

3. Discussion

The study design here is different from the ones traditionally used in multiple-dose studies of the chronic analgesic effect of an agent with unknown efficacy. To maximize response by using a highly selected study sample and to set the criteria for time to exit based on the assumption that the patch is useful to the individuals for the proposed indication, both might have introduced bias that the benefit might have been overestimated. The adequacy of blinding was not assessed by the study although it was suggested by the division (asking patients a simple question about the identity of the medication at 48 hours and the reasons for the guess). Patients might have been able to distinguish lidocaine patch from vehicle patch based on their experience with long term use of lidocaine patch. The carry over effect inherited from a crossover study design with no washout period in between the treatments, was a concern originally, because the commonly used statistical tests to detect carryover effects in the 2x2 crossover design are not considered very sensitive due to their heavy dependence on between-patient comparisons (Max, 1991). However, the consistent response pattern between the treatment phases (based on the subsequent analysis requested from the sponsor after the initial review of the study) did provide some levels of confidence. The lack of active control was due to the lack of clear standard therapy or apparent choice of therapy for the indication. The study was not designed to evaluate the time course of response, which is very useful in providing information on the onset and duration of response with respect to chronic treatment and thus providing dosing guidance for the patients. Since the increased skin sensitivity is an important aspect of the misery of neuropathic pain secondary to postherpetic neuralgia, the information on the multiple-dose effect of the lidocaine patch on allodynia reduction would be very useful but was not measured in the study. Also, the concurrent use of other PHN medication made it difficult to distinguish between the effect of lidocaine patch used alone and the added effect of patch to the oral PHN medication. The study results should be interpreted bearing all these issues/limitations in mind.

4. Conclusion

The study demonstrated that lidocaine patch performed statistically better than vehicle-control patch in terms of time to exit, daily pain relief, and patient preference of treatment, in selected patients who are considered responders after being chronically treated by lidocaine patches. However, the study was limited by the withdrawal type study design, the lack of assessment of adequate blinding, and the concurrent use of other PHN medication. The issues on the time course of response, and the multiple-dose effect on allodynia reduction remain to be resolved.

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III. Safety updates

1. Safety updates on lidocaine patch

There have been no reports of serious or unexpected adverse events since 1996 according to the most recent safety updates (covering the period of June 1996 to November 1998) and the annual reports for 1997 and 1998.

2. Literature reports on topical lidocaine formulations

Most studies in the literature reported the use of 2-10% lidocaine on limited skin surface areas for a couple of hours that resulted minimal systemic absorption, no systemic toxicities, and minor skin reactions.

There was a report of fatal case secondary to lidocaine overdose by cutaneous absorption. A 55-year old female with extensive cutaneous T cell lymphoma (patient was otherwise healthy) was treated with 5% lidocaine in lanette wax twice a day for her painful skin lesion. The daily dose was 25gm lidocaine contained in 500 gm cream, which was used to cover about 60% body surface area. The patient developed progressive neurologic and psychiatric abnormalities starting on day 5. Systemic intoxication with lidocaine was confirmed by a serum concentration of lidocaine 21.2 µg/ml accompanied by increases in the amount of lidocaine metabolites on day 8. The patient subsequently died despite discontinuation of lidocaine treatment (Lie et al., 1990).

There were allergic type reactions associated with the topical use of lidocaine as reported by Adriani *et. al.* Based on the author's review of 450 cases reported to the manufacturer of lidocaine from 1959 to 1975, 41 were classified as allergic: 20 of 41 were anaphylactic, 11 were questionable anaphylactoid, and 10 were contact allergic dermatitis. The author also identified 17 anaphylactic/anaphylactoid cases and 13 cases of contact allergic dermatitis due to the use of topical lidocaine by reviewing cases reported in the literature from 1968 to 1984. The conclusion was that allergic reactions associated with the topical use of lidocaine do occur and occur rarely (Adriani *et. al.*, 1986)

IV. Overall conclusion, benefits/risks, and recommendations

Pain secondary to postherpetic neuralgia (PHN) is very difficult to treat and remains intractable to currently used therapies.

The effect of lidocaine patch was shown in terms of patient's response to the discontinuation of treatment in an enriched sample population in a study, which might be biased by the withdrawal type study design, the lack of assessment of adequate blinding, and the concurrent use of other PHN medication. The additional evidence was the post-hoc findings of allodynia reduction based on measurements at a single time point after a single patch application. Are these together considered substantial evidence for efficacy?

In this reviewer's opinion, analgesic efficacy in terms of multiple-dose effect should be demonstrated in PHN patients who have never been treated with lidocaine patch previously, and the results should be reproducible. The time course of response should be demonstrated for pain associated with PHN (constant and touch-induced) in chronic studies of sufficient duration. Lidocaine patch may benefit some PHN patients after long term use, but the time it takes for lidocaine patch to reach the maximum effect could not be determined from the studies conducted.

It is considered safe to use lidocaine patch with recommended dosing. The relative safety profile of lidocaine patch in comparison to the other currently used PHN medication should be taken into the consideration as well.

V. Labeling review

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information

APPENDIX

Attachment 1

Table 2.1 presents the demographic characteristics of gender and age, as well as summary data on the number of days of open-label use of the patch prior to study entry.

Table 2.1
Demographic Characteristics of Period 1 Treated Subjects

	<u>ACTIVE</u>	<u>PLACEBO</u>	<u>TOTAL</u>	<u>P-VALUE</u>
Number of Patients	16	16	32	
Age (yrs)				
Mean	78.46	76.16	77.31	0.371 ^a
SD	8.56	5.39	7.14	
Range	62.0-96.6	65.1-86.2	62.0-96.6	
Not Reported	0	0	0	
Gender				
Male	7 (44%)	7 (44%)	14 (44%)	1.000 ^b
Female	9 (56%)	9 (56%)	18 (56%)	
Length of Use (Days)				
Mean	1165	1232	1198	0.777 ^a
SD	533	768	651	
Range	103-2237	81-3101	81-3101	
Not Reported	0	0	0	

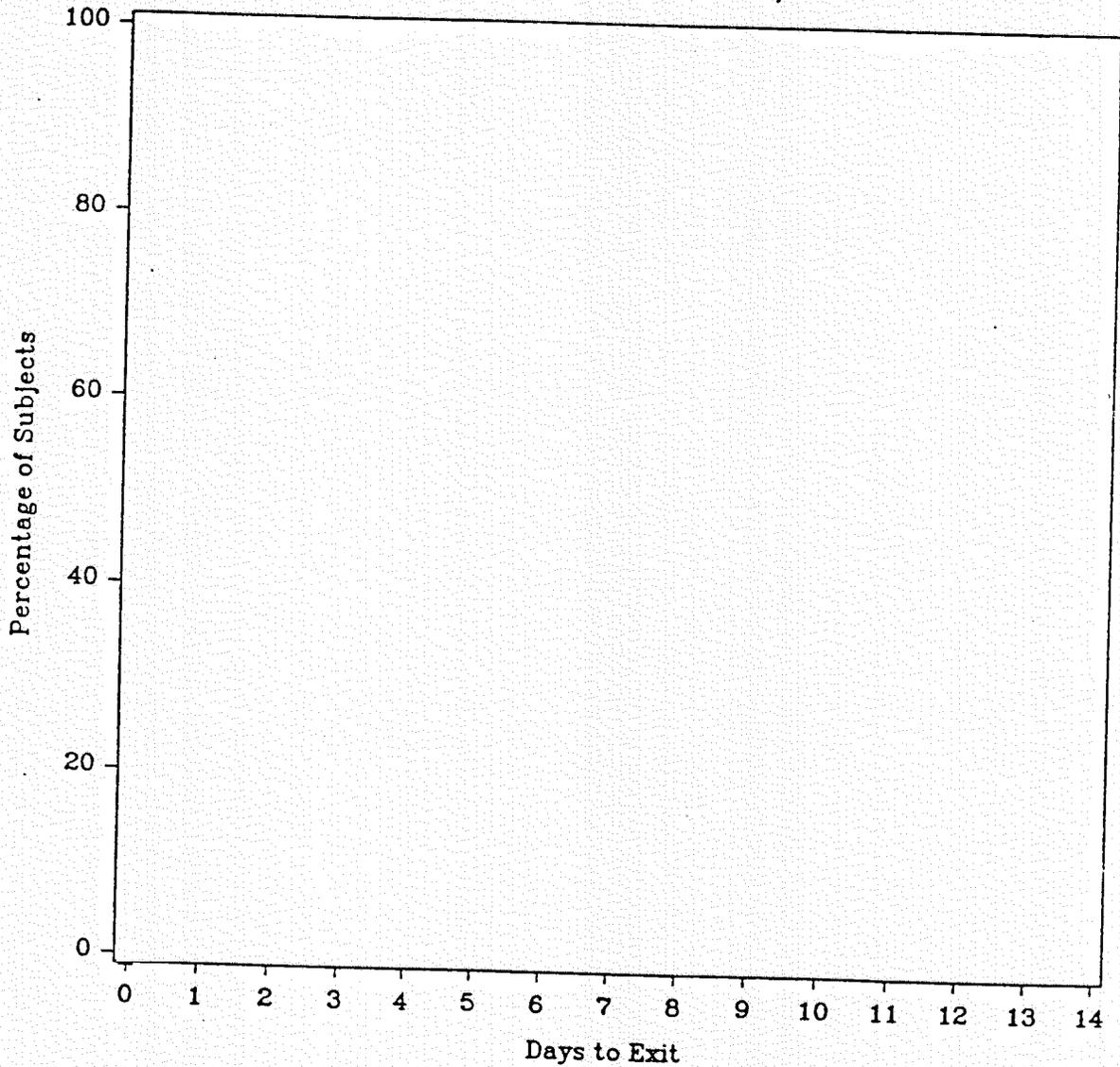
^a P-values for treatment comparisons from a one-way analysis of variance with a factor of treatment.

^b P-values for treatment comparisons from a Fisher's Exact Test.

SOURCE: JQ/HHC/CROSS-DEMO2 (Oct 14, 1998 12:14)

Attachment 2.1

Figure 1
Time to Study Exit
(Intent-to-treat Patients)



TREATMENT A A A ACTIVE P P P PLACEBO

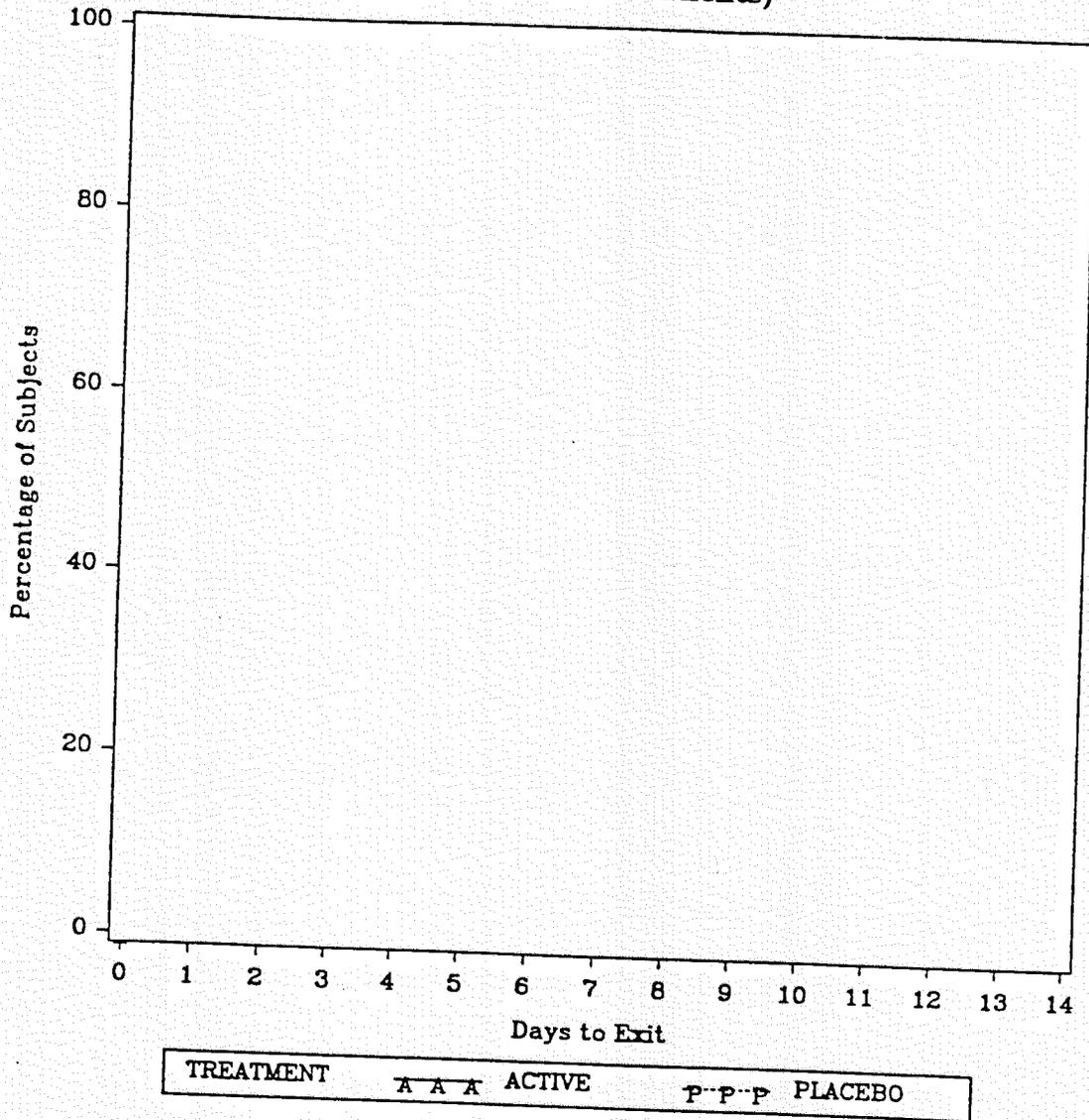
Comparison of distribution of days to exit across both treatments

	Median Time (minutes)	95% C.I. for Median Time	PLACEBO vs ACTIVE
ACTIVE	>14	(14.0, >14)	<0.001 ^a
PLACEBO	3.8	(3.0, >14)	

^a p-values obtained from WILCOXON test.

Attachment 2.2

Figure 1.1
Time to Study Exit (First Period Data Only)
(Intent-to-treat Patients)



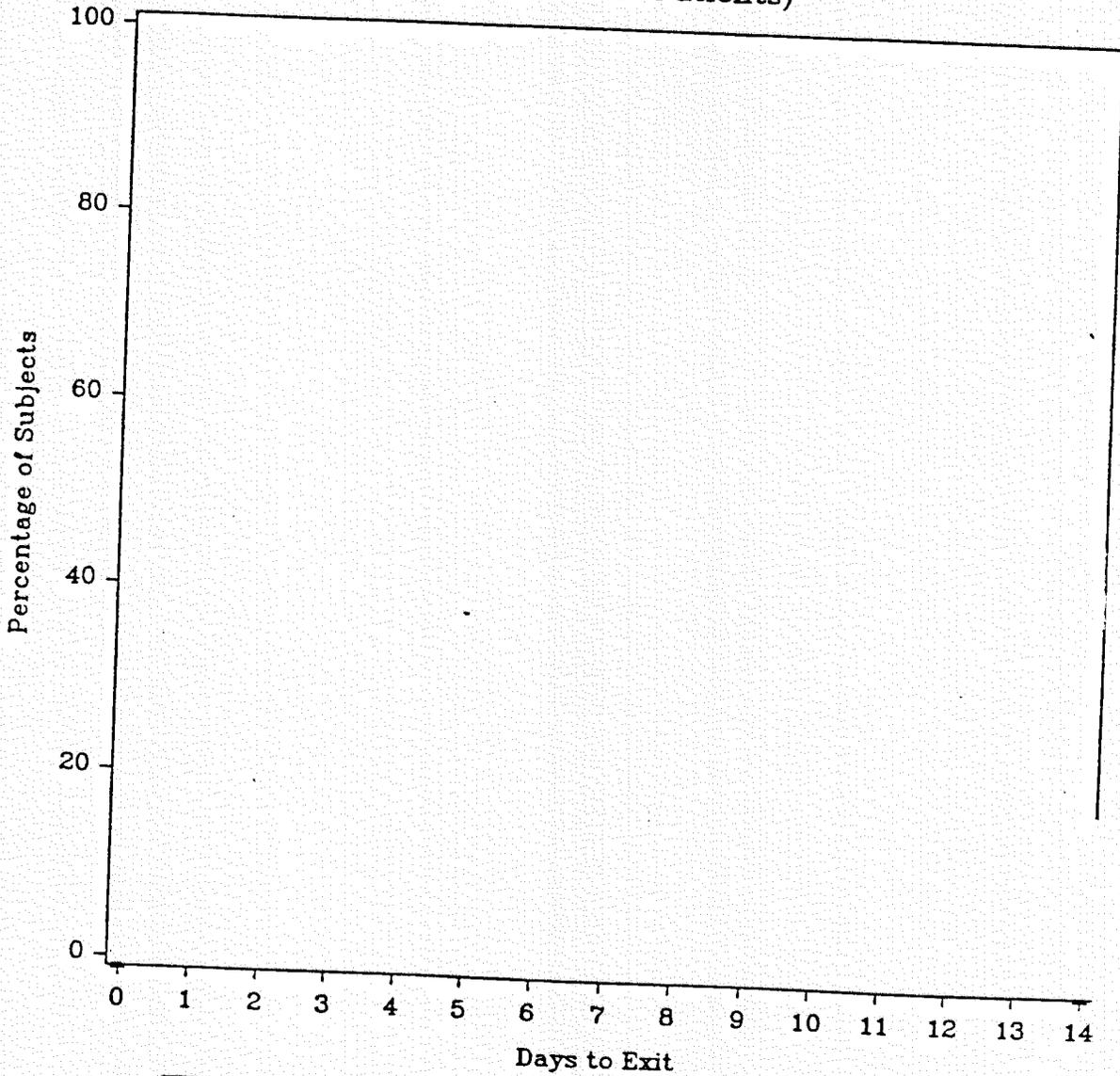
Comparison of distribution of days to exit across both treatments

	Median Time (Days)	95% C.I. for Median Time	PLACEBO vs ACTIVE
ACTIVE	>14	(14.0, >14)	<0.001 ^a
PLACEBO	2.7	(2.0, 4.0)	

^a p-values obtained from WILCOXON test.

Attachment 2.3

Figure 1.2
Time to Study Exit (Second Period Data Only)
(Intent-to-treat Patients)



TREATMENT A A A ACTIVE P P P PLACEBO

Comparison of distribution of days to exit across both treatments

	Median Time (Days)	95% C.I. for Median Time	PLACEBO vs ACTIVE
ACTIVE	>14	(14.0, >14)	<0.001 ^a
PLACEBO	6	(4.0, >14)	

^a p-values obtained from WILCOXON test.

Attachment 3.1

Table 7
Relief Scores Through Time

<u>UCL</u> ^a	<u>ACTIVE</u> <u>Mean (LCL, UCL)</u> ^a	<u>PLACEBO</u> <u>Mean (LCL,</u>
Number of Subjects ^b	31	31
Relief Scores		
Day 1	4.6 (4.3, 5.0)	3.1 (2.6, 3.6)
Day 2	4.5 (4.2, 4.8)	3.3 (2.8, 3.8)
Day 3	4.6 (4.3, 4.9)	3.1 (2.7, 3.6)
Day 4	4.6 (4.3, 4.9)	3.1 (2.6, 3.6)
Day 5	4.4 (4.1, 4.8)	3.1 (2.7, 3.6)
Day 6	4.5 (4.2, 4.8)	2.9 (2.5, 3.3)
Day 7	4.4 (4.0, 4.8)	3.1 (2.6, 3.6)
Day 8	4.5 (4.2, 4.9)	3.1 (2.7, 3.6)
Day 9	4.4 (4.1, 4.8)	3.0 (2.6, 3.5)
Day 10	4.5 (4.2, 4.9)	3.0 (2.6, 3.5)
Day 11	4.5 (4.2, 4.9)	3.1 (2.6, 3.6)
Day 12	4.6 (4.2, 5.0)	3.1 (2.6, 3.5)
Day 13	4.5 (4.1, 4.9)	3.2 (2.7, 3.7)
Day 14	4.5 (4.1, 4.8)	3.2 (2.7, 3.7)

^a (LCL, UCL) equals 95% lower and upper confidence limit.

^b Sample size is decreased by one subject due to Subject 156 not recording daily diary relief scores.

Attachment 3.2

Table 7.1
Relief Scores Through Time (First Period Data Only)

<u>UCL</u> ^a	<u>ACTIVE</u> <u>Mean (LCL, UCL)</u> ^a	<u>PLACEBO</u> <u>Mean (LCL,</u>
Number of Subjects ^b	15	16
Relief Scores		
Day 1	4.4 (3.7, 5.1)	3.0 (2.2, 3.8)
Day 2	4.3 (3.8, 4.9)	2.9 (2.1, 3.7)
Day 3	4.4 (3.8, 4.9)	2.6 (1.9, 3.2)
Day 4	4.3 (3.8, 4.9)	2.6 (1.9, 3.2)
Day 5	4.1 (3.5, 4.8)	2.5 (1.9, 3.1)
Day 6	4.3 (3.7, 4.8)	2.6 (1.9, 3.2)
Day 7	4.0 (3.3, 4.7)	2.6 (1.9, 3.2)
Day 8	4.2 (3.6, 4.9)	2.6 (1.9, 3.2)
Day 9	4.2 (3.6, 4.8)	2.6 (1.9, 3.2)
Day 10	4.0 (3.4, 4.6)	2.5 (1.9, 3.1)
Day 11	4.1 (3.5, 4.8)	2.6 (1.9, 3.2)
Day 12	4.1 (3.4, 4.8)	2.5 (1.8, 3.1)
Day 13	4.1 (3.5, 4.7)	2.5 (1.9, 3.2)
Day 14	4.0 (3.4, 4.6)	2.6 (1.9, 3.3)

^a (LCL, UCL) equals 95% lower and upper confidence limit.

^b Sample size is decreased by one subject due to Subject 156 not recording daily diary relief scores.

Attachment 3.3

Table 7.2
Relief Scores Through Time (Second Period Data Only)

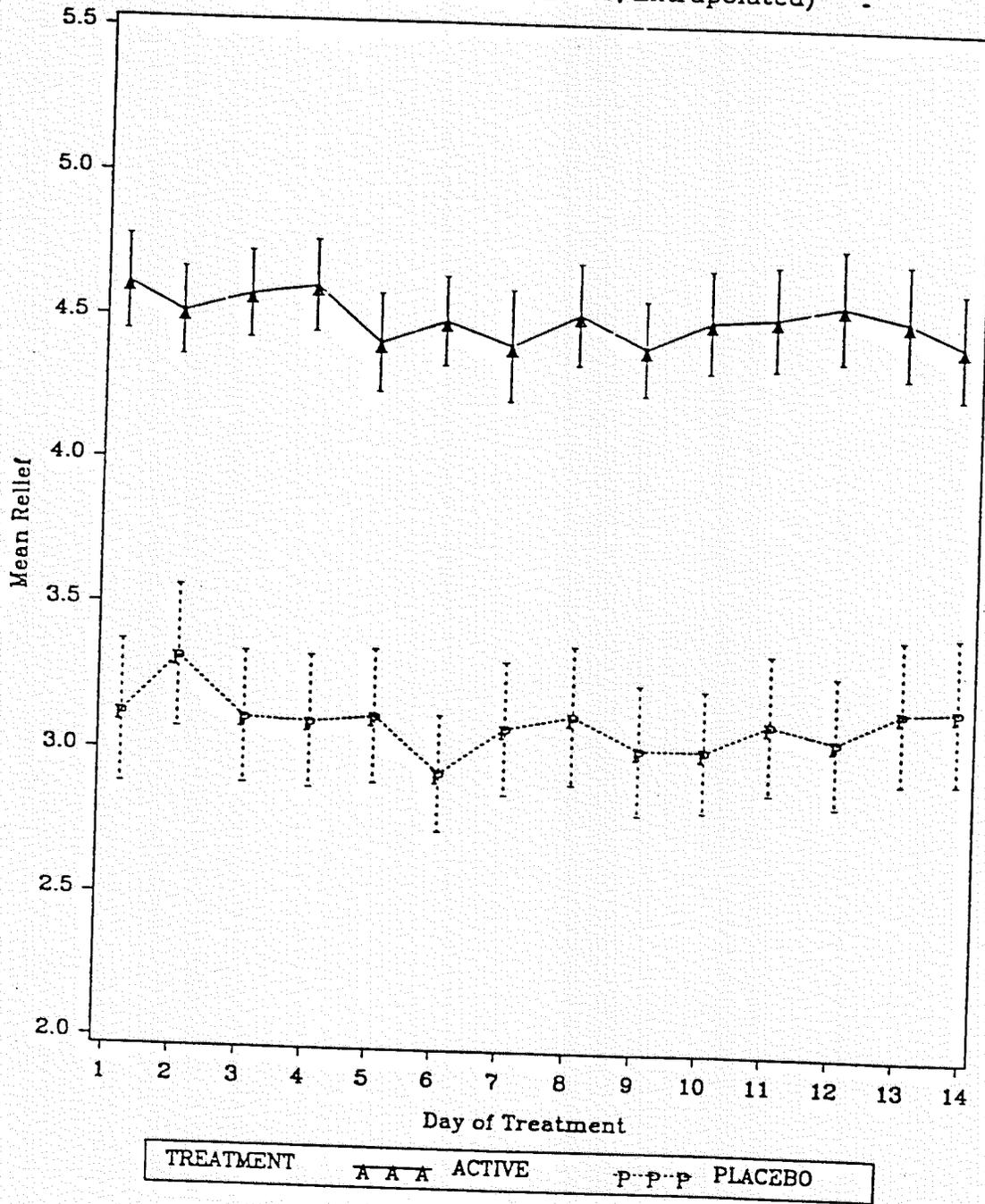
<u>UCL</u> ^a	ACTIVE Mean (LCL, UCL) ^a	PLACEBO Mean (LCL,
Number of Subjects ^b	16	15
Relief Scores		
Day 1	4.8 (4.5, 5.1)	3.3 (2.6, 3.9)
Day 2	4.7 (4.4, 5.0)	3.8 (3.2, 4.4)
Day 3	4.8 (4.5, 5.1)	3.7 (3.1, 4.3)
Day 4	4.9 (4.5, 5.2)	3.7 (3.1, 4.3)
Day 5	4.7 (4.3, 5.1)	3.8 (3.2, 4.4)
Day 6	4.7 (4.3, 5.1)	3.3 (2.8, 3.8)
Day 7	4.8 (4.4, 5.3)	3.7 (3.1, 4.3)
Day 8	4.8 (4.4, 5.2)	3.8 (3.1, 4.4)
Day 9	4.6 (4.2, 5.1)	3.5 (2.9, 4.2)
Day 10	5.0 (4.6, 5.4)	3.6 (3.1, 4.1)
Day 11	4.9 (4.5, 5.3)	3.7 (3.1, 4.4)
Day 12	5.0 (4.6, 5.4)	3.7 (3.2, 4.3)
Day 13	4.9 (4.4, 5.4)	3.9 (3.2, 4.5)
Day 14	4.9 (4.4, 5.3)	3.9 (3.2, 4.5)

^a (LCL, UCL) equals 95% lower and upper confidence limit.

^b Sample size is decreased by one subject due to Subject 156 not recording daily diary relief scores.

Attachment 3.4

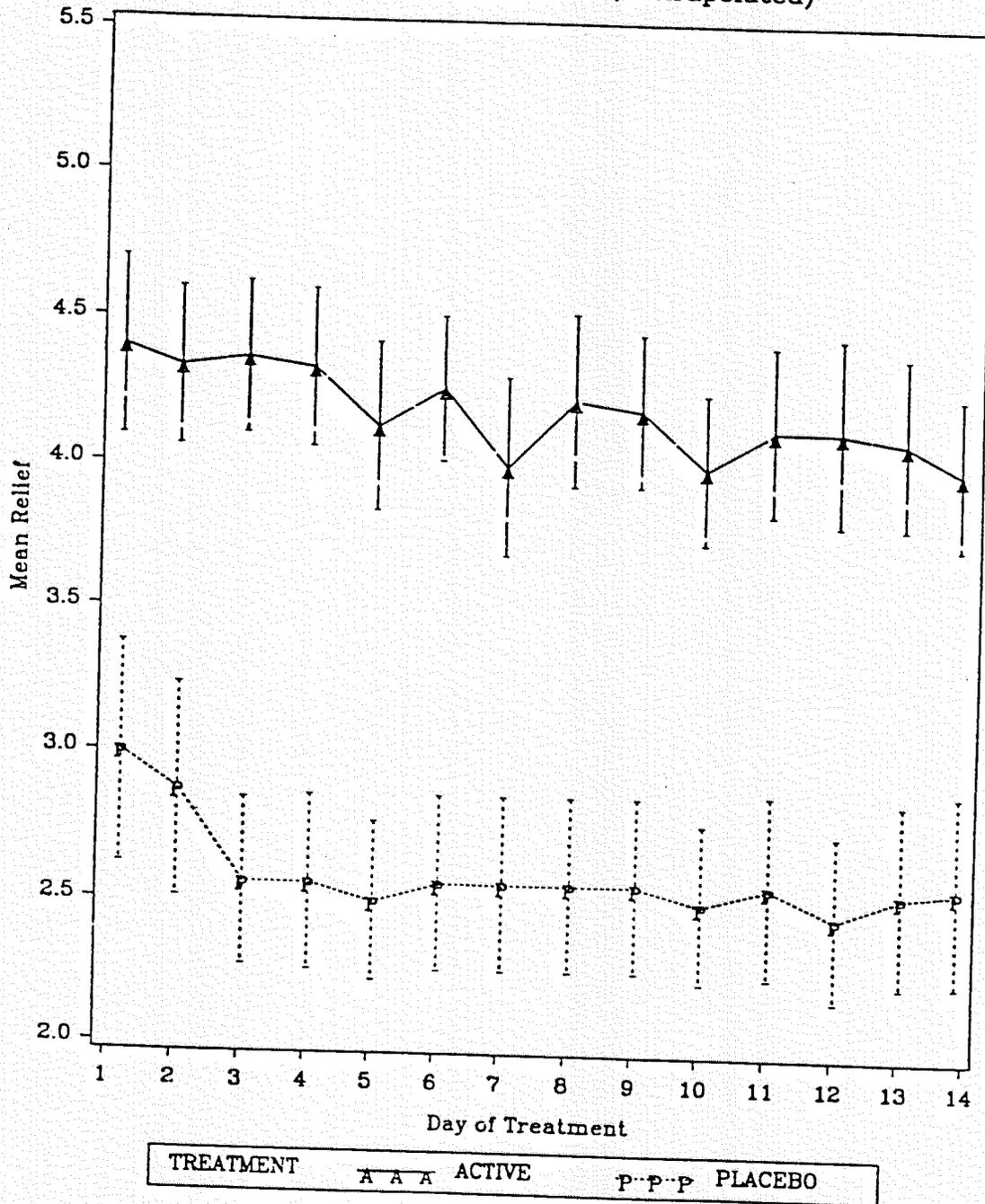
Figure 2
Mean Relief Scores
(Mean + or - Standard Error, Extrapolated)



SOURCE: TB/HHC/CROSS/RELIEF_2 (Oct 12, 1998 11:08)

Attachment 3.5

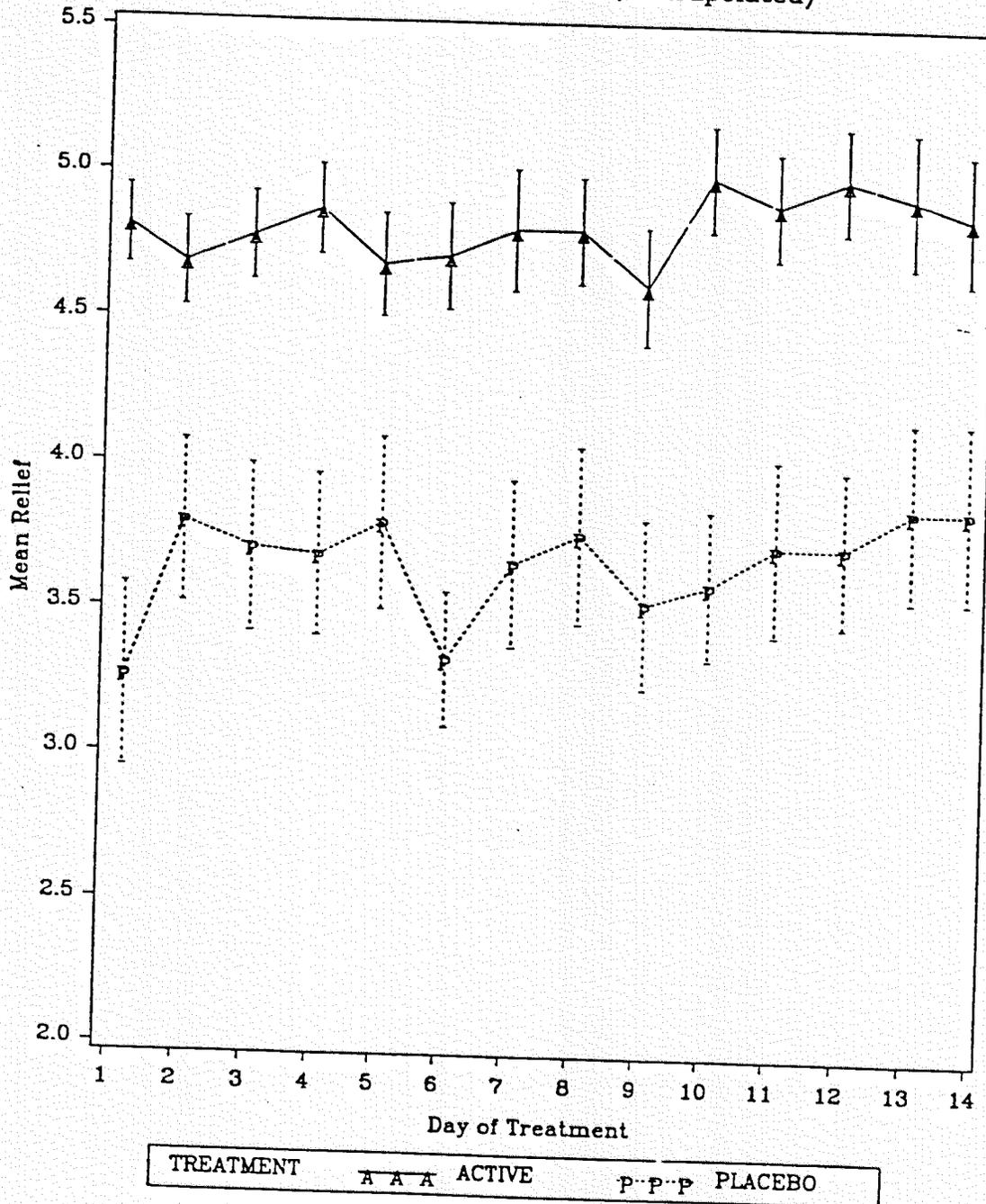
Figure 2.1
Mean Relief Scores (First Period Data Only)
(Mean + or - Standard Error, Extrapolated)



SOURCE: TB/HHC/CROSS/REL_2_1 (Oct 12, 1998 10:52)

Attachment 3.6

Figure 2.2
Mean Relief Scores (Second Period Data Only)
(Mean + or - Standard Error, Extrapolated)



SOURCE: TB/HHC/CROSS/REL_2_2 (Oct 12, 1998 10:46)

Attachment 4

Table 8
Concomitant Med Use of Period 1 & 2 Combined

	<u>ACTIVE</u>	<u>PLACEBO</u>	<u>TOTAL</u>	<u>P-VALUE*</u>
Number of Patients	32	32	64	
Number of Days of Concomitant Drug Use				
Mean	2.34	1.37	1.86	0.289 ^a
SD	4.53	2.38	3.62	
Range	0.0-14.0	0.0-10.0	0.0-14.0	
Not Reported	0	0	0	
Number of Days Subjects Remained in Period				
Mean	13.06	7.28	10.17	<0.001 ^a
SD	3.16	5.39	5.26	
Range	2.0-16.0	2.0-14.0	2.0-16.0	
Not Reported	0	0	0	
Ratio of Number of Concomitant Drug Days to Days in Period				
Mean	0.19	0.22	0.21	0.755 ^a
SD	0.36	0.39	0.37	
Range	0.0-1.0	0.0-1.5	0.0-1.5	
Not Reported	0	0	0	

* P-values for treatment comparisons from a one-way analysis of variance with a factor of treatment.

SOURCE: JQ/HHC/CROSS/MEDS0 (Oct 14, 1998 12:31)

References

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2. Hetherington RG. Herpes zoster and postherpetic neuralgia. In: Ashburn MA, Rice LJ, eds. The Management of Pain. New York: Churchill Livingstone; 1998:351-362.
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6. Adriani J, Coffman V, Naraghi M. The allergenicity of lidocaine and other amide and related local anesthetics. Anesthesiology Review 1986; 13(6):30-36.