active subjects).
(b) Model: PID $= \mu + Trt(i) + Baseline(j) + Error$
(c) Model: PID $= \mu + Trt(i) + Baseline(j) + Trt*Baseline(ij) + Error$
(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.

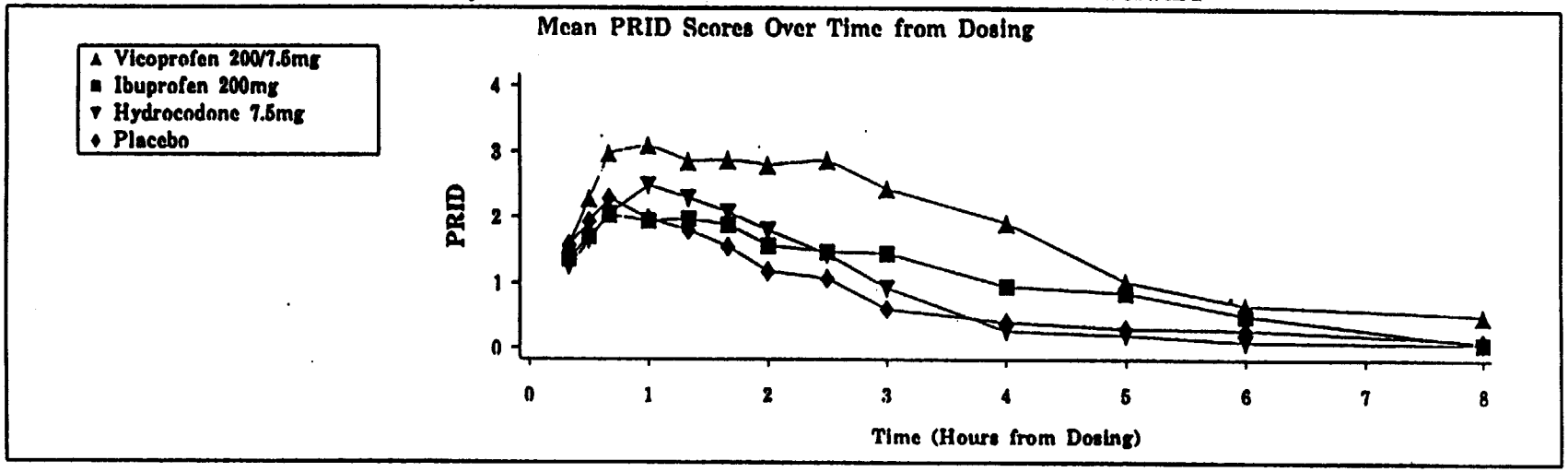
FIGURE 2
VP-23-2301 Pain Relief Scores
Means (Standard Deviations), Sample Sizes, and Fisher's Protected LSD Comparisons
All Acceptable Patients with Baseline Observations Carried-Forward



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)(d)	1.17 (1.09) [59](a)A(c)	1.61 (1.13) [59] A	2.05 (1.42) [59] A	2.10 (1.62) [59] A	1.92 (1.77) [41] A	1.95 (1.82) [34] A	1.88 (1.83) [33] A	1.93 (1.86) [32] A	1.63 (1.79) [32] A	1.27 (1.73) [26] A	0.69 (1.39) [22] A	0.44 (1.15) [14] A	0.32 (1.02) [8] A
Ibuprofen 200mg (n=60)	1.02 (1.13) [60] A	1.24 (1.10) [60] A	1.47 (1.26) [60] A	1.35 (1.54) [60] B	1.32 (1.61) [33] A	1.27 (1.64) [28] B	1.08 (1.58) [25] B	1.02 (1.58) [21] B	0.98 (1.56) [19] B	0.62 (1.38) [18] B	0.57 (1.31) [11] A	0.32 (1.03) [11] A	0.07 (0.46) [5] B
Hydrocodone 7.5mg (n=61)	0.93 (1.18) [61] A	1.20 (1.20) [61] A	1.48 (1.44) [61] A	1.69 (1.63) [61] AB	1.56 (1.64) [38] A	1.38 (1.65) [34] AB	1.21 (1.65) [30] B	0.97 (1.56) [24] B	0.62 (1.27) [21] BC	0.20 (0.75) [13] B	0.13 (0.56) [5] B	0.07 (0.40) [3] A	0.05 (0.38) [1] B
Placebo (n=60)	1.10 (1.10) [60] A	1.34 (1.20) [60] A	1.58 (1.43) [60] A	1.32 (1.53) [60] B	1.18 (1.55) [32] A	1.00 (1.53) [26] B	0.77 (1.44) [23] B	0.70 (1.34) [15] B	0.38 (0.96) [14] C	0.25 (0.77) [9] B	0.17 (0.64) [6] B	0.17 (0.64) [4] A	0.05 (0.22) [3] B
Treatment P-Value(b)	0.688	0.220	0.073	0.025	0.081	0.018	0.003	<0.001	<0.001	<0.001	0.005	0.087	0.033
RMS Error(b)	1.125	1.160	1.389	1.580	1.644	1.663	1.631	1.593	1.425	1.226	1.043	0.858	0.598

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

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

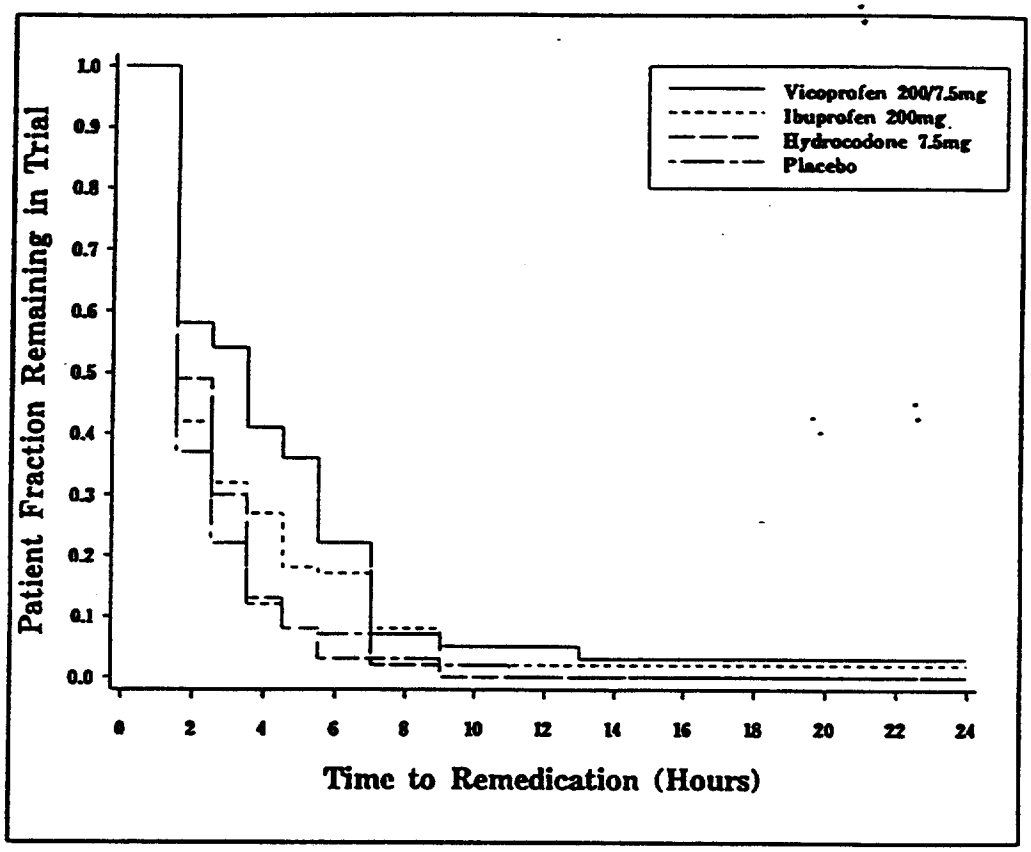


Treatment	Assessment Time Point (in Hours from Dosing)															
	0.33	0.5	0.67	1	1.33	1.67	2	2.5	3	4	5	6	8
Vicoprofen 200/7.5mg (n=59)(e)	1.59 (1.66) [59](a)A(d)	2.29 (1.69) [59] A	2.96 (2.11) [59] A	3.10 (2.40) [59] A	2.86 (2.66) [41] A	2.88 (2.75) [34] A	2.80 (2.74) [33] A	2.88 (2.79) [32] A	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 (1.5 [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	1.57 (2.34) [25] B	1.48 (2.85) [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 (0.2 [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) [5] C	0.10 (0.54) [3] A	0.07 (0. [1] B
Placebo (n=60)	1.58 (1.67) [60] A	1.94 (1.85) [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. [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	1.597	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. 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 4

Product Limit Plot of Time-to-Remedication
(All Evaluable Subjects)



Treatment	Calculated Time-to-Remedication	
	Median Time [1] (decimal hours)	95%-CI [2] (decimal hours)
Vicoprofen 200/7.5mg	3.00 A [3]	1.33 - 4.67
Ibuprofen 200mg	1.33 AB	1.00 - 2.00
Hydrocodone 7.5mg	1.67 B	1.00 - 2.50
Placebo	1.33 B	1.00 - 1.83

[1] Kaplan-Meier estimate (see Miller, Survival Analysis, page 75)

[2] Method of Simon & Lee, Cancer Treat Rep 66:37-42, 1982

[3] Logrank test applied as in Fisher's PLSD.

Knoll Pharmaceuticals
Protocol #: VP-23

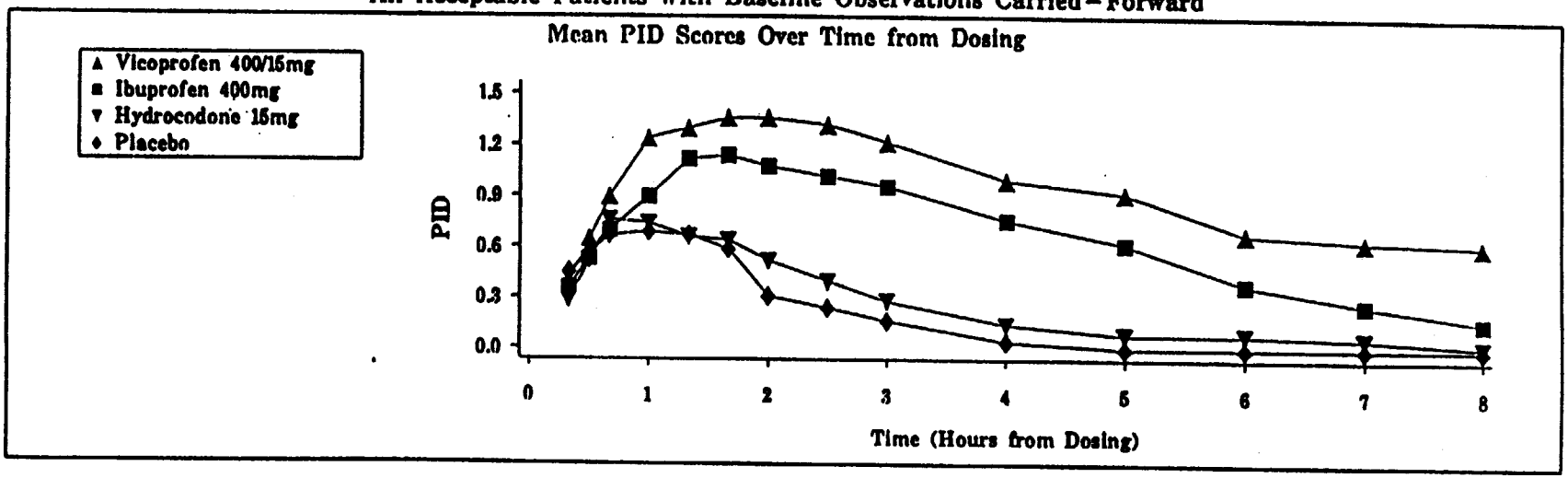
Table 1

Estimated Onset of Pain Relief (on-PR)

Treatment	PRID at 30 min			Estimated on-PR	
	Mean	SD	N	Time in min	95%-CI in min
Vicoprofen 200/7.5mg	2.29	1.69	59	13.1 A (1)	11.0 - 16.2
Ibuprofen 200mg	1.71	1.64	60	17.6 A	14.1 - 23.4
Hydrocodone 7.5mg	1.65	1.76	61	18.2 A	14.3 - 25.1
Placebo	1.94	1.83	60	15.5 A	12.4 - 20.4

Note: Onset = 30/PRID30 (Combined pain relief and pain intensity difference scores at 30 minutes).
(1) Separation based on 30 minute PRID LSmeans.

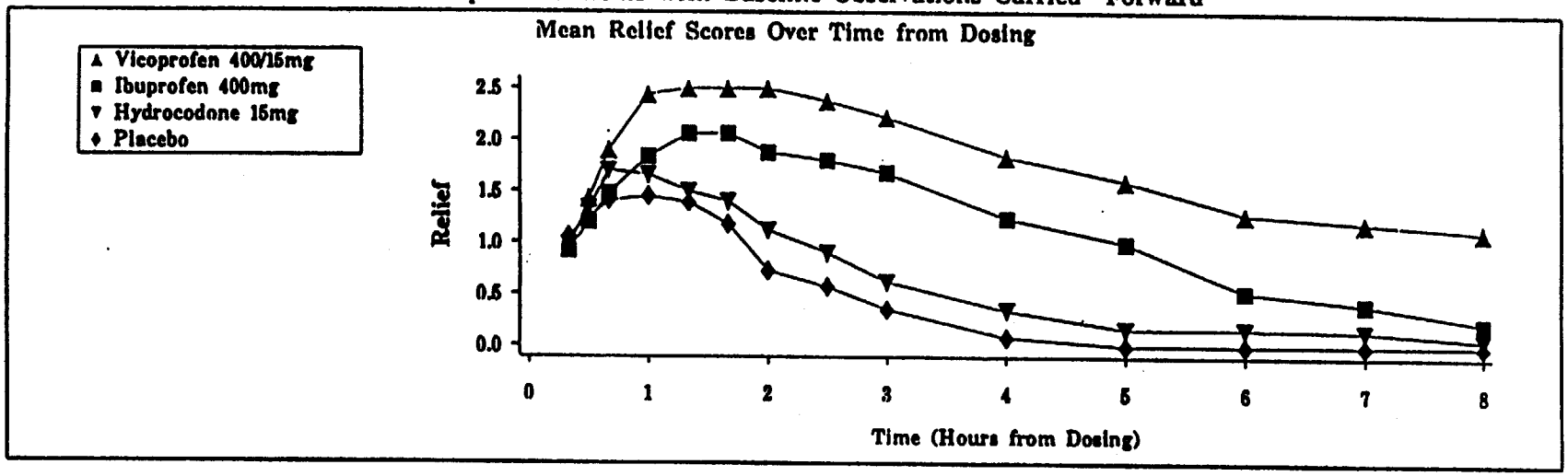
FIGURE 1
VP-29-2901 PID Scores
Means (Standard Deviations), Sample Sizes, and Fisher's Protected LSD Comparisons
All Acceptable Patients with Baseline Observations Carried-Forward



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)	0.40 (0.61) [50](a)A(d)	0.65 (0.69) [50] A	0.90 (0.89) [50] A	1.24 (0.98) [50] A	1.30 (0.97) [39] A	1.36 (1.05) [39] A	1.36 (1.06) [37] A	1.32 (1.06) [36] A	1.22 (1.02) [33] A	1.00 (0.95) [32] A	0.92 (0.84) [28] A	0.68 (0.96) [23] A	0.64 (0.94) [19] A	0.62 (0.9[illegible]) [18] A
Ibuprofen 400mg (n=50)	0.36 (0.60) [50] A	0.53 (0.63) [50] A	0.70 (0.79) [50] A	0.90 (0.97) [50] AB	1.12 (1.04) [35] A	1.14 (1.09) [33] A	1.08 (1.14) [33] A	1.02 (1.15) [29] A	0.96 (1.14) [27] A	0.76 (1.10) [26] A	0.62 (1.03) [19] B	0.38 (0.85) [15] B	0.26 (0.75) [8] B	0.16 (0.5[illegible]) [7] B
Hydrocodone 15mg (n=50)	0.28 (0.84) [50] A	0.52 (0.70) [50] A	0.76 (0.92) [50] A	0.74 (0.83) [50] B	0.66 (0.87) [33] B	0.64 (0.85) [28] B	0.52 (0.79) [27] B	0.40 (0.73) [21] B	0.28 (0.70) [18] B	0.14 (0.53) [11] B	0.08 (0.44) [6] C	0.08 (0.40) [2] C	0.06 (0.31) [2] BC	0.02 (0.1[illegible]) [2] B
Placebo (n=51)	0.45 (0.67) [51] A	0.56 (0.68) [51] A	0.67 (0.77) [51] A	0.69 (0.88) [51] B	0.67 (0.86) [31] B	0.59 (0.83) [27] B	0.31 (0.65) [23] B	0.24 (0.55) [14] B	0.16 (0.54) [13] B	0.04 (0.20) [7] B	0.00 (0.00) [2] C	0.00 (0.00) [0] C	0.00 (0.00) [0] C	0.00 (0.0[illegible]) [0] B
Treatment P-Value(b)	0.514	0.704	0.474	0.009	<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)	0.903	0.934	0.950	0.611	0.487	0.304	0.131	0.082	0.019	0.005	0.022	0.071	0.224	0.648
RMS Error(b)	0.602	0.649	0.819	0.898	0.922	0.940	0.919	0.893	0.871	0.772	0.728	0.669	0.621	0.559

(a) Represents the number of subjects evaluating efficacy at that time point (i.e. number of active subjects).
(b) Model: PID = μ + Trt(i) + Baseline(j) + Error
(c) Model: PID = 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.

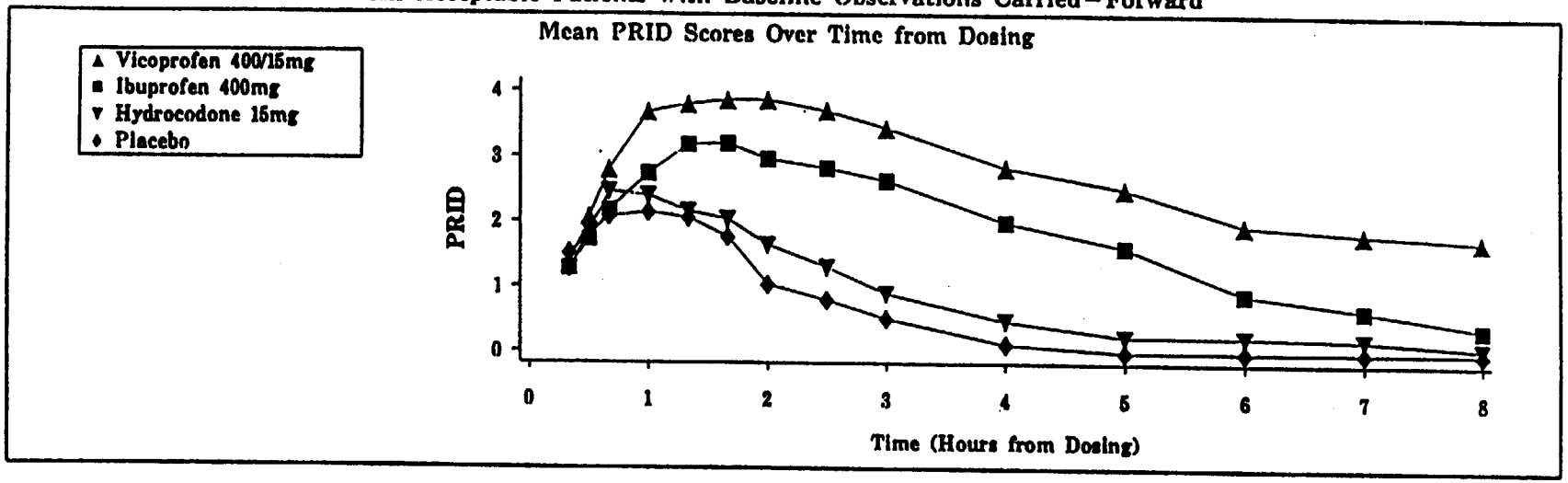
FIGURE 2
VP-29-2901 Pain Relief Scores
Means (Standard Deviations), Sample Sizes, and Fisher's Protected LSD Comparisons
All Acceptable Patients with Baseline Observations Carried-Forward



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)(d)	0.96 (1.03) [50](a)A(c)	1.43 (1.12) [50] A	1.90 (1.43) [50] A	2.44 (1.53) [50] A	2.50 (1.59) [39] A	2.50 (1.73) [39] A	2.50 (1.75) [37] A	2.38 (1.82) [36] A	2.22 (1.80) [33] A	1.84 (1.75) [32] A	1.60 (1.81) [28] A	1.28 (1.73) [23] A	1.20 (1.69) [19] A	1.12 (1.6 [18] A
Ibuprofen 400mg (n=50)	0.92 (1.03) [50] A	1.20 (1.05) [50] A	1.48 (1.23) [50] A	1.84 (1.48) [50] B	2.06 (1.66) [35] AB	2.06 (1.68) [33] A	1.88 (1.78) [33] A	1.80 (1.80) [29] A	1.68 (1.75) [27] A	1.24 (1.71) [26] B	1.00 (1.59) [19] B	0.52 (1.28) [15] B	0.40 (1.09) [8] B	0.22 (0.6 [7] B
Hydrocodone 15mg (n=50)	0.98 (1.00) [50] A	1.34 (1.10) [50] A	1.70 (1.40) [50] A	1.66 (1.48) [50] B	1.50 (1.53) [33] BC	1.40 (1.48) [28] B	1.12 (1.45) [27] B	0.90 (1.37) [21] B	0.62 (1.28) [18] B	0.34 (1.00) [11] C	0.16 (0.79) [6] C	0.16 (0.79) [2] BC	0.14 (0.70) [2] B	0.06 (0.2 [2] B
Placebo (n=51)	1.06 (1.12) [51] A	1.24 (1.12) [51] A	1.41 (1.27) [51] A	1.45 (1.46) [51] B	1.39 (1.50) [31] C	1.18 (1.51) [27] B	0.73 (1.28) [23] B	0.57 (1.12) [14] B	0.35 (0.98) [13] B	0.08 (0.44) [7] C	0.00 (0.00) [2] C	0.00 (0.00) [0] C	0.00 (0.00) [0] B	0.00 (0.0 [0] B
Treatment P-Value(b)	0.925	0.717	0.248	0.007	0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
RMS Error(b)	1.046	1.101	1.336	1.486	1.571	1.604	1.579	1.562	1.489	1.338	1.264	1.143	1.062	0.973

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

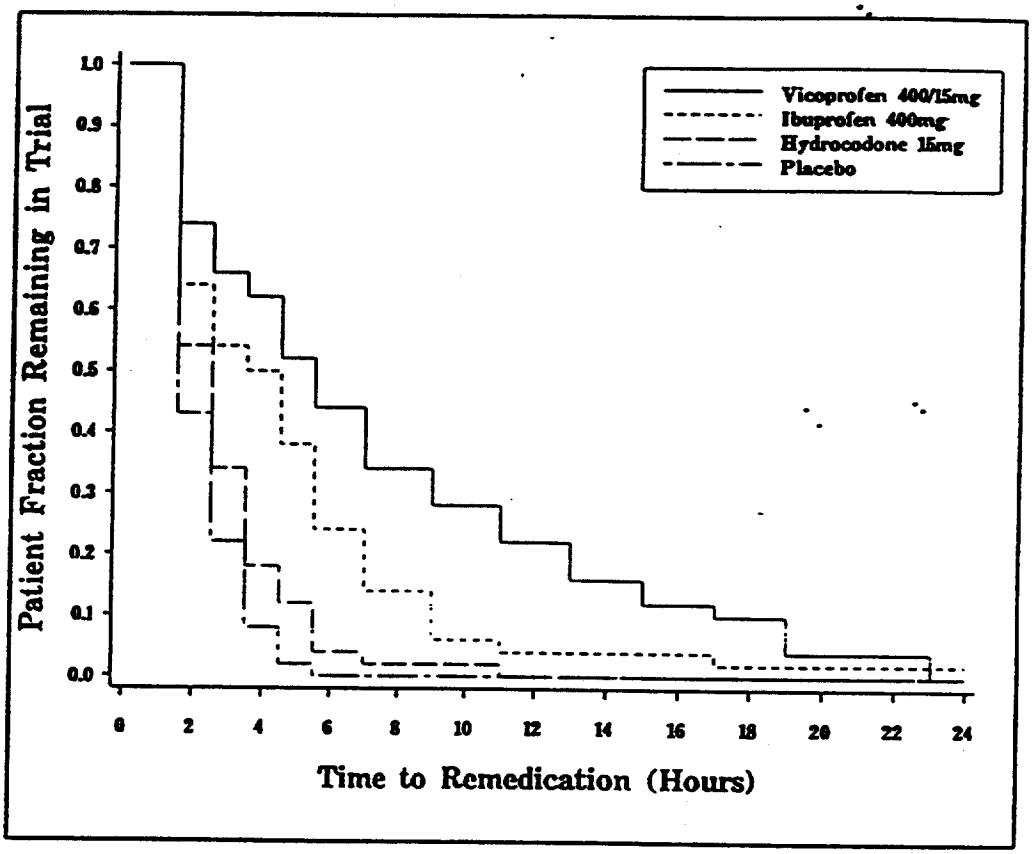


Treatment	Assessment Time Point (in Hours from Dosing)														
	0.33	0.5	0.67	1	1.33	1.67	2	2.5	3	4	5	6	7	8	
Vicoprofen 400/15mg (n=50)(e)	1.36 (1.59) [50](a)A(d)	2.08 (1.77) [50] A	2.80 (2.26) [50] A	3.68 (2.43) [50] A	3.80 (2.51) [39] A	3.86 (2.72) [39] A	3.86 (2.77) [37] A	3.70 (2.82) [36] A	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 (2.6 [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 (1.1 [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 (0.5 [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 (0.0 [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	<0.00	
Trt*Baseline P-Value(c)	0.756	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	2.115	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. 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 4

Product Limit Plot of Time-to-Remedication
(All Evaluable Subjects)



Treatment	Calculated Time-to-Remedication	
	Median Time [1] (decimal hours)	95%-CI [2] (decimal hours)
Vicoprofen 400/15mg	5.00 A [3]	3.33 - 7.00
Ibuprofen 400mg	3.71 B	2.00 - 5.00
Hydrocodone 15mg	2.00 C	1.33 - 2.50
Placebo	1.67 C	1.00 - 2.00

[1] Kaplan-Meier estimate (see Miller, Survival Analysis, page 75)

[2] Method of Simon & Lee, Cancer Treat Rep 66:37-42, 1982

[3] Logrank test applied as in Fisher's PLSD.

Date: 26APR96
Time: 16:05

Knoll Pharmaceuticals
Protocol #: VP-29

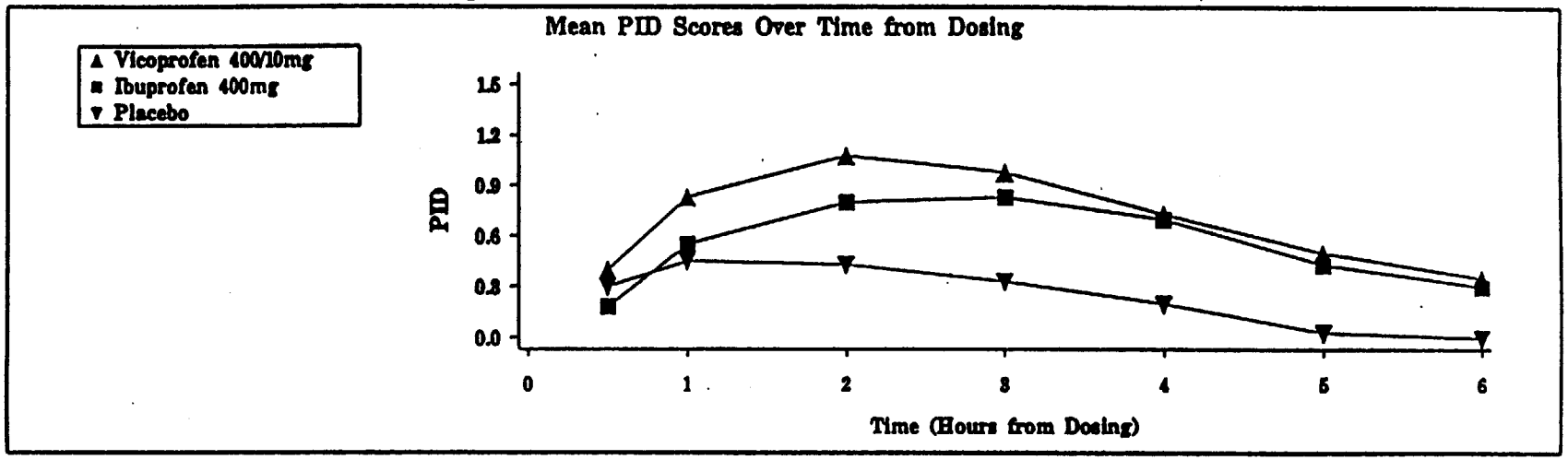
Table 1

Estimated Onset of Pain Relief (on-PR)

Treatment	PRID at 30 min			Estimated on-PR	
	Mean	SD	N	Time in min	95%-CI in min
Vicoprofen 400/15mg	2.08	1.77	50	14.4 A (1)	11.6 - 19.0
Ibuprofen 400mg	1.73	1.63	50	17.3 A	13.7 - 23.7
Hydrocodone 15mg	1.86	1.75	50	16.1 A	12.7 - 22.0
Placebo	1.79	1.75	51	16.7 A	13.1 - 23.0

Note: Onset = 30/PRID30 (Combined pain relief and pain intensity difference scores at 30 minutes).
(1) Separation based on 30 minute PRID LSmeans.

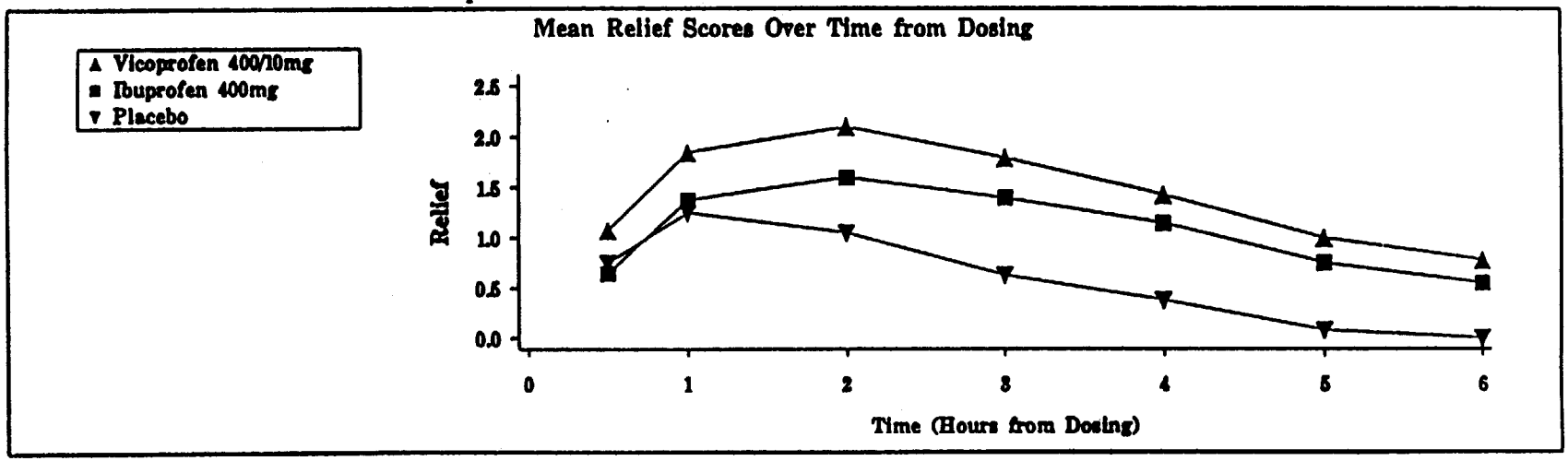
FIGURE 1
VP-01-0101 PID Scores
Means (Standard Deviations), Sample Sizes, and Fisher's Protected LSD Comparisons
All Acceptable Patients with Baseline Observations Carried-Forward



Treatment	Assessment Time Point (in Hours from Dosing)													
	0.5		1		2		3		4		5		6	
Vicoprofen 400/10mg (n=40)(e)	0.40 [40](a)	(0.50) A(d)	0.83 [40]	(0.75) A	1.08 [34]	(1.00) A	0.98 [26]	(1.00) A	0.73 [24]	(0.88) A	0.50 [16]	(0.73) A	0.35 [12]	(0.66) A
Ibuprofen 400mg (n=40)	0.18 [40]	(0.38) A	0.55 [40]	(0.81) A	0.80 [30]	(1.02) AB	0.83 [20]	(1.11) A	0.70 [17]	(1.02) A	0.43 [15]	(0.81) A	0.30 [9]	(0.72) A
Placebo (n=40)	0.30 [40]	(0.46) A	0.45 [40]	(0.68) A	0.43 [28]	(0.68) B	0.33 [14]	(0.62) B	0.20 [10]	(0.52) B	0.03 [5]	(0.16) B	0.00 [1]	(0.00) B
Treatment P-Value(b)	0.087		0.076		0.007		0.006		0.007		0.003		0.014	
Trt*Baseline P-Value(c)	0.193		0.283		0.434		0.180		0.158		0.116		0.216	
RMS Error(b)	0.452		0.749		0.902		0.911		0.821		0.659		0.568	

(a) Represents the number of subjects evaluating efficacy at that time point (i.e. number of active subjects).
(b) Model: PID = μ + Trt(i) + Baseline(j) + Error
(c) Model: PID = 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.

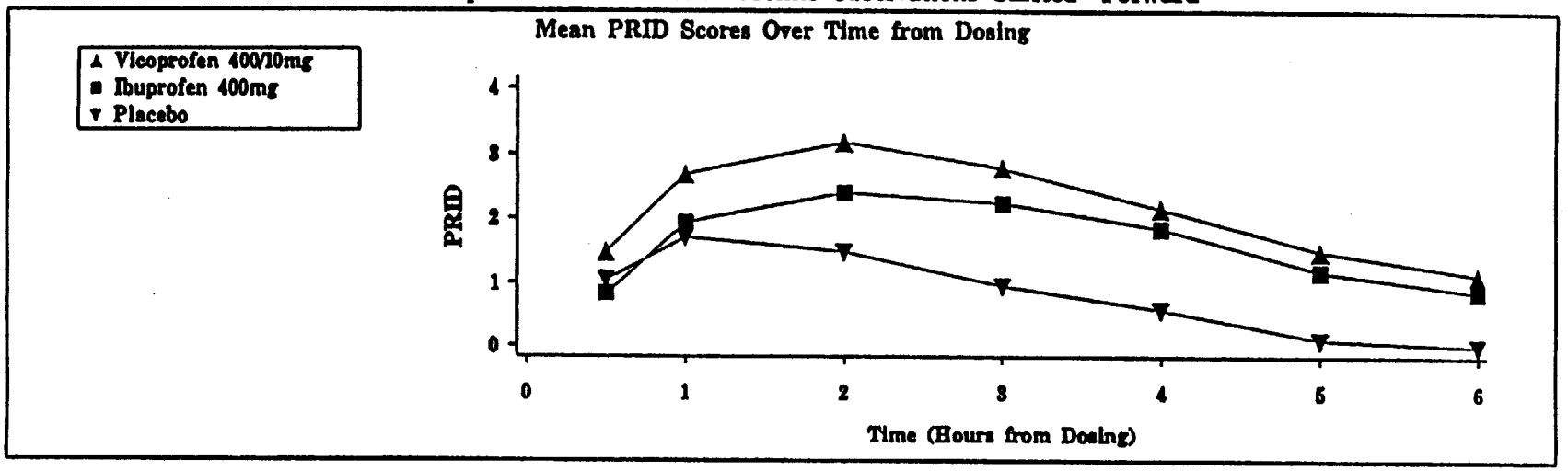
FIGURE 2
VP-01-0101 Pain Relief Scores
Means (Standard Deviations), Sample Sizes, and Fisher's Protected LSD Comparisons
All Acceptable Patients with Baseline Observations Carried-Forward



Treatment	Assessment Time Point (in Hours from Dosing)													
	0.5		1		2		3		4		5		6	
Vicoprofen 400/10mg (n=40)(d)	1.08 [40](a)	(0.86) A(c)	1.85 [40]	(1.33) A	2.10 [34]	(1.60) A	1.80 [26]	(1.64) A	1.43 [24]	(1.53) A	1.00 [16]	(1.47) A	0.78 [12]	(1.31) A
Ibuprofen 400mg (n=40)	0.65 [40]	(0.77) A	1.38 [40]	(1.25) A	1.60 [30]	(1.53) AB	1.40 [20]	(1.68) A	1.15 [17]	(1.55) A	0.75 [15]	(1.32) A	0.55 [9]	(1.20) A
Placebo (n=40)	0.75 [40]	(0.78) A	1.25 [40]	(1.03) A	1.05 [28]	(1.18) B	0.63 [14]	(1.08) B	0.38 [10]	(0.95) B	0.08 [5]	(0.27) B	0.00 [1]	(0.00) B
Treatment P-Value(b)	0.050		0.070		0.007		0.002		0.003		0.001		0.003	
RMS Error(b)	0.803		1.212		1.447		1.489		1.372		1.148		1.025	

(a) Represents the number of subjects evaluating efficacy at that time point (i.e. number of active subjects).
(b) Model: REL = μ + Trt(I) + Error
(c) 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.
(d) 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

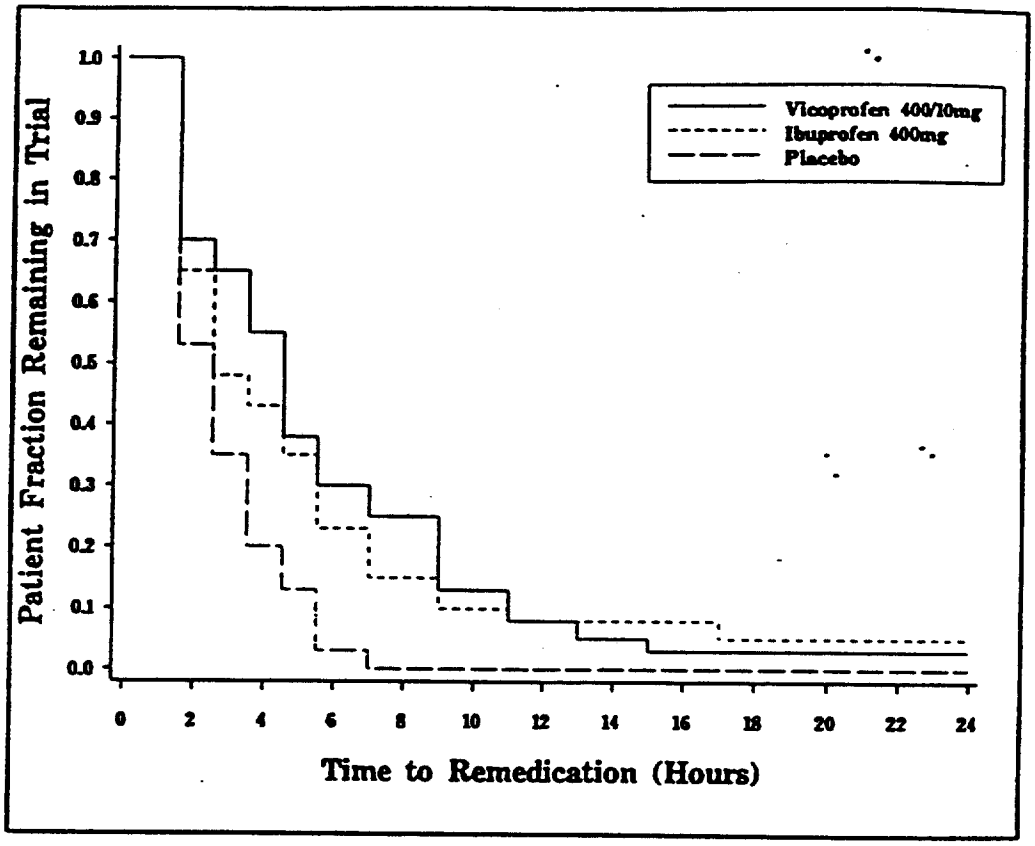


Treatment	Assessment Time Point (in Hours from Dosing)													
	0.5		1		2		3		4		5		6	
Vicoprofen 400/10mg (n=40)(e)	1.48 [40](a)	(1.30) A(d)	2.68 [40]	(2.03) A	3.18 [34]	(2.54) A	2.78 [26]	(2.60) A	2.15 [24]	(2.35) A	1.50 [16]	(2.23) A	1.13 [12]	(1.95) A
Ibuprofen 400mg (n=40)	0.83 [40]	(1.11) A	1.93 [40]	(2.02) A	2.40 [30]	(2.50) AB	2.23 [20]	(2.75) A	1.85 [17]	(2.54) A	1.18 [15]	(2.11) A	0.85 [9]	(1.90) A
Placebo (n=40)	1.05 [40]	(1.18) A	1.70 [40]	(1.65) A	1.48 [28]	(1.80) B	0.95 [14]	(1.66) B	0.58 [10]	(1.45) B	0.10 [5]	(0.32) B	0.00 [1]	(0.00) B
Treatment P-Value(b)	0.051		0.061		0.006		0.003		0.004		0.002		0.005	
Trt*Baseline P-Value(c)	0.187		0.231		0.368		0.215		0.179		0.105		0.154	
RMS Error(b)	1.200		1.914		2.312		2.378		2.177		1.793		1.579	

(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 4

Product Limit Plot of Time-to-Remedication (All Evaluable Subjects)



Treatment	Calculated Time-to-Remedication	
	Median Time [1] (decimal hours)	95%-CI [2] (decimal hours)
Vicoprofen 400/10mg	4.17 A [3]	2.33 - 5.50
Ibuprofen 400mg	2.75 A	1.67 - 5.00
Placebo	2.04 B	1.58 - 3.00

[1] Kaplan-Meier estimate (see Miller, Survival Analysis, page 75)

[2] Method of Simon & Lee, Cancer Treat Rep 66:37-42, 1982

[3] Logrank test applied as in Fisher's PLSD.

Knoll Pharmaceuticals
Protocol #: VP-01-01

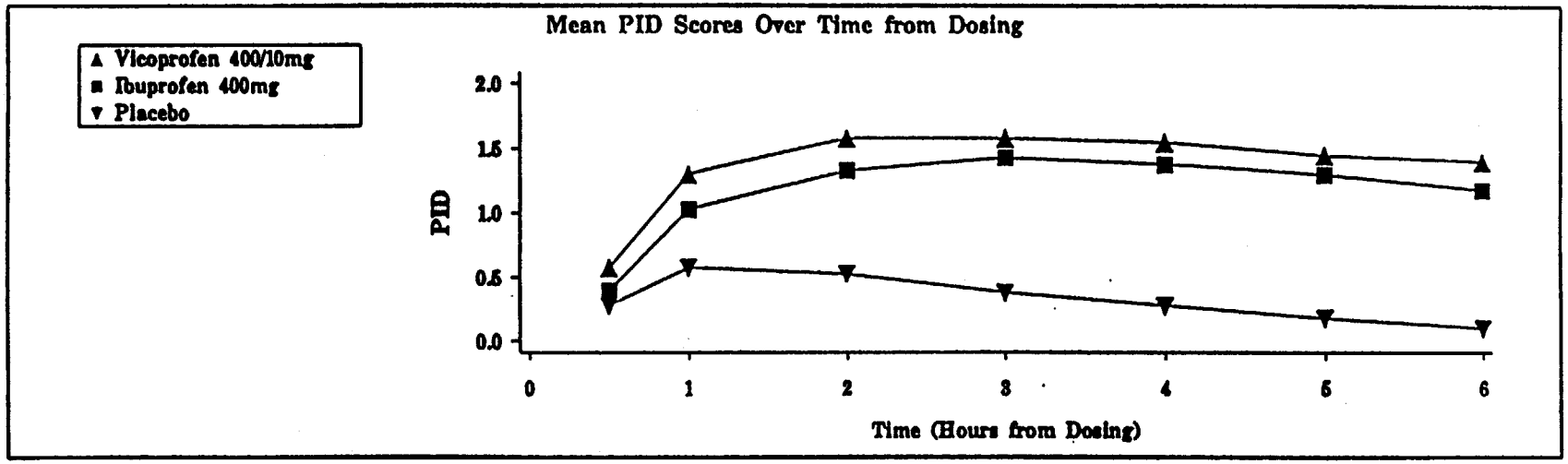
Table 1

Estimated Onset of Pain Relief (on-PR)

Treatment	PRID at 30 min			Estimated on-PR	
	Mean	SD	N	Time in min	95%-CI in min
Vicoprofen 400/10mg	1.48	1.30	40	20.3 A (1)	15.9 - 28.3
Ibuprofen 400mg	0.83	1.11	40	36.4 A	25.4 - 63.7
Placebo	1.05	1.18	40	28.6 A	21.0 - 44.5

Note: Onset = 30/PRID30 (Combined pain relief and pain intensity difference scores at 30 minutes).
(1) Separation based on 30 minute PRID LSmeans.

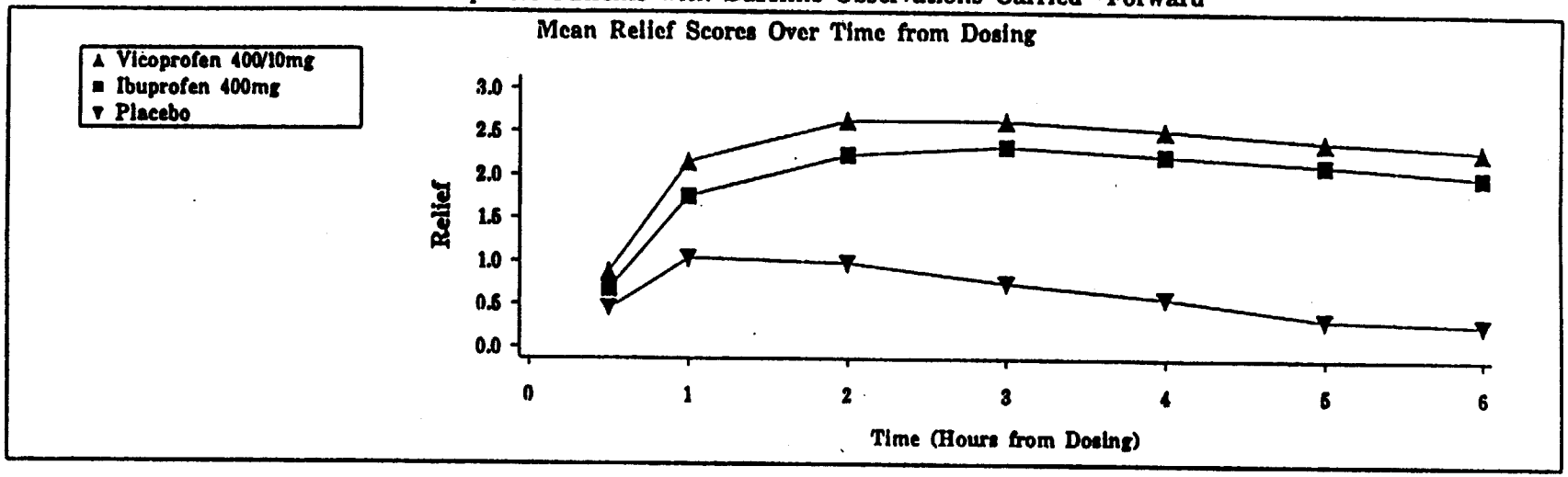
FIGURE 1
VP-01-0102 PID Scores
Means (Standard Deviations), Sample Sizes, and Fisher's Protected LSD Comparisons
All Acceptable Patients with Baseline Observations Carried-Forward



Treatment	Assessment Time Point (in Hours from Dosing)													
	0.5		1		2		3		4		5		6	
Vicoprofen 400/10mg (n=40)(e)	0.58 [40](a)	(0.68) A(d)	1.30 [40]	(0.88) A	1.58 [36]	(1.08) A	1.58 [33]	(0.98) A	1.55 [22]	(1.06) A	1.45 [29]	(1.13) A	1.40 [28]	(1.13) A
Ibuprofen 400mg (n=40)	0.40 [40]	(0.59) A	1.03 [40]	(0.95) A	1.33 [34]	(0.92) A	1.43 [30]	(1.01) A	1.38 [28]	(1.08) A	1.30 [27]	(1.04) A	1.18 [26]	(0.98) A
Placebo (n=40)	0.28 [40]	(0.45) A	0.58 [40]	(0.71) B	0.53 [20]	(0.72) B	0.38 [15]	(0.67) B	0.28 [13]	(0.58) B	0.18 [8]	(0.50) B	0.10 [7]	(0.50) B
Treatment P-Value(b)	0.055		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001	
Trt*Baseline P-Value(c)	0.086		0.094		0.037		0.028		0.205		0.136		0.277	
RMS Error(b)	0.552		0.811		0.892		0.882		0.949		0.927		0.905	

(a) Represents the number of subjects evaluating efficacy at that time point (i.e. number of active subjects).
(b) Model: PID $= \mu + Trt(i) + Baseline(j) + Error$
(c) Model: PID $= \mu + Trt(i) + Baseline(j) + Trt*Baseline(ij) + Error$
(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.

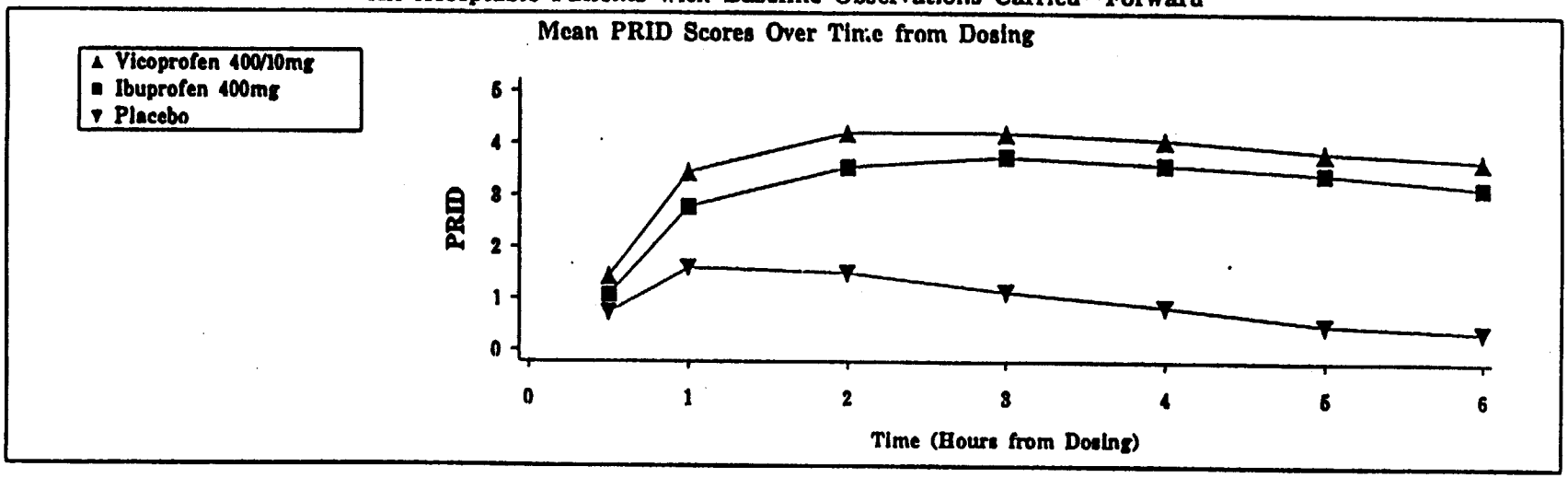
FIGURE 2
VP-01-0102 Pain Relief Scores
Means (Standard Deviations), Sample Sizes, and Fisher's Protected LSD Comparisons
All Acceptable Patients with Baseline Observations Carried-Forward



Treatment	Assessment Time Point (in Hours from Dosing)													
	0.5		1		2		3		4		5		6	
Vicoprofen 400/10mg (n=40)(d)	0.88 [40](a)	(0.97) A(c)	2.15 [40]	(1.27) A	2.63 [36]	(1.44) A	2.63 [33]	(1.35) A	2.63 [32]	(1.57) A	2.40 [29]	(1.61) A	2.30 [28]	(1.65) A
Ibuprofen 400mg (n=40)	0.68 [40]	(0.80) A	1.75 [40]	(1.32) A	2.23 [34]	(1.42) A	2.33 [30]	(1.53) A	2.23 [28]	(1.66) A	2.13 [27]	(1.65) A	2.00 [26]	(1.60) A
Placebo (n=40)	0.45 [40]	(0.71) A	1.03 [40]	(1.14) B	0.98 [20]	(1.27) B	0.75 [15]	(1.26) B	0.58 [13]	(1.20) B	0.33 [8]	(0.94) B	0.28 [7]	(0.91) B
Treatment P-Value(b)	0.078		< 0.001		< 0.001		< 0.001		< 0.001		< 0.001		< 0.001	
RMS Error(b)	0.832		1.246		1.382		1.383		1.487		1.440		1.427	

(a) Represents the number of subjects evaluating efficacy at that time point (i.e. number of active subjects).
(b) Model: REL $= \mu + Trt(I) + Error$
(c) 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.
(d) 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

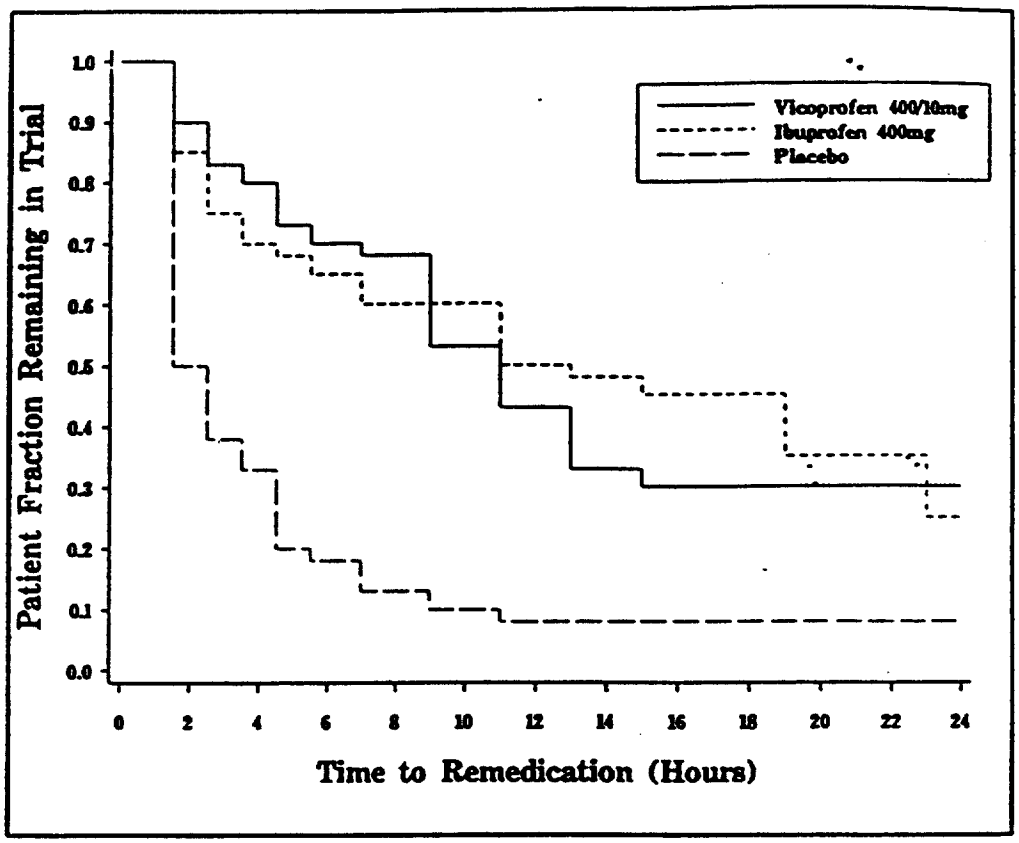


Treatment	Assessment Time Point (in Hours from Dosing)													
	0.5		1		2		3		4		5		6	
Vicoprofen 400/10mg (n=40)(e)	1.45 [40](a)	(1.60) A(d)	3.45 [40]	(2.11) A	4.20 [36]	(2.47) A	4.20 [33]	(2.28) A	4.08 [32]	(2.59) A	3.85 [29]	(2.69) A	3.70 [28]	(2.74) A
Ibuprofen 400mg (n=40)	1.08 [40]	(1.33) 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)	0.73 [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)	0.069		<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 4

Product Limit Plot of Time-to-Remedication
(All Evaluable Subjects)



Treatment	Calculated Time-to-Remedication	
	Median Time [1] (decimal hours)	95%-CI [2] (decimal hours)
Vicoprofen 400/10mg	10.50 A [3]	8.75 - 12.75
Ibuprofen 400mg	12.25 A	5.17 - 22.67
Placebo	2.00 B	1.45 - 3.25

[1] Kaplan-Meier estimate (see Miller, Survival Analysis, page 75)

[2] Method of Simon & Lee, Cancer Treat Rep 66:37-42, 1982

[3] Logrank test applied as in Fisher's PLSD.

Date: 08MAR96
Time: 16:44

Knoll Pharmaceuticals
Protocol #: VP-01-02

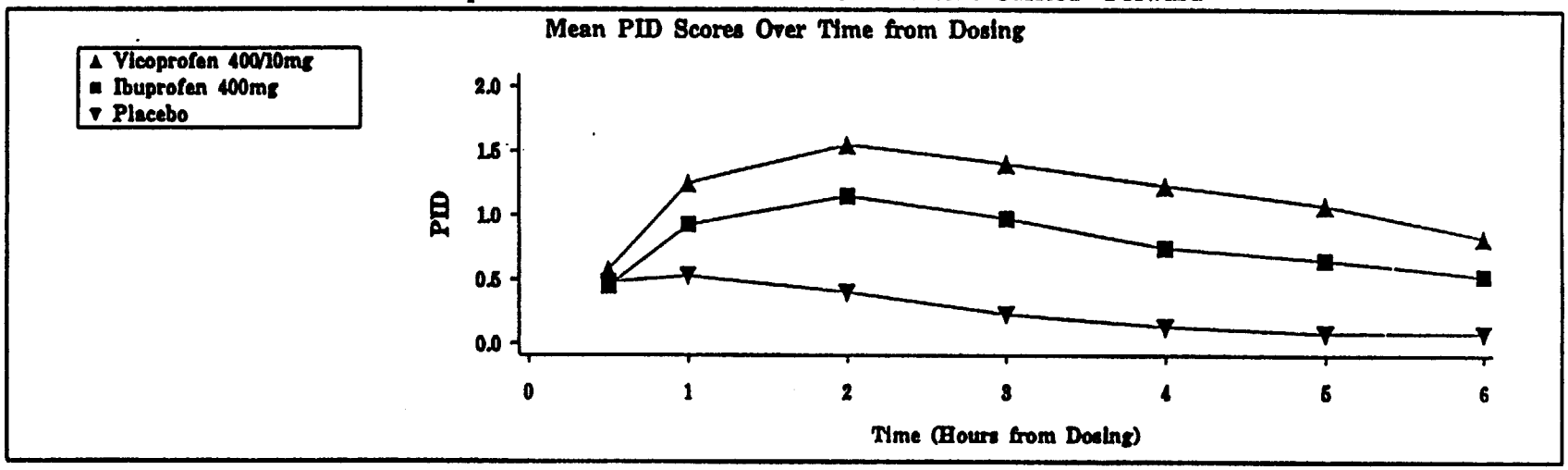
Table 1

Estimated Onset of Pain Relief (on-PR)

Treatment	PRID at 30 min			Estimated on-PR	
	Mean	SD	N	Time in min	95%-CI in min
Vicoprofen 400/10mg	1.45	1.60	40	20.7 A (1)	15.3 - 32.0
Ibuprofen 400mg	1.08	1.33	40	27.9 A	20.0 - 46.1
Placebo	0.73	1.11	40	41.4 A	27.8 - 81.0

Note: Onset = 30/PRID30 (Combined pain relief and pain intensity difference scores at 30 minutes).
(1) Separation based on 30 minute PRID LSmeans.

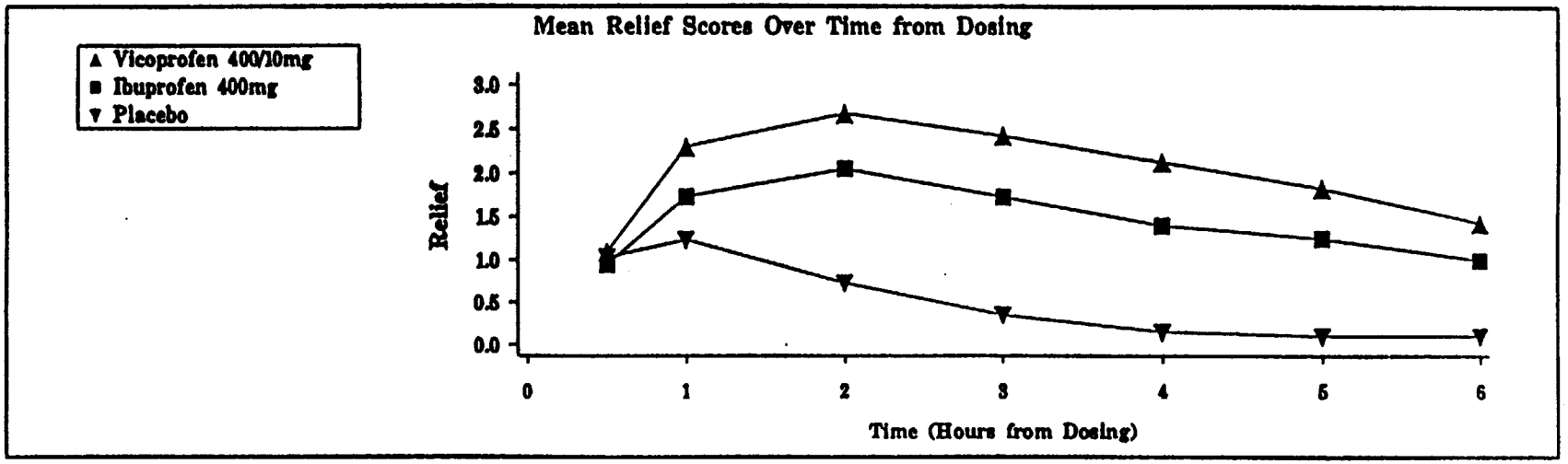
FIGURE 1
VP-01-0103 PID Scores
Means (Standard Deviations), Sample Sizes, and Fisher's Protected LSD Comparisons
All Acceptable Patients with Baseline Observations Carried-Forward



Treatment	Assessment Time Point (in Hours from Dosing)													
	0.5		1		2		3		4		5		6	
Vicoprofen 400/10mg (n=40)(e)	0.58 [40](a)	(0.81) A(d)	1.25 [40]	(1.03) A	1.55 [34]	(1.06) A	1.40 [31]	(1.03) A	1.23 [28]	(1.00) A	1.08 [27]	(1.05) A	0.83 [23]	(0.96) A
Ibuprofen 400mg (n=40)	0.45 [40]	(0.78) A	0.93 [40]	(0.83) A	1.15 [30]	(1.12) A	0.96 [25]	(1.10) B	0.75 [21]	(1.01) B	0.65 [17]	(0.95) B	0.53 [14]	(0.91) A
Placebo (n=40)	0.48 [40]	(0.78) A	0.53 [40]	(0.75) B	0.40 [27]	(0.74) B	0.23 [14]	(0.53) C	0.13 [7]	(0.40) C	0.08 [3]	(0.35) C	0.08 [2]	(0.35) B
Treatment P-Value(b)	0.745		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001	
Trt*Baseline P-Value(c)	0.273		0.168		0.488		0.810		0.735		0.729		0.949	
RMS Error(b)	0.770		0.828		0.934		0.904		0.849		0.838		0.788	

(a) Represents the number of subjects evaluating efficacy at that time point (i.e. number of active subjects).
(b) Model: PID $= \mu + Trt(i) + Baseline(j) + Error$
(c) Model: PID $= \mu + Trt(i) + Baseline(j) + Trt*Baseline(ij) + Error$
(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.

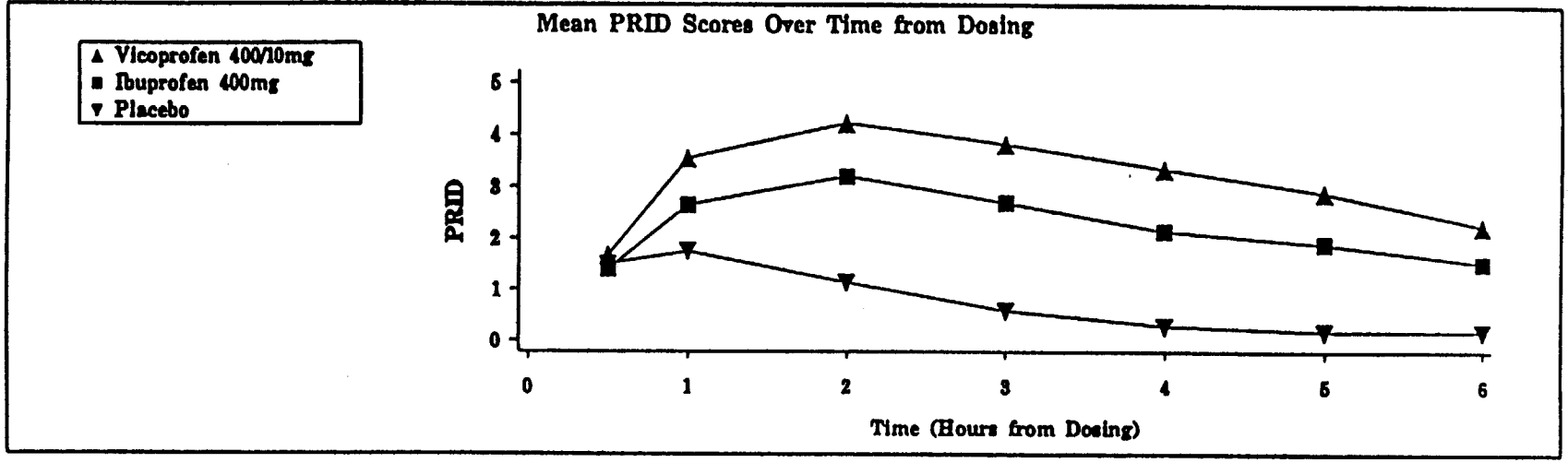
FIGURE 2
VP-01-0103 Pain Relief Scores
Means (Standard Deviations), Sample Sizes, and Fisher's Protected LSD Comparisons
All Acceptable Patients with Baseline Observations Carried-Forward



Treatment	Assessment Time Point (in Hours from Dosing)													
	0.5		1		2		3		4		5		6	
Vicoprofen 400/10mg (n=40)(d)	1.10 [40](a)	(1.26) A(c)	2.30 [40]	(1.38) A	2.68 [34]	(1.59) A	2.43 [31]	(1.65) A	2.13 [28]	(1.67) A	1.83 [27]	(1.77) A	1.43 [23]	(1.71) A
Ibuprofen 400mg (n=40)	0.95 [40]	(1.26) A	1.73 [40]	(1.38) AB	2.05 [30]	(1.66) A	1.73 [25]	(1.77) B	1.40 [21]	(1.71) B	1.25 [17]	(1.63) A	1.00 [14]	(1.67) A
Placebo (n=40)	1.03 [40]	(1.22) A	1.23 [40]	(1.25) B	0.73 [27]	(1.15) B	0.85 [14]	(0.80) C	0.15 [7]	(0.53) C	0.10 [3]	(0.50) B	0.10 [2]	(0.50) B
Treatment P-Value(b)	0.866		0.002		<0.001		<0.001		<0.001		<0.001		<0.001	
RMS Error(b)	1.249		1.338		1.487		1.470		1.411		1.417		1.369	

(a) Represents the number of subjects evaluating efficacy at that time point (i.e. number of active subjects).
(b) Model: REL = μ + Trt(1) + Error
(c) 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.
(d) 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

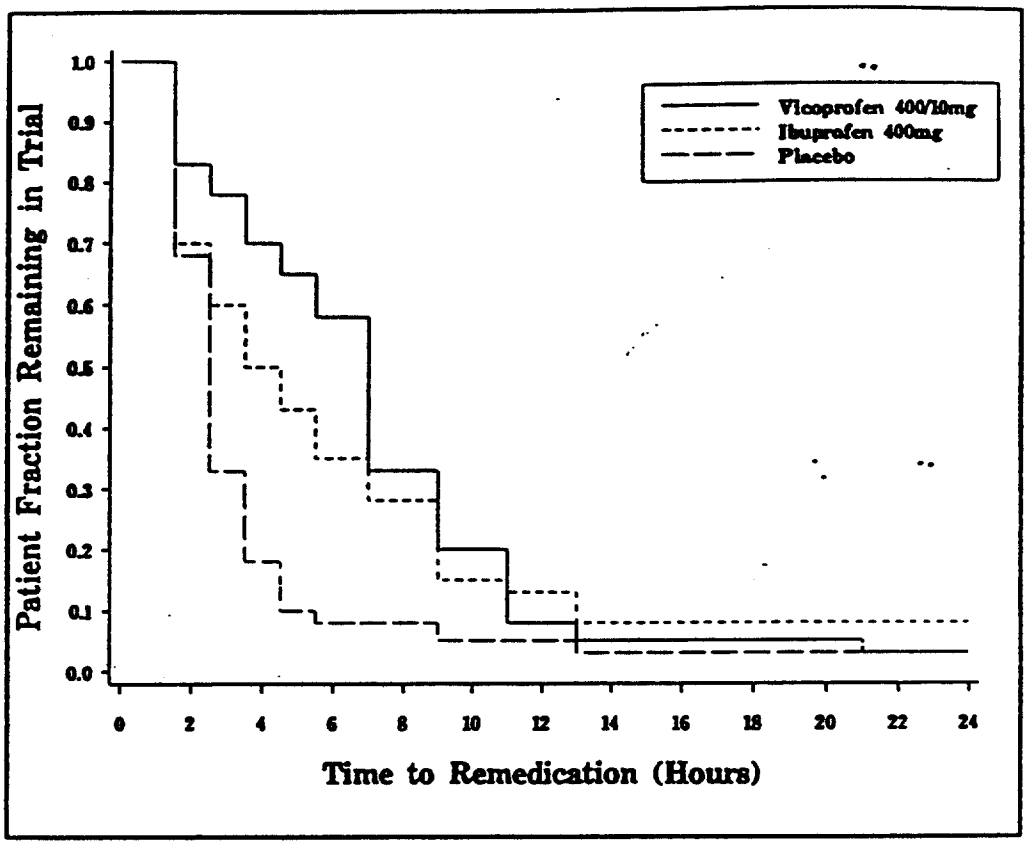


Treatment	Assessment Time Point (In Hours from Dosing)													
	0.5		1		2		3		4		5		6	
Vicoprofen 400/10mg (n=40)(e)	1.68 [40](a)	(2.02) A(d)	3.55 [40]	(2.35) A	4.23 [34]	(2.60) A	3.83 [31]	(2.62) A	3.35 [28]	(2.61) A	2.90 [27]	(2.75) A	2.25 [23]	(2.61) A
Ibuprofen 400mg (n=40)	1.40 [40]	(1.98) 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]	(2.53) 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 4

Product Limit Plot of Time-to-Remedication
(All Evaluable Subjects)



Treatment	Calculated Time-to-Remedication	
	Median Time [1] (decimal hours)	95%-CI [2] (decimal hours)
Vicoprofen 400/10mg	6.46 A [3]	4.92 - 7.58
Ibuprofen 400mg	3.92 A	2.17 - 6.00
Placebo	2.25 B	2.00 - 2.67

[1] Kaplan-Meier estimate (see Miller, Survival Analysis, page 75)

[2] Method of Simon & Lee, Cancer Treat Rep 66:37-42, 1982

[3] Logrank test applied as in Fisher's PLSD.

Date: 11MAR96
Time: 14:59

Knoll Pharmaceuticals
Protocol #: VP-01-03

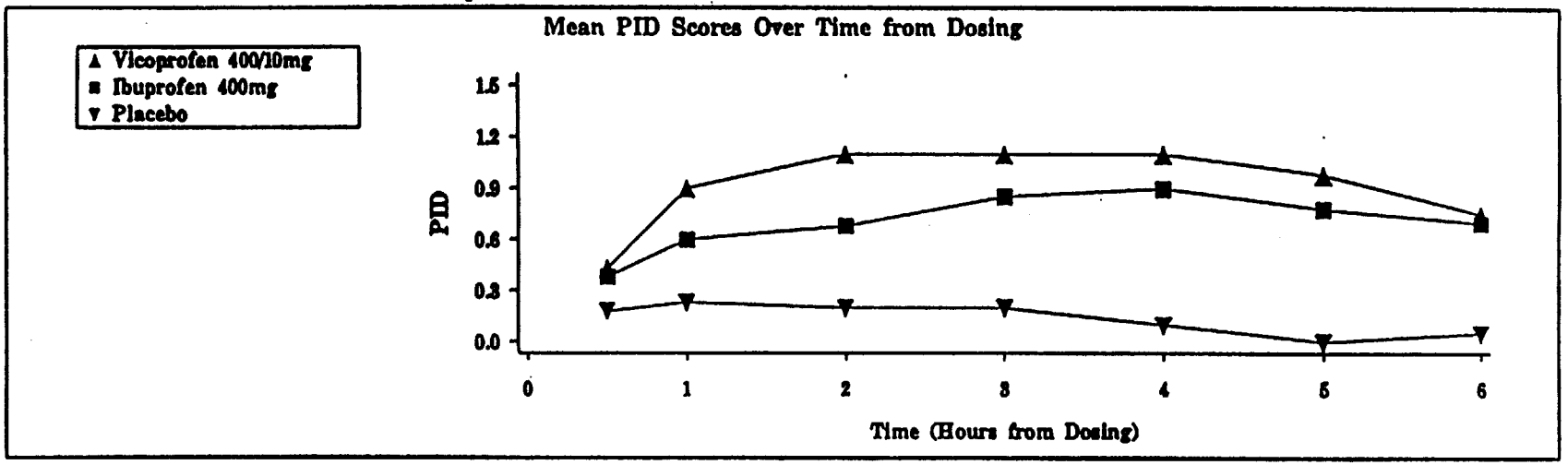
Table 1

Estimated Onset of Pain Relief (on-PR)

Treatment	PRID at 30 min			Estimated on-PR	
	Mean	SD	N	Time in min	95%-CI in min
Vicoprofen 400/10mg	1.68	2.02	40	17.9 A (1)	12.9 - 29.1
Ibuprofen 400mg	1.40	1.98	40	21.4 A	14.7 - 39.2
Placebo	1.50	1.96	40	20.0 A	14.1 - 34.4

Note: Onset = 30/PRID30 (Combined pain relief and pain intensity difference scores at 30 minutes).
(1) Separation based on 30 minute PRID LSmeans.

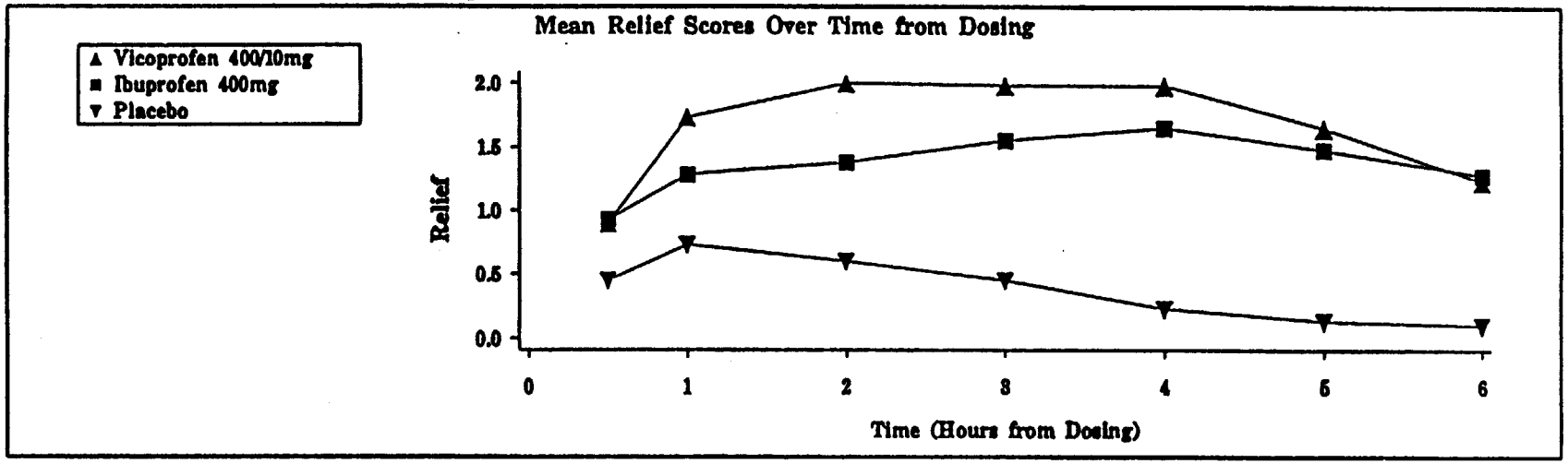
FIGURE 1
VP-01-0104 PID Scores
Means (Standard Deviations), Sample Sizes, and Fisher's Protected LSD Comparisons
All Acceptable Patients with Baseline Observations Carried-Forward



Treatment	Assessment Time Point (in Hours from Dosing)													
	0.5		1		2		3		4		5		6	
Vicoprofen 400/10mg (n=40)(a)	0.43 [40](a)	(0.68) A(d)	0.90 [40]	(1.03) A	1.10 [33]	(1.03) A	1.10 [30]	(0.98) A	1.10 [27]	(1.10) A	0.96 [26]	(1.10) A	0.76 [21]	(1.03) A
Ibuprofen 400mg (n=40)	0.28 [40]	(0.63) A	0.60 [39]	(0.74) A	0.68 [33]	(0.80) B	0.85 [27]	(1.00) A	0.90 [25]	(1.03) A	0.78 [24]	(1.05) A	0.70 [21]	(0.97) A
Placebo (n=40)	0.18 [40]	(0.50) A	0.23 [40]	(0.66) B	0.20 [27]	(0.76) C	0.20 [15]	(0.52) B	0.10 [11]	(0.44) B	0.00 [7]	(0.32) B	0.05 [4]	(0.22) B
Treatment P-Value(b)	0.149		0.001		<0.001		<0.001		<0.001		<0.001		<0.001	
Trt*Baseline P-Value(c)	0.304		0.539		0.352		0.284		0.417		0.636		0.528	
RMS Error(b)	0.601		0.808		0.849		0.842		0.891		0.884		0.818	

(a) Represents the number of subjects evaluating efficacy at that time point (i.e. number of active subjects).
(b) Model: PID $= \mu + Trt(i) + Baseline(j) + Error$
(c) Model: PID $= \mu + Trt(i) + Baseline(j) + Trt*Baseline(ij) + Error$
(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.

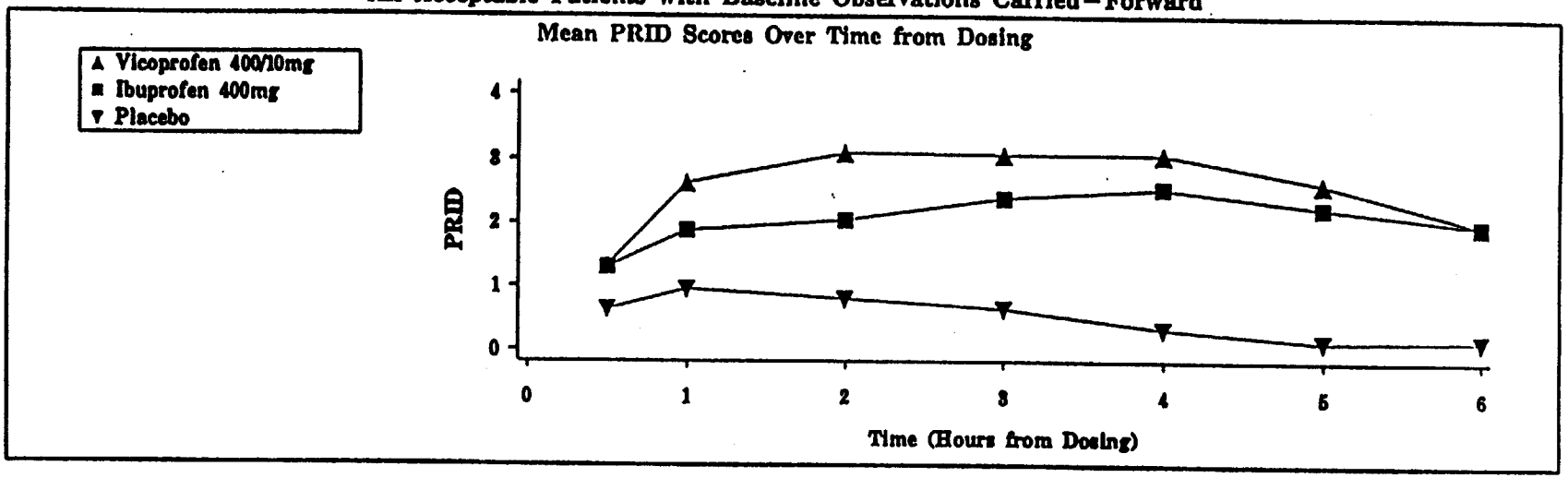
FIGURE 2
VP-01-0104 Pain Relief Scores
Means (Standard Deviations), Sample Sizes, and Fisher's Protected LSD Comparisons
All Acceptable Patients with Baseline Observations Carried-Forward



Treatment	Assessment Time Point (In Hours from Dosing)													
	0.5		1		2		3		4		5		6	
Vicoprofen 400/10mg (n=40)(d)	0.90 [40](a)	(0.96) A(c)	1.73 [40]	(1.43) A	2.00 [33]	(1.52) A	1.98 [30]	(1.51) A	1.96 [27]	(1.64) A	1.65 [26]	(1.73) A	1.23 [21]	(1.64) A
Ibuprofen 400mg (n=40)	0.93 [40]	(1.12) A	1.28 [39]	(1.18) A	1.38 [33]	(1.37) B	1.55 [27]	(1.57) A	1.65 [25]	(1.63) A	1.48 [24]	(1.63) A	1.28 [21]	(1.60) A
Placebo (n=40)	0.45 [40]	(0.71) B	0.73 [40]	(1.01) B	0.60 [27]	(1.08) C	0.45 [15]	(0.93) B	0.23 [11]	(0.70) B	0.13 [7]	(0.46) B	0.10 [4]	(0.44) B
Treatment P-Value(b)	0.047		0.002		<0.001		<0.001		<0.001		<0.001		<0.001	
RMS Error(b)	0.953		1.219		1.336		1.367		1.393		1.400		1.348	

(a) Represents the number of subjects evaluating efficacy at that time point (i.e. number of active subjects).
(b) Model: REL = μ + Trt(I) + Error
(c) 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.
(d) 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

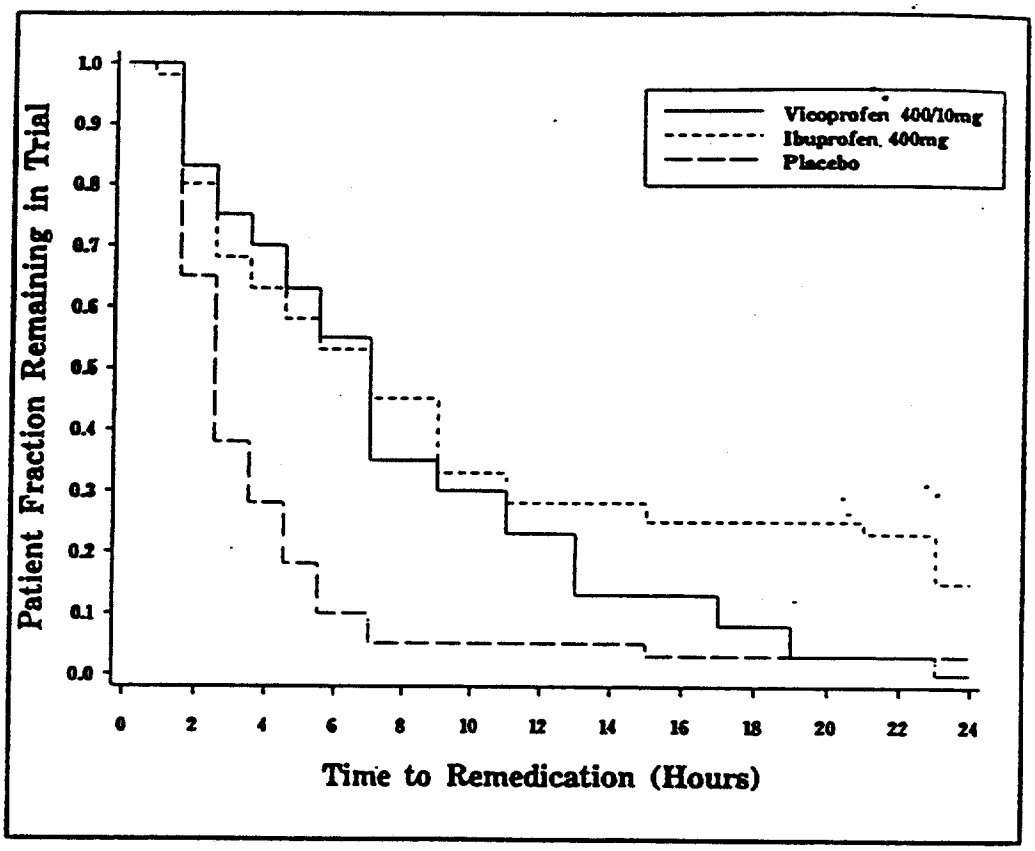


Treatment	Assessment Time Point (in Hours from Dosing)													
	0.5		1		2		3		4		5		6	
Vicoprofen 400/10mg (n=40)(e)	1.83 [40](a)	(1.59) A(d)	2.63 [40]	(2.39) A	3.10 [33]	(2.50) A	3.08 [30]	(2.43) A	3.06 [27]	(2.69) A	2.62 [26]	(2.78) A	1.98 [21]	(2.63) A
Ibuprofen 400mg (n=40)	1.30 [40]	(1.68) 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 $= \mu + Trt(i) + Baseline(j) + Error$
(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 4

Product Limit Plot of Time-to-Remedication
(All Evaluable Subjects)



Treatment	Calculated Time-to-Remedication	
	Median Time [1] (decimal hours)	95%-CI [2] (decimal hours)
Vicoprofen 400/10mg	6.08 A [3]	4.33 - 9.00
Ibuprofen 400mg	6.08 A	3.08 - 9.92
Placebo	2.21 B	1.58 - 3.17

[1] Kaplan-Meier estimate (see Miller, Survival Analysis, page 75)

[2] Method of Simon & Lee, Cancer Treat Rep 66:37-42, 1982

[3] Logrank test applied as in Fisher's PLSD.

Knoll Pharmaceuticals
Protocol #: VP-01-04

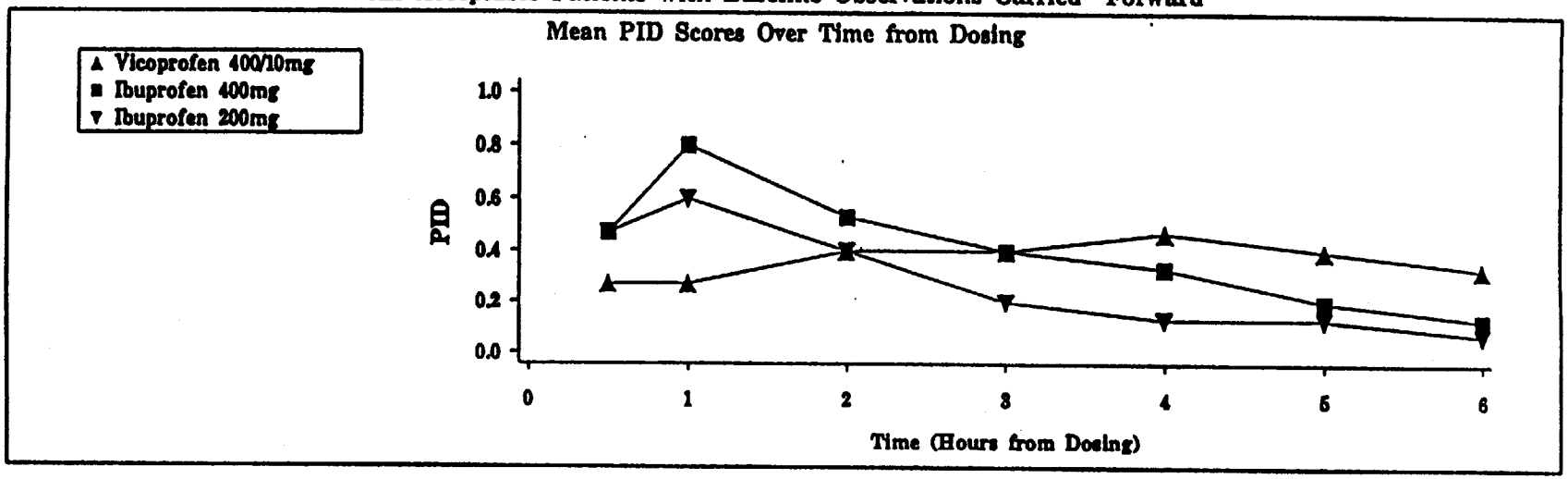
Table 1

Estimated Onset of Pain Relief (on-PR)

Treatment	PRID at 30 min			Estimated on-PR	
	Mean	SD	N	Time in min	95%-CI in min
Vicoprofen 400/10mg	1.33	1.59	40	22.6 A (1)	16.4 - 36.8
Ibuprofen 400mg	1.30	1.68	40	23.1 A	16.3 - 39.4
Placebo	0.63	1.15	40	48.0 A	30.2 - 116.3

Note: Onset = 30/PRID30 (Combined pain relief and pain intensity difference scores at 30 minutes).
(1) Separation based on 30 minute PRID LSmeans.

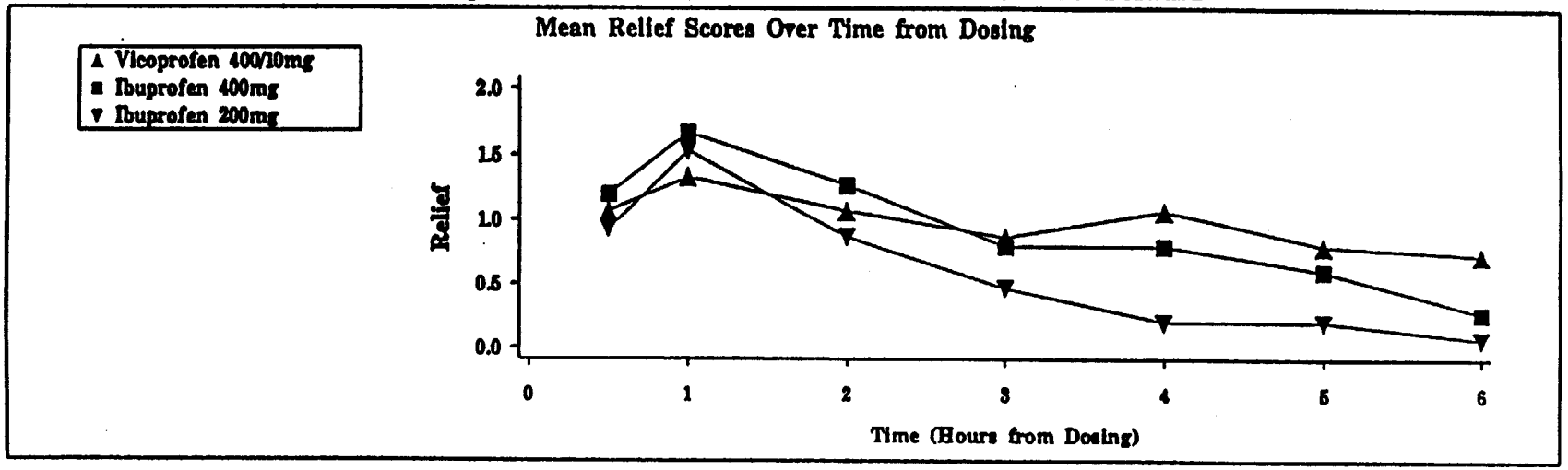
FIGURE 1
VP-12-1201 PID Scores
Means (Standard Deviations), Sample Sizes, and Fisher's Protected LSD Comparisons
All Acceptable Patients with Baseline Observations Carried-Forward



Treatment	Assessment Time Point (in Hours from Dosing)											
	0.5		1		2		3		4		5		6	
Vicoprofen 400/10mg (n=15)(e)	0.27 [15](a)	(0.46) A(d)	0.27 [15]	(0.59) A	0.40 [9]	(0.83) A	0.40 [7]	(0.74) A	0.47 [6]	(0.74) A	0.40 [5]	(0.74) A	0.33 [4]	(0.62) A
Ibuprofen 400mg (n=15)	0.47 [15]	(0.64) A	0.80 [15]	(0.86) A	0.53 [10]	(0.74) A	0.40 [6]	(0.74) A	0.33 [5]	(0.62) A	0.20 [5]	(0.41) A	0.13 [3]	(0.35) A
Ibuprofen 200mg (n=15)	0.47 [15]	(0.52) A	0.60 [15]	(0.74) A	0.40 [10]	(0.74) A	0.20 [4]	(0.56) A	0.13 [2]	(0.52) A	0.13 [1]	(0.52) A	0.07 [1]	(0.26) A
Treatment P-Value(b)	0.587		0.308		0.954		0.619		0.518		0.400		0.221	
Trt*Baseline P-Value(c)	0.506		0.209		0.022		0.394		0.881		0.230		0.605	
RMS Error(b)	0.533		0.708		0.758		0.676		0.634		0.577		0.441	

(a) Represents the number of subjects evaluating efficacy at that time point (i.e. number of active subjects).
(b) Model: PID = μ + Trt(i) + Baseline(j) + Error
(c) Model: PID = 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.

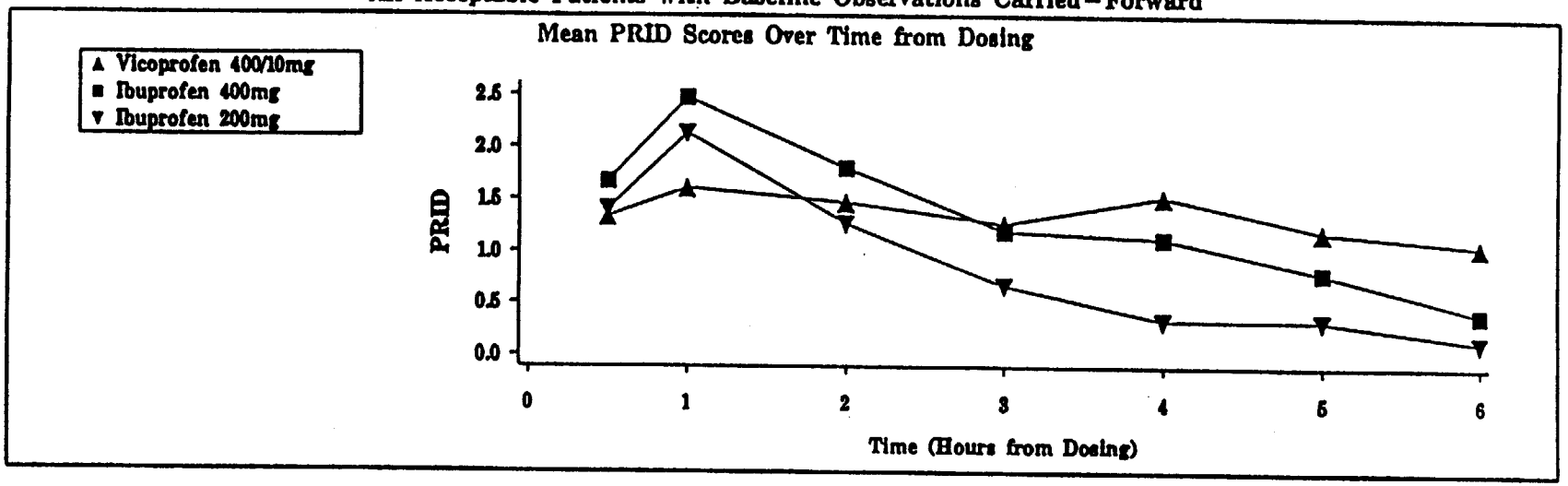
FIGURE 2
VP-12-1201 Pain Relief Scores
Means (Standard Deviations), Sample Sizes, and Fisher's Protected LSD Comparisons
All Acceptable Patients with Baseline Observations Carried-Forward



Treatment	Assessment Time Point (in Hours from Dosing)													
	0.5		1		2		3		4		5		6	
Vicoprofen 400/10mg (n=15)(d)	1.07 [15](a)	(1.22) A(c)	1.33 [15]	(0.98) A	1.07 [9]	(1.22) A	0.87 [7]	(1.19) A	1.07 [6]	(1.39) A	0.80 [5]	(1.37) A	0.73 [4]	(1.28) A
Ibuprofen 400mg (n=15)	1.20 [15]	(1.21) A	1.67 [15]	(1.35) A	1.27 [10]	(1.53) A	0.80 [6]	(1.26) A	0.80 [5]	(1.26) A	0.60 [5]	(1.12) A	0.27 [3]	(0.80) A
Ibuprofen 200mg (n=15)	0.93 [15]	(0.96) A	1.53 [15]	(1.06) A	0.87 [10]	(1.13) A	0.47 [4]	(0.92) A	0.20 [2]	(0.77) A	0.20 [1]	(0.77) A	0.07 [1]	(0.26) A
Treatment P-Value(b)	0.814		0.724		0.705		0.588		0.129		0.335		0.118	
RMS Error(b)	1.137		1.138		1.306		1.132		1.172		1.117		0.884	

(a) Represents the number of subjects evaluating efficacy at that time point (i.e. number of active subjects).
(b) Model: REL = μ + Trt(I) + Error
(c) 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.
(d) 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

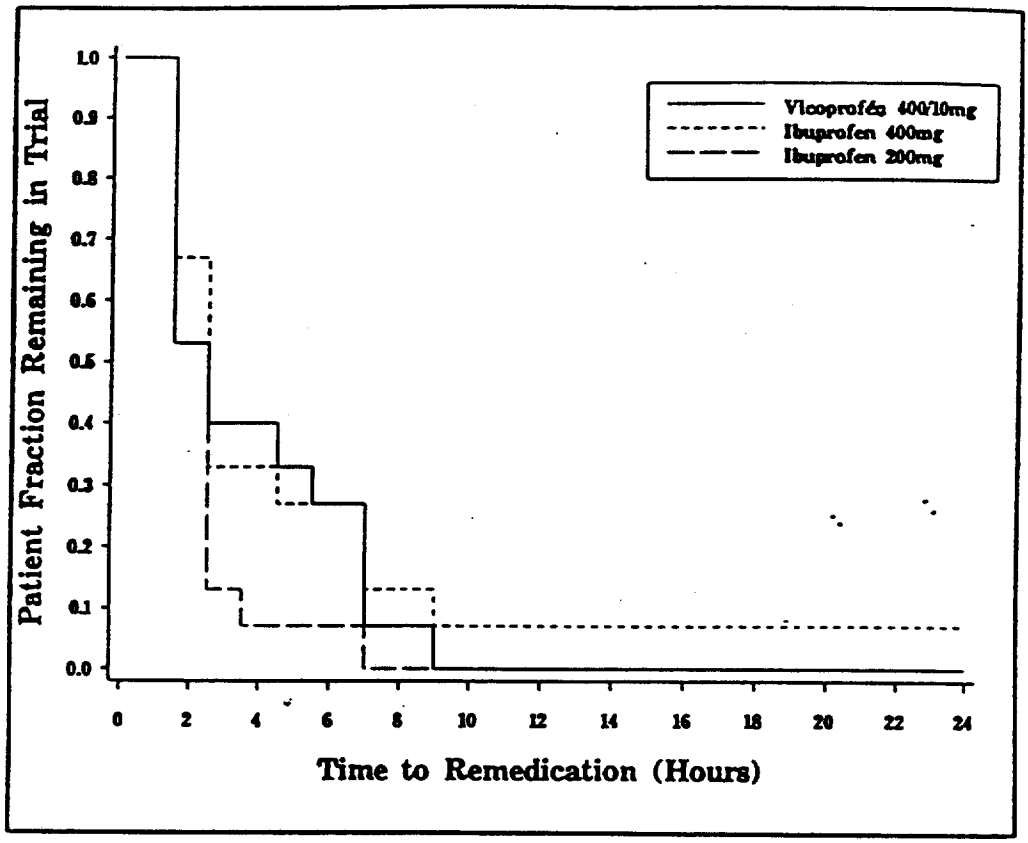


Treatment	Assessment Time Point (in Hours from Dosing)													
	0.5		1		2		3		4		5		6	
Vicoprofen 400/10mg (n=15)(e)	1.53 [15](a)	(1.64) A(d)	1.60 [15]	(1.45) A	1.47 [9]	(1.92) A	1.27 [7]	(1.83) A	1.53 [6]	(2.07) A	1.20 [5]	(2.08) A	1.07 [4]	(1.87) A
Ibuprofen 400mg (n=15)	1.67 [15]	(1.60) A	2.47 [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		0.562	
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.

FIGURE 4

Product Limit Plot of Time-to-Remedication
(All Evaluable Subjects)



Treatment	Calculated Time-to-Remedication	
	Median Time [1] (decimal hours)	95%-CI [2] (decimal hours)
Vicoprofen 400/10mg	2.08 A [3]	1.08 - 6.50
Ibuprofen 400mg	2.00 A	1.00 - 6.00
Ibuprofen 200mg	2.00 A	1.00 - 2.33

[1] Kaplan-Meier estimate (see Miller, Survival Analysis, page 75)

[2] Method of Simon & Lee, Cancer Treat Rep 66:37-42, 1982

[3] Logrank test applied as in Fisher's PLSD.

Knoll Pharmaceuticals
Protocol #: VP-12

Table 1

Estimated Onset of Pain Relief (on-PR)

Treatment	PRID at 30 min			Estimated on-PR	
	Mean	SD	N	Time in min	95%-CI in min
Vicoprofen 400/10mg	1.33	1.54	15	22.5 A (1)	13.7 - 62.7
Ibuprofen 400mg	1.67	1.80	15	18.0 A	11.3 - 44.8
Ibuprofen 200mg	1.40	1.40	15	21.4 A	13.8 - 48.2

Note: Onset = 30/PRID30 (Combined pain relief and pain intensity difference scores at 30 minutes).
(1) Separation based on 30 minute PRID LSmeans.

AUG 13 1997

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

550

MEDICAL OFFICER REVIEW

ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMIC DRUG PRODUCTS DIVISION -- HFD-550

NDA #:	**20-716.**
SUBMISSION DATES:	May 23 and June 19, 1997.
TYPE:	Response to approvable letter.
REVIEW DATE:	August 7, 1997.
REVIEWER:	John Hyde, Ph.D., M.D.
NAME:	**VICOPROFEN (hydrocodone bitartrate and ibuprofen tablets).**
SPONSOR:	Knoll Pharmaceutical Company 199 Cherry Hill Road Parsippany, NJ 07054 phone (201) 426-2600
PHARMACOLOGIC CATEGORY:	Opioid and NSAID combination analgesic.
PROPOSED INDICATIONS:	Management of pain.
DOSAGE FORM & ROUTE:	Oral tablets, 7.5 mg/200 mg
NDA DRUG CLASSIFICATION:	4S
RELATED REVIEWS:	Medical Officer NDA review, 3/31/97.
CSO:	V. Lutwak

RESUME:

Re-analysis of Study VP-04:

Item 1 of the approvable letter of 4/17/97 requested a re-anlaysis of VP-04. One of the investigators in this one-month study was Dr. Fiddes, who is under investigation by DSI. The applicant was asked to analyze the study with this investigator removed. The applicant's response is under Tab 1 of the 5/23/97 submission. The main effect of removing Dr. Fiddes' data was that several of the differences between the high dose (two tablet) arm and the other two arms (one tablet arm and APAP/codeine arm) are no longer statistically significant. However, the point estimates of the various efficacy measures and adverse event rates generally are not significantly altered. Thus there is no clear evidence of any bias introduced by the patients from Dr. Fiddes' site; the principal effect of their removal is loss of power.

Vital Signs:

Item 2 in the approvable letter requested an analysis of vital signs. This was addressed under Tab 2 of the 5/23/97 submission. Only studies VP-02, VP-27 and VP-30, collected pre- and post-dose vital signs, and VP-02 included only respiratory rate. These were all single-dose PK studies using either the 400/10 or 400/15 doses of ibuprofen/hydrocodone. A total of 93 subjects were involved. In the arms receiving vicoprofen, the greatest respiratory rate decrease was 1.1 resp/min, the greatest fall in HR was 5.2

bpm, the greatest fall in sitting SBP was 4.8 mm Hg and the greatest fall in DBP was 5.7 mm Hg. There did not appear to be any substantial overall effect on vital signs.

Dissolution:
Item 3 in the approvable letter requested dissolution data for study VP-09. This was addressed under Tab 3 of the 5/23/97 submission. At 30 minutes the vicoprofen tablet averaged % dissolution for ibuprofen and dissolution for hydrocodone. The ibuprofen comparator tablet was dissolved at 30 minutes. Thus the superiority of vicoprofen over ibuprofen is reasonably attributable to the hydrocodone component, and not to a substantially inferior formation of ibuprofen.

Safety Update:
This was presented under Tab 10 of the 5/23/97 submission. Since the initial safety summary, two studies have been completed and two are ongoing. The completed studies are VP-28, a single-dose post-op pain study with 181 patients; and VP-41, a 2-arm PK study in 25 subjects. The ongoing studies are VP-40, a single-dose post-op pain study with 50 patients recruited; and VP-43, a single-dose dental pain study with 42 patients recruited.

Studies VP-28 and VP40 have not reported any serious adverse events or dropouts for adverse events. VP-41 (the PK study) had no serious adverse events, but one subject dropped out because of bruised arms from phlebotomy.

One serious adverse event was reported in dental pain study VP-43:

> A 25 y.o. white female took two vicoprofen tablets (400/15) an hour following extraction of two molars. After 50 minutes she began feeling lightheaded. Over the next hour her blood pressure fell from 130/84 to 90/68 and she complained of chest tightness and nausea. She was transferred to an emergency room where she was found to have SVT. She was treated with Benadryl IV, Solu-Medrol IV, Tagamet IV, Maalox and Reglan. She was discharged after 5 hours in the ER with no sequelae. The diagnosis was allergic reaction/idiosyncratic reaction to study medication. She had taken ibuprofen in the past without problem.

This appears to be an allergic reaction. The labeling already includes allergic reaction as a listed adverse event, and there is an Anaphylactoid Reactions section under WARNINGS.

Phase 4:

Maximum daily dose:
At the meeting on 5/19/97 the sponsor argued for daily dosing greater than 4 tablets per day. Data from the clinical studies and the well-know safety profiles of the two components were used in support. The applicant is

agreeing to additional safety studies without any quid pro quo; the 4 tablet daily maximum is adequately supported by the NDA. This reviewer feels it would be reasonable to extend the daily maximum to 5 tablets (which would allow dosing of q4h while awake), with the possibility of increasing this to 6 pending results of the Phase 4 study.

Labeling:
Labeling was submitted under Tab 9 of the 5/23/97 submission. A few modifications need to be made, some of which were already reflected in the applicant's submitted labeling:

In the labeling sent with the approvable letter, the division inadvertently allowed the term "moderate to severe pain" to remain in INDICATION AND USAGE. This is at odds with recent division decisions to omit mention of pain severity in the indication section. At any rate, the term "severe" has been reserved for pain in which potent narcotics are usually required; that is not appropriate for this drug. The pain qualifiers should be removed.

The maximum daily dose can be increased to 5 tablets per day (see discussion above).

Propylene glycol has been deleted from the list of inactive ingredients as requested by the reviewing chemist. This had been left in the approvable letter labeling, but was removed in the applicant's response.

At the 5/19/97 meeting the applicant asked to reverse the order of listing of ibuprofen and hydrocodone; this was considered acceptable. The sponsor has made some additional minor changes that are acceptable.

Appended is revised labeling reflecting the recommended changes; these are shown as revisions to the labeling sent with the 4/17/97 approvable letter.

CONCLUSIONS:
The applicant has responded adequately to the clinical deficiencies in the approvable letter of 4/17/97, and has made the requested Phase 4 commitment. There are no new recommendations to add to the original safety review as a result of the re-analysis of VP-04 or as a result of the safety update. The labeling should be changed to remove the pain qualifier "moderate to severe" in the INDICATION AND USAGE section, and the applicant should be allowed to increase the daily maximum number of tablets to 5. The sponsor's other changes to the labeling are acceptable.

RECOMMENDATIONS:
Pending acceptability of the Chemistry and Biopharmaceutics responses, this NDA can be approved if the applicant submits labeling with the changes as discussed above and shown in the attached labeling.

John E Hyde 8-7-97
John E. Hyde, Ph.D., M.D.

MW 8/13/97

Orig NDA # 20-716
HFD-550/Div File
HFD-340
HFD-550/CSO/Lutwak
HFD-550/Chem/Yaciw
HFD-880/Biopharm/Bashaw
HFD-550/MO/JHyde