

MEANS, (SD), SAMPLE SIZES, AND FISHER'S PROTECTED LSD COMPARISON (VERTICALLY)
 FOR PATIENTS VALID FOR EFFICACY ANALYSIS
 HOURS

DRUG	.25	.5	1	1.5	2	3	3.5	4	5	6
KETO 25 MG	0.68 (1.24) 35	2.50 (2.07) 35 A	4.24 (2.14) 35 A	4.66 (2.20) 32 AB	4.97 (2.06) 32 A	4.74 (2.52) 31 A	4.39 (2.77) 28 A	3.80 (2.90) 24 A	3.07 (2.91) 19 A	2.97 (2.86) 18 A
KETO 12.5 MG	0.68 (1.28) 35	1.99 (1.65) 35 AB	4.30 (1.69) 35 A	4.89 (1.73) 34 A	5.25 (1.68) 34 A	4.63 (2.29) 31 A	4.51 (2.64) 30 A	4.25 (2.75) 26 A	3.70 (2.82) 24 A	3.17 (2.73) 20 A
KETO 6.25 MG	0.45 (0.88) 35	1.50 (1.62) 35 BC	3.07 (2.14) 35 B	3.52 (2.49) 29 C	3.17 (2.60) 25 B	2.37 (2.65) 19 B	2.25 (2.68) 16 B	1.74 (2.50) 12 B	1.58 (2.33) 11 B	1.66 (2.38) 11 B
IBU 200 MG	0.34 (0.90) 35	1.13 (1.58) 35 C	3.10 (2.43) 35 B	3.81 (2.72) 27 BC	4.23 (2.79) 26 AB	4.31 (2.94) 25 A	4.19 (2.98) 24 A	4.02 (2.90) 24 A	3.84 (2.88) 24 A	3.60 (2.86) 22 A
PLACEBO	0.28 (0.85) 35	0.73 (1.27) 35 C	1.13 (1.56) 35 C	1.09 (1.94) 18 D	0.96 (2.10) 14 C	0.98 (2.25) 7 C	1.07 (2.29) 6 B	1.02 (2.29) 6 B	1.01 (2.29) 6 B	1.04 (2.21) 6 B
TRT P (b)	0.3448	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0002
T*BASE (c)	0.1955	0.5930	0.6958	0.6357	0.6295	0.8789	0.8150	0.5574	0.3136	0.2392
RMS (b)	1.0505	1.6496	2.0179	2.2520	2.2893	2.5467	2.6791	2.6816	2.6631	2.6153

(i) SAME LETTER INDICATES ABSENCE OF SIGNIFICANT DIFFERENCE (0.05 LEVEL).
 (a) SAMPLE SIZES ARE NOT EXTRAPOLATED
 (b) MODEL: PRID = u + T(i) + B(j) + error
 (c) MODEL: PRID = u + T(i) + B(j) + TB(ij) + error
 (d) PLSD BASED ON MODEL (b) LSMEANS

Result - Study S91-008 (See graphs and tables on pages 6.1-6.3)

<i>Statistically significant difference</i>	<i>Pain parameter</i>	<i>Time interval</i>
Keto12.5 > PLA	PR	0.5 through 4 hours
	PID	0.5 through 6 hours
	PRID	0.5 through 5 hours

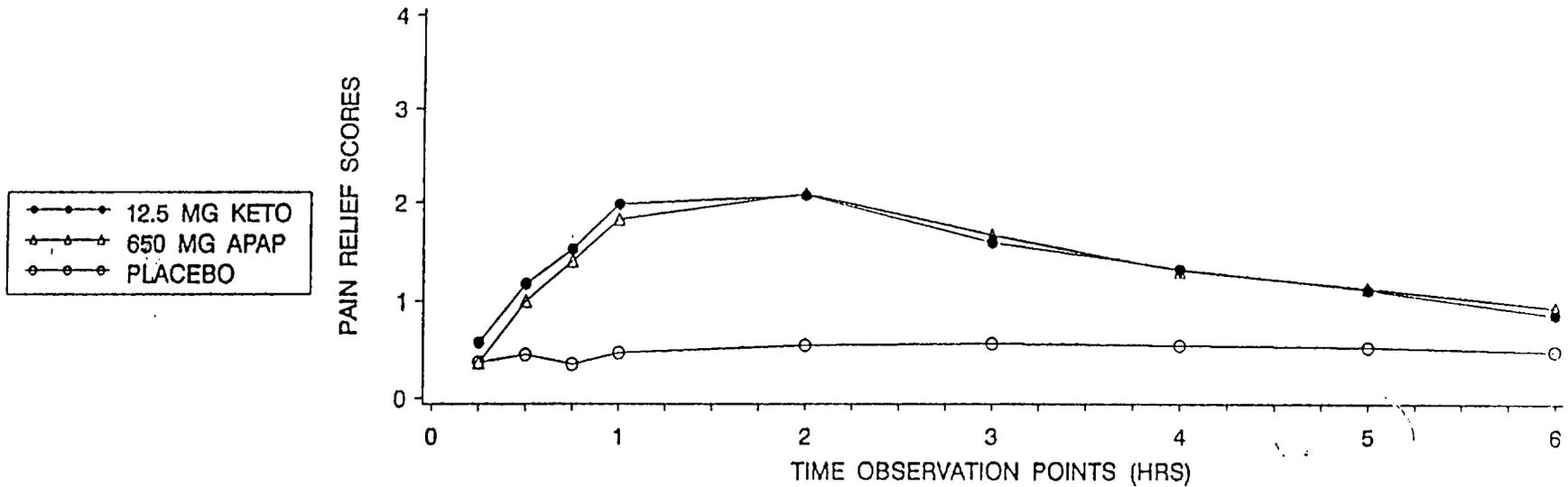
(Note: The statistically significant differences were obtained by applying the Protected Fisher's LSD at the 0.05 level.)

In terms of PR, PID, and PRID, statistically significant differences were shown in favor of ketoprofen 12.5mg and acetaminophen 650mg over placebo. No statistically significant differences were detected between ketoprofen 12.5mg and acetaminophen 650mg.

**APPEARS THIS WAY
ON ORIGINAL**

MEAN PAIN RELIEF (1) (EXTRAPOLATED)

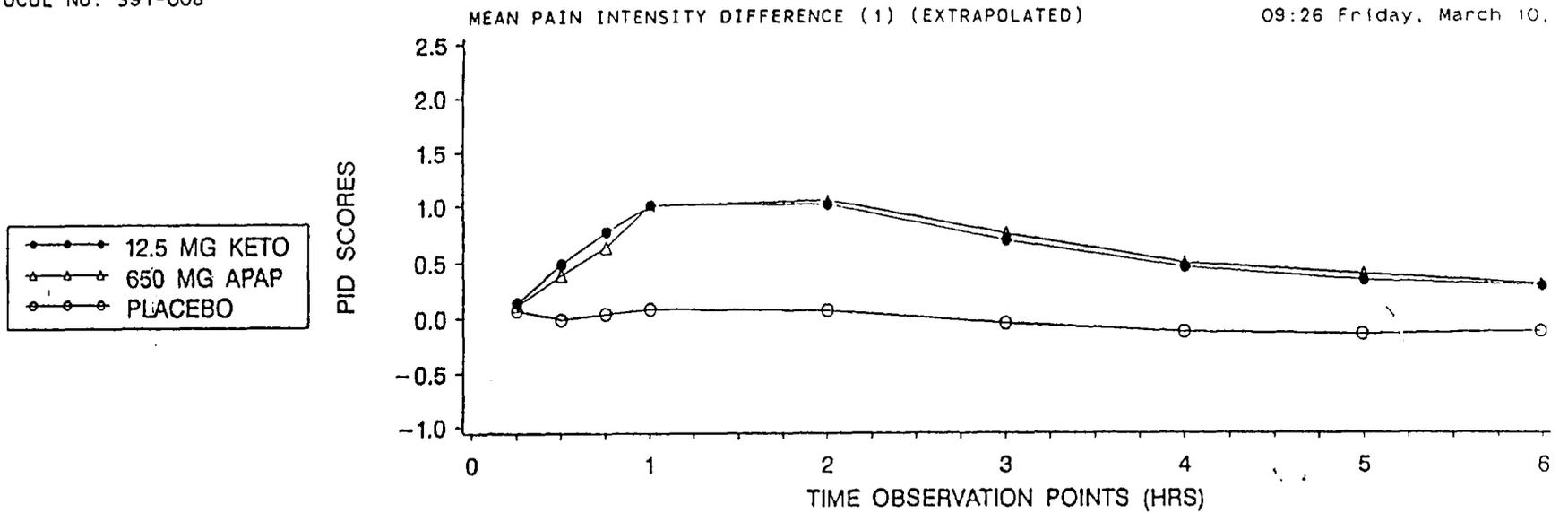
09:26 Friday, March 10, 1995



MEANS, (SD), SAMPLE SIZES, AND FISHER'S PROTECTED LSD COMPARISON (VERTICALLY)
 FOR PATIENTS VALID FOR EFFICACY ANALYSIS
 HOURS

DRUG	.25	.5	.75	1	2	3	4	5	6
KETOPROFEN 12.5 MG	0.58 (0.82) 52	1.17 (1.08) 52 A	1.52 (1.20) 52 A	1.98 (1.39) 52 A	2.08 (1.54) 45 A	1.60 (1.64) 32 A	1.33 (1.70) 22 A	1.12 (1.58) 20	0.87 (1.47) 17
ACETAMINOPHEN 650 MG	0.37 (0.60) 52	1.00 (1.05) 52 A	1.40 (1.19) 52 A	1.83 (1.28) 52 A	2.10 (1.40) 46 A	1.67 (1.56) 34 A	1.31 (1.58) 25 A	1.13 (1.61) 20	0.94 (1.39) 18
PLACEBO	0.37 (0.56) 51	0.45 (0.78) 51 B	0.35 (0.66) 51 B	0.47 (0.83) 51 B	0.55 (0.99) 19 B	0.57 (1.19) 12 B	0.55 (1.30) 8 B	0.53 (1.30) 8	0.49 (1.27) 7
TRT P (b)	0.1944	0.0007	0.0001	0.0001	0.0001	0.0002	0.0156	0.0716	0.2100
RMS (b)	0.6722	0.9803	1.0486	1.1952	1.3349	1.4745	1.5371	1.5045	1.3804

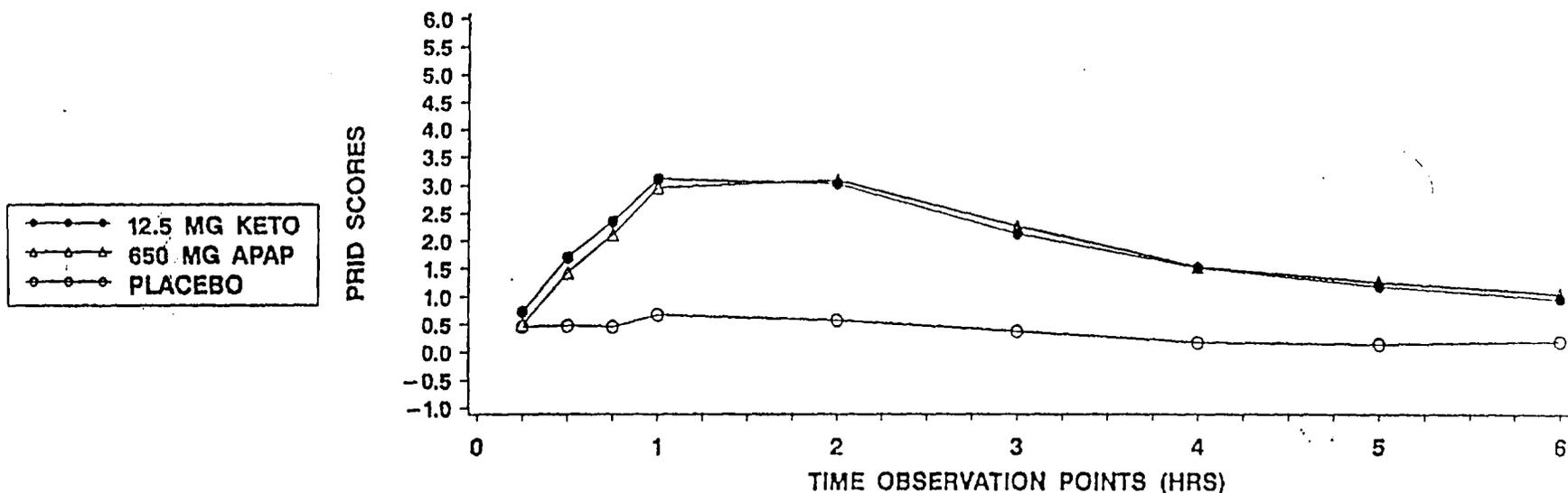
(1) SAME LETTER INDICATES ABSENCE OF SIGNIFICANT DIFFERENCE (0.05 LEVEL).
 (a) SAMPLE SIZES ARE NOT EXTRAPOLATED
 (b) MODEL: PR = u + T(i) + error
 (c) PLSD BASED ON MODEL (b) LSMEANS



MEANS, (SD), SAMPLE SIZES, AND FISHER'S PROTECTED LSD COMPARISON (VERTICALLY)
 FOR PATIENTS VALID FOR EFFICACY ANALYSIS
 HOURS

DRUG	.25	.5	.75	1	2	3	4	5	6
KETOPROFEN 12.5 MG	0.14 (0.64) 52	0.48 (0.78) 52 A	0.77 (0.83) 52 A	1.01 (1.00) 52 A	1.01 (1.10) 45 A	0.70 (1.07) 32 A	0.46 (1.02) 22 A	0.35 (0.94) 20 A	0.30 (0.90) 17 A
ACETAMINOPHEN 650 MG	0.12 (0.44) 52	0.39 (0.74) 52 A	0.64 (0.77) 52 A	1.01 (0.82) 52 A	1.05 (0.91) 46 A	0.76 (0.93) 34 A	0.50 (0.87) 25 A	0.40 (0.84) 20 A	0.32 (0.72) 18 A
PLACEBO	0.07 (0.40) 51	-.01 (0.57) 51 B	0.04 (0.63) 51 B	0.08 (0.72) 51 B	0.07 (0.81) 19 B	-.04 (0.82) 12 B	-.12 (0.88) 8 B	-.14 (0.90) 8 B	-.11 (0.90) 7 B
TRT P (b)	0.7921	0.0007	0.0001	0.0001	0.0001	0.0001	0.0010	0.0044	0.0170
T*BASE (c)	0.2268	0.4332	0.1837	0.0938	0.1779	0.6462	0.9677	0.8981	0.9738
RMS (b)	0.4970	0.6831	0.7193	0.8199	0.9252	0.9429	0.9285	0.9005	0.8476

(1) SAME LETTER INDICATES ABSENCE OF SIGNIFICANT DIFFERENCE (0.05 LEVEL).
 (a) SAMPLE SIZES ARE NOT EXTRAPOLATED (b) MODEL: PID = u + T(i) + B(j) + error
 (c) MODEL: PID = u + T(i) + B(j) + TB(ij) + error (d) PLSD BASED ON MODEL (b) LSMEANS



MEANS, (SD), SAMPLE SIZES, AND FISHER'S PROTECTED LSD COMPARISON (VERTICALLY)
 FOR PATIENTS VALID FOR EFFICACY ANALYSIS
 HOURS

DRUG	.25	.5	.75	1	2	3	4	5	6
KETOPROFEN 12.5 MG	0.73 (1.38) 52	1.70 (1.78) 52 A	2.36 (1.95) 52 A	3.12 (2.34) 52 A	3.05 (2.58) 45 A	2.14 (2.64) 32 A	1.52 (2.66) 22 A	1.20 (2.46) 20 A	0.97 (2.31) 17
ACETAMINOPHEN 650 MG	0.50 (0.93) 52	1.43 (1.72) 52 A	2.11 (1.88) 52 A	2.97 (2.02) 52 A	3.11 (2.25) 46 A	2.28 (2.43) 34 A	1.54 (2.39) 25 A	1.28 (2.40) 20 A	1.07 (2.05) 18
PLACEBO	0.46 (0.82) 51	0.48 (1.23) 51 B	0.46 (1.16) 51 B	0.68 (1.46) 51 B	0.58 (1.71) 19 B	0.38 (1.92) 12 B	0.18 (2.10) 8 B	0.15 (2.13) 8 B	0.20 (2.09) 7
TRT P (b)	0.3814	0.0004	0.0001	0.0001	0.0001	0.0001	0.0051	0.0252	0.0850
T*BASE (c)	0.2525	0.4166	0.2982	0.1066	0.2702	0.6453	0.9846	0.9674	0.9966
RMS (b)	1.0667	1.5870	1.6869	1.9483	2.2150	2.3608	2.3938	2.3350	2.1576

(1) SAME LETTER INDICATES ABSENCE OF SIGNIFICANT DIFFERENCE (0.05 LEVEL).

(a) SAMPLE SIZES ARE NOT EXTRAPOLATED

(c) MODEL: PRID = u + T(i) + B(j) + TB(ij) + error

(b) MODEL: PRID = u + T(i) + B(j) + error

(d) PLSD BASED ON MODEL (b) LSMEANS

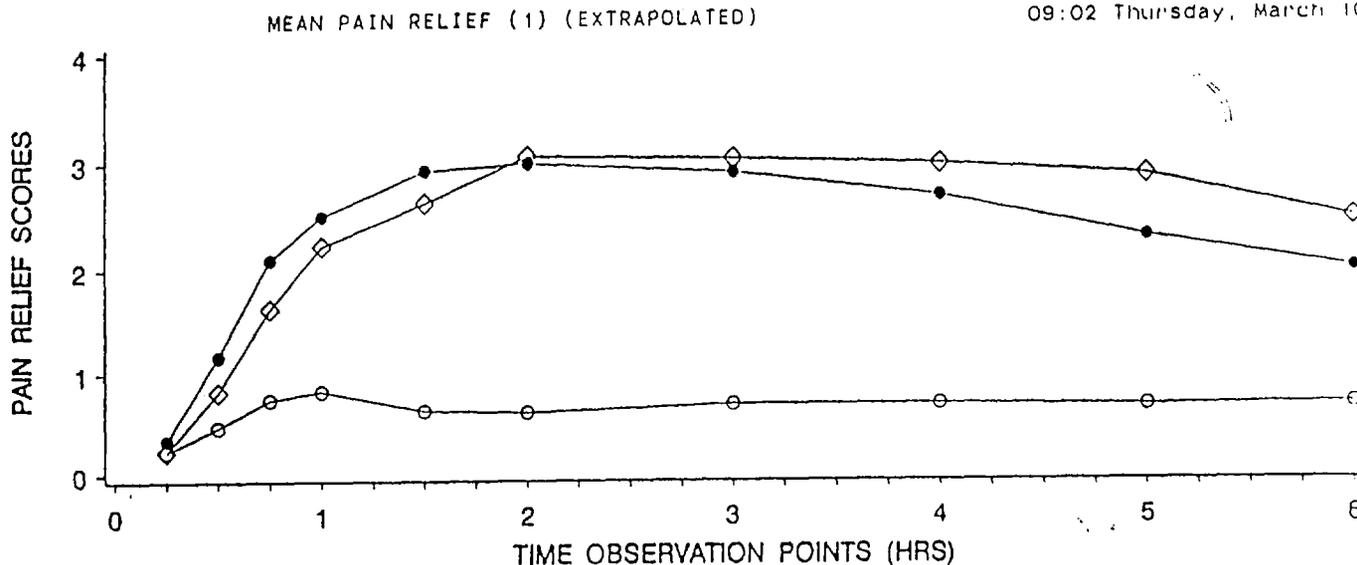
Result - Study S92-008 (See graphs and tables on pages 7.1-7.3)

<i>Statistically significant difference</i>	<i>Pain parameter</i>	<i>Time interval</i>
Keto12.5 > PLA	PR	0.5 through 6 hour
	PID	0.5 through 6 hour
	PRID	0.5 through 6 hour

(Note: The statistically significant differences were obtained by applying the Protected Fisher's LSD at the 0.05 level.)

Statistically significant differences were shown in favor of ketoprofen 12.5mg and acetaminophen 650mg over placebo, in terms of PR, PID, and PRID. No meaningful differences were shown between ketoprofen 12.5mg and ibuprofen 200mg.

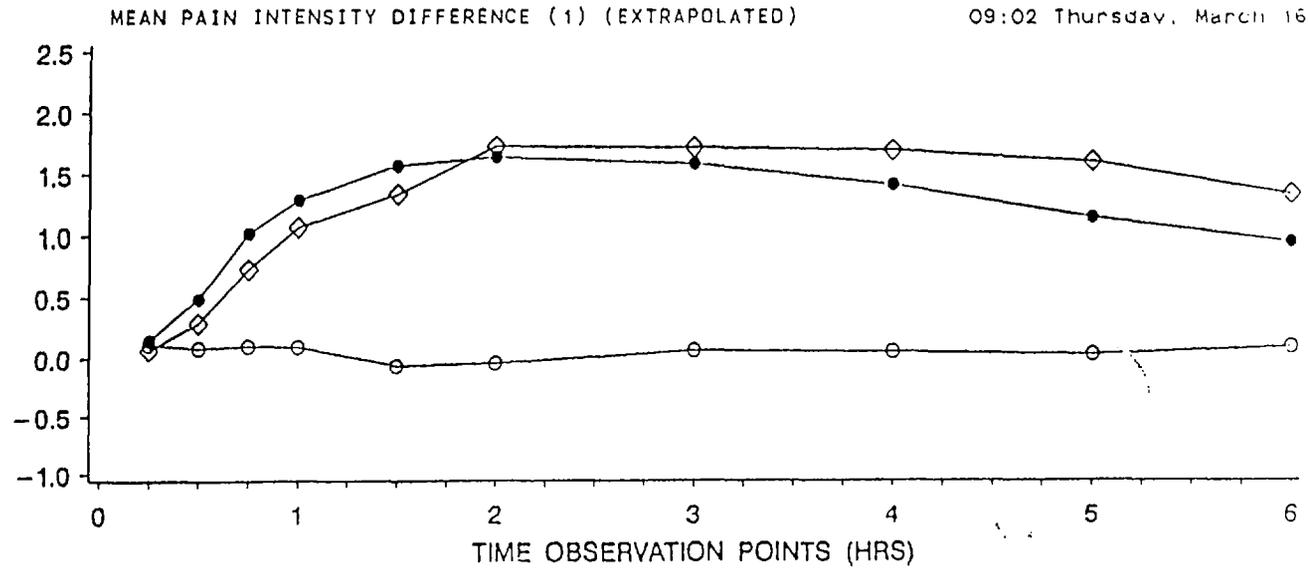
**APPEARS THIS WAY
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FOR PATIENTS VALID FOR EFFICACY ANALYSIS
 HOURS

DRUG	.25	.5	.75	1	1.5	2	3	4	5	6
KETO 12.5 MG	0.34 (0.68) 62	1.16 (1.09) 62 A	2.10 (1.21) 62 A	2.52 (1.22) 62 A	2.94 (1.14) 60 A	3.00 (1.13) 57 A	2.92 (1.27) 55 A	2.71 (1.41) 53 A	2.32 (1.56) 48 B	2.02 (1.62) 40 A
IBU 200 MG	0.23 (0.46) 61	0.82 (0.99) 61 B	1.62 (1.23) 61 B	2.23 (1.26) 61 A	2.64 (1.30) 55 A	3.07 (1.33) 53 A	3.05 (1.31) 53 A	3.00 (1.40) 52 A	2.90 (1.45) 51 A	2.51 (1.55) 47 A
PLACEBO	0.23 (0.46) 62	0.47 (0.72) 62 C	0.74 (0.96) 62 C	0.82 (1.12) 62 B	0.63 (1.12) 26 B	0.61 (1.19) 15 B	0.69 (1.39) 14 B	0.69 (1.41) 13 B	0.68 (1.41) 12 C	0.69 (1.44) 12 B
TRT P (b)	0.4226	0.0003	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
RMS (b)	0.5422	0.9459	1.1378	1.2028	1.1913	1.2190	1.3231	1.4063	1.4723	1.5396

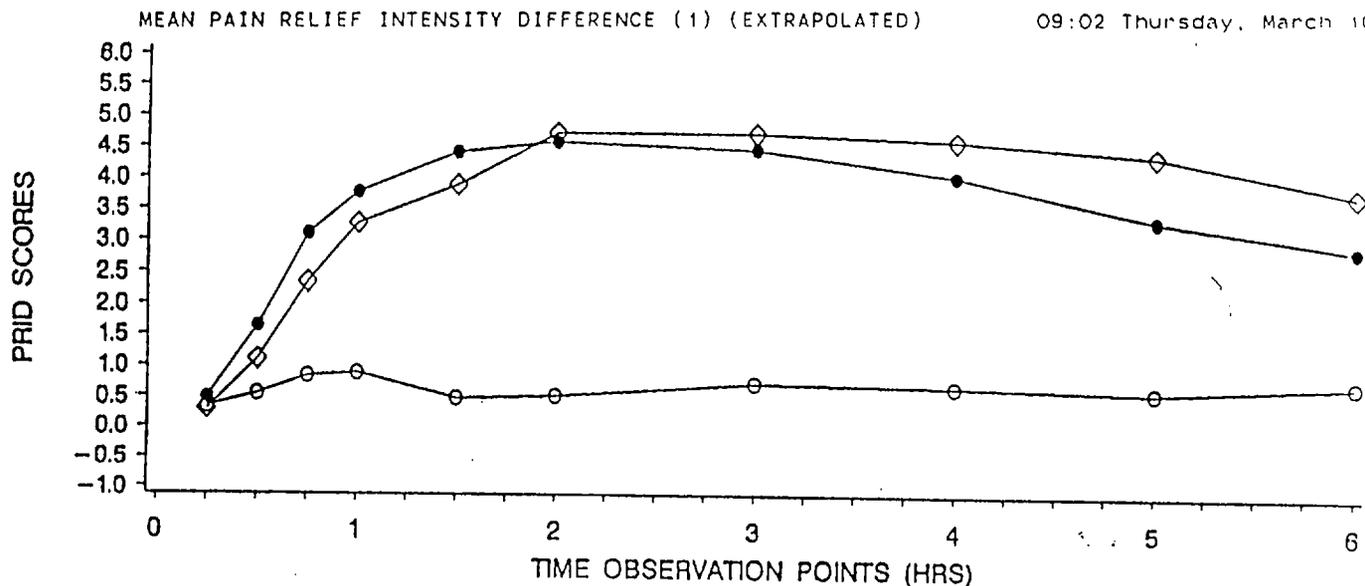
(1) SAME LETTER INDICATES ABSENCE OF SIGNIFICANT DIFFERENCE (0.05 LEVEL).
 (a) SAMPLE SIZES ARE NOT EXTRAPOLATED
 (b) MODEL: PR = μ + T(1) + error
 (c) PLSD BASED ON MODEL (b) LSMEANS



FOR PATIENTS VALID FOR EFFICACY ANALYSIS
 HOURS

DRUG	.25	.5	.75	1	1.5	2	3	4	5	6
KETO 12.5 MG	0.15 (0.46) 62	0.49 (0.75) 62 A	1.02 (0.90) 62 A	1.29 (0.97) 62 A	1.56 (1.00) 60 A	1.63 (0.96) 57 A	1.58 (1.05) 55 A	1.41 (1.12) 53 A	1.14 (1.17) 48 B	0.95 (1.18) 40 A
IBU 200 MG	0.07 (0.30) 61	0.29 (0.62) 61 AB	0.73 (0.85) 61 B	1.07 (0.98) 61 A	1.34 (1.07) 55 A	1.72 (1.06) 53 A	1.71 (1.04) 53 A	1.68 (1.12) 52 A	1.60 (1.19) 51 A	1.33 (1.19) 47 A
PLACEBO	0.11 (0.36) 62	0.09 (0.55) 62 B	0.10 (0.71) 62 C	0.09 (0.87) 62 B	-0.06 (0.82) 26 B	-0.04 (0.90) 15 B	0.06 (1.09) 14 B	0.05 (1.12) 13 B	0.03 (1.12) 12 C	0.09 (1.15) 12 B
FRT P (b)	0.5108	0.0020	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
T*BASE (c)	0.6421	0.6584	0.4068	0.6723	0.9245	0.6990	0.6221	0.8121	0.6966	0.5093
RMS (d)	0.3778	0.6261	0.7940	0.8853	0.8837	0.9071	1.0001	1.0506	1.0900	1.1221

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MEANS, (SD), SAMPLE SIZES, AND FISHER'S PROTECTED LSD COMPARISON (VERTICALLY)
 FOR PATIENTS VALID FOR EFFICACY ANALYSIS
 HOURS

DRUG	.25	.5	.75	1	1.5	2	3	4	5	6
KETO 12.5 MG	0.49 (1.10) 62	1.65 (1.80) 62 A	3.11 (2.06) 62 A	3.77 (2.15) 62 A	4.42 (2.10) 60 A	4.59 (2.05) 57 A	4.48 (2.28) 55 A	4.06 (2.49) 53 A	3.37 (2.69) 48 B	2.94 (2.76) 40 A
IBU 200 MG	0.30 (0.70) 61	1.10 (1.56) 61 A	2.35 (2.03) 61 B	3.27 (2.17) 61 A	3.90 (2.32) 55 A	4.74 (2.35) 53 A	4.74 (2.31) 53 A	4.62 (2.48) 52 A	4.40 (2.60) 51 A	3.81 (2.69) 47 A
PLACEBO	0.34 (0.77) 62	0.55 (1.20) 62 B	0.84 (1.60) 62 C	0.89 (1.93) 62 B	0.49 (1.89) 26 B	0.53 (2.05) 15 B	0.74 (2.44) 14 B	0.68 (2.49) 13 B	0.61 (2.49) 12 C	0.76 (2.56) 12 D
TRT P (b)	0.4605	0.0005	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
T*BASE (c)	0.6779	0.7087	0.4207	0.5023	0.8863	0.5726	0.4742	0.7168	0.7733	0.4909
RMS (b)	0.8769	1.5343	1.8995	2.0613	2.0559	2.1164	2.3168	2.4473	2.5482	2.6521

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 (c) MODEL: PRID = u + T(i) + B(j) + TB(ij) + ERROR (d) PLSD BASED ON MODEL (b) LSMEANS

Result - Study S92-009 (See graphs and tables on pages 8.1-8.3)

<i>Statistically significant difference</i>	<i>Pain parameter</i>	<i>Time interval</i>
Keto12.5 > PLA	PR	0.75 through 3 hours
	PID	0.75 through 4 hours
	PRID	0.75 through 4 hours

(Note: The statistically significant differences were obtained by applying the Protected Fisher's LSD at the 0.05 level.)

Statistically significant differences were shown in favor of ketoprofen 12.5mg and acetaminophen 650mg over placebo, in terms of PR, PID, and PRID. No statistically significant differences were demonstrated between ketoprofen 12.5mg and aspirin 650mg.

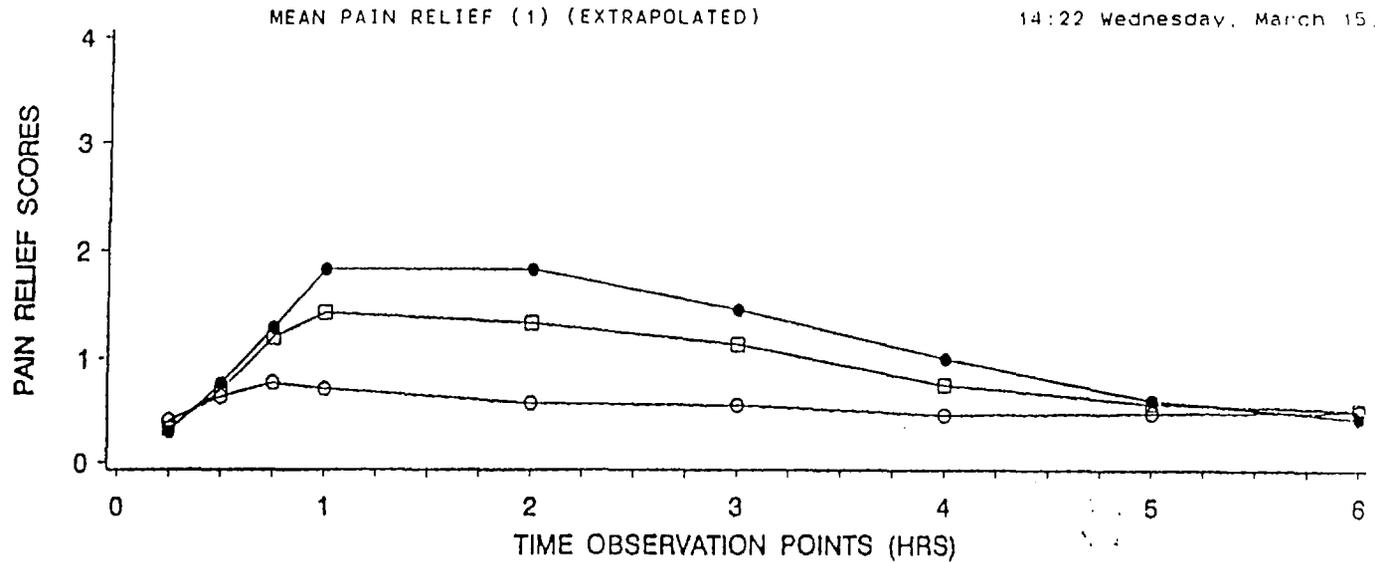
Conclusion - the Efficacy of Ketoprofen OTC for the Dental Pain

Ketoprofen 12.5mg was shown to be effective in all of the 4 dental studies. Ketoprofen 25mg was shown to be effective in study S90-002, the only study in which it was tested. The results of these studies provided substantial evidence that ketoprofen is an effective analgesic at proposed 12.5 to 25mg OTC dosage levels.

There was no substantial evidence to support a significant difference in analgesic efficacy between ketoprofen and the other treatments used as active-controls in these studies.

A dose-response was shown between ketoprofen 6.25mg and ketoprofen 12.5 to 25mg (only one trial included 6.25mg dose of ketoprofen) but not between ketoprofen 25 and 12.5mg (see study S90-002 for details).

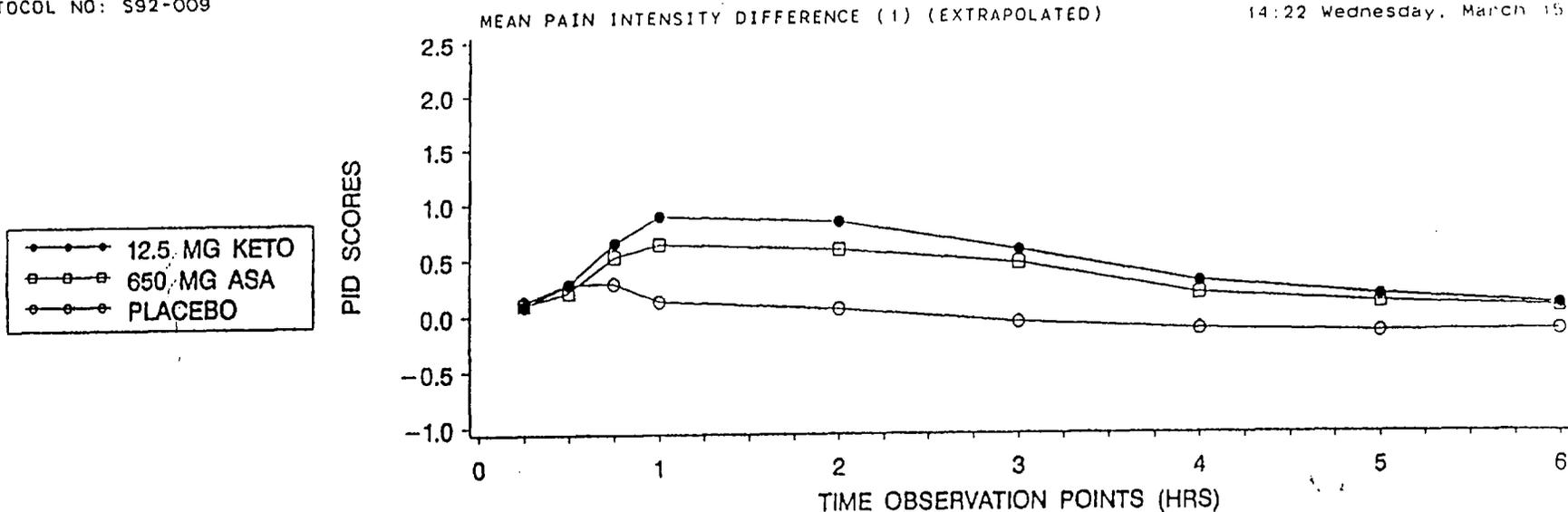
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 FOR PATIENTS VALID FOR EFFICACY ANALYSIS
 HOURS

DRUG	.25	.5	.75	1	2	3	4	5	6
KETOPROFEN 12.5 MG	0.29 (0.64) 51	0.76 (0.93) 51	1.28 (1.20) 51 A	1.82 (1.29) 51 A	1.82 (1.42) 44 A	1.45 (1.58) 28 A	1.00 (1.41) 20	0.61 (1.17) 12	0.43 (0.98) 9
ASPIRIN 650 MG	0.33 (0.68) 52	0.69 (0.85) 52	1.19 (1.09) 52 A	1.42 (1.21) 52 A	1.33 (1.45) 38 A	1.13 (1.46) 26 A	0.75 (1.23) 18	0.58 (1.21) 11	0.52 (1.13) 10
PLACEBO	0.40 (0.72) 52	0.63 (0.89) 52	0.77 (0.98) 52 B	0.71 (0.94) 52 B	0.58 (1.02) 25 B	0.56 (1.18) 12 B	0.46 (1.06) 9	0.48 (1.15) 9	0.50 (1.20) 8
TRT P (D)	0.7032	0.7590	0.0413	0.0001	0.0001	0.0059	0.0921	0.8485	0.9146
RMS (b)	0.6813	0.8897	1.0904	1.1550	1.3118	1.4131	1.2425	1.1749	1.1077

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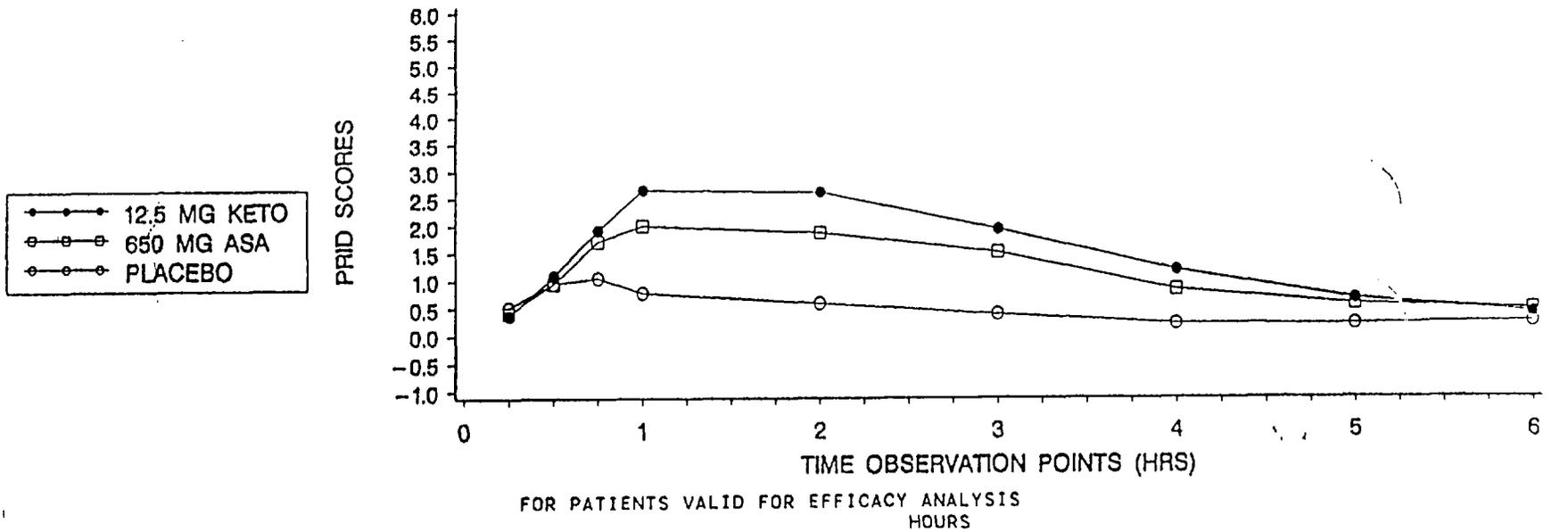


MEANS, (SD), SAMPLE SIZES, AND FISHER'S PROTECTED LSD COMPARISON (VERTICALLY)
 FOR PATIENTS VALID FOR EFFICACY ANALYSIS
 HOURS

DRUG	.25	.5	.75	1	2	3	4	5	6
KETOPROFEN 12.5 MG	0.09 (0.49) 51	0.29 (0.59) 51	0.65 (0.78) 51 A	0.89 (0.88) 51 A	0.84 (0.91) 44 A	0.58 (0.96) 28 A	0.30 (0.80) 20 A	0.18 (0.72) 12	0.09 (0.63) 9
ASPIRIN 650 MG	0.10 (0.46) 52	0.22 (0.73) 52	0.53 (0.76) 52 AB	0.64 (0.83) 52 A	0.59 (0.98) 38 A	0.47 (0.92) 26 A	0.20 (0.77) 18 A	0.11 (0.73) 11	0.07 (0.67) 10
PLACEBO	0.13 (0.39) 52	0.29 (0.55) 52	0.29 (0.74) 52 B	0.13 (0.70) 52 B	0.06 (0.82) 25 B	-0.06 (0.82) 12 B	-0.12 (0.78) 9 B	-0.15 (0.76) 9	-0.14 (0.81) 8
TRT P (b)	0.9035	0.7974	0.0426	0.0001	0.0001	0.0007	0.0172	0.0576	0.1915
T*BASE (c)	0.8753	0.2839	0.6276	0.7892	0.8258	0.6961	0.6946	0.9932	0.9198
RMS (d)	0.4442	0.5992	0.7320	0.7860	0.8867	0.8965	0.7814	0.7327	0.7048

(1) SAME LETTER INDICATES ABSENCE OF SIGNIFICANT DIFFERENCE (0.05 LEVEL).
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 (d) PLSD BASED ON MODEL (b) LSMEANS

MEAN PAIN RELIEF INTENSITY DIFFERENCE (1) (EXTRAPOLATED)



DRUG	.25	.5	.75	1	2	3	4	5	6
KETOPROFEN 12.5 MG	0.37 (1.03) 51	1.08 (1.43) 51	1.92 (1.90) 51 A	2.66 (2.11) 51 A	2.62 (2.28) 44 A	1.93 (2.49) 28 A	1.18 (2.14) 20 A	0.66 (1.81) 12	0.41 (1.53) 9
ASPIRIN 650 MG	0.42 (1.03) 52	0.94 (1.46) 52	1.71 (1.74) 52 AB	2.01 (1.97) 52 A	1.87 (2.36) 38 A	1.51 (2.30) 26 A	0.83 (1.92) 18 AB	0.57 (1.85) 11	0.48 (1.71) 10
PLACEBO	0.52 (1.00) 52	0.95 (1.33) 52	1.05 (1.61) 52 B	0.78 (1.52) 52 B	0.59 (1.73) 25 B	0.40 (1.92) 12 B	0.22 (1.74) 9 B	0.21 (1.81) 9	0.25 (1.91) 8
TRT P (b)	0.7509	0.8488	0.0330	0.0001	0.0001	0.0022	0.0418	0.4078	0.7826
T*BASE (c)	0.7036	0.6106	0.7826	0.9265	0.7549	0.6299	0.5260	0.9468	0.8014
RMS (b)	1.0174	1.3951	1.7503	1.8831	2.1447	2.2546	1.9497	1.8281	1.7296

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 (a) SAMPLE SIZES ARE NOT EXTRAPOLATED
 (b) MODEL: PRID = u + T(i) + B(j) + error
 (c) MODEL: PRID = u + T(i) + B(j) + TB(ij) + error
 (d) PLSD BASED ON MODEL (b) LSMEANS

2. Ketoprofen for Dysmenorrhea (See Appendix A1 for abbreviation and definition)

Three protocols (NDA volumes 44-58)

<i>Protocol # Investigator</i>	<i>Design</i>	<i>Drug (mg)</i>	<i># of patients- efficacy/safety</i>	<i>Evaluation time (initial dose)</i>
S92-001 Fulmer	Double-blind randomized 4-way crossover single-center PRN dose up to qid and for up to 3 days	Keto 25 Keto 12.5 Ibu 200 Placebo	70/71 66/68 68/69 70/70	30 and 60 mins 2, 3, 4 hrs
S92-004 Dawood Nelson Gordon	Same as above except three-center	Keto 25 Keto 12.5 Ibu 200 Placebo	91/92 94/94 92/92 91/92	30 and 60 mins 2, 3, 4 hrs
S92-012 Kisicki DeVries	Same as above except two-center	Keto 25 Keto 12.5 Ibu 200 Placebo	93/93 92/92 94/94 93/93	30 and 60 mins 2, 3, 4 hrs

<i>Study population</i>	Regularly menstruating females age 18 to 45 with a history of mild to moderate primary dysmenorrhea in the majority of cycles during the previous year, which typically responded to treatment with a non-narcotic oral analgesic
<i>Baseline condition</i>	Mild to moderate pain intensity (PI _{≥2}) at the onset of dysmenorrhea
<i>Rescue medication</i>	Not encouraged during the first hour after the initial dose. If remedicated within an hour, pain scores were excluded from efficacy analysis. If remedicated after 1 hour, the pain scores for the time interval after remedication were extrapolated.
<i>Raw efficacy data</i>	PI, PR, and onset of meaningful pain relief by stopwatch for the initial dose in each treatment cycle, global assessment at the end of each treatment period (up to three days), and time to remedication from patient diary

Execution

Study #	Drug (mg)	Pt exp (N)	Age (yr) Mean (range)	Gender (N) females only	Race (N) W/B/O	Drop-Outs (N)			Excl from PRID analysis (N)	Baseline mean PI (N) mild/mod
						Lack of efficacy	A E	Other		
92-1	TOTAL	72	32(18-45)	72	61/2/9	0	0	4		
	Keto 25	71							1	1.63 (26/44)
	Keto12.5	68							2	1.64 (24/42)
	Ibu 200	69							1	1.69 (21/47)
	Placebo	70							0	1.71 (20/50)
92-4	TOTAL	102	30(19-43)	102	44/29/29	0	1	15		
	Keto 25	92							1	1.56 (40/51)
	Keto12.5	94							0	1.64 (34/60)
	Ibu 200	92							0	1.58 (39/53)
	Placebo	92							1	1.51 (45/46)
92-12	TOTAL	95	33(19-45)	95	90/3/2	0	1	4		
	Keto 25	93							0	1.47 (49/44)
	Keto12.5	92							0	1.50 (46/46)
	Ibu 200	94							0	1.57 (40/54)
	Placebo	93							0	1.48 (48/45)

There were no statistically significant differences among treatment groups with regard to demographic characters such as age, height, weight and race, dysmenorrhea history, the mean time from onset of dysmenorrhea to the initial dose, or the mean baseline pain intensity (except in study 92-004, the percentage of patients with moderate pain at baseline for ketoprofen 12.5mg and ibuprofen 200mg groups was significantly greater than that for the placebo group).

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ON ORIGINAL**

Efficacy Result of the Dysmenorrhea Study

Result - Study S92-001 (See graphs and tables on pages 11.1-11.3)

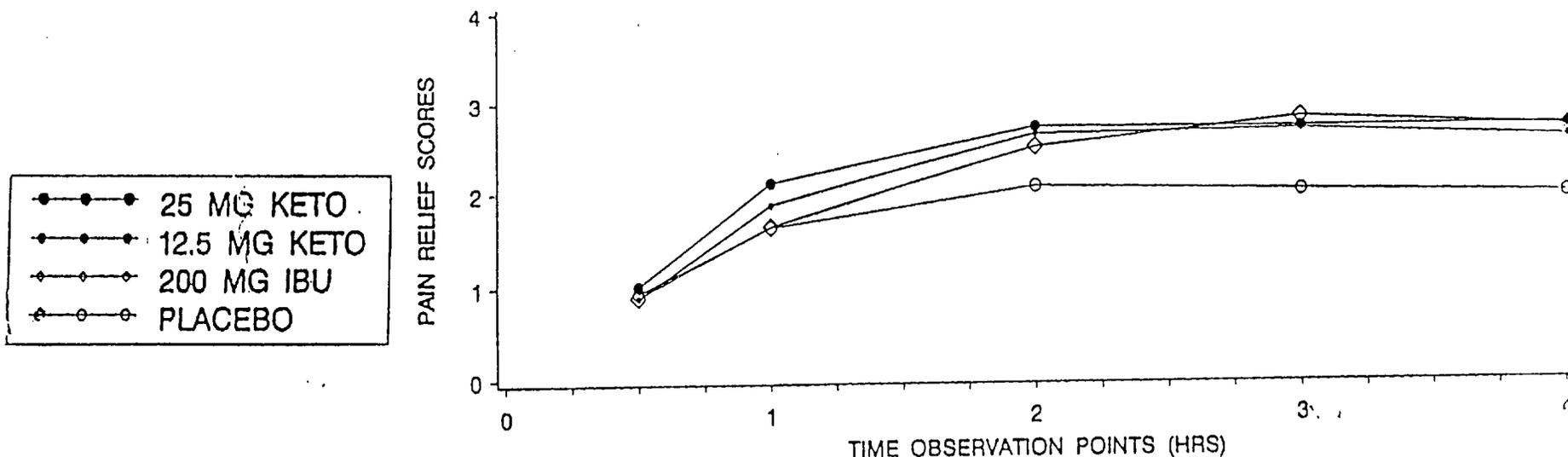
<i>Statistically significant difference</i>	<i>Pain parameter</i>	<i>Time interval</i>
Keto25 > PLA Keto12.5 > PLA	PR	3 and 4 hours
	PID	2 through 4 hours
	PRID	2 through 4 hours

(Note: The statistically significant differences were obtained by applying the Protected Fisher's LSD at the 0.05 level.)

In terms of PR, PID, and PRID, statistically significant differences in favor of ketoprofen 25mg and 12.5mg and ibuprofen 200mg over placebo started at 2 hours after dosing. The delayed statistical separation was probably due to low pain intensity at baseline, which did not leave much room for improvement. No statistically significant differences were demonstrated between the ketoprofen treatments and ibuprofen. No dose-response was shown between the two ketoprofen doses.

**APPEARS THIS WAY
ON ORIGINAL**

MEAN PAIN RELIEF (1) (EXTRAPOLATED)



MEANS, (SD), SAMPLE SIZES(a), AND FISHER'S LSD COMPARISON (VERTICALLY)(c)
 FOR PATIENTS VALID FOR EFFICACY ANALYSIS
 HOURS

DRUG	.5	1	2	3	4
KETOPROFEN 25 MG	1.01 (1.20) 70	2.09 (1.46) 70	2.70 (1.42) 69	2.68 (1.48) 66 A	2.68 (1.51) 65 A
KETOPROFEN 12.5 M	0.89 (1.14) 66	1.86 (1.47) 66	2.62 (1.51) 65	2.66 (1.59) 60 A	2.55 (1.68) 60 A
IBUPROFEN 200 MG	0.90 (1.17) 68	1.64 (1.48) 68	2.47 (1.53) 67	2.79 (1.57) 65 A	2.67 (1.60) 65 A
PLACEBO	0.94 (1.29) 70	1.63 (1.49) 70	2.05 (1.62) 65	1.99 (1.63) 62 B	1.94 (1.68) 61 B
TRT P (b)	0.9074	0.1525	0.0534	0.0102	0.0136
RMS (b)	1.0806	1.3663	1.4897	1.5370	1.5271

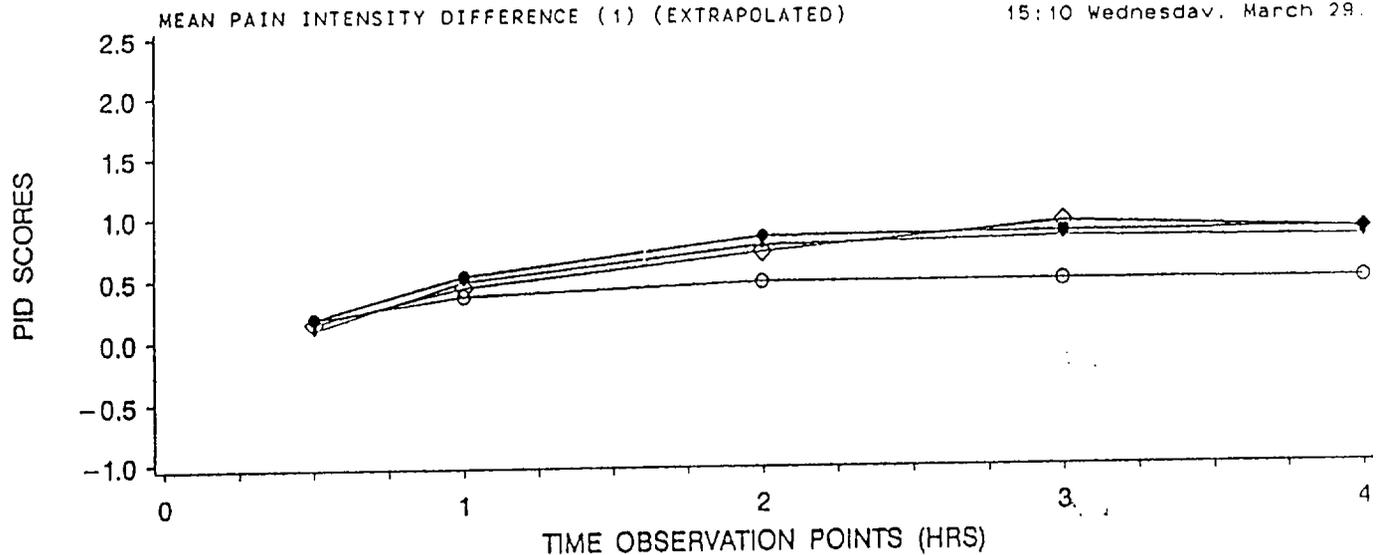
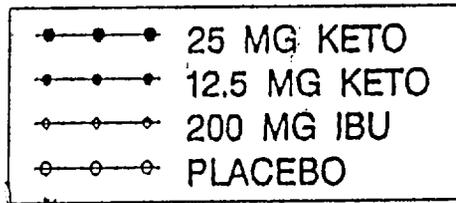
SAME LETTER INDICATES ABSENCE OF SIGNIFICANT DIFFERENCE (0.05 LEVEL).

STATISTICS ARE BASED ON THE EVALUABLE CYCLE FOR A TREATMENT.

(a) SAMPLE SIZES ARE NOT EXTRAPOLATED

(b) MODEL: $PR = u + T(i) + P(k) + S(1) + \text{error}$

(c) PLSD BASED ON MODEL (b) LSMEANS



MEANS, (SD), SAMPLE SIZES(a), AND FISHER'S LSD COMPARISON (VERTICALLY)(c)
 FOR PATIENTS VALID FOR EFFICACY ANALYSIS
 HOURS

DRUG	.5		1		2		3		4	
KETOPROFEN 25 MG	0.18	(0.51)	0.52	(0.74)	0.83	(0.79)	0.85	(0.81)	0.85	(0.79)
	70		70		69	A	66	A	65	A
KETOPROFEN 12.5 M	0.09	(0.45)	0.48	(0.72)	0.75	(0.71)	0.81	(0.74)	0.79	(0.73)
	66		66		65	A	60	A	60	A
IBUPROFEN 200 MG	0.14	(0.58)	0.43	(0.80)	0.70	(0.86)	0.93	(0.86)	0.85	(0.94)
	68		68		67	A	65	A	65	A
PLACEBO	0.18	(0.65)	0.36	(0.79)	0.46	(0.87)	0.46	(0.92)	0.46	(0.93)
	70		70		65	B	62	B	61	B
TRT P (b)	0.6764		0.4536		0.0155		0.0011		0.0026	
T*BASE (d)	0.5530		0.9936		0.5956		0.6407		0.2105	
RMS (b)	0.4783		0.6223		0.6900		0.7142		0.7020	

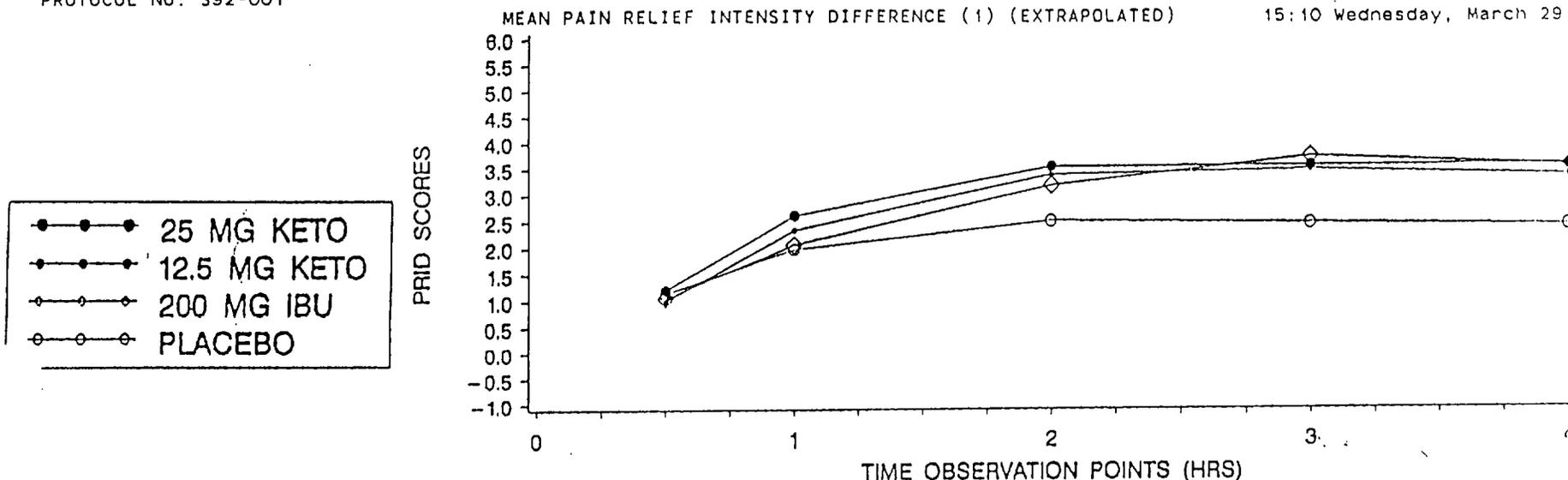
(1) SAME LETTER INDICATES ABSENCE OF SIGNIFICANT DIFFERENCE (0.05 LEVEL).
 STATISTICS ARE BASED ON THE EVALUABLE CYCLE FOR A TREATMENT.

(a) SAMPLE SIZES ARE NOT EXTRAPOLATED

(b) MODEL: PID = u + T(i) + B(j) + P(k) + S(1) + error

(c) PLSD BASED ON MODEL (b) LSMEANS

(d) MODEL: PID = u + T(i) + B(j) + P(k) + S(1) + TB(ij) + error



MEANS, (SD), SAMPLE SIZES(a), AND FISHER'S LSD COMPARISON (VERTICALLY)(c)
 FOR PATIENTS VALID FOR EFFICACY ANALYSIS
 HOURS

DRUG	.5	1	2	3	4
KETOPROFEN 25 MG	1.21 (1.62) 70	2.61 (2.11) 70	3.52 (2.08) 69 A	3.53 (2.17) 66 A	3.54 (2.17) 65 A
KETOPROFEN 12.5 M	1.00 (1.48) 66	2.34 (2.07) 66	3.36 (2.11) 65 A	3.46 (2.23) 60 A	3.34 (2.32) 60 A
IBUPROFEN 200 MG	1.06 (1.61) 68	2.06 (2.18) 68	3.17 (2.27) 67 AB	3.71 (2.33) 65 A	3.52 (2.45) 65 A
PLACEBO	1.14 (1.85) 70	1.98 (2.18) 70	2.50 (2.39) 65 B	2.44 (2.45) 62 B	2.39 (2.52) 61 B
TRT P (b)	0.8518	0.2133	0.0315	0.0043	0.0070
T*BASE (d)	0.7326	0.9849	0.7654	0.7728	0.4278
RMS (b)	1.4722	1.9268	2.1357	2.2113	2.1901

(1) SAME LETTER INDICATES ABSENCE OF SIGNIFICANT DIFFERENCE (0.05 LEVEL).

STATISTICS ARE BASED ON THE EVALUABLE CYCLE FOR A TREATMENT.

(a) SAMPLE SIZES ARE NOT EXTRAPOLATED

(b) MODEL: PRID = u + T(i) + B(j) + P(k) + S(1) + error

(c) PLSD BASED ON MODEL (b) LSMEANS

(d) MODEL: PRID = u + T(i) + B(j) + P(k) + S(1) + TB(ij) + error

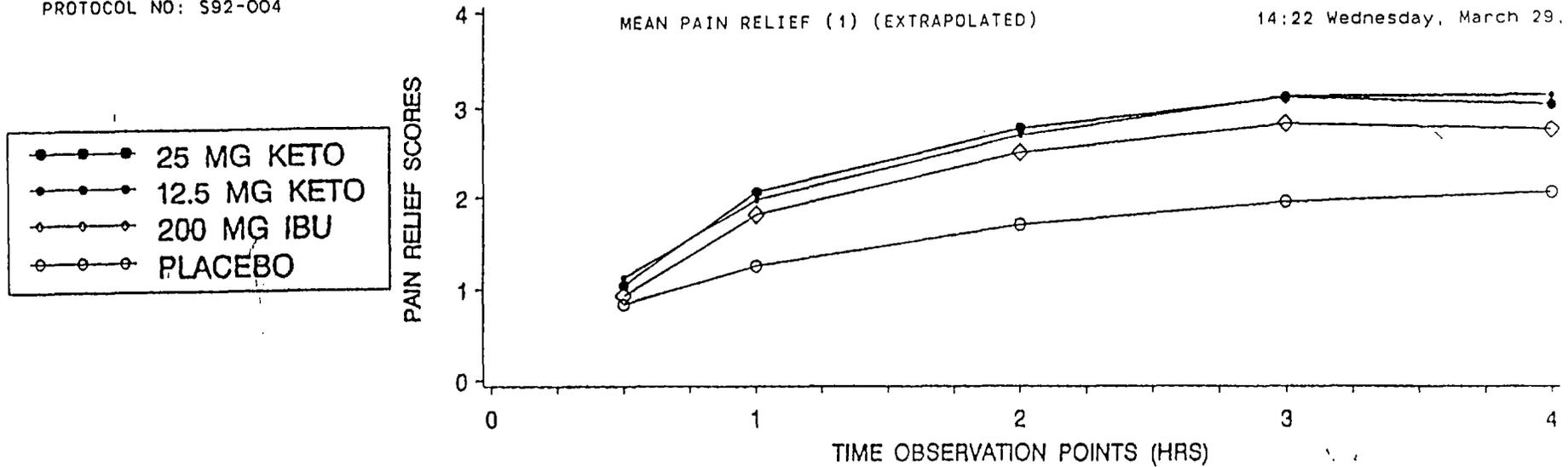
Result - Study S92-004 (See graphs and tables on pages 12.1-12.3)

<i>Statistically significant difference</i>	<i>Pain parameter</i>	<i>Time interval</i>
Keto25 > PLA Keto12.5 > PLA	PR	1 through 4 hours
	PID	1 through 4 hours
	PRID	1 through 4 hours

(Note: The statistically significant differences were obtained by applying the Protected Fisher's LSD at the 0.05 level.)

In terms of PR, PID, and PRID, statistically significant differences were shown in favor of ketoprofen 25mg and 12.5mg and ibuprofen 200mg over placebo starting at 1 hour. No statistically significant differences were demonstrated between the ketoprofen treatments and ibuprofen. No dose-response between the two ketoprofen doses was shown in the study.

**APPEARS THIS WAY
ON ORIGINAL**



MEANS, (SD), SAMPLE SIZES(a), AND FISHER'S LSD COMPARISON (VERTICALLY)(c)
 FOR PATIENTS VALID FOR EFFICACY ANALYSIS
 HOURS

DRUG	.5	1	2	3	4
KETOPROFEN 25 MG	1.05 (1.18) 91	2.06 (1.43) 91 A	2.78 (1.27) 90 A	3.11 (1.21) 90 A	3.05 (1.33) 90 AB
KETOPROFEN 12.5 M	1.13 (1.19) 94	1.97 (1.48) 94 A	2.70 (1.37) 93 A	3.13 (1.20) 93 A	3.15 (1.24) 93 A
IBUPROFEN 200 MG	0.93 (1.03) 92	1.82 (1.34) 92 A	2.51 (1.42) 92 A	2.83 (1.44) 91 A	2.77 (1.50) 91 B
PLACEBO	0.84 (1.09) 91	1.26 (1.28) 91 B	1.71 (1.53) 87 B	1.96 (1.61) 84 B	2.07 (1.68) 83 C
TRT P (b)	0.1599	0.0001	0.0001	0.0001	0.0001
T*CNTR (d)	0.7114	0.1240	0.1736	0.5850	0.5394
RMS (b)	0.9416	1.1859	1.2611	1.2100	1.2474

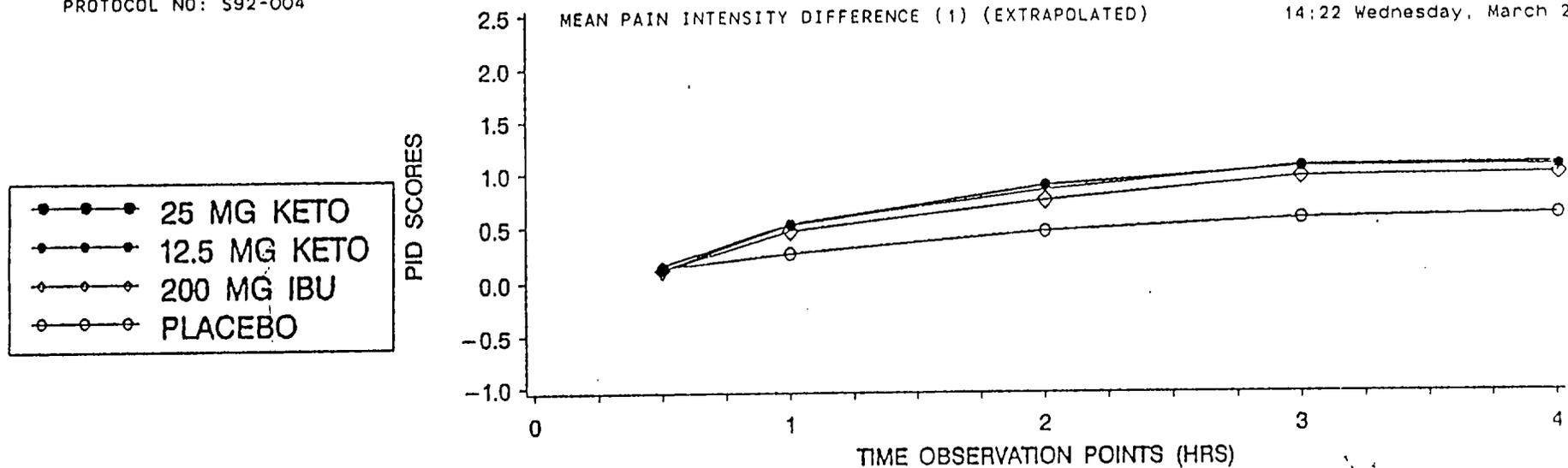
(1) SAME LETTER INDICATES ABSENCE OF SIGNIFICANT DIFFERENCE (0.05 LEVEL).
 STATISTICS ARE BASED ON THE EVALUABLE CYCLE FOR A TREATMENT.

(a) SAMPLE SIZES ARE NOT EXTRAPOLATED

(b) MODEL: $PR = u + T(i) + P(k) + S(r) + C(r) + \text{error}$

(c) PLSD BASED ON MODEL (b) LSMEANS

(d) MODEL: $PR = u + T(i) + P(k) + S(r) + C(r) + TC(tr) + \text{error}$



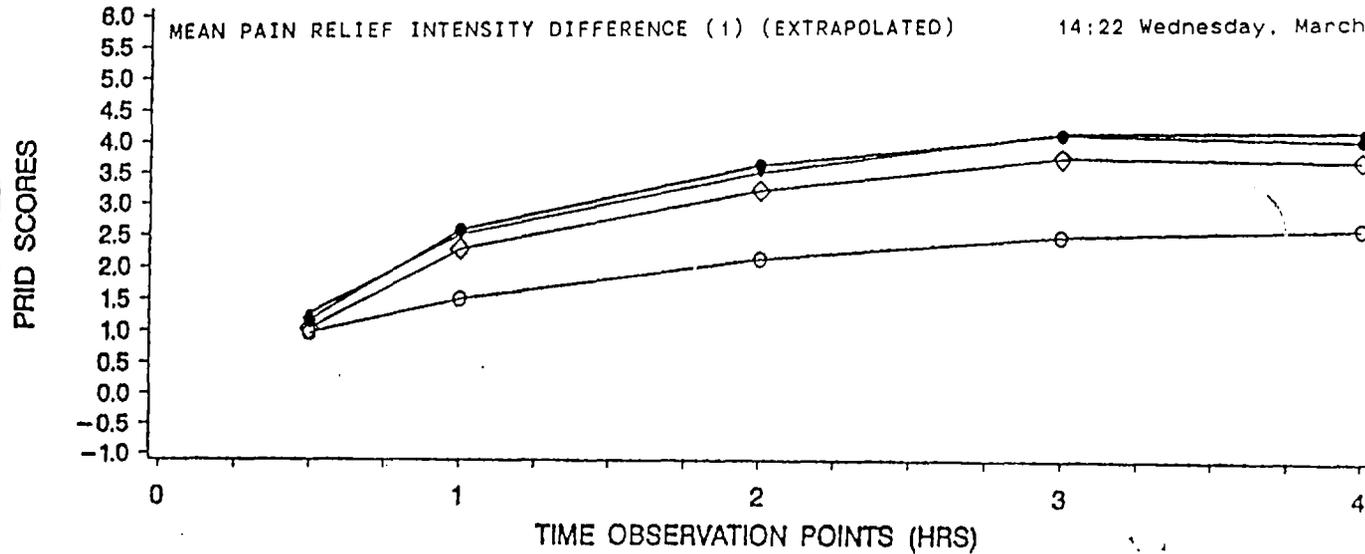
MEANS, (SD), SAMPLE SIZES(a), AND FISHER'S LSD COMPARISON (VERTICALLY)(c)
 FOR PATIENTS VALID FOR EFFICACY ANALYSIS
 HOURS

DRUG	.5		1		2		3		4	
KETOPROFEN 25 MG	0.12 91	(0.57)	0.52 91	(0.79) A	0.88 90	(0.75) A	1.06 90	(0.76) A	1.06 90	(0.81) A
KETOPROFEN 12.5 M	0.16 94	(0.58)	0.52 94	(0.82) A	0.84 93	(0.81) A	1.07 92	(0.77) A	1.09 92	(0.80) A
IBUPROFEN 200 MG	0.12 92	(0.53)	0.46 92	(0.64) A	0.74 92	(0.78) A	0.96 91	(0.84) A	0.99 91	(0.85) A
PLACEBO	0.13 91	(0.61)	0.26 91	(0.77) B	0.45 87	(0.92) B	0.57 84	(0.94) B	0.61 83	(1.01) B
TRT P (b)	0.9460		0.0085		0.0001		0.0001		0.0001	
T*CNTR (d)	0.1281		0.0955		0.0850		0.3670		0.2579	
T*BASE (e)	0.3828		0.0761		0.9102		0.9400		0.7544	
RMS (b)	0.4839		0.5836		0.6193		0.5850		0.6053	

(1) SAME LETTER INDICATES ABSENCE OF SIGNIFICANT DIFFERENCE (0.05 LEVEL).
 STATISTICS ARE BASED ON THE EVALUABLE CYCLE FOR A TREATMENT.

(a) SAMPLE SIZES ARE NOT EXTRAPOLATED
 (b) MODEL: PID = u + T(i) + B(j) + P(k) + S(r1) + C(r) + error
 (c) PLSD BASED ON MODEL (b) LSMEANS
 (d) MODEL: PID = u + T(i) + B(j) + P(k) + S(r1) + C(r) + TC(ir) + error
 (e) MODEL: PID = u + T(i) + B(j) + P(k) + S(r1) + C(r) + TB(ij) + error

●—● 25 MG KETO
 ●—● 12.5 MG KETO
 ◆—◆ 200 MG IBU
 ○—○ PLACEBO



MEANS, (SD), SAMPLE SIZES(a), AND FISHER'S LSD COMPARISON (VERTICALLY)(c)
 FOR PATIENTS VALID FOR EFFICACY ANALYSIS
 HOURS

DRUG	.5	1	2	3	4
KETOPROFEN 25 MG	1.16 (1.57) 91	2.59 (2.06) 91 A	3.66 (1.82) 90 A	4.17 (1.80) 90 A	4.11 (1.95) 90 A
KETOPROFEN 12.5 M	1.28 (1.61) 94	2.52 (2.19) 94 A	3.55 (2.05) 93 A	4.20 (1.84) 92 A	4.25 (1.90) 92 A
IBUPROFEN 200 MG	1.04 (1.38) 92	2.30 (1.84) 92 A	3.25 (2.05) 92 A	3.80 (2.12) 91 A	3.77 (2.17) 91 A
PLACEBO	0.97 (1.55) 91	1.51 (1.85) 91 B	2.16 (2.30) 87 B	2.53 (2.40) 84 B	2.68 (2.52) 83 B
TRT P (b)	0.3897	0.0001	0.0001	0.0001	0.0001
T*CNTR (d)	0.5418	0.0825	0.1171	0.5013	0.4726
T*BASE (e)	0.9081	0.2892	0.8084	0.9393	0.7743
RMS (b)	1.2862	1.6709	1.8007	1.7352	1.7861

(1) SAME LETTER INDICATES ABSENCE OF SIGNIFICANT DIFFERENCE (0.05 LEVEL).
 STATISTICS ARE BASED ON THE EVALUABLE CYCLE FOR A TREATMENT.

(a) SAMPLE SIZES ARE NOT EXTRAPOLATED (b) MODEL: PRID = u + T(i) + B(j) + P(k) + S(r1) + C(r) + error
 (c) PLSD BASED ON MODEL (b) LSMEANS
 (d) MODEL: PRID = u + T(i) + B(j) + P(k) + S(r1) + C(r) + TC(ir) + error
 (e) MODEL: PRID = u + T(i) + B(j) + P(k) + S(r1) + C(r) + TB(ij) + error

Result - Study S92-012 (See graphs and tables on pages 13.1-13.3)

<i>Statistically significant difference</i>	<i>Pain parameter</i>	<i>Time interval</i>
Keto25 > PLA	PR	2 through 4 hours
	PID	2 through 4 hours
	PRID	2 through 4 hours
Keto12.5 > PLA	PR	2 through 4 hours
	PID	1 through 4 hours
	PRID	2 through 4 hours

(Note: The statistically significant differences were obtained by applying the Protected Fisher's LSD at the 0.05 level.)

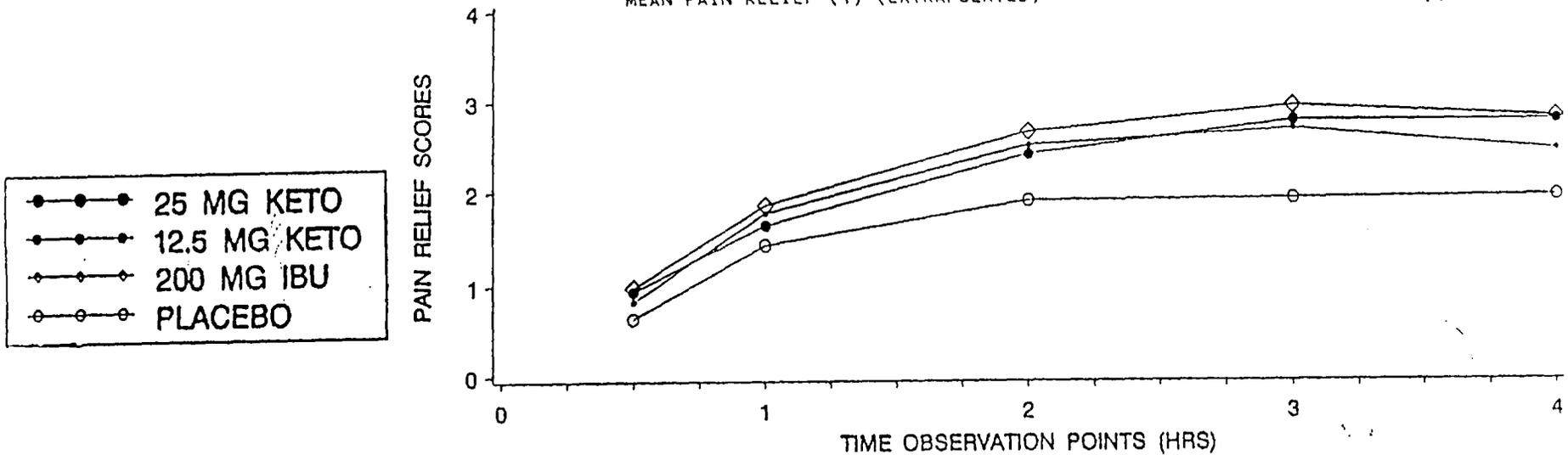
In terms of PR, PID, and PRID, statistically significant differences in favor of ketoprofen 25mg and 12.5mg and ibuprofen 200mg over placebo started at 2 hours after dosing. The delayed statistical separation was probably due to low pain intensity at baseline, which did not leave much room for improvement. No consistent pattern of statistically significant differences was demonstrated between the ketoprofen treatments and ibuprofen. No dose-response between the two ketoprofen doses was shown.

Conclusion - the Efficacy of Ketoprofen for Pain due to Primary Dysmenorrhea

The result of the study S92-004 provided substantial evidence for the analgesic efficacy of ketoprofen 25mg and 12.5mg for the treatment of primary dysmenorrhea. The results from the studies S92-001 and S92-012 were supportive of the efficacy claim.

There was no substantial evidence to show a significant difference in analgesic efficacy between ketoprofen and ibuprofen.

A dose-response between ketoprofen 12.5 and 25mg was not shown in these studies.



MEANS, (SD), SAMPLE SIZES(a), AND FISHER'S LSD COMPARISON (VERTICALLY)(c)
 FOR PATIENTS VALID FOR EFFICACY ANALYSIS
 HOURS

DRUG	.5	1	2	3	4
KETOPROFEN 25 MG	0.94 (1.18) 93	1.65 (1.42) 93	2.42 (1.41) 92 A	2.79 (1.43) 92 A	2.79 (1.42) 91 AB
KETOPROFEN 12.5 M	0.83 (1.00) 92	1.78 (1.40) 92	2.52 (1.47) 90 A	2.70 (1.49) 88 A	2.46 (1.52) 88 B
IBUPROFEN 200 MG	0.98 (1.09) 94	1.86 (1.37) 94	2.67 (1.25) 94 A	2.95 (1.27) 94 A	2.83 (1.40) 93 A
PLACEBO	0.65 (0.99) 93	1.44 (1.46) 93	1.92 (1.65) 90 B	1.94 (1.61) 88 B	1.96 (1.61) 87 C
TRT P (b)	0.0699	0.0891	0.0005	0.0001	0.0001
T*CNTR (d)	0.0467	0.1845	0.4815	0.2144	0.4735
RMS (b)	0.9283	1.2112	1.2743	1.2200	1.1911

(1) SAME LETTER INDICATES ABSENCE OF SIGNIFICANT DIFFERENCE (0.05 LEVEL).
 STATISTICS ARE BASED ON THE EVALUABLE CYCLE FOR A TREATMENT.

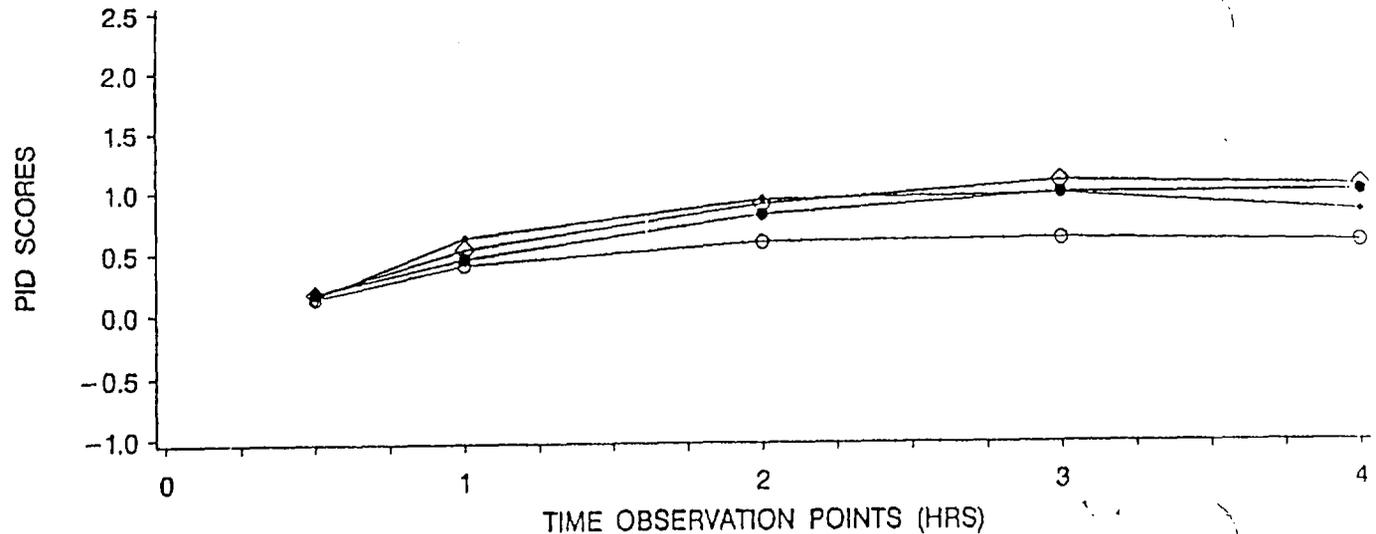
(a) SAMPLE SIZES ARE NOT EXTRAPOLATED

(b) MODEL: $PR = u + T(i) + P(k) + S(r1) + C(r) + error$

(c) PLSD BASED ON MODEL (b) LSMEANS

(d) MODEL: $PR = u + T(i) + P(k) + S(r1) + C(r) + TC(ir) + error$

MEAN PAIN INTENSITY DIFFERENCE (1) (EXTRAPOLATED)



●—● 25 MG KETO
 ●—● 12.5 MG KETO
 ◆—◆ 200 MG IBU
 ○—○ PLACEBO

MEANS, (SD), SAMPLE SIZES(a), AND FISHER'S LSD COMPARISON (VERTICALLY)(c)
 FOR PATIENTS VALID FOR EFFICACY ANALYSIS
 HOURS

DRUG	.5		1		2		3		4	
KETOPROFEN 25 MG	0.17 93	(0.50)	0.45 93	(0.70) B	0.80 92	(0.75) A	0.98 92	(0.77) A	0.98 91	(0.74) AB
KETOPROFEN 12.5 M	0.14 92	(0.49)	0.62 92	(0.77) A	0.92 90	(0.81) A	0.96 88	(0.80) A	0.81 88	(0.84) B
IBUPROFEN 200 MG	0.16 94	(0.61)	0.52 94	(0.75) AB	0.89 94	(0.76) A	1.07 94	(0.70) A	1.03 93	(0.79) A
PLACEBO	0.12 93	(0.40)	0.40 93	(0.69) B	0.58 90	(0.83) B	0.60 88	(0.76) B	0.57 87	(0.80) C
TRT P (b)	0.8816		0.0482		0.0006		0.0001		0.0001	
T*CNTR (d)	0.7240		0.5300		0.1918		0.7267		0.7460	
T*BASE (e)	0.0438		0.3659		0.4569		0.5285		0.8683	
RMS (b)	0.4292		0.5649		0.6121		0.5450		0.5704	

(1) SAME LETTER INDICATES ABSENCE OF SIGNIFICANT DIFFERENCE (0.05 LEVEL).
 STATISTICS ARE BASED ON THE EVALUABLE CYCLE FOR A TREATMENT.

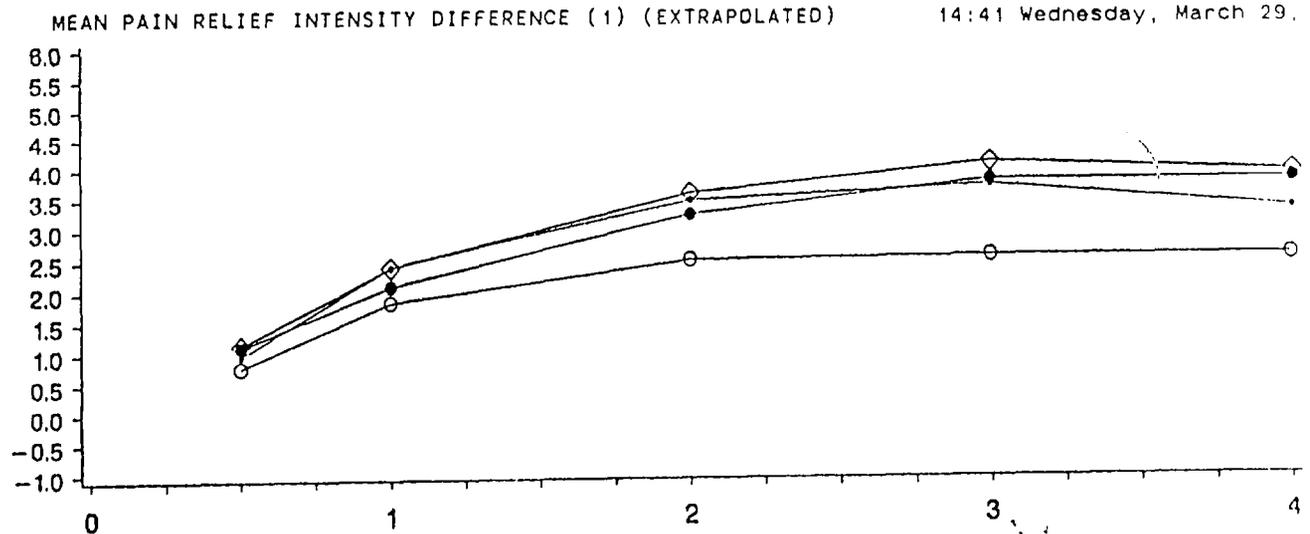
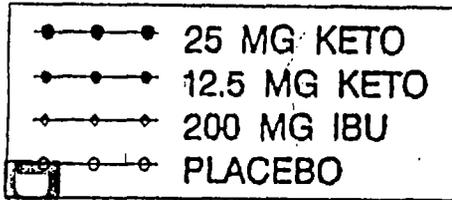
(a) SAMPLE SIZES ARE NOT EXTRAPOLATED

(b) MODEL: $PID = u + T(i) + B(j) + P(k) + S(r1) + C(r) + error$

(c) PLSD BASED ON MODEL (b) LSMEANS

(d) MODEL: $PID = u + T(i) + B(j) + P(k) + S(r1) + C(r) + TC(tr) + error$

(e) MODEL: $PID = u + T(i) + B(j) + P(k) + S(r1) + C(r) + TB(ij) + error$



MEANS, (SD), SAMPLE SIZES(a), AND FISHER'S LSD COMPARISON (VERTICALLY)(c)
 FOR PATIENTS VALID FOR EFFICACY ANALYSIS
 HOURS

DRUG	.5	1	2	3	4
KETOPROFEN 25 MG	1.11 (1.50) 93	2.09 (1.92) 93	3.22 (1.98) 92 A	3.76 (2.00) 92 A	3.76 (1.97) 91 AB
KETOPROFEN 12.5 M	0.97 (1.34) 92	2.40 (2.02) 92	3.45 (2.12) 90 A	3.67 (2.11) 88 A	3.28 (2.23) 88 B
IBUPROFEN 200 MG	1.14 (1.55) 94	2.39 (2.01) 94	3.56 (1.86) 94 A	4.05 (1.81) 94 A	3.88 (2.06) 93 A
PLACEBO	0.77 (1.28) 93	1.83 (2.03) 93	2.49 (2.37) 90 B	2.54 (2.25) 88 B	2.53 (2.28) 87 C
TRT P (b)	0.1564	0.0645	0.0003	0.0001	0.0001
T*CNTR (d)	0.1287	0.2211	0.3423	0.3374	0.5865
T*BASE (e)	0.0260	0.3087	0.3624	0.8553	0.9538
RMS (b)	1.2230	1.6673	1.8041	1.6906	1.6740

(1) SAME LETTER INDICATES ABSENCE OF SIGNIFICANT DIFFERENCE (0.05 LEVEL).
 STATISTICS ARE BASED ON THE EVALUABLE CYCLE FOR A TREATMENT.

(a) SAMPLE SIZES ARE NOT EXTRAPOLATED (b) MODEL: PRID = u + T(i) + B(j) + P(k) + S(r1) + C(r) + error
 (c) PLSD BASED ON MODEL (b) LSMEANS
 (d) MODEL: PRID = u + T(i) + B(j) + P(k) + S(r1) + C(r) + TC(lr) + error
 (e) MODEL: PRID = u + T(i) + B(j) + P(k) + S(r1) + C(r) + TB(lj) + error

3. Analgesic Onset of Ketoprofen

<i>Estimated ONSET in minutes (95% confidence interval)</i>					
Dental study	S90-002	S91-008	S92-008	S92-009	
Keto25	12 A				
Keto12.5	15 AB	18 A	18 A	28	
Keto6.25	20 BC				
Active-Control	<i>Ibu 200</i> 27 C	<i>APAP 650</i> 21 A	<i>Ibu 200</i> 27 A	<i>ASA 650</i> 32	
Placebo	41 C	63 B	55 B	32	

<i>Estimated ONSET in minutes (95% confidence interval)</i>			
Dysmenorrhea study	S92-001	S92-004	S92-012
Keto25	25	26	27
Keto12.5	30	24	31
Active-Control	<i>Ibu 200</i> 28	<i>Ibu 200</i> 29	<i>Ibu 200</i> 26
Placebo	26	31	39

(Note: The statistically significant differences were obtained by applying the Protected Fisher's LSD at the 0.05 level. The outcomes of the pairwise comparison were denoted by upper case letters, where letter A stands for the most effective treatment(s), B for the next most effective treatment, and so forth.)

Conclusion - Analgesic onset of Ketoprofen

The onset of analgesia for ketoprofen was basically within half-an-hour. In terms of analgesic onset, statistically significant differences were shown in favor of ketoprofen over placebo in 3 of the 4 dental trials. A significant separation in terms of the analgesic onset of ketoprofen from that of placebo was not demonstrated in dysmenorrhea trials. There was no substantial evidence differentiating the analgesic onset between ketoprofen and the active-controls. A dose-response between ketoprofen 12.5 and 25mg was not shown in these studies.

4. Analgesic Duration of Ketoprofen (See graphs and tables in Appendix A2)

<i>Estimated DURATION in minutes (95% confidence interval)</i>					
Dental study	S90-002	S91-008	S92-008	S92-009	
Keto25	>6h(4:10->6h) A				
Keto12.5	>6h(5:07->6h) A	3:26' A	>6h(>6h->6h) A	3:01	A
Keto6.25	3:00' B				
Active-Control	<i>Ibu 200</i> >6h(5:02->6h) A	<i>APAP 650</i> 3:19 A	<i>Ibu 200</i> >6h(>6h->6h) A	<i>ASA 650</i> 2:46	AB
Placebo	1:36' C	1:36 B	1:20 B	1:50	B

(Note: The statistically significant differences were obtained by applying the Protected Fisher's LSD at the 0.05 level. The outcomes of the pairwise comparison were denoted by upper case letters, where letter A stands for the most effective treatment(s), B for the next most effective treatment, and so forth.)

The median time to the rescue medication intake was used to estimate the duration of analgesia.

The estimation for the analgesic duration had analytic complexities based on the time-to-remediation data in dysmenorrhea studies because of the crossover study design. The estimated analgesic duration (both the median and the 95% confidence interval for the time-to-remediation) was >4 hours for all treatment groups. A statistical separation between the treatment groups was not detected based on the Log-Rank test.

Conclusion - Analgesic Duration of Ketoprofen

In all 4 dental trials, statistically significant differences in analgesic duration were shown in favor of ketoprofen over placebo. The range was from 2 hours to more than 6 hours. There was no substantial evidence for differentiating the analgesic duration of ketoprofen from that of active-controls. A dose-response between ketoprofen 12.5 and 25mg in analgesic duration was not demonstrated.

B. ANTIPYRETIC STUDIES OF KETOPROFEN

1. Ketoprofen for Induced Pyrexia

One protocol (NDA Volume 37-39)

<i>Protocol # Investigator</i>	<i>Design</i>	<i>Drug (mg)</i>	<i># of patients evaluated for efficacy/safety</i>	<i>Temperature evaluation time</i>
92-002 McMahon	single-dose double-blind randomized parallel single-center	Keto 25 Keto 12.5 APAP 650 Placebo	30/30 30/30 30/30 30/30	- q15 minutes x 3 before test medication (baseline) - prior to endotoxin - q15 minutes x 8 hrs after endotoxin

<i>Study population</i>	18 to 55 years old male healthy volunteers within 20% of their idea body weight, who had normal and stable baseline body temperature, i.e. 3 oral readings taken 15 minutes apart between 97.4°F and 98.8°F with the highest being within 0.2°F of the lowest
<i>Endotoxin administration</i>	Reference Standard Endotoxin EC-5 at a standard dose of 20 endotoxin unit (EU) per kg body weight given intravenously and 30 minutes after the test medication
<i>Rescue medication</i>	Not encouraged. If remedicated within an hour, temperature measurements were excluded from efficacy analysis. If remedicated after 1 hour, temperature measurements for the time interval after remedication were extrapolated based on the highest temperature from baseline to the end of observation.
<i>Raw efficacy data</i>	On-site evaluation of oral temperature at the time intervals as specified above

Execution

<i>Drug (mg)</i>	<i>Pt exp (N)</i>	<i>Age (yr) Mean (range)</i>	<i>Gender (N) M/F</i>	<i>Race (N) W/B/O</i>	<i>Drop-Outs (N)</i>			<i>Excl from efficacy analysis (N)</i>
					<i>Lack of efficacy</i>	<i>AE</i>	<i>Other</i>	
Keto 25	30	35(20-55)	30/0	16/14/0	0	0	0	0
Keto 12.5	30	36(20-49)	30/0	19/10/1	0	0	0	0
APAP 650	30	36(21-51)	30/0	16/13/1	0	0	0	0
Placebo	30	38(20-55)	30/0	16/13/1	0	0	0	0

There were no statistically significant differences among the treatment groups with regard to demographic characters such as age, height, weight and race, and the mean baseline temperature.

Result of the Antipyretic Study Using Induced Fever Model (See Table 1 in Appendix A3)

<i>Drug (mg)</i>	<i>6-hour average temperature elevation: mean (range) in °F</i>		<i>8-hour average temperature elevation: mean (range) in °F</i>		<i>8-hour maximum temperature elevation: mean (range) in °F</i>	
Keto25	0.69	A	0.71	A	1.50	A
Keto12.5	1.15	B	1.14	BC	2.13	B
APAP650	0.70	A	0.72	A	1.47	A
Placebo	1.41	C	1.35	C	2.57	C

(Note: The average temperature elevation was obtained by averaging the Area Under the Curve for the temperature difference from the baseline over the hours of measurements. The maximum temperature elevation was the maximum temperature difference from the baseline during the entire observation period. The statistically significant differences were obtained by applying the Protected Fisher's LSD at the 0.05 level.)

In terms of the average and maximum temperature reduction, statistically significant differences were shown in favor of the ketoprofen treatments over placebo. (One exception was the lack of significant separation between ketoprofen 12.5mg and placebo in mean temperature reduction over 8 hours.) Both ketoprofen 25mg and acetaminophen 650mg performed significantly better than ketoprofen 12.5mg.

2. Ketoprofen for Pyrexia Secondary to Upper Respiratory Infection

One protocol (NDA volume 40-43)

<i>Protocol # Investigator</i>	<i>Design</i>	<i>Drug (mg)</i>	<i># of patients evaluated for efficacy/safety</i>	<i>Temperature evaluation time</i>
S92-003 Schachtel	single-dose double-blind randomized parallel 14-center	Keto 25 Keto 12.5 APAP 650 Placebo	28/28 29/29 26/26 29/29	30, 60, 90, 120 minutes 3, 4, 5, 6, 7, 8 hours

<i>Study population</i>	Males and females age 18 or older with a diagnosis of acute viral upper respiratory infection accompanied with an elevated oral temperature lasting not for more than 3 days
<i>Stratification at randomization</i>	Baseline temperature Baseline temperature
<i>Rescue medication</i>	Not encouraged. If re-medicated within an hour, temperature measurements were excluded from efficacy analysis. If re-medicated after 1 hour, temperature measurements for the time interval after re-medication were extrapolated based on the highest temperature from baseline to the end of observation.
<i>Raw efficacy data</i>	On-site evaluation during the first 2 hours and out-patient evaluation during the last 6 hours for the oral temperature measurements (and pain measurements if myalgia intensity was at least moderate at baseline. Here, PI was measured on a 100mm VAS scale and PR on a 7-point categorical scale)

Execution

<i>Drug (mg)</i>	<i>Pt exp (N)</i>	<i>Age (yr) Mean (range)</i>	<i>Gender (N) M / F</i>	<i>Race (N) W/B/O</i>	<i>Drop-Outs (N)</i>			<i>Excl. from efficacy analysis (N)</i>
					<i>Lack of efficacy</i>	<i>AE</i>	<i>Other</i>	
Keto 25	28	26(18-57)	17/11	25/3/0	0	0	0	0
Keto 12.5	29	29(18-57)	21/8	23/3/3	0	0	1	1
APAP 650	26	26(18-48)	10/16	25/1/0	0	0	3	1
Placebo	29	28(18-61)	19/10	27/1/1	0	0	2	0

There were no statistically significant differences among the treatment groups with regard to demographic characters such as age, gender, height, weight and race, medical history, presentation of upper respiratory tract infection, and the mean baseline body temperature.

Result of the Antipyretic Study Using Natural Fever Model (See Table 2 in Appendix A3)

<i>Drug (mg)</i>	<i>6-hour average temperature reduction: mean (range) in °F</i>		<i>8-hour average temperature reduction: mean (range) in °F</i>		<i>8-hour maximum temperature reduction: mean (range) in °F</i>	
Keto25	1.2	A	1.0	A	2.1	A
Keto12.5	0.9	A	0.7	A	1.9	A
APAP650	1.1	A	1.1	A	2.2	A
Placebo	-0.2	B	-0.3	B	0.8	B

(Note: The average temperature reduction was obtained by averaging the Area Under the Curve for the temperature difference from the baseline over the hours of measurements. The maximum temperature reduction was the maximum temperature difference from the baseline during the entire observation period. The statistically significant differences were obtained by applying the Protected Fisher's LSD at the 0.05 level.)

Statistically significant differences were shown in favor of the ketoprofen treatments over placebo, in terms of the average and maximum temperature reduction. Statistically significant difference was not demonstrated between ketoprofen and acetaminophen or between ketoprofen 25mg and 12.5mg.

<i>Stratum</i>	<i>Drug</i>	<i>6-hour average temp reduction mean (range)(°F)</i>	<i>8-hour average temp reduction mean (range)(°F)</i>	<i>8-hour maximum temp reduction mean (range)(°F)</i>
low fever	Keto25	1.0	0.8	1.9
	Keto12.5	0.7	0.6	1.7
	APAP650	1.1	1.0	2.0
	Placebo	-0.3	-0.4	0.6
high fever	Keto25	1.5	1.3	2.6
	Keto12.5	1.3	1.1	2.5
	APAP650	1.3	1.2	2.5
	Placebo	0.0	0.0	1.0

There were no statistically significant interactions between the treatment differences and baseline temperature (in terms of stratum). Patients started with higher fever might get slightly more fever reduction numerically as shown in the table.

Conclusion - the Efficacy of Ketoprofen OTC for the Fever Treatment

Ketoprofen is an effective antipyretic at proposed 12.5 to 25mg OTC dosage levels based on the results of the studies using both induced fever model and natural fever model. No substantial evidence was provided in differentiating the three active treatment groups: ketoprofen 25mg, ketoprofen 12.5mg, and acetaminophen 650mg.

**APPEARS THIS WAY
ON ORIGINAL**

C. OVERALL EFFICACY CONCLUSION

Ketoprofen at recommended OTC doses of 12.5 to 25mg is an effective analgesic as demonstrated by the studies using dental and dysmenorrhea pain models. Adequate pain relief starts within 30 minutes; and the analgesic duration ranged from 2 hours to longer than 6 hours. The proposed OTC dosing recommendation for ketoprofen seems to be adequate for the drug to be used for temporary relief of occasional aches and pains.

Ketoprofen 12.5 to 25mg was also shown to be effective in reducing fever.

There was no substantial evidence to significantly differentiate the analgesic or antipyretic effectiveness of ketoprofen (12.5 to 25mg) from that of other treatments used as active-controls in the studies. A dose-response between ketoprofen 12.5mg and 25mg was not clearly demonstrated.

**APPEARS THIS WAY
ON ORIGINAL**

IV. ACTUAL-USE STUDY

ACTUAL-USE STUDY OF KETOPROFEN

One protocol (NDA Volume 59-85)

<i>Protocol #/Investigator</i>	<i>Design</i>	<i>Drug (mg)</i>	<i># of patient exposed</i>
S90-3 143 investigators	Single-blind randomized parallel 143 centers PRN up to 6 cap/24 hr for up to 10 days	Keto 12.5-25	3111
		Ibu 200-400	3094

(Note: The blind was applied to the random assignment of treatment groups in the parallel study, since the size of tablets were recognizably different to investigators.)

<i>Study population</i>	Male and female healthy adults (age 18 or older), with a history of OTC analgesics use, at least once a month, for the past three months, for at least one of the following indications: common cold, headache, toothache, muscle ache, backache, minor pain of arthritis, menstrual cramps, and fever
<i>Dosing instruction</i>	<p>Indications: For the temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular aches, backache, for the minor pain of arthritis, for the pain of menstrual cramps and for reduction of fever.</p> <p>Directions: Take one tablet every 4 to 6 hours while symptoms persist. If pain or fever does not respond to one tablet, two tablets may be used but do not exceed 6 tablets in 24 hours unless directed by a doctor. The smallest effective dose should be used. Do not take for pain for more than 10 days or for fever for more than 3 days unless directed by a doctor.</p>
<i>Raw data</i>	Daily record of study medication including the amount of drug per dose, the time of dosing, the indications for use, the onset and baseline severity of the symptoms, the use of concomitant medications or rescue medications, the overall effectiveness on a 5-point categorical scale after the last dose of study medication, and adverse experiences, as well as body temperature prior to each dose for the fever indication.

Execution

<i>Drug (mg)</i>	<i>Patient exposure (N)</i>	<i>Age (yr) Mean (range)</i>	<i>Gender (N) M/F</i>	<i>Race (N) W/B/O</i>	<i>Drop-Outs (N)</i>		
					<i>Lack of efficacy</i>	<i>AE</i>	<i>Other</i>
Keto12.5-25	3111	34(17-85)	916/2195	2834/141/136	219	21	0
Ibu 200-400	3094	35(14-86)	924/2170	2822/135/137	219	14	0

There were no statistically significant differences among the treatment groups with regard to demographic characters (such as age, gender and race), medical history, and previous analgesics usage.

Result of the Actual-Use Study

More than 50% of subjects took the study medication for headaches; more than 20% for musculoskeletal pain; more than 10% for menstrual cramps; and the remainder for common cold, toothache, fever, etc. About 50% of subjects in each group reported good overall pain relief, and 15 to 20% reported excellent overall pain relief. Rescue medications were taken by 7% of subjects in each group.

There were 492 (7.9%) subjects who reported at least one adverse event among 6205 who received study medication. The counting of adverse events was based on the number of subjects who had an AE that did not exist at baseline or that was worse than the AE at baseline. The number and percentage of subjects with AEs by treatment groups and the figures for drug-related AEs and severe AEs are summarized in Table 1.

Table 1.

	<i>Number of subjects with AE and % (with respect to subjects exposed)</i>		
	<i>Total</i>	<i>Severe</i>	<i>Drug-related</i>
Ketoprofen	284/3111(9.1%)	24 (0.8%)	230 (7.4%)
Ibuprofen	208/3094(6.7%)	15 (0.5%)	160 (5.2%)

(Note: One subject could have multiple counts of adverse events. Severe AEs included both drug-related and non-drug-related events. Drug-related events could be severe or non-severe.)

Statistically more AEs were reported from subjects on ketoprofen for the following categories: total count of AEs, total count of drug-related AEs, and individual AEs listed in Table 2.

Table 2.

	<i>Abdominal pain</i>	<i>Headache</i>	<i>Dizziness</i>	<i>Insomnia</i>
Ketoprofen	32 (1.0%)	18 (0.6%)	37 (1.2%)	0
Ibuprofen	16 (0.5%)	7 (0.2%)	20 (0.6%)	5 (0.2%)

The differences in the rates or AE reports of individual symptoms between the two treatments might not be clinically meaningful, since only a very small proportion of subjects reported these symptoms. However, in patients with a prior history of gastrointestinal disease (patients with a history of peptic ulcer or GI bleeding were excluded from the study), those taking ketoprofen had statistically higher reporting rates of GI adverse events (36 of 266, or 13.5%) than those taking ibuprofen (11 of 253, or 4.3%). The difference persisted after all the confounding factors were taken into consideration in the data analysis, suggesting less tolerance to ketoprofen GI toxicity in patients with prior GI abnormalities. There was no statistically significant difference shown between ketoprofen and ibuprofen with regard to severe adverse events. Most adverse events were of mild to moderate severity. No deaths or serious or unexpected adverse events were reported. The most frequently reported adverse events for ketoprofen were dyspepsia (71 counts or 2.3%), nausea (35 counts or 1.1%), abdominal pain (32 counts or 1.0%), somnolence (32 counts or 1.0%), and dizziness (37 counts or 1.2%).

About 70% of subjects in the study were females and 2.3% were elderly (age 65 or older). The incidence of adverse events by different gender and age groups is summarized in Table 3.

Table 3.

	<i>Number and % (with respect to sub-population at risk) of subjects with AE</i>				
<i>Groups</i>	<i>Total</i>	<i>Male</i>	<i>Female</i>	<i>Age < 65</i>	<i>Age ≥ 65</i>
Ketoprofen	284/3111 (9.1%)	66/916 (7.2%)	218/2195 (9.9%)	275/3056 (9.0%)	9/54 (16.7%)
		p = 0.016		p = 0.088	
Ibuprofen	208/3094 (6.7%)	58/924 (6.3%)	150/2170 (6.9%)	198/3002 (6.6%)	10/91 (11.0%)
		p = 0.518		p = 0.099	
Total	492/6205 (7.9%)	124/1840 (6.7%)	368/4365 (8.4%)	473/6058 (7.8%)	19/145 (13.1%)
		p = 0.024		p = 0.028	

Females reported AEs more frequently than males across treatment groups, and the difference reached statistical significance for ketoprofen. The data were not considered sufficient to draw a firm conclusion about treatment-gender interactions due to the low occurrence and mild nature of adverse reactions in subjects on low dose and short exposure of the study drugs. Elderly seemed to report AEs more frequently, but the differences between the elderly and young were not statistically significant for individual treatments.

About 40 to 50% of subjects did not follow dosing instructions. The major categories of non-compliance included: taking more than 2 tablets at once; taking more than 6 tablets in 24 hours; taking more than 6 tablets in a calendar day; taking drug for more than 10 days for pain, or 3 days for fever; taking drug for unlabeled indications. The incidence of non-compliance to the dosing instructions and the incidence of adverse events in non-compliant subjects were summarized in Tables 1 and 2 in Appendix B. The reasons for dosing deviations were not obtained from the subjects and could not be clearly elicited from available data. It was probably multifactorial. Nevertheless, no significant differences were found among the treatment groups, in terms of individual non-compliant categories, except that more subjects in the ibuprofen group took the study medication for more than 10 days (or more than 3 days for fever). Apparently significant differences between the 2 treatments were shown in AE reporting rate in non-compliant subjects, or AE reporting rate in subjects taking more than one tablet at initial dose. These differences might not be meaningful, because the non-compliant sub-populations were not randomly selected. About 43% of subjects who experienced adverse events in each of the two treatment groups were non-compliant to dosing instructions, approximately the same non-compliant rate as for the entire study population. A positive correlation between adverse events and non-compliance to dosing instructions was not suggested based on these findings.

About one third of subjects in each treatment group exceeded the recommended OTC dosing, mostly in the categories of taking more than one tablet at initial dose, having a dosing interval less than 4 hours, or taking more than 6 tablets in 24 hours. The maximum excessive dosing was 350mg in 10 divided doses in 24 hours. The recommended maximum prescription daily dose is 300mg, which is four times of the proposed maximum OTC daily dose of 75mg, thus creating a reasonably wide safety margin.

Conclusion for the Actual-Use Study

The most common indications, for OTC use of ketoprofen 12.5 to 25mg or ibuprofen 200 to 400mg, were headache, musculoskeletal pain, and dysmenorrhea. Subjects received either medication appeared to be satisfied with the overall pain relief. The rate of overall non-compliance to the dosing instructions approached 50% and was generally treatment independent. The non-compliance to specific dosing instructions was not shown to be related to the incidence of adverse events in general. Ketoprofen 12.5 to 25mg were considered reasonably safe for OTC usage under the proposed OTC dosing instructions.

V. SAFETY REVIEW

A. CLINICAL TRIAL SAFETY DATA

The safety data submitted in this NDA was collected from 10183 patients who received study medications in 22 clinical trials. Of these, 5278 received ketoprofen; 3800 received ibuprofen; 707 received placebo; 190 received acetaminophen; 123 received aspirin; and 85 received naproxen. (In the three dysmenorrhea trials, each with 4 treatments given in a crossover fashion, 269 subjects were counted more than once.) The exposure to ketoprofen in 16 single-dose trials ranged from 3.125mg to 50mg. In the 6 multidose trials, the maximum daily dose of ketoprofen was 150mg for 7 days; and the longest duration on ketoprofen was 10 days at 75mg per day.

The safety data obtained from these trials are of limited use because of the low dosage levels, short exposure to study drugs, and the small sample size of individual studies. Nevertheless, they were pooled to give some information on the type, frequency, and severity of adverse events and their relationship with study drugs. The counting of AEs was based on the number of subjects who had an AE that did not exist at baseline or that was worse than the AE at baseline. The adverse events were summarized for ketoprofen, ibuprofen, placebo, acetaminophen, and aspirin, based on the pooled data from 10 studies valid for efficacy analysis in Table 1 in Appendix C. Pooled data from the rest of the clinical studies (clinical pharmacological studies, foreign studies, dental studies using old formulations) for these treatments plus naproxen were summarized in a similar fashion in Table 2 in Appendix C.

For patients on ketoprofen, there was one count of allergic reaction, one count of edema, 3 counts of facial edema, 3 counts of peripheral edema, 6 counts of rash, and 3 counts of urticaria, not all thought to be drug-related, and all were rated non-severe. There was also 1 count of colitis, 1 count of esophagitis, and 1 count of severe melena, all were considered ketoprofen-related. Eleven of the 24 healthy volunteers had vein irritation upon receiving ketoprofen 50mg intravenously in bioavailability study 0284, and one was rated severe. There was 1 report of death from a headache study conducted in Germany. The patient had melanoma resected from the leg, 11 years prior to the study enrollment and unknown brain metastasis and was misdiagnosed at the study entry. Three days after a single oral dose of ketoprofen 25mg, the patient died of intracranial hemorrhage. Ketoprofen was not considered the primary cause of the event. For patients on ibuprofen, there was one count of severe allergic reaction, 2 counts of facial edema, 3 counts of rash (one of which was rated severe), not all thought to be drug-related. There was also 1 count of gastritis probably related to ibuprofen, and 1 severe case of convulsion, not considered to be ibuprofen-related. Most adverse events reported were of mild to moderate severity and non-serious in nature. Subjects on acetaminophen seemed to have higher overall reporting rates of adverse events. In general, there were no striking differences among treatment groups.

The incidence of adverse events was also summarized by gender and for the elderly groups in Table 1.

Table 1.

<i>Number and % (with respect to sub-population at risk) of subjects with AE</i>				
Groups	Total	Male	Female	Age ≥ 65
Ketoprofen	470/4030 (12%)	149/1120 (13%)	321/2910 (11%)	9/54 (17%)
		p = 0.0466		
Ibuprofen	247/3446 (7%)	59/954 (6%)	188/2492 (8%)	10/91 (11%)
		p = 0.1603		
Placebo	101/515 (20%)	49/124 (40%)	52/391 (13%)	
		p = 0.000		
Acetaminophen	53/108 (49%)	39/60 (65%)	14/48 (29%)	
		p = 0.0002		
Aspirin	11/52 (21%)	3/23 (13%)	8/29 (28%)	
		p = 0.1938		

It is not valid to draw a conclusion about treatment-gender interactions based on pooled data because of the inconsistency in trial design (e.g. not all trials included both male and female subjects), data collection, etc. The p-values were provided for information only. For the treatment groups with at least 100 subjects across studies, males had apparently statistically higher reporting rates of AEs than females with ketoprofen, placebo, and acetaminophen treatments but not with ibuprofen. The elderly sub-groups were too small to provide any useful information.

There were 40 cases of drop-outs due to adverse reactions. These cases were listed in Table 3 in Appendix C. Of the 25 drop-outs in the ketoprofen group, 50% were due to minor GI symptoms; and 20% were CNS symptoms. Except the fatal case described above, none had serious outcomes. Most events resolved spontaneously.

B. WORLD WIDE SAFETY SURVEILLANCE

At present time, a system for accurate and complete post-marketing monitoring for drug safety does not exist. Only limited safety information is available. To learn about how the safety of ketoprofen would fit into the safety spectrum of the other currently available over-the-counter analgesics (aspirin, acetaminophen, ibuprofen, and naproxen), the safety information from the following sources were reviewed: Medline search, FDA's Spontaneous Reporting System (SRS) database, and the World Health Organization (WHO) database available at FDA.

The SRS reporting system started in 1969. Very few spontaneous reports were received at FDA before a drug was in the market. In 1985, there was a change in terms of the definition of seriousness, which excluded the adverse events requiring medical treatments as being serious. (Serious events refer to events with outcomes of death, hospitalization, disabled, congenital abnormality, and life-threatening). The WHO reporting system started in 1968.

Attempts to interpret data based on the computer printouts of the spontaneous reports could be misleading for many reasons. Not all adverse events are reported and there are a number of ways to have counts duplicated for a single event. The number of reports submitted to the FDA, WHO, and literature are influenced by the pattern of usage (intermittent versus chronic), time of approval, length of time in the market, and familiarity with or novelty of an observed adverse reaction. The counts of events reflect reporting frequency, but not the actual incidence of adverse reactions. A given reaction may be due to underlying disease, concomitant medication, or other causes. The assessment of the likelihood that a pharmaceutical product caused the suspected reaction is not included in the computer printouts, and in many cases, is not available. No information is provided on the number of patients exposed to the product for the purpose of risk ratio estimation.

For the purpose of this review, ketoprofen safety data will be discussed under each of the 12 body systems based on the COSTART Body-System Classification, a terminology system developed and used by FDA. The adverse reactions listed in the current labels will be presented at the beginning of each body-system section for reference and followed by SRS database summary and then by WHO database summary.

In both of these summaries, the event counts for acetaminophen, aspirin, ibuprofen, and naproxen are presented along with that for ketoprofen. Tolmetin and zomepirac are added to the list for the discussion of anaphylaxis; and piroxicam, indomethacin, and diclofenac sodium are added for the discussion of major gastrointestinal complications.

The type of adverse reactions will be selected for discussion based on their clinical significance. For each type of adverse event in the SRS database summary, the count of events (not equivalent to the number of cases because of the multiple reporting of the same case from different sources and multiple COSTART terms used to describe a single case), the count of events with serious

outcomes, and the count of deaths related to the event will be presented. The percentages of each (count of events, serious events, and deaths) are calculated by dividing the count of a specific AE by the total count of AEs reported for the drug, and similarly, dividing the count of a specific AE with serious outcomes by the total count of serious AEs reported for the drug, etc. In the WHO database summary, the counts of serious events and deaths related to a specific AE are not available. Only the count of events and their percentages are presented. The denominators for all the calculations are summarized in Tables 1 and 2.

**APPEARS THIS WAY
ON ORIGINAL**

Table 1. Totals in SRS and WHO database summaries

<i>Drug</i>	<i>SRS database</i>				<i>WHO database</i>
	<i>Year of US approval</i>		<i>Total report</i>	<i>Total count (used as denominators)</i>	<i>Total count (used as denominators)</i>
Ketoprofen	1986	Count	823	1774	9620
		Serious	217	590	
		Death	38	103	
Acetaminophen	Before 1969	Count	1877	4100	6647
		Serious	819	2345	
		Death	358	978	
Aspirin	Before 1969	Count	1758	3697	13656
		Serious	683	1857	
		Death	125	301	
Ibuprofen	1974	Count	8757	16926	18850
		Serious	2073	5609	
		Death	314	738	
Naproxen	1976	Count	8063	16519	19818
		Serious	1837	4898	
		Death	366	875	

**APPEARS THIS WAY
ON ORIGINAL**

Table 2. Totals in SRS and WHO database summaries - addendum

<i>Drug</i>	<i>SRS database</i>				<i>WHO database</i>
	<i>Year of US approval</i>		<i>Total report</i>	<i>Total count (used as denominators)</i>	<i>Total count (used as denominators)</i>
Diclofenac sodium	1988	Count	3812	8001	20617
		Serious	1349	3540	
		Death	530	1278	
Indomethacin	1965	Count	3668	6792	18268
		Serious	1192	2795	
		Death	402	875	
Piroxicam	1982	Count	4989	9098	18355
		Serious	1384	3125	
		Death	302	740	
Tolmetin	1976	Count	2001	4881	3924
		Serious	574	1736	
		Death	102	271	
Zomepirac	1980 (discontinued in 1984)	Count	5336	12292	10481
		Serious	1206	3087	
		Death	220	433	

**APPEARS THIS WAY
ON ORIGINAL**

I. BODY AS A WHOLE

1. Present label

Incidence	3 to 9%	≥1% (<3%)	<1%	<1%
Causal relationship	Probable	Probable	Probable	Unknown
Adverse event			Chills, facial edema, infection, pain, allergic reaction, anaphylaxis	Septicemia, shock

2. SRS database summary

Adverse event	Anaphylaxis			Allergic reactions		
	event %	serious %	death %	event %	serious %	death %
Ketoprofen	21	16	2	25	5	0
	1.18%	2.71%	1.94%	1.41%	0.85%	
Acetaminophen	27	11	0	26	5	1
	0.66%	0.47%		0.63%	0.2% ¹	0.10%
Aspirin	23	10	0	26	8	0
	0.62%	0.54%		0.70%	0.43%	
Ibuprofen	147	90	11	307	42	2
	0.87%	1.60%	1.49%	1.81%	0.75%	0.27%
Naproxen	220	112	10	364	77	9
	1.33%	2.29%	1.14%	2.20%	1.57%	1.03%

Tolmetin	393	191	11	126	25	1
	8.05%	11.0%	4.06%	2.58%	1.44%	0.37%
Zomepirac	611	265	9	401	70	1
	4.97%	8.58%	2.08%	3.26%	2.27%	0.23%

3. WHO database summary

<i>Adverse event</i>	<i>Anaphylaxis</i>		<i>Allergic reactions</i>	
	<i>count</i>	<i>%</i>	<i>count</i>	<i>%</i>
Ketoprofen	78	0.81%	46	0.48%
Acetaminophen	89	1.34%	34	0.51%
Aspirin	114	0.83%	70	0.51%
Ibuprofen	173	0.92%	204	1.08%
Naproxen	248	1.25%	160	0.81%

Tolmetin	305	7.77%	96	2.45%
Zomepirac	398	3.80%	274	2.61%

(Note: The COSTART term used in SRS reporting system and the WHOART term in WHO reporting system are converted to make the data presentation consistent with each other. In the WHO database summary table, anaphylaxis refers to WHOART terms anaphylactic shock and anaphylactoid reactions; and allergic reactions refer to WHOART terms allergy and allergic reactions.)

4. Discussion

There appear to be more cases of anaphylaxis associated with tolmetin and zomepirac. The latter was discontinued from the U.S. market because of dramatically increased reports of fatal anaphylaxis cases. Ketoprofen 25mg was switched back from OTC to prescription status in Italy after a single case of fatal anaphylaxis. The episode occurred in a patient with a prior history of asthma after taking a combination product of ketoprofen 25 mg and sucralfate 200mg. There has not been a noticeable increase in reports of anaphylaxis for ketoprofen to the spontaneous reporting systems. Anaphylactic reaction is a safety concern with OTC usage of NSAIDs since severe hypersensitivity reactions have been noticed to appear more frequently after intermittent use of NSAIDs and to occur independent of dose levels of NSAIDs. Patients with asthma and urticaria/angioedema seem to be particularly prone to the allergic reactions induced by aspirin and NSAIDs. NSAIDs are contraindicated in patients with aspirin intolerance.

II. CARDIOVASCULAR SYSTEM

1. Present sable

Incidence	3 to 9%	≥1% (<3%)	<1%	<1%
Causal relationship	Probable	Probable	Probable	Unknown
Adverse event			Hypertension, palpitation, tachycardia, congestive heart failure, peripheral vascular disease, vasodilation.	Arrhythmias, myocardial infarction

2. SRS database summary

Adverse event	Congestive heart failure			Hypertension		
	event %	serious %	death %	event %	serious %	death %
Ketoprofen	8	7	4	13	5	0
	0.45%	1.19%	3.88%	0.73%	0.85%	
Acetaminophen	1	1	1	12	5	1
	0.02%	0.04%	0.10%	0.29%	0.21%	0.10%
Aspirin	1	1	0	16	4	1
	0.03%	0.05%		0.43%	0.22%	0.33%
Ibuprofen	38	18	9	108	20	0
	0.22%	0.32%	1.22%	0.64%	0.36%	
Naproxen	26	16	3	85	21	0
	0.16%	0.33%	0.34%	0.51%	0.43%	