CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-200

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA#: 21-260

Name of Drug: Avinza (morphine tablets)

Applicant: Elan Pharmaceutical Research Corporation

Documents Reviewed: Vols 2.147, 2.164

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Background

The sponsor has submitted two randomized, double-blind, multi center, placebo controlled trials investigating the efficacy and safety of Avinza in two pain models: moderate to severe osteoarthritis (Trial 04) and malignant and non-malignant cancer pain (Trial 02).

Trial 04

This trial compared Avinza 30 mg in the AM, Avinza 30 mg in the PM, and MS Contin 15 mg (MS) to placebo in a 4-week trial in patients with moderate to severe OA of the hip or knee. There were two primary efficacy variables: Overall Arthritis Pain Intensity Visual Analogue Scale (100 mm) and the Western Ontario and McMaster Universities (WOMAC) OA Index Pain Subscale (the sum of 5 scales: walking on a flat surface, going up and down stairs, at night while in bed, sitting or lying, standing upright, each 100 mm, maximum score=500).Once the index joint was chosen during a week-long screening period, the patient was eligible for randomization when the pain score reached at least 40 mm on a 100 mm VAS. The **primary endpoints** were absolute and percent change from baseline in the VAS scores. Secondary endpoints include various other subscales of the WOMAC, physician and patient global evaluations, and SF-36 health survey. **This review examines only the primary endpoints.**

The protocol does not stipulate any function of the data over time or any time point as the primary clinical endpoint. Further, there is no plan to account for both comparisons of the AM and PM Avinza to placebo. It does mention two-way ANOVA (treatment & investigator) with baseline as a covariate as the statistical procedure. Nor is there any plan to compare Avinza to MS Contin. In fact, the study report states: 'This study was not designed to show equivalence to an active control'.

Results

A total of 27 investigators randomized 295 patients to the 4 study arms. See **Table 1** for demographics and mean baseline pain measurements and reasons for dropout. Ten (10) of the investigators had very sparse enrollment with at least 1 treatment cell having no observations.

The major impediment to the statistical analysis and interpretation of this trial is the fact that 63 of the 295 patients have *no* evaluations after baseline (19 placebo, 14 MS Contin, 30 combined AP & PM Avinza). The table below displays the percentage of these totals which were due to AE's and Lack of Efficacy.

	Adverse Experience	Lack of Efficacy
Placebo	26%	58%
MS Contin	71%	14%
Avinza AM&PM	63%	33%

Further, 36 have *one*, 10 have *two* and 3 have *three*, and 183 have *four*. The sponsor has identified those who left the trial before week 1 (not all of those who are missing week 1 observations in the data set). Of the 12 in the placebo group, 6 left due to Lack of Efficacy (LOE). In the MS Contin group, none of the 10 withdrawals were for LOE, and, combining the Avinza groups, 4 of 23 withdrew for LOE. **The ultimate result of this pattern of missingness is that the data is divided fairly clearly into two groups: those with none or virtually no information during the double-blind period, and those who had complete data vectors.**

The sponsor has analyzed two data sets: The **Full** data set which consists of all randomized patients who took at least one dose of study drug. Thus, their LOCF analysis carries forward 63 baseline scores. The **Efficacy** data set consists of the patients with baseline and week 1 observations and patients with no data after baseline who were dropped for lack of efficacy prior to week 1. Those who dropped before week 1 for any other reason were not included.

WOMAC Scores

Figure 1 is the sponsor's display of the mean change from baseline of the WOMAC scale over time using LOCF, which, in this case, means carrying forward the baseline measurement in 21% of the total number of randomized patients. Note that another 12% of patients have their sole observation carried forward. **Table 2** displays the weekly results and p-values for both absolute and relative change from baseline for the **Full** data set. **Figure 2** and **Table 3** display analogous results for the **Efficacy** data set. Note that all the sponsor's analyses use ANCOVA with baseline as the covariate and 'center' is *not* in the model. This is understandable from the point of view of coherence because the randomization within centers is fairly unbalanced, thus complicating the interpretation of any analysis of variance.

At **Week 1**, the overall statistic is statistically significant with QAM and QPM p-values of .009 and .017, respectively. Although the overall p-value at **Week 4** is .115 in the Full Analysis Set (see **Table 2**), the comparison of QAM and QPM to placebo yield p-values of .024 and .059, respectively. Further, the pattern of missing data described above suggests supplementary analyses which **1) retain only those patients who have all four observations, i.e., complete double-blind data vectors and 2) pool the two Avinza groups.** Fortunately, means of the baseline values of the WOMAC Scores are similar between the subgroups with and without complete vectors. The same is true for the Overall Arthritis Scale. Of course, using a covariate in

the analysis is highly questionable since its legitimacy rests upon the original randomization. Clearly, subsets used by either the sponsor or this reviewer cannot be assumed to be generated by random deletion of subjects. Nevertheless, analysis shows that baseline does have an effect which decreases the root mean square error by 20%.

As far as power is concerned, little is lost. For instance, the protocol states that a sample size of 60 per group will provide 90% power to detect a 64 mm difference between any two groups with a 2-sided .05 test. This assumes a standard deviation of 107 mm. Pooling the complete vectors of the AM and PM Avinza groups gives 85 patients in the pooled Avinza group and 50 in the placebo group. These numbers retain the 90% power. **Finally, this reviewer has chosen what appear to be three clinically relevant endpoints: mean scores at week 1 with baseline as covariate, mean scores at week 4 with baseline as covariate, and area under the curve (AUC). Analyses do not account for center.**

Reviewer's Analyses

Figure 3 displays the weekly means of the complete vector cohort for the WOMAC Score for all original treatment groups. Note that there is an initially steep drop between baseline and **Week 1** in the active groups with slower improvement and eventual leveling off by **Week 4**. The p-value for comparing the placebo and pooled Avinza groups at week 1 was .04 with a difference of 40 mm in favor of Avinza. The p-value at week 4 was .12 with a difference of 31 mm. A two-sample t-test comparison of AUC's yielded p=.04. For completeness, the LOCF analysis using all patients with at least one observation on double-blind treatment (N=169) yielded p=.14 with a treatment difference of 27 mm. The LOCF's diminished signal may be a result of the clear imbalance between the groups with respect to dropping out for AE's. This would tend to carry forward 'bad' scores of Avinza patients who did not have the chance to improve on study.

Figure 4 and **Figure 5** display the means over time for hip and knee, respectively, using the pooled Avinza group. The ratio of 'hip' to 'knee' patients was 1:3 in the entire randomized sample with the Avinza groups having greater percentages of hip patients than the MS Contin or placebo: 23% placebo, 16% MS Contin, 30% Avinza AM, 37% Avinza PM. In the 'complete vector' sample, 9 of the 50 placebo patients (18%) are hip patients, whereas 33 of the 85 Avinza patients (39%) are hip patients. Fortunately, there is no statistical evidence of a treatment by index joint interaction using change to week 1, change to week 4, or AUC.

Another way to look at the effect of Avinza is examine the number and percentage of patients who achieve at least a 50% change from baseline at **any** week. The table below displays numbers and percentages (in parentheses):

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Number (%) of patients with at least 50% change from baseline

		Week 1	Week 2	Week 3	Week 4
Placebo	(N=50)	1(2)	1(2)	3(6)	9(18)
MS Contin	(N=48)	3(6)	3(6)	4(8)	14(29)
Avinza	(N=85)	3 (4)	6(7)	13(15)	18(21)

Thus, for example, 15% of the Avinza patients in the complete vector subgroup achieved a 50% decrease in WOMAC Score at week 3. This does not imply anything about their 'response' statuses at other times. The percent of patients who **never** achieved a 50% change from baseline was 72% in the placebo group and 53% in the Avinza group.

Overall Arthritis Pain Intensity Scores

Figure 6 and **Table 4** display the results for the Full data set, while **Table 5** displays statistical results for the Efficacy data set.

Reviewer's Analyses

The p-value comparing the Avinza group to placebo with respect to change from baseline to week 1 was .09 with a difference of 8 mm. The p-value at 4 weeks is .67 with a difference of 2 mm. A comparison of AUC yielded p=.10. **Figure 7** illustrates the loss of any apparent benefit from active treatment at 4 weeks. The seemingly more positive results using the WOMAC scores may be due to enhanced sensitivity by using 5 separate scales. If these scales are only weakly correlated with each other, the sum should provide more power than one scale alone.

Discussion

Conversion of Trial 04 to one with two treatment groups but with 1) similar nominal power to the designed trial and 2) complete data over 4 weeks, produces results which are similar to the sponsor's Full Analysis Set, indicating a statistically significant treatment effect between baseline and **Week 1**. Results at subsequent weeks suggest a lessening of effect with time. The failure of mean Overall Arthritis Score to remain separated at 4 weeks may be due to a less sensitive statistic than the sum of 5 WOMAC scales.

The sponsor also did two inappropriate exploratory analyses. One supposedly corrected for an 'imbalance' in the use of physical devices at baseline. Presumably patients continued to use those devices on trial. Thus, use of physical devices is a confounder on treatment, not a baseline covariate. Another was a repeated measures analysis which searched for the covariance structure that 'fit the data best'. Neither of these analyses contributes to the overall picture.

Finally, the sponsor has not provided a statistical plan to assess what, if anything, could be put in the label regarding the comparative efficacy of Avinza and MS Contin.

Trial 02

This **seven-day** trial randomized 272 subjects with malignant or nonmalignant pain to 4 treatment groups using 37 investigator sites. Two of the declared objectives were 1) to 'demonstrate that once-daily Avinza relieves pain' and 2) 'to evaluate the relative potency of once-daily Avinza and twice daily MS Contin'.

Subjects were first stabilized on MS Contin during a maximum of 3 weeks before randomization. During this period patients could receive daily oxycodone as rescue medication. Patients were then randomized to one of four treatment groups within site: Avinza at doses equal to 50%, 100%, or 133% of their MS Contin dose, or the stabilized MS Contin dose. Avinza was given qd while MS Contin was given bid. **Change in the amount of rescue medication (mg)** was a primary endpoint. The baseline amount was defined as the average of the amount of rescue medication over the last 3 days of the stabilization period. The amount on double-blind therapy was defined as the average over days 5, 6, and 7. **Two pain scales were also designated as primary endpoints in the protocol: a Pain Intensity Visual Analogue Scale (VAS) and Pain Descriptor Scale (PDS).** ANCOVA with baseline score as the covariate was the specified analysis.

The sample size of 44 evaluable patients per treatment group was based on detecting a 30 mg average difference in rescue medication between the 50% and 100% Avinza groups with 80% power (SD=50 mg). The protocol states that 'differences between groups will be tested using analysis of covariance' and 'the dose-response trend among the 50%, 100%, and 133% dose levels will be evaluated'. **There is no plan to control Type I error associated with multiple treatment comparisons, nor is there any plan (besides p-values associated with two-sample treatment comparisons) to evaluate what the sponsor calls the 'relative potency of once-daily Avinza and twice daily MS Contin'.** Presumably, the sponsor would like to advocate a qd Avinza regimen over a bid MS Contin regimen.

Results

Figure 1 displays the patient disposition of the trial. **Table 1** displays the baseline characteristics of the subjects by treatment group. Eighty-five percent of the patients had non-malignant pain. The sponsor has defined two data sets. The Full Analysis set consists of patients who took at least 1 dose of blinded medication and who had at least 1 post-baseline efficacy measurement. The Efficacy Evaluable Population included all patients in the Full Analysis Set who had efficacy data recorded at both baseline and on at least 1 of days 5, 6, or 7. Of the 279 randomized patients, the sponsor states that 272 were in the Full Set while 261 were in the Efficacy Evaluable Set. This reviewer has found 259 patients with at least 1 measurement during the last 3 days of the stabilization period and at least one measurement on day 5, 6, or 7 (N=64: Avinza 50%, N=65: Avinza 100%, N=64: Avinza 133%, N=66: MS Contin. With respect to missing data, both the sponsor and the reviewer have averaged any available observations over the 3-day windows. As in trial 04, there were numerous sites with sparse data. Of the 37 sites, 15 had at least one treatment cell with no data. Sites were ignored in these analyses.
Table 2 displays the sponsor's results of the **change in rescue medication**. This review has confirmed these results in substance. The [redacted] mg for the MS Contin group in the Efficacy Evaluable Population on page 40 of the Study Report (Volume 2.147) is a misprint. It should be

6.83 mg as taken from the sponsor's Table 02-4B in the ISE. However, as the sponsor notes, all groups *increased* rescue medication after baseline, with the MS Contin's average lying in the range of the three Avinza groups.

Table 3 and **Table 4** display the results of the **VAS and PDS** scales, respectively. There is a statistically significant relation between increasing dose of Avinza and *lesser increase* in pain. That is, on average, pain increased after baseline in patients treated with Avinza, **this despite the administration of rescue medication**. The Avinza 50% and 100% groups' average pain on both scales was statistically significantly greater than their baseline averages. This was not true in the Avinza 133% or the MS Contin groups. There was evidence of interaction between treatment and malignant vs non-malignant pain.

Discussion

I. Trial 02 was characterized by a tendency for patients to suffer greater pain and take more rescue medication after baseline than before baseline. However, the sponsor claims that there is statistically significant evidence that patients who received greater doses of Avinza tended to have a smaller increases in pain and rescue medication, on average. The 50% increase in patient enrollment over that specified in the protocol is noteworthy but unexplained by the sponsor. In the protocol, the sponsor overestimated the standard deviation of change from baseline rescue medication by 100% (25 mg vs 50 mg), but also overestimated the treatment difference by a factor of ten (3 mg vs 30 mg). These errors 'canceled' each other to an extent which preserved high power with either sample size.

II. A major feature of this data is the high correlation between baseline and final measurement. The table below displays the mean baseline and final doses of rescue medication:

	Baseline Rescue Dose (mg)	Ending Rescue Dose (mg)
55%	16.6	27.4
100%	19.2	26.5
133%	19.9	23.1

Note the close clustering of final doses. There is nothing close to statistical significance when these final doses are compared among the Avinza groups with either a linear trend or ANOVA *as long as baseline rescue dose is not a covariate in the model.* In fact, the correlation between final and baseline rescue dose is .83, meaning that baseline dose has a very strong influence on final dose and thus a strong variance-reducer. When the sponsor analyzed **change from baseline dose** and *used the **baseline dose** as the covariate*, the mean square error fell from 953 to 287. As regards 'adjusted' means, in the 55% group, 27.4 increased to 29.8, in the 100% group, 26.5 decreased to 25.7, and in the 133% group, 23.1 decreased to 21.5.

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The table below displays the mean baseline and final VAS pain:

	Baseline VAS	Ending VAS
55%	45.1	53.7
100%	48.4	53.2
133%	40.2	41.7

Note that the higher mean baseline pain in the 55% group relative to the 133% group is not consistent with the lower mean baseline rescue medication in the 55% group (see prior table). In analyzing VAS pain, however, the sponsor has not taken account of the fact that the patients' intake of rescue medication changed during the trial. However, the confounding of rescue medication and Avinza dose is not a problem as long as we recognize that less pain went along with reduced rescue medication and we do not attempt to quantify the contribution of Avinza to the change in pain.

From a speculative point of view, one might have anticipated that the treatment groups would have *similar* levels of pain at the end of the trial as a result of taking [redacted] as rescue. The protocol does not mention any limit on the amount of rescue medication allowed during the study week. One explanation for the apparent difference among Avinza groups might be that [redacted] is considerably less effective than morphine. In that case, the 50% Avinza group may have taken more [redacted] as rescue but with less effect than necessary to control increasing pain as much as Avinza 100% would have. However, the data does not directly support that possibility. There is a low correlation between final dose and final VAS pain in the 55% group with R=.22 and a higher correlation in the 100% group (R=.49) .**Figure 2** displays the scatterplot of final VAS by final rescue dose (mg) and **Figure 3** the predicted regression lines for each group. The simple linear regression slopes are .16 in the 55% group and .50 in the 133% group (p=.01 for comparison of slopes). In other words, it appears that the rate of increase in pain for a given intake of rescue medication was higher in the 133% Avinza group than in the 55% group even though there was less mean pain in the group with more Avinza.

There would be some rationale in comparing the predicted means in each group at the mean final dose of the 133% group (23.1) if the lines had been parallel. The question would have then been:'*Given a common mean ending dose*, is there statistical evidence that the 133% Avinza group suffered less of an increase in pain than the 50% Avinza group?'. Despite the lack of parallelism, this reviewer has conducted a two-group t-test using the raw means since the 'adjustment' of the 50% group mean pain to the mean dose of the 133% is so small due to the small slope (.16). In that case the z-statistic is near 2.9, suggesting that there was less of an increase in pain due to Avinza in the 133% group than the 50% group. However, this analysis is exploratory, only. It should be recognized that there is no unbiased way to distinguish the effect of the rescue medication from Avinza dose on final VAS or PDS pain scores in this trial. Caution is required also due to the seemingly two paradoxical patterns: 1) the 55% group got less rescue medication at baseline than the 133% group, yet had more pain at baseline, and 2) the rate of increase of pain per mg of rescue medication was statistically higher in the 133% group despite having **seemingly** lower pain scores on average.

III. Finally, the sponsor has made at attempt to deal with the bivariate structure of the outcome (final dose and VAS score) by contructing an 'integrated score'. It is computed by:

First- Taking the average for each patient during the last three days of the period for VAS pain intensity and rescue medication (mg).

Second- Ranking the averages of VAS pain intensity and rescue medication separately, and calculate the percent differences from the mean rank.

Third- Adding the differences from mean rank in each group, followed by a one-way ANOVA.

Table 5 displays the sponsor's results. Not surprisingly, there are low p-values when Avinza 55% and Avinza 133% are elements in a contrast.

Conclusions

A comparison of the 55% dose of Avinza to its 100% dose provides statistical evidence of Avinza's efficacy in patients with malignant or non-malignant pain.

Due to there being only one dose of MS Contin, this trial is not capable of addressing the issue of relative potency between Avinza and MS Contin; nor is there an alternative plan in the protocol for comparing the active drugs' efficacy.

Overall Conclusions

The sponsor has conducted two clinical trials, one providing statistically significant evidence that Avinza is more effective than placebo in reducing osteoarthritic pain, possibly over 4 weeks, and the other in diminishing the need for rescue medication in patients with increasing malignant or non-malignant pain over 1 week.

The sponsor's analysis of opioid-related adverse events confirms that patients taking Avinza were more likely than patients on placebo to experience constipation, nausea, somnolence, and dizziness.

In patients with osteoarthritis, there was no statistical evidence that treatment benefit differed by age (63% were 65 or older) , race (84% were Caucasian) or gender (62% were female). In the study of malignant and non-malignant pain, there was no evidence of interaction between treatment with age (86% were younger than 65 years), race (88% were Caucasian) or gender (55% were female) with respect to change in rescue medication.

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TABLE 1

Patient Demographics - All Randomized Patients

	Placebo	MS Contin	QAM	QPM	Overall
	N=73	N=76	N=73	N=73	N=295
Characteristic					
Age (years)					
Mean ± SD	61.9±10.68	61.9±10 41	62.6±9.51	63.1±11.14	62.4±10 41
Range	41-83	42-87	39-82	39-84	39-87
Gender [N (%)]					
Males	22 (30%)	28 (37%)	30 (41%)	31 (42%)	111 (38%)
Female	51 (70%)	48 (63%)	43 (59%)	42 (58%)	184 (62%)
Ethnicity [N (%)]					
Caucasian	58 (80%)	68 (90%)	63 (86%)	60 (82%)	249 (84%)
Black	14 (19%)	8 (11%)	7 (10%)	11 (15%)	40 (14%)
Asian	1 (1%)	0	1 (1%)	1 (1%)	3 (1%)
Hispanic	0	0	2 (3%)	0	2 (1%)
Other	0	0	0	1(1%)	1 (<1%)

Baseline WOMAC OA Index Pain VAS Subscale Scores and Overall Arthritis Pain Intensity VAS Scores - All Randomized Patients

	Placebo	MS Contin	QAM	QPM	Overall
	N=72	N=76	N=73	N=73	N=295
Characteristic					
WOMAC OA Index Pain VAS Subscale Score					
Mean ± SD	317.43±102.28	322.39±100.13	313.16±107.06	326.27±89.68	319.85±104.24
Range	50-487	85-491	64-484	108-500	50-500
Overall Arthritis Pain Intensity VAS Score					
Mean ± SD	78.3±13.86	78.8±15 74	76.5±18.47	79.3±15.53	78.2±15.94
Range	43-98	40-99	11-100	46-100	11-100

Patient Disposition

	Placebo	MS Contin	QAM	QPM	Overall
Total No. of Patients Screened					335
No not randomized					40
No. randomized	73	76	73	73	295
No completed	50	48	46	40	184
No. entered open label	50	48	44	39	181
No. Discontinued					
- total	23	28	27	33	111
- for AEs	5	18	17	18	58
- lack of efficacy	14	8	9	12	43
- unable to return	2	0	0	1	3
- death	0	0	0	0	0
- non-compliant	0	1	0	0	1
- lost to follow-up	0	0	1	2	3
- request withdrawal	1	0	0	0	1
- other	1	1	0	0	2

TABLE 2

Change and Percent Change from Baseline in WOMAC OA Index Pain VAS Subscale Scores[a] –Full Analysis Set

	Placebo N= 73	MS Contin N=76	QAM N=73	QPM N=73	Overall p-value	Placebo N= 73	MS Contin N=76	QAM N=73	QPM N=73	Overall p-value
Change from Baseline in WOMAC OA Index Pain VAS Subscale Score[b]						Percent Change from Baseline in WOMAC OA Index Pain VAS Subscale Score[b]				
Full Analysis Set:										
Week 1					0.017					0.017
Mean ± Std. Error	-12.43±11.84	-61.70±12.70	-56.34±13.97	-56.23±11.68		1.6±5.49	-16.1±4.19	-12.1±5.32	-18.0±3.72	
LS Mean ± Std. Error	-13.15±12.16	-60.94±11.84	-58.32±12.08	-54.33±12.08		1.3±4.62	-15.8±4.50	-12.7±4.59	-17.3±4.59	
Week 2					0.066					0.084
Mean ± Std. Error	-26.93±11.92	-63.43±12.72	-68.70±13.99	-67.34±13.29		-4.0±5.34	-18.4±4.24	-15.2±5.79	-21.0±4.00	
LS Mean ± Std. Error	-27.63±12.67	-62.70±12.34	-70.62±12.59	-65.50±12.59		-4.2±4.62	-16.2±4.70	-15.8±4.79	-20.4±4.79	
Week 3					0.054					0.090
Mean ± Std. Error	-30.01±13.62	-64.91±12.85	-76.67±13.48	-73.67±14.13		-6.3±5.58	-19.6±4.21	-19.3±5.48	-23.1±4.33	
LS Mean ± Std. Error	-30.65±13.29	-64.24±12.93	-76.44±13.20	-71.97±13.20		-6.4±4.92	-19.5±4.79	-19.7±4.69	-22.7±4.69	
Week 4					0.115					0.204
Mean ± Std. Error	-34.26±13.05	-65.33±12.64	-74.33±13.04	-71.21±14.05		-8.1±5.34	-19.4±4.18	-19.6±5.38	-21.4±4.18	
LS Mean ± Std. Error	-34.93±12.91	-64.63±12.57	-76.18±12.83	-69.43±12.83		-8.3±4.79	-19.3±4.67	-20.0±4.76	-21.0±4.76	

(a) Last observation carried forward (LOCF) approach was used

(b) Analysis of covariance model with change from baseline to each of weeks 1, 2, 3, and 4 as the outcome, treatment as a factor, and baseline value as a covariate

Source data: Appendix 16.6, Tables 11.1a, and 11.2a

Table 11.3.1.1-2 Treatment Comparison P-values for Change and Percent Change from Baseline in WOMAC OA Index Pain VAS Subscale Scores[a] – Full Analysis Set

	QAM vs. Placebo	QPM vs. Placebo	MS Contin vs. Placebo	QAM vs. MS Contin	QPM vs. MS Contin	QAM vs. QPM	QAM vs. Placebo	QPM vs. Placebo	MS Contin vs. Placebo	QAM vs. MS Contin	QPM vs. MS Contin	QAM vs. QPM
Change from Baseline in WOMAC OA Index Pain VAS Subscale Score[b,c]							Percent Change from Baseline in WOMAC OA Index Pain VAS Subscale Score[b,c]					
Full Analysis Set:												
Week 1	0.009	0.017	0.005	0.877	0.696	0.815	0.032	0.005	0.008	0.630	0.817	0.481
Week 2	0.017	0.035	0.048	0.654	0.674	0.774	0.091	0.018	0.039	0.718	0.741	0.494
Week 3	0.011	0.028	0.071	0.443	0.676	0.729	0.056	0.019	0.059	0.969	0.634	0.666
Week 4	0.024	0.059	0.101	0.521	0.769	0.710	0.065	0.061	0.101	0.921	0.797	0.877

(a) Last observation carried forward (LOCF) approach was used

(b) Analysis of covariance model with change from baseline to each of weeks 1, 2, 3, and 4 as the outcome, treatment as a factor, and baseline value as a covariate

(c) Contrast statements from an analysis of covariance model in (b)

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TABLE 3

Change and Percent Change from Baseline in WOMAC OA Index Pain VAS Subscale Scores[a] –Efficacy Evaluable Population

	Placebo N=67	MS Contin N=66	QAM N=66	QPM N=61	Overall p-value	Placebo N=67	MS Contin N=66	QAM N=66	QPM N=61	Overall p-value
Change from Baseline in WOMAC OA Index Pain VAS Subscale Score[b]						Percent Change from Baseline in WOMAC OA Index Pain VAS Subscale Score[b]				
Week 1					0.023					0.025
Mean ± Std Error	-15.34±12.97	-66.09±14.64	-55.59±15.20	-65.86±14.19		1.4±6.17	-17.0±4.88	-10.8±5.85	-20.1±4.36	
LS Mean ± Std. Error	-14.90±13.36	-67.90±13.36	-58.81±13.37	-60.72±14.18		1.5±5.10	-17.6±5.10	-12.0±5.11	-18.3±5.42	
Week 2					0.120					0.118
Mean ± Std. Error	-30.58±12.83	-66.09±14.28	-67.03±14.85	-77.37±15.74		-4.7±5.80	-19.1±4.80	-13.5±6.22	-23.1±4.59	
LS Mean ± Std. Error	-31.53±13.60	-67.51±13.61	-68.71±13.61	-72.84±14.42		-5.0±5.20	-19.6±5.20	-14.0±5.20	-21.6±5.51	
Week 3					0.096					0.134
Mean ± Std. Error	-33.94±14.69	-67.79±14.43	-75.85±14.27	-85.20±16.75		-7.2±6.06	-20.5±4.76	-18.1±5.88	-25.7±5.01	
LS Mean ± Std. Error	-34.81±14.31	-69.08±14.31	-77.38±14.31	-81.06±15.16		-7.4±5.33	-20.8±5.33	-18.4±5.33	-24.7±5.65	
Week 4					0.193					0.300
Mean ± Std. Error	-38.56±14.05	-68.27±14.18	-73.26±13.76	-82.15±16.68		-9.2±5.79	-20.3±4.73	-18.3±5.77	-23.6±4.62	
LS Mean ± Std. Error	-39.49±13.87	-69.63±13.87	-74.87±13.88	-77.81±14.70		-9.5±5.18	-20.6±5.18	-18.7±5.18	-22.6±5.49	

(a) Last observation carried forward (LOCF) approach was used.

(b) Analysis of covariance model with change from baseline to each of weeks 1, 2, 3, and 4 as the outcome, treatment as a factor, and baseline value as a covariate

Source data: Appendix 16.6, Tables 11.1b, and 11.2b

Table 11.3.1.2-2 Treatment Comparison P-values for Change and Percent Change from Baseline in WOMAC OA Index Pain VAS Subscale Scores[a] – Efficacy Evaluable Population

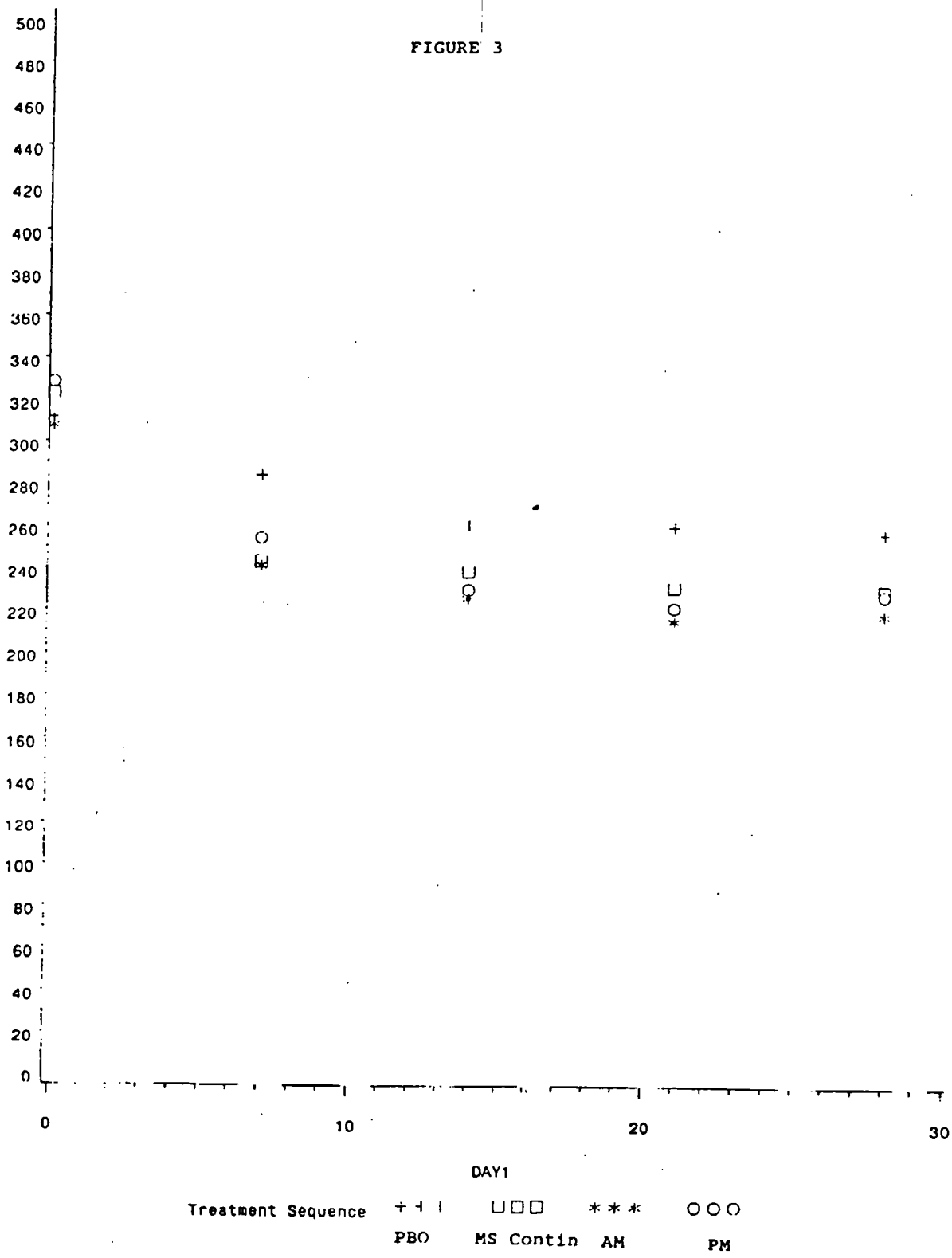
	QAM vs. Placebo	QPM vs. Placebo	MS Contin vs. Placebo	QAM vs. MS Contin	QPM vs MS Contin	QAM vs. QPM	QAM vs. Placebo	QPM vs. Placebo	MS Contin vs. Placebo	QAM vs. MS Contin	QPM vs. MS Contin	QAM vs. QPM
	Change from Baseline in WOMAC OA Index Pain VAS Subscale Score[b,c]						Percent Change from Baseline in WOMAC OA Index Pain VAS Subscale Score[b,c]					
Week 1	0.021	0.019	0.005	0.630	0.713	0.922	0.063	0.008	0.008	0.434	0.933	0.400
Week 2	0.054	0.038	0.063	0.950	0.788	0.835	0.223	0.030	0.049	0.449	0.793	0.319
Week 3	0.036	0.028	0.092	0.682	0.567	0.860	0.144	0.027	0.076	0.751	0.621	0.423
Week 4	0.073	0.059	0.126	0.790	0.686	0.884	0.208	0.083	0.126	0.793	0.798	0.609

(a) Last observation carried forward (LOCF) approach was used.

(b) Analysis of covariance model with change from baseline to each of weeks 1, 2, 3, and 4 as the outcome, treatment as a factor, and baseline value as a covariate.

(c) Contrast statements from an analysis of covariance model in (b)

FIGURE 3



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Index Joint: Hip or Knec=1: HIP

FIGURE 4

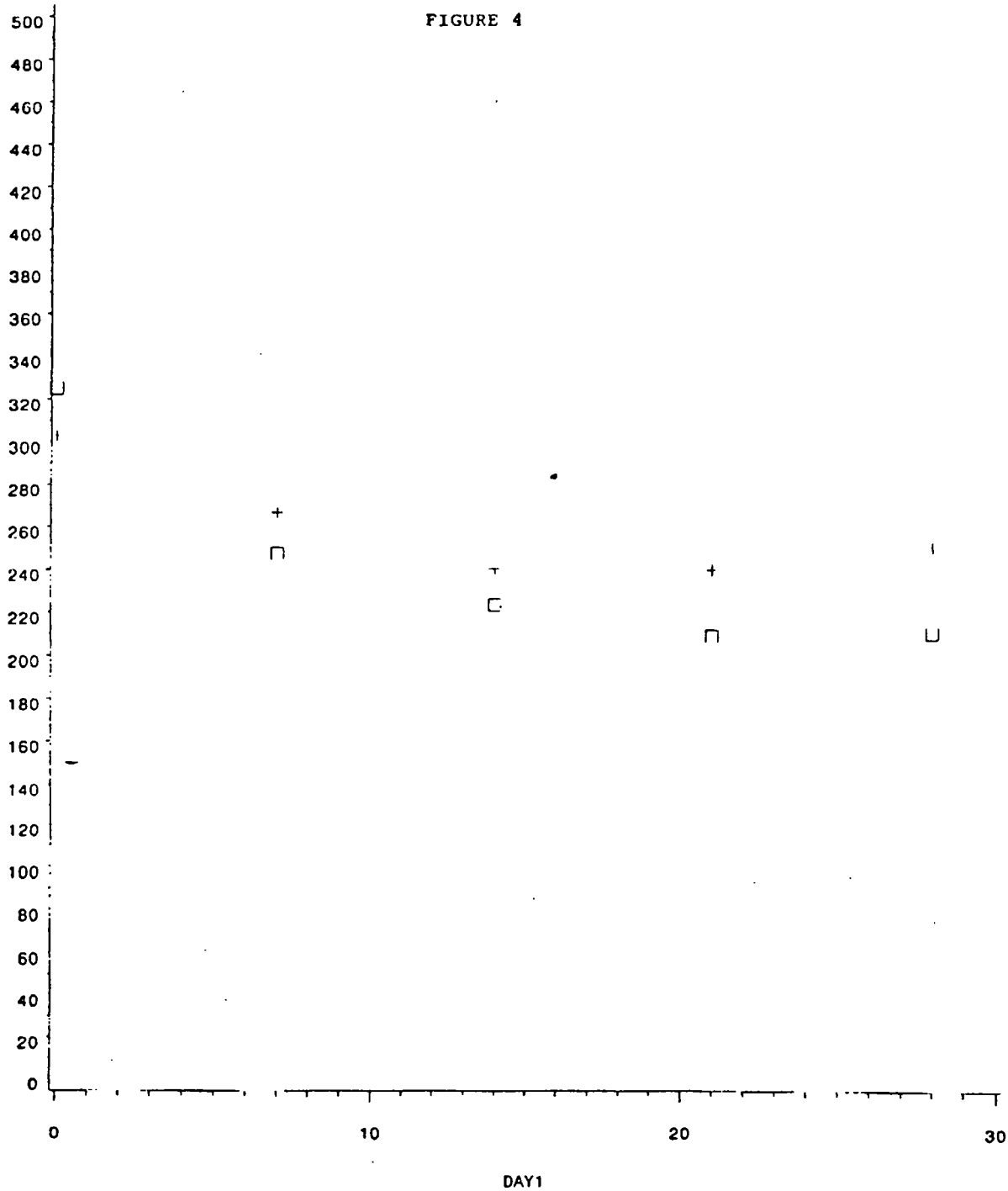
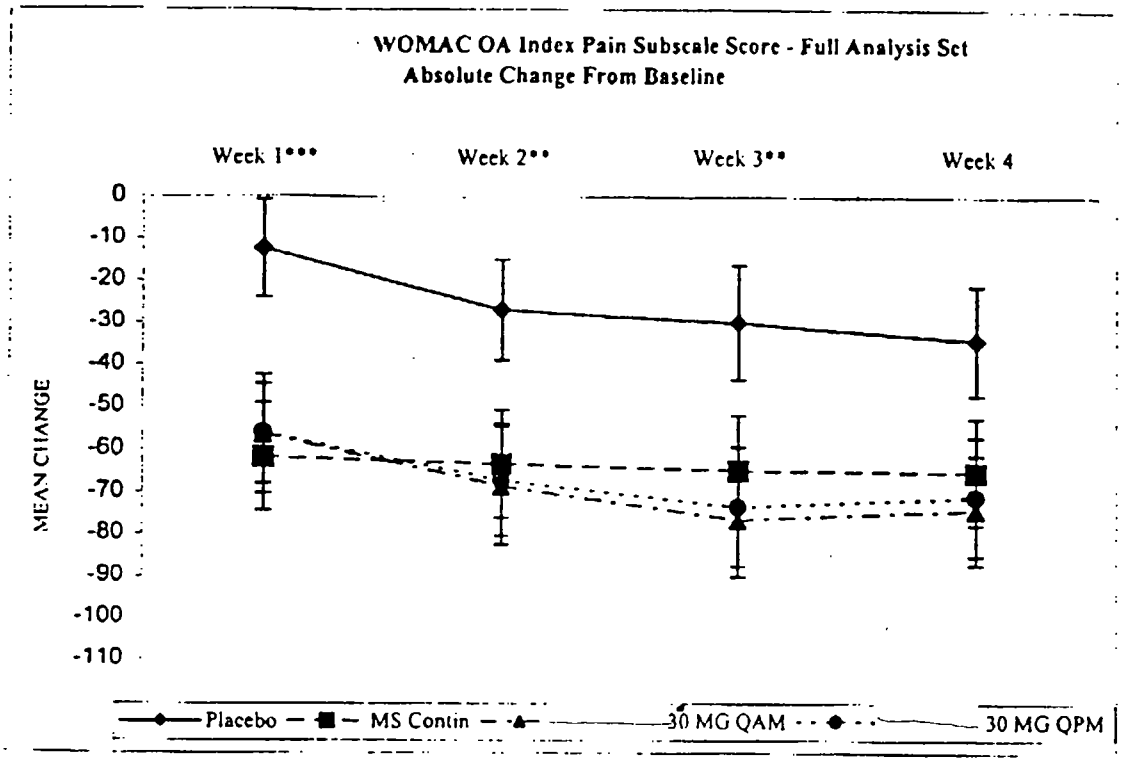


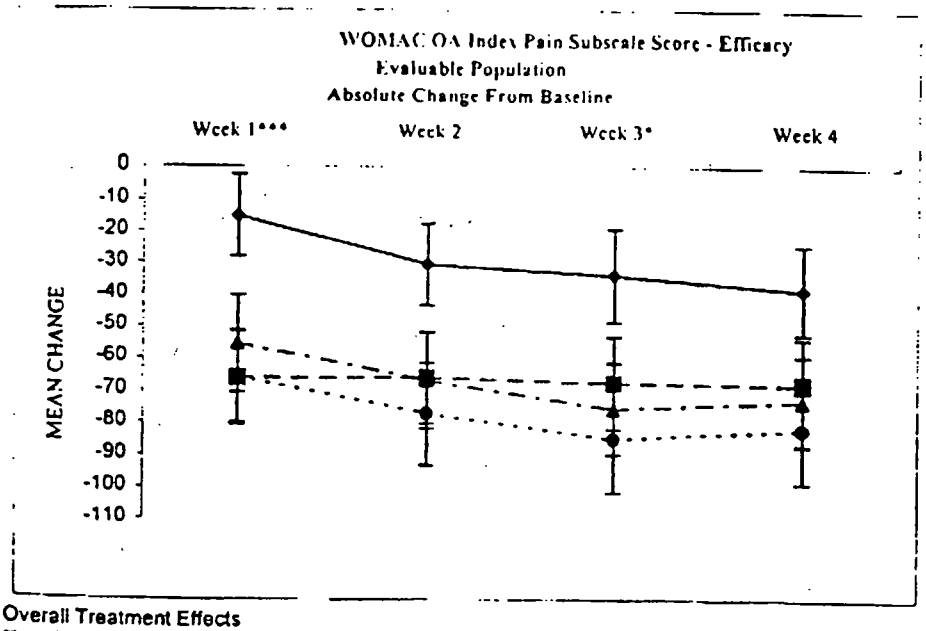
FIGURE 1



Overall Treatment Effects:

*** = Significant p≤0.05), ** = Strong Trend 0.05< p≤0.07; * = Trend 0.07<p≤0.10

FIGURE 2



Overall Treatment Effects

*** = Significant p≤0.05, ** = Strong Trend 0.05< p≤0.07; * = Trend 0.07<p≤0.10

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Index Joint: Hip or Knee=2: KNEE

FIGURE 5

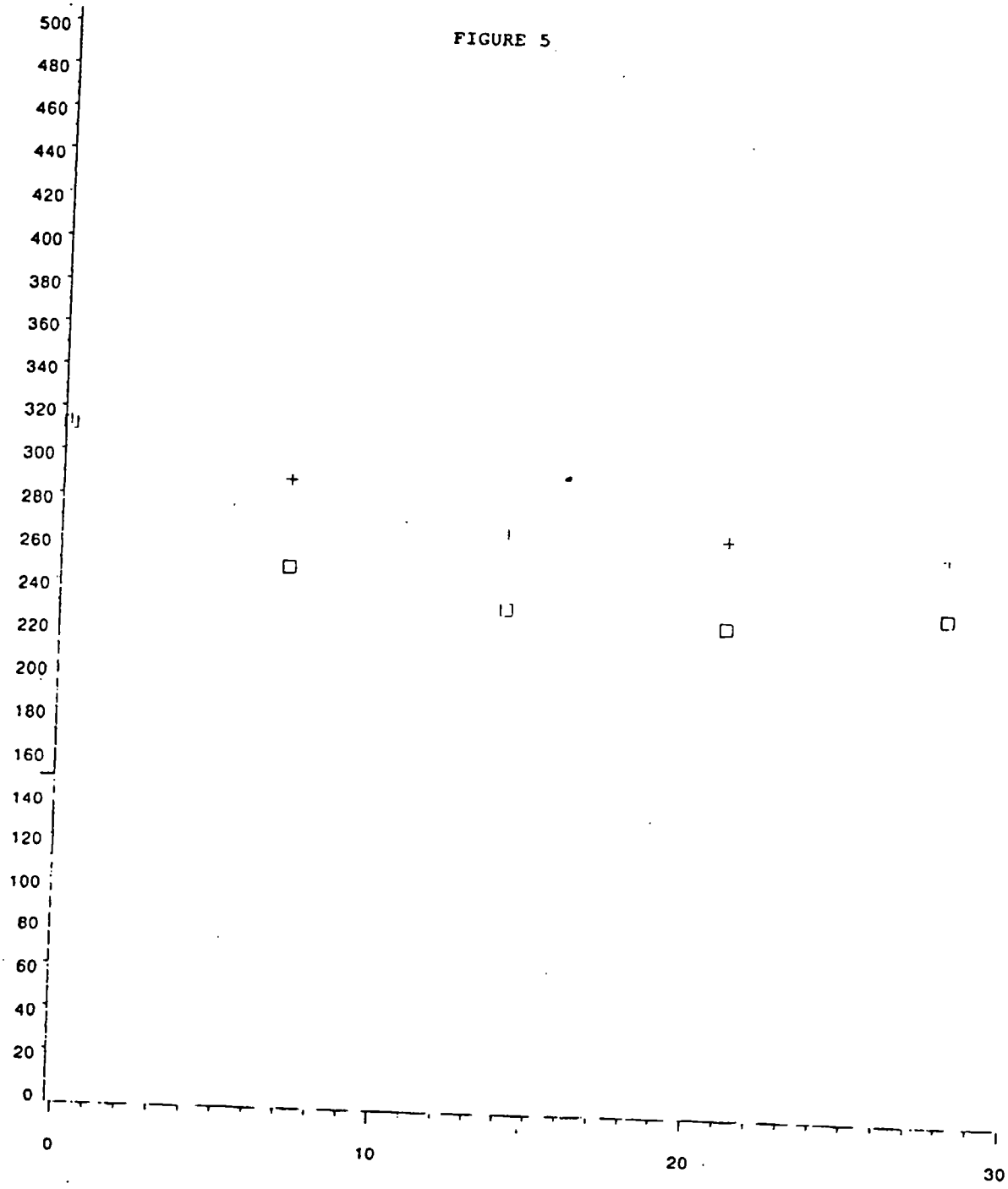

FIGURE 6

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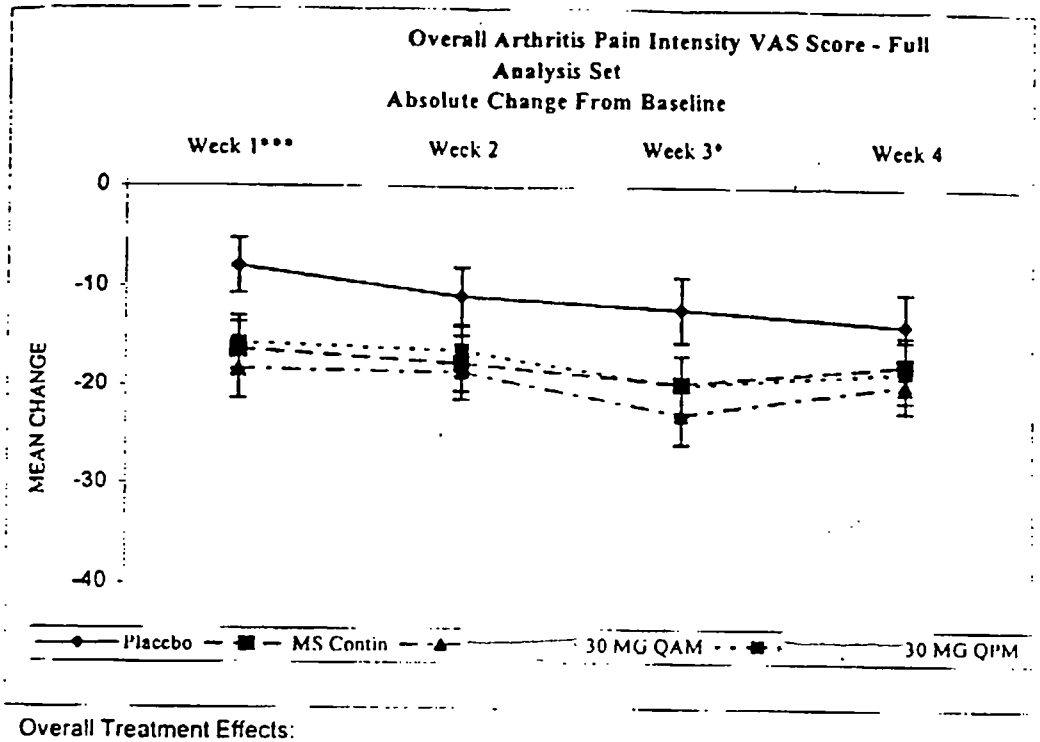
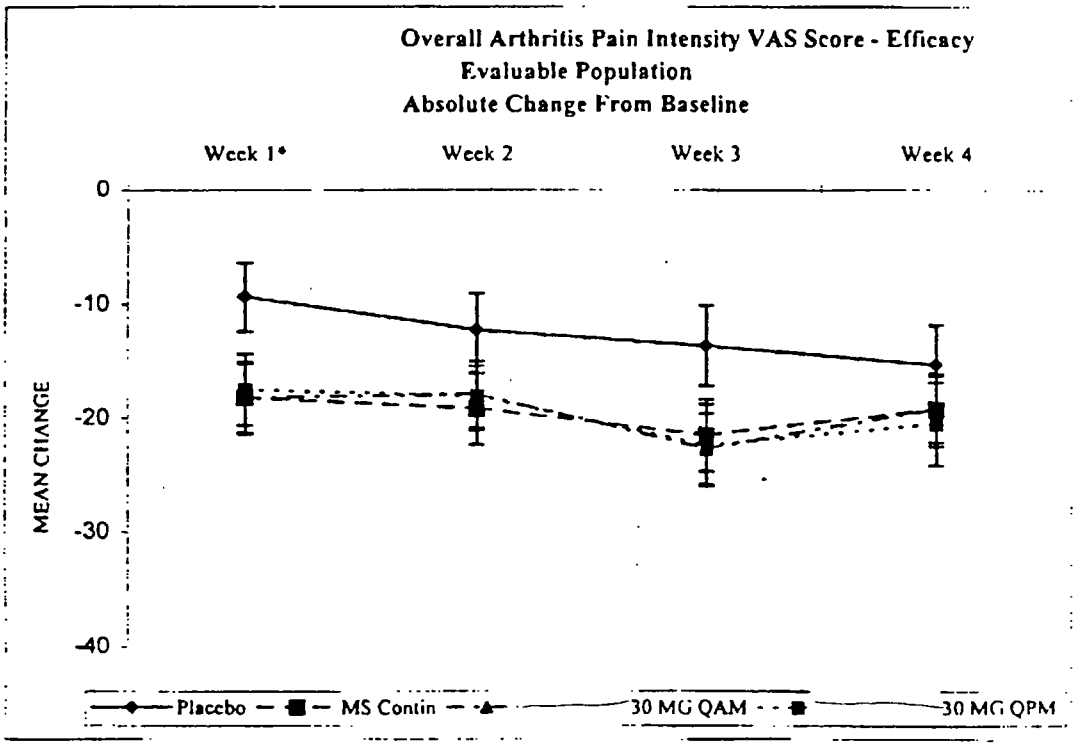


Overall Treatment Effects:
*** = Significant p≤0.05, ** = Strong Trend 0.05< p≤0.07; * = Trend 0.07<p≤0.10



Overall Treatment Effects:
*** = Significant p≤0.05), ** = Strong Trend 0.05< p≤0.07; * = Trend 0.07<p≤0.10

FIGURE 7

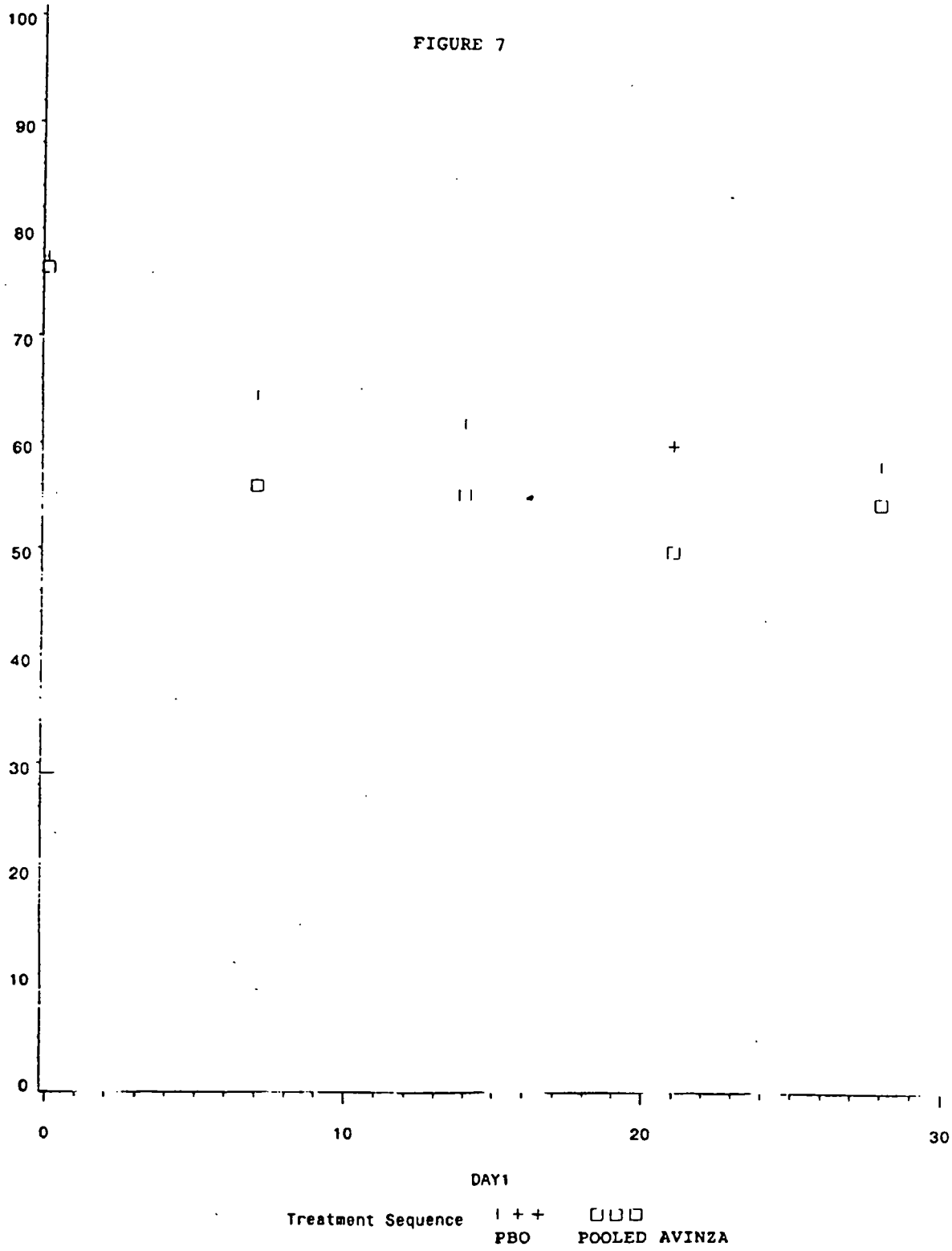


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TABLE 4

Change and Percent Change from Baseline in Overall Arthritis Pain Intensity VAS Scores[a] – Full Analysis Set

	Placebo N= 73	MS Contin N=76	QAM N=73	QPM N=73	Overall p-value	Placebo	MS Contin	QAM	QPM	Overall p-value
Change from Baseline in Overall OA Pain Intensity VAS Score[b]						Percent Change from Baseline in Overall OA Pain Intensity VAS Score[b]				
Week 1					0.042					0.053
Mean ± Std. Error	-7.96±2.72	-16.30±2.73	-16.30±3.06	-15.64±2.71		-9.3±3.77	-20.6±3.59	-23.0±3.96	-19.8±3.69	
LS Mean ± Std. Error	-7.94±2.80	-16.14±2.72	-16.78±2.78	-15.35±2.78		-9.3±3.79	-20.5±3.69	-23.2±3.77	-19.6±3.76	
Week 2					0.196					0.139
Mean ± Std. Error	-10.92±2.97	-17.67±2.89	-16.55±2.88	-16.38±2.64		-12.8±3.90	-22.6±3.79	-24.1±3.96	-20.6±3.45	
LS Mean ± Std. Error	-10.89±2.83	-17.50±2.76	-19.06±2.82	-16.07±2.81		-12.6±3.82	-22.5±3.72	-24.3±3.80	-20.5±3.60	
Week 3					0.072					0.052
Mean ± Std. Error	-12.19±3.27	-19.72±2.93	-22.92±2.96	-19.93±3.09		-14.4±4.37	-25.1±3.83	-30.1±3.98	-25.2±4.17	
LS Mean ± Std. Error	-12.17±3.06	-19.57±2.98	-23.39±3.05	-19.64±3.05		-14.4±4.13	-25.0±4.02	-30.2±4.11	-25.1±4.11	
Week 4					0.486					0.418
Mean ± Std. Error	-13.65±3.21	-17.67±2.94	-19.66±2.82	-18.32±3.13		-16.7±4.38	-21.9±3.75	-26.1±3.99	-22.5±4.02	
LS Mean ± Std. Error	-13.63±3.02	-17.50±2.94	-20.16±3.00	-18.01±3.00		-16.7±4.08	-21.9±3.97	-26.3±4.06	-22.3±4.05	

(a) Last observation carried forward (LOCF) approach was used

(b) Analysis of covariance model with change from baseline to each of weeks 1, 2, 3, and 4 as the outcome, treatment as a factor, and baseline value as a covariate

Source data: Appendix 16.6, Tables 12.1a, and 12.2a

Treatment Comparison P-values for Change and Percent Change from Baseline in Overall Arthritis Pain Intensity VAS Scores[a] – Full Analysis Set

	QAM vs. Placebo	QPM vs. Placebo	MS Contin vs. Placebo	QAM vs. MS Contin	QPM vs. MS Contin	QAM vs.QPM	QAM vs. Placebo	QPM vs. Placebo	MS Contin vs. Placebo	QAM vs. MS Contin	QPM vs. MS Contin	QAM vs.QPM
	Change from Baseline in Overall OA Pain Intensity VAS Score[b,c]						Percent Change from Baseline in Overall OA Pain Intensity VAS Score[b,c]					
Week 1	0.006	0.061	0.036	0.498	0.839	0.384	0.010	0.055	0.035	0.613	0.861	0.500
Week 2	0.042	0.195	0.098	0.694	0.717	0.455	0.031	0.143	0.062	0.744	0.698	0.480
Week 3	0.010	0.085	0.085	0.371	0.986	0.365	0.007	0.066	0.066	0.370	0.988	0.383
Week 4	0.126	0.304	0.358	0.528	0.904	0.614	0.094	0.325	0.362	0.434	0.935	0.486

(a) Last observation carried forward (LOCF) approach was used

(b) From an analysis of covariance model with change from baseline to each of weeks 1, 2, 3, and 4 as the outcome, treatment as a factor, and baseline value as a covariate

(c) Contrast statements from an analysis of covariance model from (b)

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TABLE 5

Change and Percent Change from Baseline in Overall Arthritis Pain Intensity VAS Scores[a] – Efficacy Evaluable Population

	Placebo N= 67	MS Contin N=66	QAM N=66	QPM N=61	Overall p-value
Change from Baseline in Overall OA Pain Intensity VAS Score[b]					
Week 1					0 094
Mean ± Std. Error	-9 30±2.99	-18 17±3.05	-18 17±3 22	-17.45±3.19	
LS Mean ± Std. Error	-9.16±3 04	-18 26±3.04	-18 73±3 03	-16.89±3 20	
Week 2					0.341
Mean ± Std. Error	-12.24±3.17	-19.20±3 17	-17 94±2.98	-18 07±3 05	
LS Mean ± Std. Error	-12.20±3.00	-19.26±3.00	-18 47±3 01	-17 46±3.18	
Week 3					0 148
Mean ± Std. Error	-13.64±3.50	-21.56±3.19	-22 77±3 11	-22.46±3.60	
LS Mean ± Std. Error	-13 59±3.27	-21.62±3.27	-23 25±3 27	-21 90±3.46	
Week 4					0.702
Mean ± Std. Error	-15.23±3.42	-19 20±3.23	-19 17±2.92	-20 46±3.67	
LS Mean ± Std. Error	-15 18±3.21	-19.26±3.21	-19 88±3 22	-19 87±3.41	

	Placebo N=67	MS Contin N=66	QAM N=66	QPM N=61	Overall p-value
Percent Change from Baseline in Overall OA Pain Intensity VAS Score[b]					
					0.121
	-11.2±4.13	-23.2±4.03	-22.7±4.16	-21.6±4.27	
	-11.1±4.11	-23.3±4 11	-23.0±4.08	-21.3±4.32	
					0.265
	-14 4±4.13	-24 8±4.17	-23.2±4 14	-22.2±3 87	
	-14.3±4.04	-24.8±4.04	-23.4±4.05	-22.0±4.28	
					0.123
	-16 4±4.65	-27.7±4 19	-29 8±4.17	-27.9±4.80	
	-16 4±4 40	-27.7±4 40	-29.9±4 40	-27.8±4.66	
					0 701
	-16 9±4.64	-24.0±4 13	-25 4±4.18	-24.5±4 63	
	-16 8±4.34	-24.1±4 34	-25.8±4.35	-24.3±4.60	

(a) Last observation carried forward (LOCF) approach was used

(b) Analysis of covariance model with change from baseline to each of weeks 1, 2, 3, and 4 as the outcome, treatment as a factor and baseline value as a covariate.

Source data: Appendix 16.6, Tables12.1b, and 12.2b

Treatment Comparison P-values for Change and Percent Change from Baseline in Overall Arthritis Pain Intensity VAS Scores[a] –Efficacy Evaluable Population

	QAM vs. Placebo	QPM vs. Placebo	MS Contin vs. Placebo	QAM vs. MS Contin	QPM vs. MS Contin	QAM vs.QPM
Change from Baseline in Overall OA Pain Intensity VAS Score[b, c]						
Week 1	0.027	0.081	0.036	0.913	0.757	0.677
Week 2	0.142	0.230	0.098	0.852	0 682	0.819
Week 3	0.038	0.082	0.084	0.724	0.952	0.777
Week 4	0.324	0.318	0.371	0.927	0 896	0.967

	QAM vs. Placebo	QPM vs. Placebo	MS Contin vs. Placebo	QAM vs. MS Contin	QPM vs. MS Contin	QAM vs.QPM
Percent Change from Baseline in Overall OA Pain Intensity VAS Score [b, c]						
	0.042	0.089	0 038	0.962	0.744	0.779
	0.117	0.196	0.068	0.799	0.630	0.816
	0.030	0 075	0 070	0 718	0.963	0.742
	0.270	0 388	0.395	0.799	0.969	0 835

(a) Last observation carried forward (LOCF) approach was used

(b) From an analysis of covariance model with change from baseline to each of weeks 1, 2, 3 and 4 as the outcome, treatment as a factor, and baseline value as a covariate

(c) Contrast statements from an analysis of covariance model from (b)

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TRIAL 02

FIGURE 1

Patient Disposition

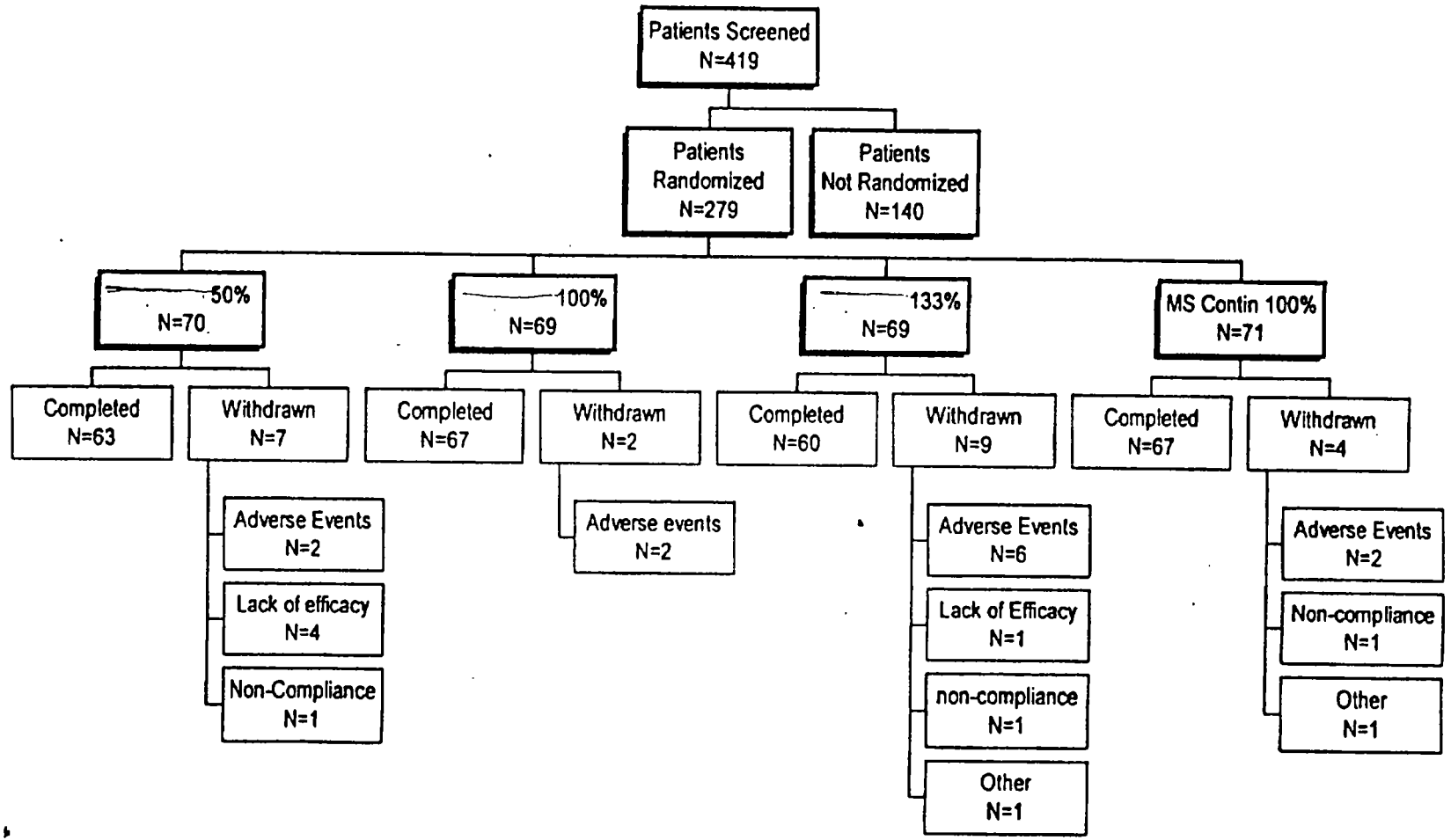

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TABLE 1

Demographics and Baseline Characteristics

	50% N=70	100% N=69	133% N=69	MS Contin® 100% N=71
Age (yr.)				
N	70	69	69	71
Mean ± SD	51.3 ± 13.08	49.7 ± 11.94	49.8 ± 11.06	49.6 ± 11.71
Range	29 – 81	29 – 81	28 – 79	26 – 78
Gender [n (%)]				
Male	32 (45.7%)	28 (40.6%)	33 (47.8%)	33 (46.5%)
Female	38 (54.3%)	41 (59.4%)	36 (52.2%)	38 (53.5%)
Race				
Caucasian	60 (85.7%)	64 (92.8%)	57 (82.6%)	64 (90.1%)
African-American	4 (5.7%)	1 (1.4%)	5 (7.2%)	2 (2.8%)
Asian	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hispanic	4 (5.7%)	4 (5.8%)	7 (10.1%)	4 (5.6%)
Other	1 (1.4%)	0 (0.0%)	0 (0.0%)	1 (1.4%)
Karnofsky Performance				
N	70	69	69	71
Mean ± SD	81.21 ± 9.026	80.65 ± 7.372	80.22 ± 8.064	80.49 ± 8.708
Range	70.0 – 100.0	70.0 – 90.0	70.0 – 100.0	70.0 – 100.0
Pain History				
Nonmalignant	58 (82.9%)	61 (88.4%)	59 (85.5%)	60 (84.5%)
Malignant	12 (17.1%)	8 (11.6%)	10 (14.5%)	11 (15.5%)

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TABLE 2

TRG004-02: CHANGE IN RESCUE MEDICATION DOSE (MG)
EFFICACY EVALUABLE POPULATION

	STATISTICS BY TREATMENT				INFERENTIAL STATISTICS	
	50% (N=64)	100% (N=66)	133% (N=65)	MS CONTIN 100% (N=66)	SOURCE	P-VALUE
DAY 5-7					TREATMENT (a)	0.057
MEAN OF CHANGE	10.76	7.33	3.24	6.83	BASELINE (a)	<0.001
STANDARD ERROR	2.756	1.664	2.006	2.224	TREND (b)	0.006
LSMEAN OF CHANGE (a)	11.19	7.21	2.95	6.83	AGE GROUP(<65 VS >=65) (c)	0.299
STANDARD ERROR (a)	2.115	2.097	2.114	2.091	TREATMENT*AGE GROUP (d)	0.876
					GENDER (c)	0.921
					TREATMENT*GENDER (d)	0.590
					RACE (WHITE VS NON-WHITE) (c)	0.505
					TREATMENT*RACE (d)	0.490
					MALIGNANCY (c)	0.155
					TREATMENT*MALIGNANCY (d)	0.809
					DOSE CORRECTION FACTOR (c)	0.732
					TREATMENT*DOSE CORRECTION FACTOR (d)	0.989
					COMPARISON (a):	
					MORPH 50% VS MORPH 100%	0.183
					MORPH 50% VS MORPH 133%	0.006
					MORPH 50% VS MS CONT	0.140
					MORPH 100% VS MORPH 133%	0.153
					MORPH 100% VS MS CONT	0.889
					MORPH 133% VS MS CONT	0.195

(a) From an analysis of covariance (ANCOVA) model with treatment as the factor and baseline value as a covariate.
(b) From a contrast statement in (a) excluding MS Contin. A significant p-value indicates evidence of a linear treatment response as the dose of Morphelan increases.
(c) From an analysis of covariance (ANCOVA) model as in (a) with the effect term added.
(d) From an analysis of covariance (ANCOVA) model as in (a) with the interaction term and necessary lower-ordered terms added.

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TABLE 3

TRG004-02: VAS PAIN SCORE
EFFICACY EVALUABLE POPULATION

	STATISTICS BY TREATMENT					
	50% (N=64)	100% (N=66)	133% (N=65)	MS CONTIN 100% (N=66)	INFERENTIAL STATISTICS SOURCE	P-VALUE
DAY 5-7						
MEAN OF CHANGE	8.62	4.81	1.72	0.46	TREATMENT (a)	<0.001
STANDARD ERROR	1.832	1.526	1.636	1.390	BASELINE (a)	0.022
LSMEAN OF CHANGE (a)	8.80	5.26	1.50	0.06	TREND (b)	0.003
STANDARD ERROR (a)	1.598	1.596	1.599	1.581	AGE GROUP(<65 VS >=65) (c)	0.056
					TREATMENT*AGE GROUP (d)	0.862
					GENDER (c)	0.396
					TREATMENT*GENDER (d)	0.037
					RACE (WHITE VS NON-WHITE) (c)	0.104
					TREATMENT*RACE (d)	0.304
					MALIGNANCY (c)	0.002
					TREATMENT*MALIGNANCY (d)	0.504
					DOSE CORRECTION FACTOR (c)	0.144
					TREATMENT*DOSE CORRECTION FACTOR (d)	0.777
					COMPARISON (a):	
					50% VS 100%	0.117
					50% VS 133%	0.001
					50% VS MS CONT	<0.001
					100% VS 133%	0.099
					100% VS MS CONT	0.022
					133% VS MS CONT	0.520

(a) From an analysis of covariance (ANCOVA) model with treatment as the factor and baseline value as a covariate.
(b) From a contrast statement in (a) excluding MS Contin. A significant p-value indicates evidence of a linear treatment response as the dose of Morphelan increases.
(c) From an analysis of covariance (ANCOVA) model as in (a) with the effect term added.
(d) From an analysis of covariance (ANCOVA) model as in (a) with the interaction term and necessary lower-ordered terms added.

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TABLE 4

TRG004-02: PDS PAIN SCORE
EFFICACY EVALUABLE POPULATION

PART 2 OF 2: ANALYSIS OF CHANGE FROM BASELINE

	STATISTICS BY TREATMENT				INFERENTIAL STATISTICS	
	50% (N=64)	100% (N=66)	133% (N=65)	MS CONTIN 100% (N=66)	SOURCE	P-VALUE
DAY 5-7						
MEAN OF CHANGE	20.97	9.51	3.80	-0.66	TREATMENT (a)	<0.001
STANDARD ERROR	4.355	3.073	3.527	2.303	BASELINE (a)	0.005
LSMEAN OF CHANGE (a)	21.28	10.44	3.59	-1.67	TREND (b)	<0.001
STANDARD ERROR (a)	3.355	3.343	3.354	3.321	AGE GROUP(<65 VS >=65) (c)	0.074
					TREATMENT*AGE GROUP (d)	0.696
					GENDER (c)	0.534
					TREATMENT*GENDER (d)	0.662
					RACE (WHITE VS NON-WHITE) (c)	0.343
					TREATMENT*RACE (d)	0.776
					MALIGNANCY (c)	0.006
					TREATMENT*MALIGNANCY (d)	0.497
					DOSE CORRECTION FACTOR (c)	0.300
					TREATMENT*DOSE CORRECTION FACTOR (d)	0.652
					COMPARISON (a):	
					50% VS ——— 100%	0.023
					50% VS ——— 133%	<0.001
					50% VS MS CONT	<0.001
					100% VS ——— 133%	0.150
					100% VS MS CONT	0.011
					133% VS MS CONT	0.265

(a) From an analysis of covariance (ANCOVA) model with treatment as the factor and baseline value as a covariate.
(b) From a contrast statement in (a) excluding MS Contin. A significant p-value indicates evidence of a linear treatment response as the dose of ——— increases.
(c) From an analysis of covariance (ANCOVA) model as in (a) with the effect term added.
(d) From an analysis of covariance (ANCOVA) model as in (a) with the interaction term and necessary lower-ordered terms added.

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TABLE 5

INTEGRATED SCORE FROM PAIN INTENSITY (VAS) AND RESCUE MEDICATION DOSE (MG) (a)
FULL ANALYSIS SET

PART 2 OF 2: ANALYSIS OF CHANGE FROM BASELINE

	STATISTICS BY TREATMENT				INFERENTIAL STATISTICS	
	50% (N=67)	100% (N=67)	133% (N=69)	MS CONTIN 100% (N=69)	SOURCE	P-VALUE
DAY 5-7						
MEAN OF CHANGE	20.74	2.89	-12.80	-10.55	TREATMENT (a)	<0.001
STANDARD ERROR	6.523	7.042	6.050	7.002	BASELINE (a)	<0.001
LSMEAN OF CHANGE (a)	21.45	4.63	-12.91	-12.80	TREND (b)	<0.001
STANDARD ERROR (a)	6.518	6.579	6.467	6.445	AGE GROUP(<65 VS >=65) (c)	0.016
					TREATMENT*AGE GROUP (d)	0.423
					GENDER (c)	0.744
					TREATMENT*GENDER (d)	0.144
					RACE (WHITE VS NON-WHITE) (c)	0.280
					TREATMENT*RACE (d)	0.070
					MALIGNANCY (c)	<0.001
					TREATMENT*MALIGNANCY (d)	0.727
					DOSE CORRECTION FACTOR (c)	0.233
					TREATMENT*DOSE CORRECTION FACTOR (d)	0.707
					COMPARISON (a):	
					50% VS 100%	0.070
					50% VS 133%	<0.001
					50% VS MS CONT	<0.001
					100% VS 133%	0.058
					100% VS MS CONT	0.060
					133% VS MS CONT	0.990

(a) From an analysis of covariance (ANCOVA) model with treatment as the factor and baseline value as a covariate.
(b) From a contrast statement in (a) excluding MS Contin. A significant p value indicates evidence of a linear treatment response as the dose of [redacted] increases.
(c) From an analysis of covariance (ANCOVA) model as in (a) with the effect term added.
(d) From an analysis of covariance (ANCOVA) model as in (a) with the interaction term and necessary lower ordered terms added.

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FIGURE 2

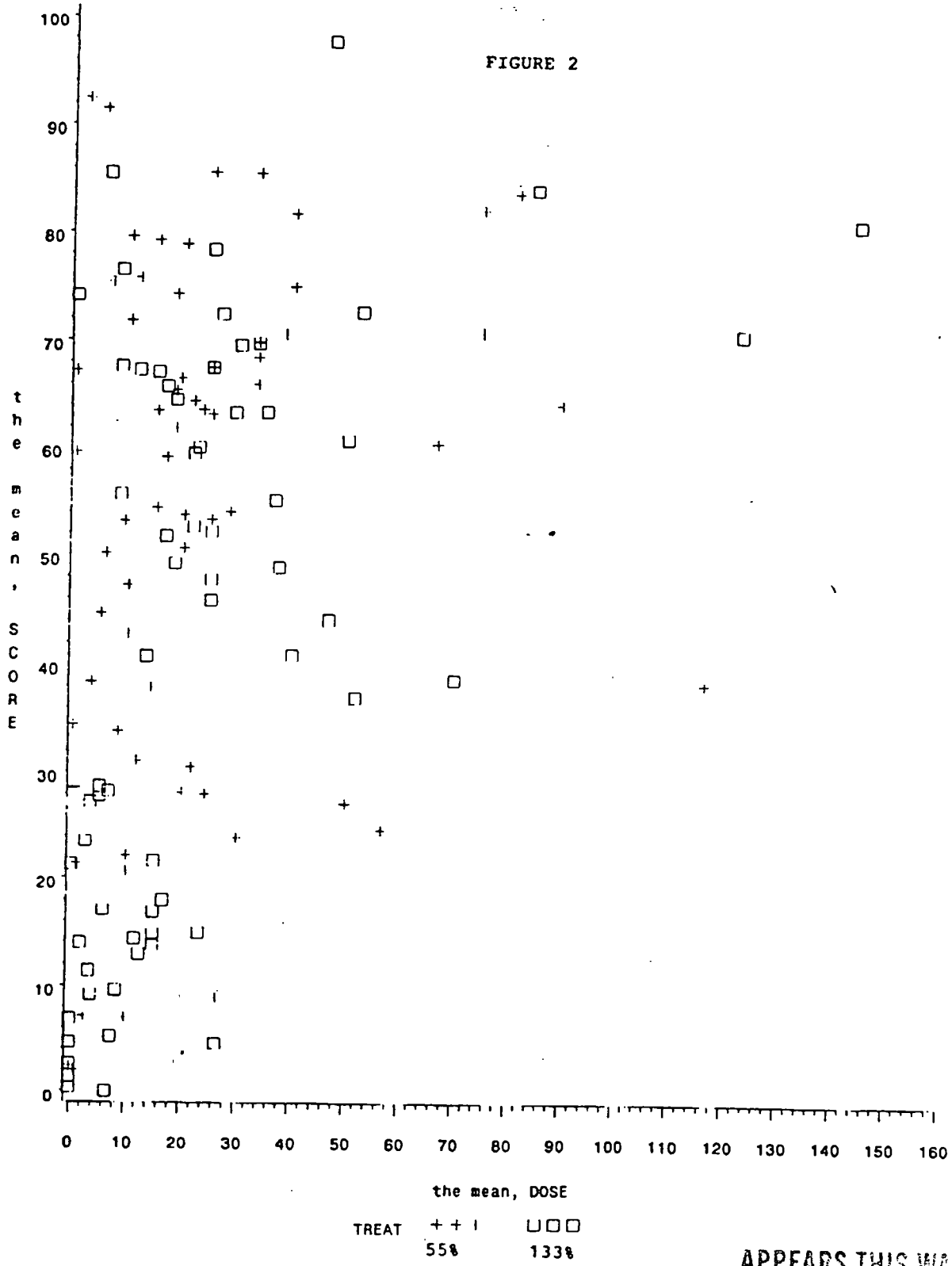

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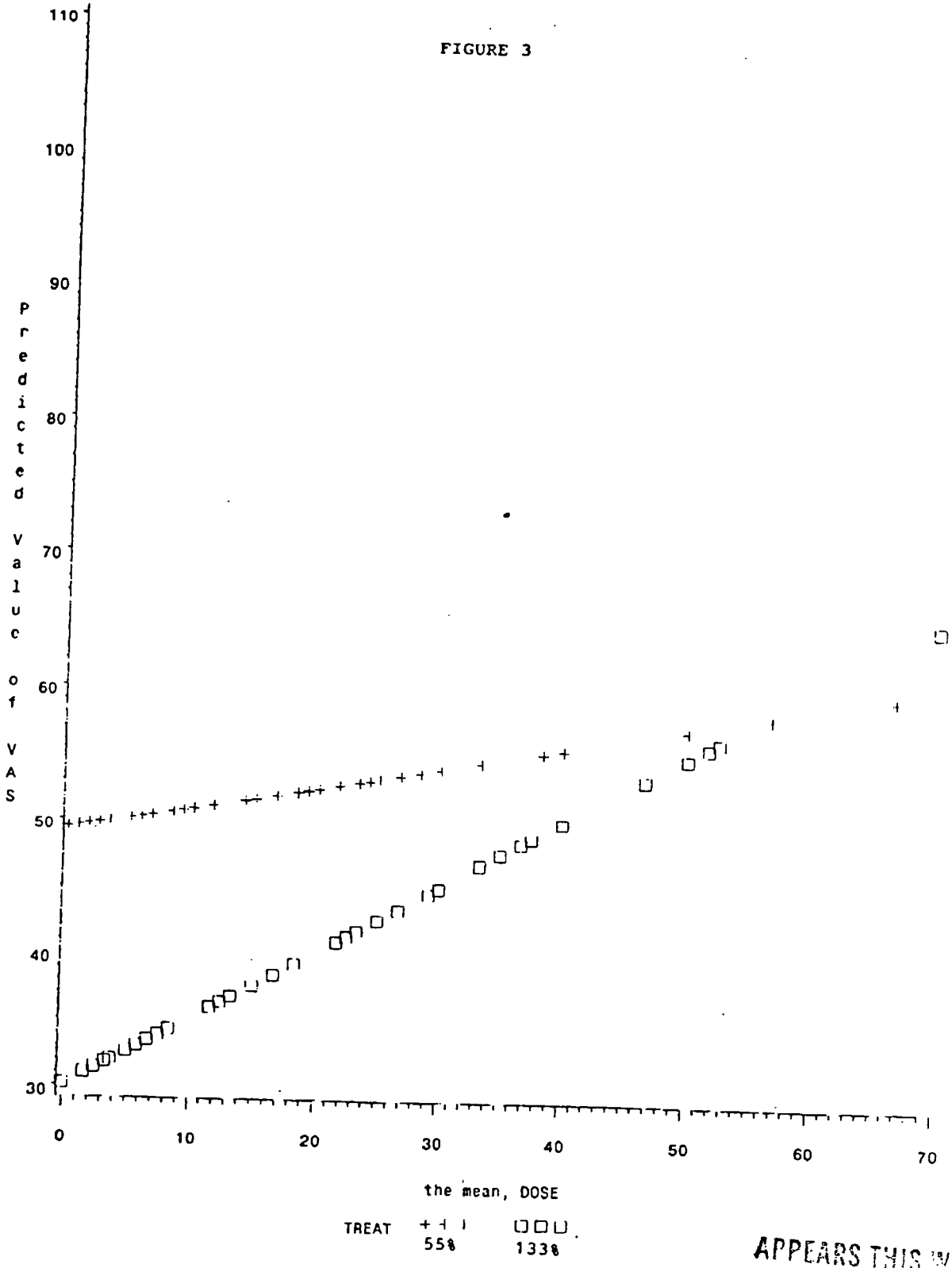
FIGURE 3



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/s/

David Hoberman
3/22/01 09:53:54 AM
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