IV. Sponsor's Statistical Analyses (ITT with LOCF) and Results

Post-Dental Surgery Pain Studies: 066, 071

An intent-to-treat (ITT) analysis was performed and considered the primary efficacy analysis. Intent-to-treat dataset contained all those patients who took study medication, recorded a baseline pain intensity score, and recorded at least one pain evaluation postdose. Missing pain relief and pain intensity scores were estimated by last observation carried forward approach (LOCF). In this approach, the missing pain scores after a patient took rescue medication were estimated by using the score recorded just prior to the patient took rescue medication. Patients who took rescue medication early (prior to 90 minutes) were included in the ITT analysis.

Sponsor's 5-page summary results from the ITT analyses with LOCF of (1) Pain Relief, (2) PID, (3) PRID, (4) Time to Confirmed Perceptible Pain Relief, and (5) Time to Taking Rescue Medication are included in the Appendix (pages 9-18 of this review).

Both studies confirmed the statistical effectiveness of a single Rofecoxib 50 mg dose for pain relief. The analgesic effect of a single Rofecoxib 50 mg dose was similar to 400 mg of ibuprofen in these studies.

The study 071 also demonstrated that the doses of 100 and 200 mg Rofecoxib were more effective than 50 mg Rofecoxib dose, but there is no safety data available for 100 and 200 mg doses of Rofecoxib. Thus, recommended dose has to be 50 mg of Rofecoxib.

Primary Dysmenorrhea Studies: 055, 056

An intent-to-treat (ITT) analysis was performed and considered the primary efficacy analysis. Intent-to-treat dataset contained all those patients who took study medication, recorded a baseline pain intensity score, and recorded at least one pain evaluation postdose. Missing pain relief and pain intensity scores were estimated by last observation carried forward approach (LOCF). In this approach, the missing pain scores after a patient took rescue medication were estimated by using the score recorded just prior to the patient took rescue medication. However, baseline pain intensity or data from previous periods were not carried forward. Patients who took rescue medication early (prior to 120 minutes) were included in the ITT analysis.

Sponsor's 5-page summary results from the ITT analyses with LOCF of (1) Pain Relief, (2) PID, (3) PRID, (4) Time to Onset of Analgesia (PID≥1), and (5) Time to

Taking Rescue Medication are included in the Appendix (pages 19-28 of this review).

Both studies confirmed the statistical effectiveness of a Rofecoxib 50 mg dose for pain relief. The analgesic effect of a single Rofecoxib 50 mg dose was similar to 550 mg of naproxen sodium in these studies after 2 hours post-dose.

Post-Orthopedic Surgery Pain Study: 072

An intent-to-treat (ITT) analysis was performed and considered the primary efficacy analysis. Intent-to-treat dataset contained all those patients who took study medication, recorded a baseline pain intensity score, and recorded at least one pain evaluation postdose. Missing pain relief and pain intensity scores were estimated by last observation carried forward approach (LOCF). In this approach, the missing pain scores after a patient took rescue medication were estimated by using the score recorded just prior to the patient took rescue medication. Patients who took rescue medication early were included in the ITT analysis.

Sponsor's 5-page summary results from the ITT analyses with LOCF of (1) Pain Relief, (2) PID, (3) PRID, (4) Time to Confirmed Perceptible Pain Relief, and (5) Time to Taking Rescue Medication are included in the Appendix (pages 29-33 of this review).

This study confirmed the statistical effectiveness of a Rofecoxib 50 mg dose for pain relief. The analgesic effect of Rofecoxib 50 mg daily dose was similar to 550 mg of naproxen sodium in this study.

Comment: *Please note that the Division's primary efficacy endpoints (namely, PR, PI, PID and PRID) and Sponsor's primary efficacy endpoint (TOPAR8) yielded similar conclusions for all the five pivotal studies.*

V.   FDA-Requested Analyses (ITT with BOCF) and Results

The FDA requested the sponsor to perform an ITT analysis using the Baseline Observation Carried Forward (BOCF) approach for missing values for the first 24 hours. In this approach, the missing pain scores after a patient took rescue medication are estimated by setting to zero both the PID and the PR at all time points after the patient remedicated.

The sponsor complied with the request and analyzed the data utilizing ITT with BOCF. Results from the ITT analyses with BOCF of (1) Pain Relief, (2) PID, and (3) PRID are included in the Appendix (pages 34-48 of this review) for studies 066, 071, 055, 056 and 072. The analytical methods are identical to those used to produce the 5-page summaries in the original NDA submission.

In general, results of these analyses were consistent with those presented in the original NDA submission.

VI. Statistical Issues

There were two statistical issues that needed to be resolved. These are described below with a possible resolution.

1. **Missing Values in studies 066 and 071:** In studies 066 and 071, the number of patients rapidly decreases after 8 hours of treatment. In Study 066, at 24 hours, percentage of patients remaining in Placebo, Rofecoxib 50 mg, and Ibuprofen 400 mg groups are 10%, 46% and 22% respectively. In Study 071, at 24 hours, percentage of patients remaining in Placebo, Rofecoxib 50 mg, Rofecoxib 100 mg, Rofecoxib 200 mg, and Ibuprofen 400 mg groups are 2%, 40%, 62%, 62% and 8% respectively. With such a large percentage of missing values at 24 hours, a claim of persistent analgesic effect of 50 mg of Rofecoxib up to 24 hours is questionable.

   Comment: As the sponsor's primary endpoint was total pain relief over the 8-hour postdose period (TOPAR8) and the percentage of missing values is not as large at 8 hours as at 24 hours, a claim of persistent analgesic effect of 50 mg of Rofecoxib up to 8 hours is reasonable.

2. **Carryover Effects in studies 055 and 056:** In studies 055 and 056, there were significant carryover effects for several endpoints. In Study 055, there were significant carryover effects in TOPAR8 ($p=0.025$), SPID8 ($p=0.018$) and GLOBAL8 ($p<0.001$). In Study 056, there were significant carryover effects in Peak PID ($p=0.032$).

   Comment: For both the studies, analyses of the above endpoints were performed with carryover effects included in the model to adjust the treatment means for carryover effects. Adjusted treatment means (for carryover effects) were then compared and found to be similar to the unadjusted treatment means. Thus, the impact of these significant carryover effects was negligible on the overall results of these studies. All the results are included in the Appendix (pages 49-56 of this review).

VII. Statistical Reviewer's Comments

1. Post-Dental Surgery Pain studies confirmed the statistical effectiveness of a single Rofecoxib 50 mg dose for pain relief. The analgesic effect of a single Rofecoxib 50 mg dose was similar to 400 mg of ibuprofen in these studies.
2. Primary Dysmenorrhea studies confirmed the statistical effectiveness of a Rofecoxib 50 mg dose for pain relief. The analgesic effect of a single Rofecoxib 50 mg dose was similar to 550 mg of naproxen sodium in these studies after 2 hours post-dose.
3. Post-Orthopedic Surgery Pain study confirmed the statistical effectiveness of a Rofecoxib 50 mg dose for pain relief. The analgesic effect of Rofecoxib 50 mg daily dose was similar to 550 mg of naproxen sodium in this study.
4. In Post-Dental Surgery Pain studies, the persistency of the analgesic effect of Rofecoxib 50 mg daily dose up to 24 hours is questionable as there are not many patients left in the studies at 24 hours. This result is purely analysis-driven. Thus, a claim of persistent analgesic effect of 50 mg of Rofecoxib up to 24 hours is not justified.
5. In Primary Dysmenorrhea studies, there were significant carryover effects for several endpoints. But, the impact of these significant carryover effects was negligible on the overall results of these studies.

/S/

Baldeo K. Taneja, Ph.D.
Mathematical Statistician (Biomed)

Concur: Dr. Lin   /S/

Dr. Huque   /S/   7/29/99.

APPEARS THIS WAY
ON ORIGINAL

cc: Archival NDA 21-042
HFD-550/Cook, Averbuch, Hyde, Division File
HFD-725/Taneja, Lin, Huque, Division File, Chron.

There are total 56 pages (8 pages of text and 48 pages of Appendix) in this review.

MK-0966 Prot. No. 066
Phase III Trial for Postoperative Dental Pain

APPENDIX 4.1

4.1.29: Five-Page Summary of Efficacy Results

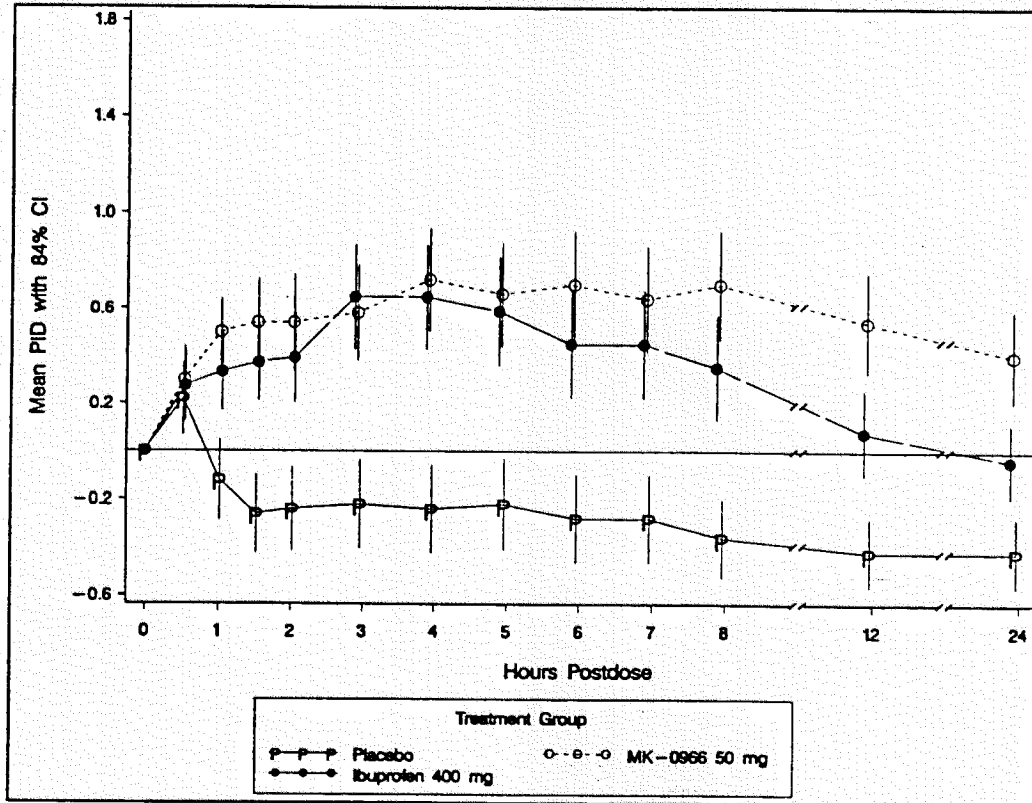### Analysis of Pain Relief Over Time (Intention-to-Treat)
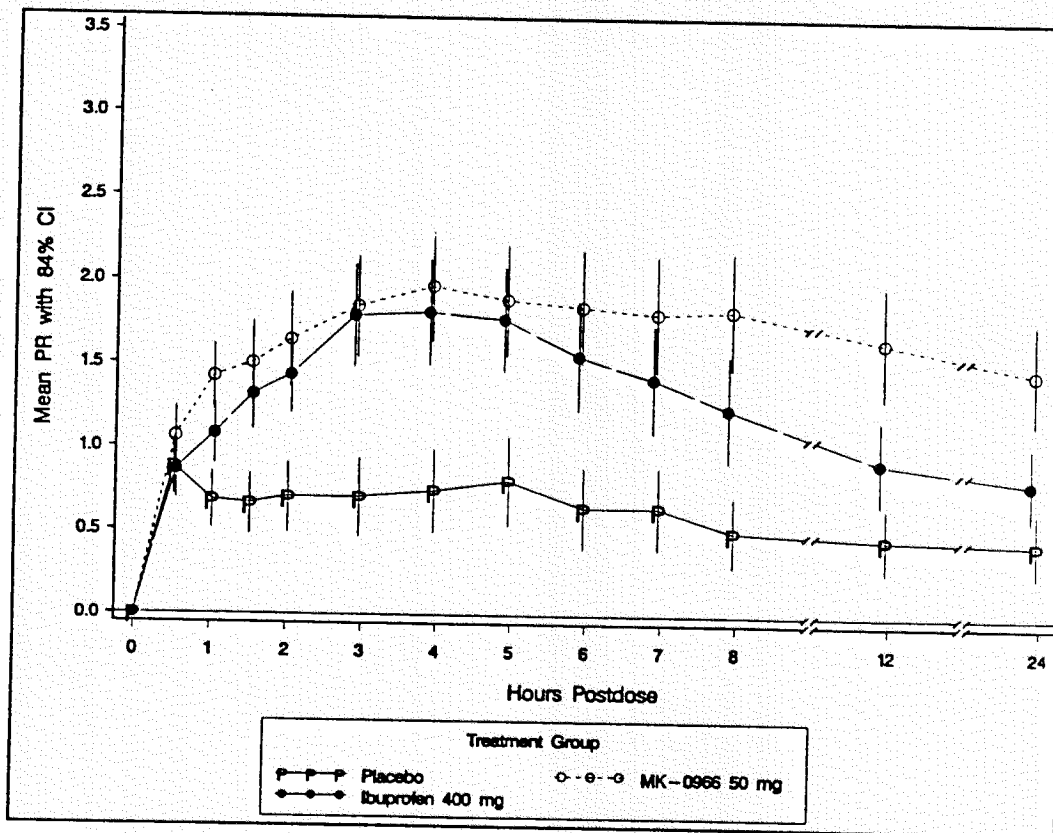
Treatment		Analysis of Pain Relief Over Time (Hours Post Dose, Last Value Carried Forward)											
		0.5	1	1.5	2	3	4	5	6	7	8	12	24
Placebo	N †	50	50	50	41	21	14	13	13	10	10	6	5
	MEAN	0.9 A	0.7 B	0.7 B	0.7 B	0.7 B	0.7 B	0.8 B	0.6 B	0.6 B	0.5 B	0.5 B	0.4 B
	STD	0.8	0.9	0.9	1.1	1.2	1.3	1.4	1.2	1.2	1.1	1.0	1.0
MK-0966 50 mg	N †	50	50	50	45	36	33	30	28	27	26	25	23
	MEAN	1.1 A	1.4 A	1.5 A	1.6 A	1.8 A	2.0 A	1.9 A	1.8 A	1.8 A	1.8 A	1.6 A	1.5 A
	STD	0.9	1.0	1.3	1.4	1.5	1.7	1.7	1.7	1.7	1.7	1.7	1.5
Ibuprofen 400 mg	N †	51	51	51	45	35	32	31	29	23	21	18	11
	MEAN	0.9 A	1.1 A	1.3 A	1.4 A	1.8 A	1.8 A	1.8 A	1.5 A	1.4 A	1.2 A	0.9 B	0.8 B
	STD	0.9	0.9	1.1	1.2	1.6	1.6	1.6	1.6	1.6	1.6	1.3	1.1
Pooled SD		0.9	0.9	1.1	1.2	1.4	1.5	1.5	1.5	1.5	1.5	1.4	1.2
Effect		p-Values by Time Point (Hours Postdose)											
Treatment ††		0.494	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Stratum(Baseline PI) ††		0.548	0.575	0.697	0.991	0.574	0.628	0.955	0.613	0.494	0.752	0.544	0.722
Rx-by-Stratum Interaction †††		0.634	0.854	0.895	0.710	0.806	0.861	0.696	0.638	0.563	0.979	0.811	0.673

† — Observed sample size
†† — Model included treatment, baseline Pain Intensity (PI) as factors.
††† — Model included treatment, baseline PI and treatment-by-baseline PI interaction as factors.
A, B, C — Based on Model †† LSMeans. Letter A indicates the most effective dose(s), B indicates the next most effective, and so forth. Treatments sharing at least one letter were not significantly different from each other at the 5% significance level.
All p-values from the pairwise comparisons are provided in APPENDIX [4.1.1] of the CSR.

9

MK-0966 Prot. No. 066
Phase III Trial for Postoperative Dental Pain

APPENDIX 4.1

4.1.29: Five-Page Summary of Efficacy Results (Cont.)

Analysis of PID Over Time (Intention-to-Treat)

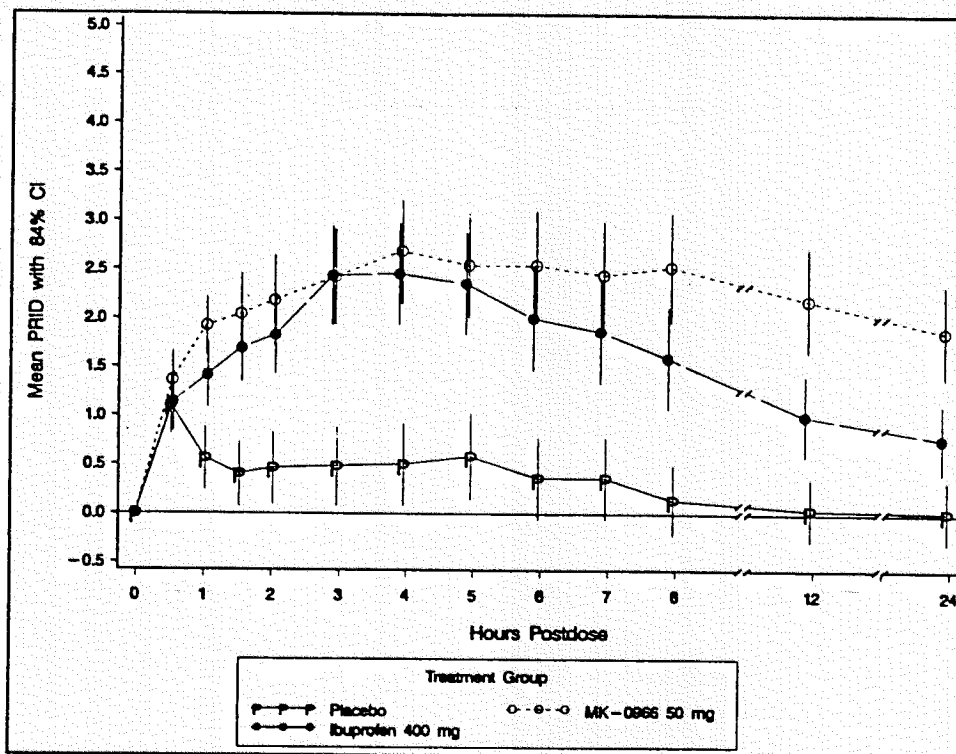| Treatment		Analysis of PID Over Time (Hours Post Dose, Last Value Carried Forward)											
		0.5	1	1.5	2	3	4	5	6	7	8	12	24
Placebo	N †	50	50	50	41	21	14	13	13	10	10	6	5
	MEAN	0.2 A	-0.1 B	-0.3 B	-0.2 B	-0.2 B	-0.2 B	-0.2 B	-0.3 B	-0.3 B	-0.4 B	-0.4 C	-0.4 C
	STD	0.8	0.8	0.8	0.9	0.9	0.9	1.0	0.9	0.9	0.8	0.7	0.7
MK-0966 50 mg	N †	50	50	50	45	36	33	30	28	27	26	25	23
	MEAN	0.3 A	0.5 A	0.5 A	0.5 A	0.6 A	0.7 A	0.7A	0.7 A	0.6 A	0.7 A	0.5 A	0.4 A
	STD	0.7	0.7	0.9	1.0	1.0	1.1	1.1	1.1	1.1	1.1	1.1	1.0
Ibuprofen 400 mg	N †	51	51	51	45	35	32	31	29	23	21	18	11
	MEAN	0.3 A	0.3 A	0.4 A	0.4 A	0.6 A	0.6 A	0.6 A	0.5 A	0.5 A	0.4 A	0.1 B	-0.0 B
	STD	0.8	0.8	0.8	1.0	1.1	1.1	1.2	1.2	1.2	1.1	0.9	0.8
Pooled SD		0.7	0.8	0.8	0.9	1.0	1.0	1.1	1.1	1.0	1.0	0.9	0.8
Effect		p-Values by Time Point (Hours Postdose)											
Treatment ††		0.862	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Stratum(Baseline PI) ††		0.045	0.023	0.012	0.002	0.066	0.052	0.022	0.005	0.004	0.077	0.061	0.005
Rx-by-Stratum Interaction†††		0.938	0.857	0.838	0.985	0.796	0.764	0.542	0.470	0.457	0.961	0.998	0.825

† — Observed sample size
†† — Model included treatment, baseline Pain Intensity (PI) as factors.
††† — Model included treatment, baseline PI and treatment-by-baseline PI interaction as factors.
A, B, C — Based on Model †† LSMeans. Letter A indicates the most effective dose(s), B indicates the next most effective, and so forth. Treatments sharing at least one letter were not significantly different from each other at the 5% significance level.
All p-values from the pairwise comparisons are provided in APPENDIX [4.1.2] of the CSR.

MK-0966 Prot. No. 066
Phase III Trial for Postoperative Dental Pain

APPENDIX 4.1

4.1.29: Five-Page Summary of Efficacy Results (Cont.)

Analysis of PRID Over Time (Intention-to-Treat)

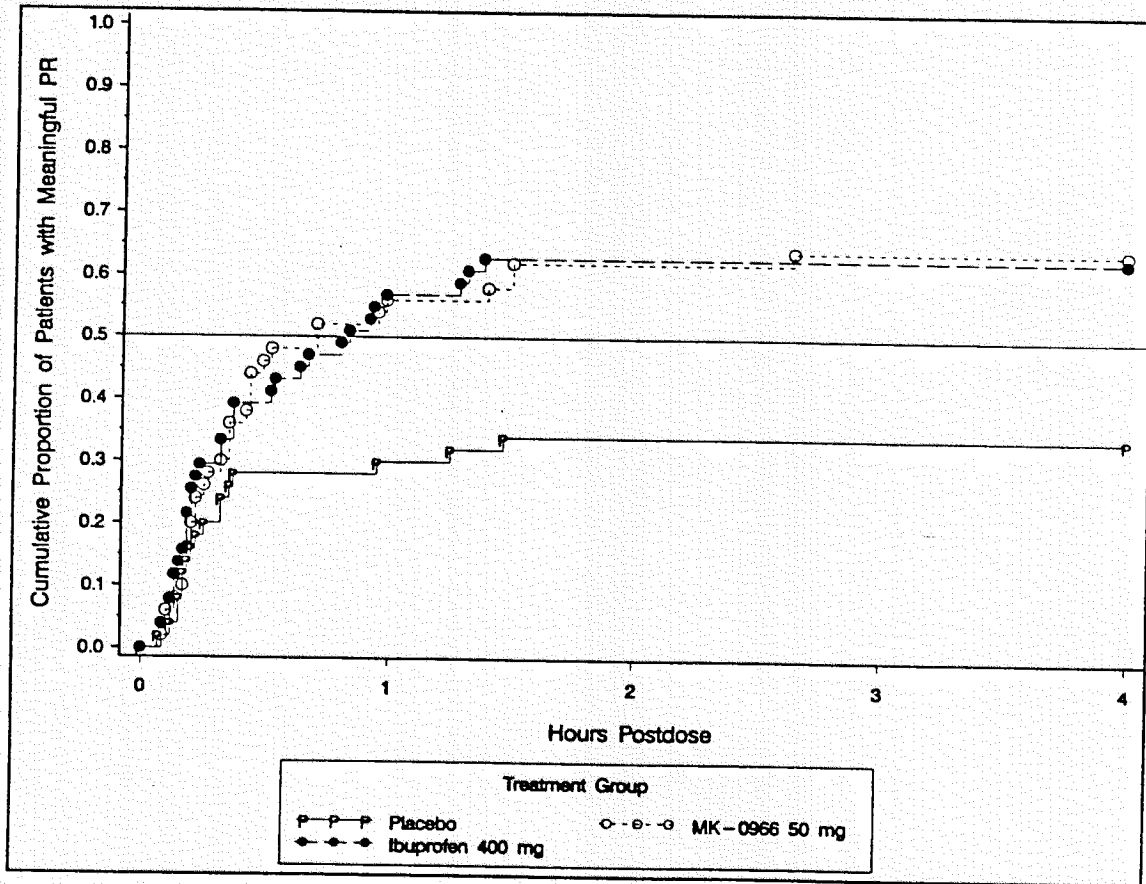| Treatment		Analysis of PRID Over Time (Hours Post Dose, Last Value Carried Forward)											
		0.5	1	1.5	2	3	4	5	6	7	8	12	24
Placebo	N †	50	50	50	41	21	14	13	13	10	10	6	5
	MEAN	1.1 A	0.6 B	0.4 B	0.5 B	0.5 B	0.5 B	0.6 B	0.4 B	0.4 B	0.1 B	0.0 C	0.0 B
	STD	1.5	1.6	1.7	1.9	2.1	2.1	2.3	2.1	2.1	1.8	1.6	1.6
MK-0966 50 mg	N †	50	50	50	45	36	33	30	28	27	26	25	23
	MEAN	1.4 A	1.9 A	2.0 A	2.2 A	2.4 A	2.7 A	2.5 A	2.5 A	2.4 A	2.5 A	2.2 A	1.9 A
	STD	1.5	1.5	2.1	2.3	2.5	2.7	2.7	2.8	2.8	2.8	2.7	2.4
Ibuprofen 400 mg	N †	51	51	51	45	35	32	31	29	23	21	18	11
	MEAN	1.1 A	1.4 A	1.7 A	1.8 A	2.4 A	2.5 A	2.4 A	2.0 A	1.9 A	1.6 A	1.0 B	0.8 B
	STD	1.5	1.7	1.8	2.0	2.6	2.6	2.7	2.7	2.7	2.7	2.1	1.8
Pooled SD		1.5	1.6	1.9	2.1	2.4	2.5	2.5	2.5	2.5	2.5	2.2	2.0
Effect		p-Values by Time Point (Hours Postdose)											
Treatment ††		0.638	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Stratum(Baseline PI) ††		0.534	0.424	0.354	0.158	0.653	0.606	0.355	0.141	0.107	0.584	0.688	0.159
Rx-by-Stratum Interaction†††		0.769	0.841	0.861	0.918	0.807	0.816	0.630	0.562	0.505	0.971	0.917	0.792

† — Observed sample size.
†† — Model included treatment, baseline Pain Intensity (PI) as factors.
††† — Model included treatment, baseline PI and treatment-by-baseline PI interaction as factors.
A, B, C — Based on Model †† LSMeans. Letter A indicates the most effective dose(s); B indicates the next most effective, and so forth. Treatments sharing at least one letter were not significantly different from each other at the 5% significance level.
All p-values from the pairwise comparisons are provided in APPENDIX [4.1.3] of the CSR.

11

MK-0966 Prot. No. 066
Phase III Trial for Postoperative Dental Pain

APPENDIX 4.1

4.1.29: Five-Page Summary of Efficacy Results (Cont.)

Analysis of Time to Confirmed Perceptible Pain Relief
### (Stopwatch Time of Perceptible Pain)

Treatment	N	Number (%[@]) of Patients Confirmed Perceptible Pain Relief	Time (Hour) to Confirmed Perceptible Pain Relief by Percentile		
			25th	50th (95% CI)	75th
Placebo	50	17 (34.0)	0.4	NE, B	NE
MK-0966 50 mg	50	32 (64.0)	0.3	0.7 (0.4, 2.7) A	NE
Ibuprofen 400 mg	51	32 (62.7)	0.2	0.8 (0.4, NE) A	NE

Effect		p-Value
Treatment		0.010
Stratum (Baseline PI)		0.479

@: Kaplan-Meier estimate of incidence rate (This may be different from the crude rate).
NE: Not estimable. Percentile NE due to low percentage (≤x% for the x'th percentile).
A, B, C —Letter A indicates the most effective dose(s), B indicates the next most effective, and so forth. Treatments sharing at least one letter were not significantly different from each other at the 5% significance level.
All p-values from the pairwise comparisons are provided in Table 20 of the CSR.

MK-0966 Prot. No. 066
Phase III Trial for Postoperative Dental Pain

APPENDIX 4.1

4.1.29: Five-Page Summary of Efficacy Results (Cont.)

Analysis of Time to Taking Rescue Medication Within 24 Hours
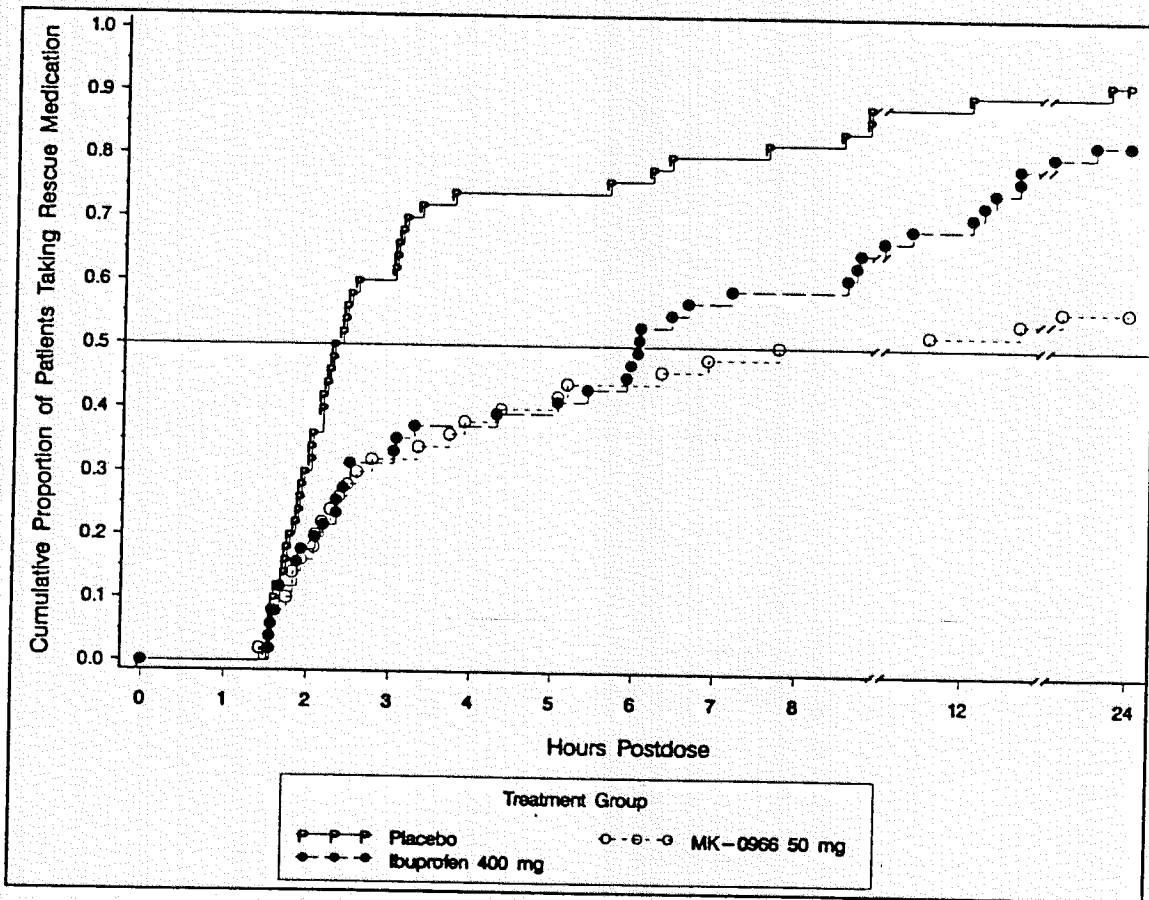
Treatment	N	Number(% [@]) of Patients Rescue Medication	Time (Hour) to Rescue Medication by Percentile		
			25th	50th (95% CI)	75th
Placebo	50	46 (92.0)	1.9	2.4 (2.2, 3.1) C	5.7
MK-0966 50 mg	50	28 (56.0)	2.4	9.5 (3.9, NE) A	NE
Ibuprofen 400 mg	51	42 (82.4)	2.3	6.1 (3.3, 9.5) B	16.0

Effect				p-Value	p-Value
Treatment				<0.001	<0.001
Stratum (Baseline PI)				0.646	0.677

@: Kaplan-Meier estimate of incidence rate (This may be different from the crude rate).

NE: Not estimable. Percentile NE due to low percentage (≤x% for the x'th percentile).

A, B, C —Letter A indicates the most effective dose(s), B indicates the next most effective, and so forth. Treatments sharing at least one letter were not significantly different from each other at the 5% significance level.

All p-values from the pairwise comparisons are provided in Table 26 of the CSR.

MK-0966 Prot. No. 071
Phase III Trial for Postoperative Dental Pain

APPENDIX 4.1

4.1.30: Five-Page Summary

Analysis of Pain Relief Over Time (Intention-to-Treat Approach)

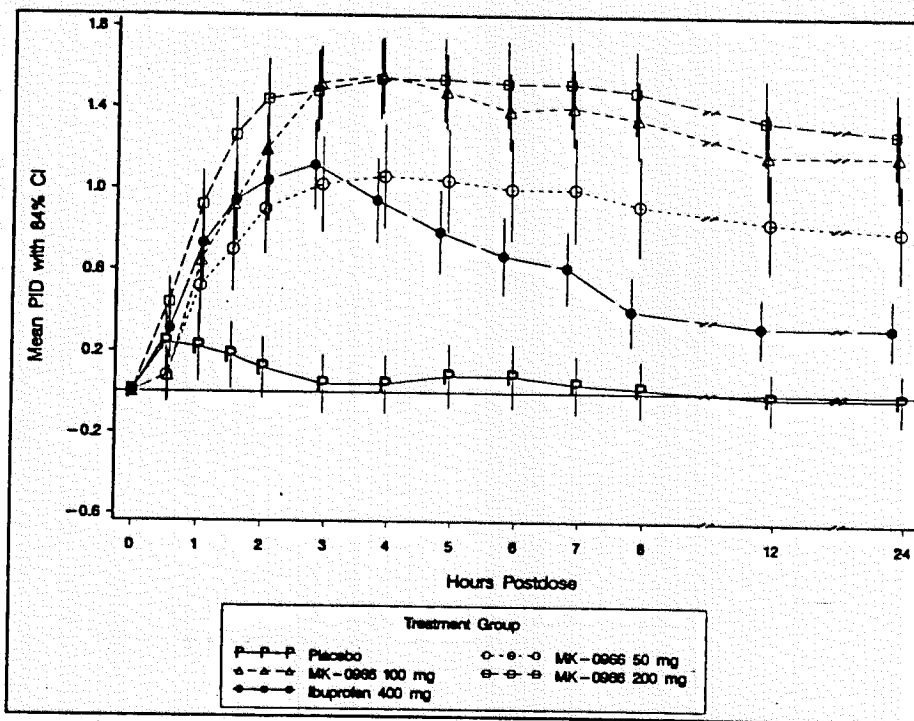| Treatment		Summary Statistics by Time Point (Hours Postdose)											
		0.5	1	1.5	2	3	4	5	6	7	8	12	24
Placebo	N †	50	50	50	24	12	5	4	4	4	4	2	1
	MEAN	0.7 A	0.9 C	0.9 C	0.7 C	0.6 C	0.6 C	0.6 D	0.6 D	0.6 D	0.6 C	0.5 C	0.5 C
	STD	0.9	0.9	0.9	0.9	0.8	0.9	1.0	1.0	0.9	0.8	0.7	0.7
MK-0966 50 mg	N †	50	50	50	38	34	32	30	28	26	25	23	20
	MEAN	0.6 A	1.3 B	1.6 B	1.9 B	2.1 B	2.2 B	2.1 B	2.0 B	2.0 B	1.9 B	1.7 B	1.6 B
	STD	0.8	1.1	1.3	1.3	1.4	1.5	1.6	1.6	1.6	1.6	1.5	1.6
MK-0966 100 mg	N †	51	51	52	46	45	45	44	44	39	38	36	31
	MEAN	0.6 A	1.4 AB	1.9 AB	2.3 AB	2.8 A	2.8 A	2.7 A	2.6 A	2.6 A	2.5 A	2.2 A	2.3 A
	STD	0.7	0.9	1.0	1.1	1.2	1.2	1.2	1.3	1.3	1.4	1.5	1.5
MK-0966 200 mg	N †	50	50	50	44	42	39	38	38	37	36	34	31
	MEAN	0.9 A	1.7 A	2.3 A	2.6 A	2.7 A	2.8 A	2.8 A	2.7 A	2.7 A	2.6 A	2.4 A	2.3 A
	STD	0.9	1.2	1.3	1.4	1.4	1.4	1.4	1.5	1.5	1.5	1.5	1.6
Ibuprofen 400 mg	N †	52	52	52	42	38	33	27	21	19	15	6	4
	MEAN	0.9 A	1.6 AB	1.9 AB	2.1 B	2.1 B	1.8 B	1.6 C	1.4 C	1.3 C	0.9 C	0.8 C	0.8 C
	STD	1.0	1.2	1.3	1.4	1.6	1.5	1.4	1.3	1.2	1.0	0.9	0.9
Pooled SD		0.9	1.1	1.2	1.2	1.3	1.3	1.3	1.3	1.3	1.2	0.9	1.3
Effect		p-Values by Time Point (Hours Postdose)											
Treatment ††		0.148	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Stratum(Baseline PI) ††		0.057	0.025	0.005	0.063	0.134	0.174	0.136	0.125	0.171	0.336	0.440	0.588
Rx-by-Stratum Interaction †††		0.791	0.395	0.713	0.892	0.859	0.505	0.641	0.737	0.489	0.170	0.130	0.239

† — Observed sample size . †† — Model included treatment, baseline Pain Intensity (PI) as factors.

††† — Model included treatment, baseline PI and treatment-by-baseline PI interaction as factors.

A,B,C,D — Based on Model †† LSMeans. Letter A indicates the most effective dose(s). B indicates the next most effective, and so forth. Treatments sharing the same letter were not significantly different from each other at the 5% significance level.

All p-values from the pairwise comparisons are provided in Appendix [4.1.1] of the CSR.

MK-0966 Prot. No. 071
Phase III Trial for Postoperative Dental Pain

APPENDIX 4.1

4.1.30: Five-Page Summary (Cont.)

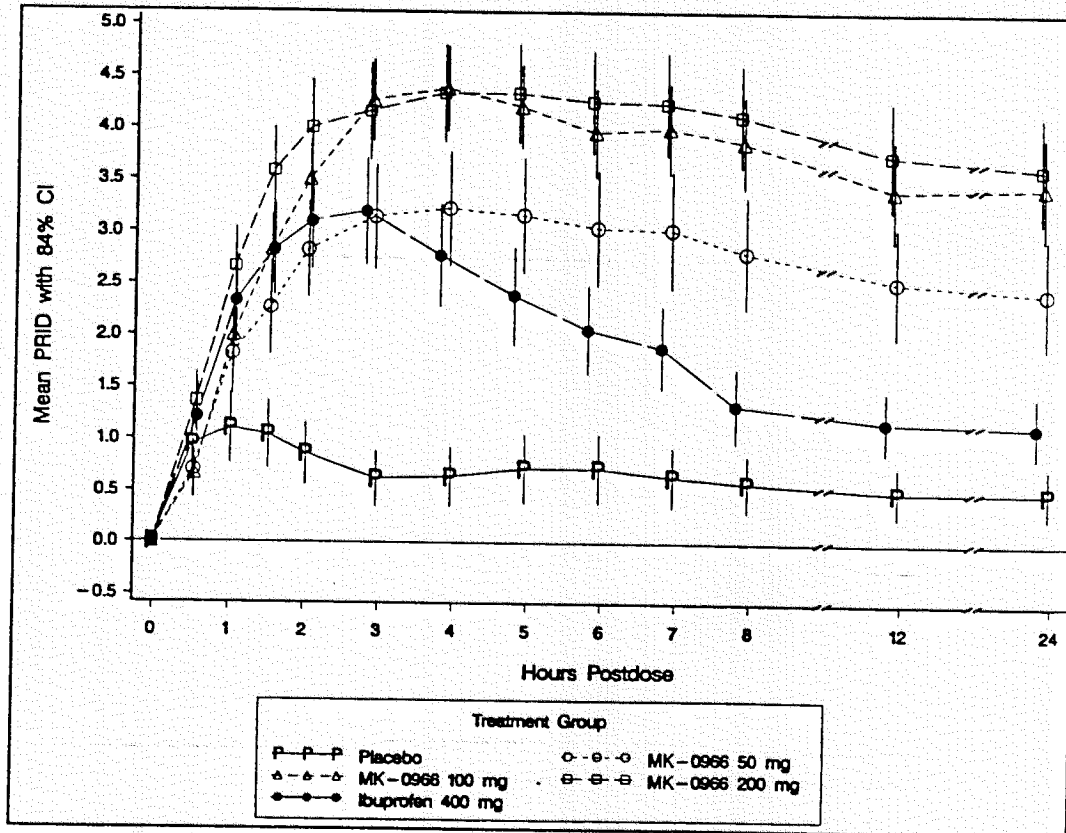### Analysis of PID Over Time (Intention-to-Treat Approach)

Treatment		Summary Statistics by Time Point (Hours Postdose)											
		0.5	1	1.5	2	3	4	5	6	7	8	12	24
Placebo	N †	50	50	50	24	12	5	4	4	4	4	2	1
	MEAN	0.2 AB	0.2 C	0.2 C	0.1 C	0.0 C	0.0 C	0.1 C	0.1 C	0.0 D	0.0 D	-0.0 D	-0.0 D
	STD	0.7	0.9	0.8	0.8	0.7	0.7	0.8	0.8	0.7	0.7	0.7	0.7
MK-0966 50 mg	N †	50	50	50	38	34	32	30	28	26	25	23	20
	MEAN	0.1 B	0.5 B	0.7 B	0.9 B	1.0 B	1.1 B	1.0 B	1.0 B	1.0 B	0.9 B	0.8 B	0.8 B
	STD	0.7	1.0	1.0	1.1	1.2	1.3	1.3	1.3	1.3	1.2	1.2	1.2
MK-0966 100 mg	N †	51	51	52	46	45	45	44	44	39	38	36	31
	MEAN	0.1 B	0.6 AB	0.9 B	1.2 AB	1.5 A	1.6 A	1.5 A	1.4 A	1.4 A	1.3 A	1.2 AB	1.2 A
	STD	0.6	0.7	0.8	0.9	0.9	1.0	1.0	1.0	1.0	1.0	1.1	1.1
MK-0966 200 mg	N †	50	50	50	44	42	39	38	38	37	36	34	31
	MEAN	0.4 A	0.9 A	1.3 A	1.4 A	1.5 A	1.5 A	1.5 A	1.5 A	1.5 A	1.5 A	1.4 A	1.3 A
	STD	0.6	0.8	0.9	1.0	1.0	1.0	1.1	1.1	1.1	1.0	1.1	1.1
Ibuprofen 400 mg	N †	52	52	52	42	38	33	27	21	19	15	6	4
	MEAN	0.3 AB	0.7 AB	0.9 B	1.0 B	1.1 B	0.9 B	0.8 B	0.7 B	0.6 C	0.4 C	0.3 C	0.3 C
	STD	0.8	1.0	1.0	1.0	1.1	1.1	1.1	1.0	0.9	0.9	0.8	0.8
Pooled SD		0.6	0.8	0.8	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9
Effect		p-Values by Time Point (Hours Postdose)											
Treatment ††		0.011	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Stratum(Baseline PI) ††		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Rx-by-Stratum Interaction †††		0.769	0.181	0.901	0.497	0.481	0.143	0.235	0.356	0.257	0.216	0.049	0.156

† — Observed sample size , †† — Model included treatment, baseline Pain Intensity (PI) as factors.

††† — Model included treatment, baseline PI and treatment-by-baseline PI interaction as factors.

A,B,C,D — Based on Model †† LSMeans. Letter A indicates the most effective dose(s). B indicates the next most effective, and so forth. Treatments sharing the same letter were not significantly different from each other at the 5% significance level.

All p-values from the pairwise comparisons are provided in Appendix [4.1.2] of the CSR.

MK-0966 Prot. No. 071
Phase III Trial for Postoperative Dental Pain

APPENDIX 4.1

4.1.30: Five-Page Summary (Cont.)

Analysis of PRID Over Time (Intention-to-Treat Approach)

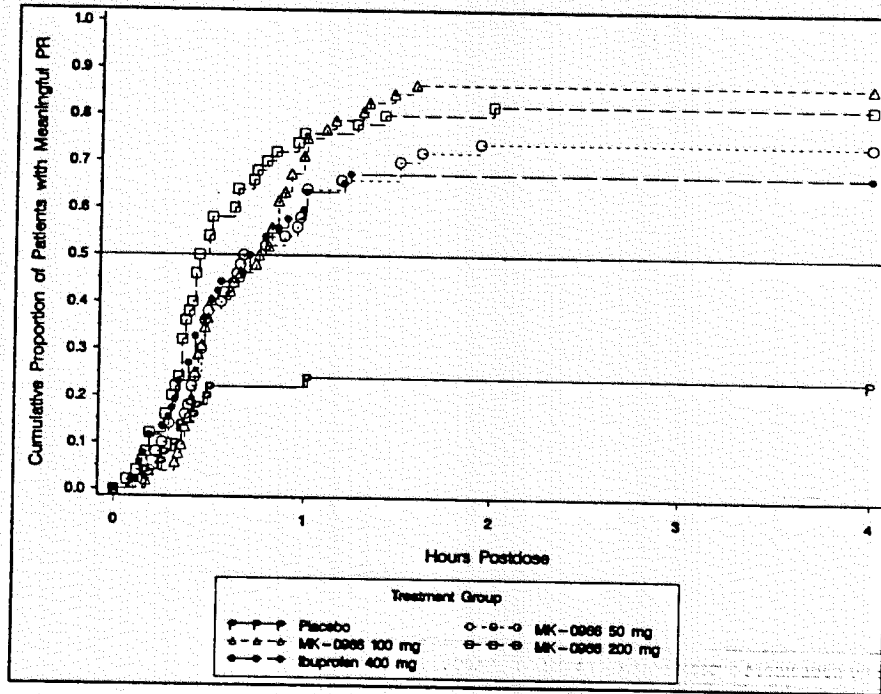| Treatment		Summary Statistics by Time Point (Hours Postdose)											
		0.5	1	1.5	2	3	4	5	6	7	8	12	24
Placebo	N †	50	50	50	24	12	5	4	4	4	4	2	1
	MEAN	0.9 ABC	1.1 C	1.0 C	0.9 C	0.6 C	0.6 C	0.7 C	0.7 D	0.6 D	0.6 C	0.5 C	0.5 C
	STD	1.5	1.7	1.7	1.5	1.4	1.5	1.7	1.7	1.5	1.4	1.2	1.2
MK-0966 50 mg	N †	50	50	50	38	34	32	30	28	26	25	23	20
	MEAN	0.7 BC	1.8 B	2.3 B	2.8 B	3.1 B	3.2 B	3.2 B	3.0 B	3.0 B	2.8 B	2.5 B	2.4 B
	STD	1.4	2.0	2.3	2.3	2.5	2.8	2.8	2.8	2.8	2.7	2.7	2.7
MK-0966 100 mg	N †	51	51	52	46	45	45	44	44	39	38	36	31
	MEAN	0.7 C	2.0 AB	2.8 B	3.5 AB	4.3 A	4.4 A	4.2 A	4.0 A	4.0 A	3.9 A	3.4 A	3.4 A
	STD	1.2	1.6	1.7	1.9	2.0	2.1	2.1	2.2	2.2	2.3	2.5	2.5
MK-0966 200 mg	N †	50	50	50	44	42	39	38	38	37	36	34	31
	MEAN	1.4 A	2.7 A	3.6 A	4.0 A	4.2 A	4.3 A	4.3 A	4.3 A	4.2 A	4.1 A	3.7 A	3.6 A
	STD	1.5	1.9	2.2	2.4	2.3	2.4	2.4	2.5	2.5	2.5	2.6	2.6
Ibuprofen 400 mg	N †	52	52	52	42	38	33	27	21	19	15	6	4
	MEAN	1.2 AB	2.3 AB	2.8 B	3.1 B	3.2 B	2.8 B	2.4 B	2.1 C	1.9 C	1.3 C	1.2 C	1.1 C
	STD	1.6	2.2	2.3	2.4	2.6	2.5	2.4	2.2	2.1	1.9	1.6	1.5
Pooled SD		1.4	1.8	1.9	2.0	2.2	2.2	2.2	2.2	2.2	2.1	2.1	2.2
Effect		p-Values by Time Point (Hours Postdose)											
Treatment ††		0.044	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Stratum(Baseline PI) ††		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Rx-by-Stratum Interaction †††		0.780	0.273	0.810	0.743	0.725	0.473	0.603	0.404	0.197	0.091	0.216	

All p-values from the pairwise comparisons are provided in Appendix [4.1.3] of the CSR.

16

MK-0966 Prot. No. 071
Phase III Trial for Postoperative Dental Pain

APPENDIX 4.1

4.1.30: Five-Page Summary (Cont.)

Analysis of Time to Confirmed Perceptible Pain Relief (Stopwatch Time
of Perceptible Pain Relief, Confirmed by the Second Stopwatch)
(Intention-to-Treat Approach)

Treatment	N	Number(% @) of Patients Confirmed Perceptible Pain Relief	Time (Hour) to Confirmed Perceptible Pain Relief by Percentile		
			25th	50th (95% CI)	75th
Placebo	50	12 (24.0)	NE	NE B	NE
MK-0966 50 mg	50	37 (74.0)	0.5	0.7 (0.5, 1.0) A	NE
MK-0966 100 mg	52	45 (86.5)	0.4	0.8 (0.5, 0.9) A	1.1
MK-0966 200 mg	50	41 (82.0)	0.4	0.5 (0.4, 0.6) A	1.0
Ibuprofen 400 mg	52	35 (67.3)	0.4	0.7 (0.5, 1.0) A	NE

Effect	p-Value
Treatment	<0.001
Stratum (Baseline PI)	0.053

@: Kaplan-Meier estimate of incidence rate (This may be different from the crude rate).

NE: Not estimable. Percentile NE due to low percentage ($\leq$x% for the x'th percentile).

A,B,C — Letter A indicates the most effective dose(s), B the next most effective dose(s), and so forth. Treatments sharing the same letter were not significantly different from each other at the 5% significance level.

All p-values from the pairwise comparisons are provided in Table 20 of the CSR.