4.3 Evaluation of Data Quality and Integrity

As described above, methods used to evaluate data integrity included a comparison of summary reports, primary and secondary tabulations, relevant appendices, case report tabulations, and case report forms for specific patients and for a randomly selected group. A routine DSI inspection on two high-volume sites returned no unexpected, invalid, or potentially troublesome concerns.

4.4 Financial Disclosure

The sponsor has provided certification of financial disclosure for each study. According to the submitted information (Form OMB 0910-0396), the sponsor has not entered into any financial arrangement with the study investigators.

5 DESCRIPTION OF DATA SOURCES

5.1 Overall Data

Data from the NDA (including clinical trial reports, CRTs, CRFs, safety information), from the IND, from other reviewers' assessments, and from relevant literature were used to compile this reviewer's final evaluation of the efficacy and safety profiles of Morphelan.

5.2 Primary Source Data

To date, the ———— clinical development program has consisted of seven clinical trials - three clinical pharmacology studies in patients, two controlled clinical studies, and two uncontrolled clinical studies. These studies were conducted to evaluate efficacy, safety, and pharmacokinetics/pharmacodynamics in patients with chronic, moderate to severe pain. The seven clinical studies differed with respect to their design, number of patients exposed, demographic profiles, dosage of ———— administered, treatment duration, and efficacy variables analyzed. For a more detailed description of these categories in all trials, see Appendix B. For a summary of the CRFs examined in this review, see Appendix C.

5.3 Secondary Source Data

No secondary source data for this NDA submission were identified.

5.4 Postmarketing Experience

Although ———— has not been used in either US or foreign markets, there is extensive information on the use of morphine and morphine combination agents. Adverse experiences have ranged from the typical opioid side effects (nausea, somnolence, constipation, dizziness, pruritus) to more severe occurrences of respiratory depression, dependency, abuse, overdose, and withdrawal syndromes.

5.5 Literature Search

The sponsor conducted and submitted a search of relevant literature for this NDA. The subjects included pain control in cancer patients, control of chronic non-cancer pain,

control in pediatric cancer pain, and control of pain for osteoarthritis. There were numerous articles discussing the pharmacokinetic and pharmacodynamic profiles of morphine coginers and the pharmacotoxicity of these agents. Information was also provided on experience with and evaluation of various assessment measures. The literature submitted was an accurate representation of the known published information.

6 REVIEW OF EFFICACY

6.1 Individual Review of Studies (by indication)

6.1.1 Study TRG004-02: A Multicenter, Randomized, Double-Blind, Double-Dummy, Parallel Groups Study of ——— in Patients with Chronic, Moderate to Severe Pain

6.1.1.1 Summary of Findings

This study was a double-blind trial in which patients with chronic malignant or non-malignant pain were randomized to four treatment groups. Patients were initially entered into a non-randomized stabilization period of up to three weeks during which they received MS Contin for pain and were allowed ——— as a rescue medication. Subsequently, patients were randomized into one of four treatment groups, based upon the established dose of MS Contin during the prior period, and in three of the groups, based upon conversion from MS Contin to ——— using "morphine equivalents". The four treatment groups were as follows: 1) ——— 50%, 2) ——— 100%, 3) ——— 133%, and 4) MS Contin 100%. The randomization period was conducted for a total of 7 days, during which time patients were also allowed to take ——— as a rescue medication. The sponsor chose change in total daily rescue medication dose, change in VAS Pain Intensity Score (100 mm), and change in Pain Descriptor Score (PDS, seven-item categorical scale, – see Appendix D) as primary efficacy variables.

Subgroup analyses of efficacy based on age were of limited value due to very low enrollment of patients over 65 years of age and even lower enrollment of patients over the age of 75 years. No analyses based on gender, age, or other special population category were performed.

Change in Rescue Medication Dose (See Table 6.5)

All treatment groups required more rescue medication at the start of the double blind phase than at the end of the stabilization period. The average increase in rescue medication use for patients taking ——— 133% or MS Contin 100% was statistically significantly less than that for ——— 50% (p=0.003 and p=0.045 respectively). There were no statistically significant differences between ——— 100% and any of the other three treatment groups. Although the differences were not statistically significant, use of rescue medication in the ——— 133% was less than in the MS Contin group while the use of rescue medication in the ——— 100% group was higher than in the MS Contin group. The largest difference in mean rescue mediation dose between any two treatment groups was 8.2 mg.

Change in VAS Pain Intensity Score (See Table 6.6)

The average VAS pain scores increased slightly, although not statistically significantly from the end of the stabilization period to the baseline double-blind measurement for all treatment groups.

All treatment groups had an increase in VAS score over the randomized treatment period. The increase in VAS score was statistically significantly smaller for the [redacted] 133% and MS Contin 100% groups compared with the [redacted] 50% group ($p<0.001$, $p=0.001$ respectively). The increase in VAS score was also statistically significantly less for MS Contin 100% than for [redacted] 100% ($p=0.019$). The increase in pain intensity of the [redacted] 133% treated group was less than the increase of the [redacted] 100% treated group, but this difference did not reach statistical significant ($p=0.150$). The largest difference in change in VAS score between any two treatment groups was 8.9 mm.

Change in Pain Descriptor Scale (PDS) Score (See Table 6.7)

In the [redacted] groups, using the change in PDS score from the beginning to the end of the randomization period, MS Contin 100% was most effective and [redacted] 50% was least effective in the reduction of pain. Both [redacted] 133% and [redacted] 100% demonstrated less worsening in PDS than [redacted] 50% ($p<0.001$ and $p=0.008$, respectively). The change in PDS score for the MS Contin 100% group was statistically significantly smaller than the change for both the [redacted] 50% ($p<0.001$) and the [redacted] 100% ($p=0.016$) groups.

Secondary Efficacy Variables

The results of the secondary variables of number of doses/day of rescue medication, adjusted number of doses/day of rescue medication, quality of sleep and amount of rescue medication also demonstrated superiority of the MS Contin 100% and [redacted] 133% over [redacted] 50%.

Overall Conclusions

While the absolute changes in outcome measures were small, there were many differences between treatment groups that were statistically significantly different. The p-values from the pair-wise, between-group comparisons are presented in Table 6.1. MS Contin 100% and [redacted] 133% were consistently better in managing pain than [redacted] 50%, as demonstrated by the comparisons across all primary and secondary outcome measures. [redacted] 100% was better than [redacted] 50% as reflected by one primary outcome measure, change in mean PDS score, and as reflected by all of the secondary outcome measures except mean amount of rescue medication. In addition, MS Contin 100% was somewhat more effective than [redacted] 100% as reflected in two primary outcome measures, change in mean VAS score and change in mean PDS score. In no comparison did [redacted] 100% demonstrate superiority over MS Contin 100%.

Table 6. 1 p-values For Pair-wise Comparisons Between Treatment Groups Primary And Secondary Outcome Measures						
	MS Contin 100% vs					
	MSC vs. 133	MSC vs. 100	MSC vs. 50	133 vs. 100	133 vs. 50	100 vs. 50
1° Outcome Measures						
Δ Rescue Medication	NS*	NS	0.045	NS	0.003	NS
Δ VAS score	NS	0.019	<0.001	NS	<0.001	NS
Δ PDS score	NS	0.016	<0.001	NS	<0.001	0.008
2° Outcome Measures						
Δ Number Doses	NS	NS	<0.001	NS	<0.001	0.014
Adjusted Δ # Doses	NS	NS	<0.001	NS	<0.001	0.036
Δ QOS score	NS	NS	<0.001	NS	<0.001	<0.001
Amount of Rescue	NS	NS	0.045	NS	0.003	NS

*= Not significant

There are several possible explanations for superiority of MS Contin 100% over [redacted] 100% for change in VAS score and change in PDS score and for the more consistent superiority of MS Contin 100% over [redacted] 50% than [redacted] 100% compared with [redacted] 50%. There could be differences in bioavailability between the formulations so that more morphine becomes available from MS Contin than [redacted] The manner in which morphine is released over time from MS Contin may better suit chronic pain management. The timing of outcome measures may have occurred at a time when morphine levels from MS Contin were higher than the morphine levels from [redacted] The information obtained from the PK study, TRG004-01, demonstrated differences in the PK profiles of MS Contin and [redacted] with a lower serum peak measured following administration of [redacted] as compared to MS Contin. It may be that patients achieve a greater sense of pain relief associated with a higher peak serum concentration even if the overall bioavailability is comparable.

There is no apparent explanation for the increased pain intensity scores and the increased use of rescue across all treatment groups over the randomized period. Over a one week period, particularly among non-malignant chronic pain patients, one would not expect progression of underlying disease. These findings might reflect an artifact created by the frequent reporting of pain scores (four times each day) imposed on patients.

In patients with pain of malignant origin, [redacted] 133% showed the greatest decrease in usage of rescue medication and the smallest increase in the Pain Descriptor Scale Score than all other treatment groups. Conclusions based on this finding must be conservative as patients with pain of malignant origin only constituted 15% of the study population.

6.1.1.2 Study Plan

6.1.1.2.1 Population, Design, and Objectives

In-patients or out-patients 21 years of age and older with chronic, moderate to severe pain (malignant or non-malignant) requiring treatment with 60-1000 mg oral morphine equivalents daily were to be eligible for enrollment. Patients were to be ineligible if they had an expected survival of <3 months, if they had significant systemic disease, or if they had received external beam radiation to currently painful sites within 6 weeks of beginning the stabilization period. The design called for the enrollment of a minimum of 192 evaluable patients.

The objectives of the study were to:

- Demonstrate that once-daily ——— relieved pain in patients with chronic moderate to severe pain
- Evaluate the relative potency of once daily ——— and twice daily MS Contin
- Acquire information concerning conversion from twice daily MS Contin to once daily ———

6.1.1.2.2 Treatment Summary

Stabilization Phase:

Patients were to have been stabilized on MS Contin for a minimum of 7 days during which time an attempt would be made to identify the dose which would balance analgesia and side effects while requiring ≤4 rescue doses of ——— daily. The rescue medication dose was to have been 10% of the total daily dose of morphine given as ——— every 2 hours as needed. Patients were to have maintained a diary during this time in which dose and timing of all pain medications, including rescue medication, Pain Intensity Visual Analog Scale (VAS) results, Pain Descriptor Scale (PDS) results and quality of sleep results, were to have been recorded.

Double-Blind Phase

After a minimum of 7 days in the stabilization period, patients were to have been randomized in a blinded fashion into one of four groups:

- Group 1 – 50% equivalent daily morphine dose of once-daily ———
- Group 2 – 100% equivalent daily morphine dose of once-daily ———
- Group 3 - 133% equivalent daily morphine dose of once-daily ———
- Group 4 - 100% equivalent daily morphine dose of twice-daily MS Contin

Medications were to be administered in a double-blind, double-dummy fashion. Rescue medication was to have been continued at 10% of the total daily dose of morphine established during the stabilization period given as ——— every 2 hours as needed. Patients were to have continued to keep a daily diary recording VAS, PDS, and quality of sleep results. This phase of the study was to have continued for a period of 7 days at

which time patients were to be offered the option to participate in an open-label extension trial of once-daily ——— use.

6.1.1.2.3 Assessments

According to the protocol, the following assessments were to have been considered primary efficacy measures:

- Change or percent change in total daily rescue medication dose
- Change in Visual Analog Scale (VAS) pain intensity score
- Change in Pain Descriptor Scale (PDS) score

The following assessments were to have been considered secondary efficacy measures:[1]

- Number of daily rescue medication doses required during the 3-day period from Days 5-7
- Quality of sleep score (see Appendix E)
- Rate of drop out
- Quality of life score[2]

6.1.1.2.4 Analysis Plan

Patients were to be randomized to one of the four treatment groups. The sponsor defined three populations for the study:

- Full Analysis Set - those who were randomized to a treatment, took at least one dose of the blinded study medication, and had at least one post-baseline efficacy measurement
- Efficacy Evaluable Population - those who had efficacy data recorded at both baseline and on at least one of Days 5, 6, or 7
- Safety Population - those who were randomized and took at least one dose of blinded study medication

Descriptive statistics were to be provided for all demographic and efficacy parameters. Differences between treatment groups were to be analyzed by analysis of covariance (ANCOVA) with change from baseline to days 5-7 as the dependent variable. Covariates were to include malignancy, site, treatment-by-malignancy, treatment-by-site interaction, and baseline rescue medications and pain scores. The dose response trend was to be evaluated. All statistical tests were to be at the 5% level of significance for treatment difference and at 10% for interactions. Comparisons of rescue medication use, pain scores, and drop-out rates were to be made using the general linear model and the Cochran-Mantel-Haenszel test.

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[1] In the final study report, the Sponsor added three secondary efficacy measures not included in the original protocol: 1) Time to drop out from study, 2) Adjusted number of daily rescue medication dose required, and 3) Amount of rescue medication dose (mg) required per day.

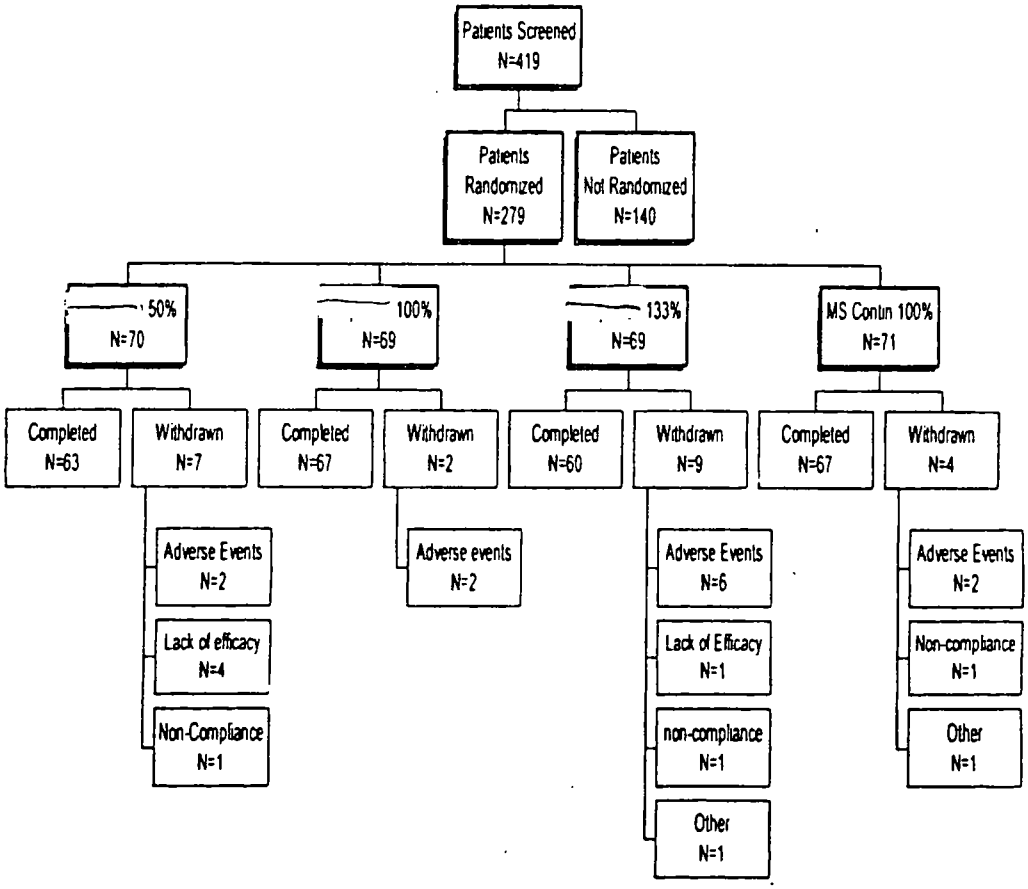
[2] Quality of life was listed as a secondary efficacy measure in the original protocol and was not deleted by any amendments. However, a recording format was not included on the sample CRF's, patient data on this variable was not submitted, and an analysis of this factor is not presented in the final study report.

6.1.1.3 Study Conduct

6.1.1.3.1 Patient Disposition

A total of 419 patients were screened for the study and 279 of these were randomized into one of the four groups. Three patients were excluded from the safety population after randomization (117-007, 131-013, 157-004) because they did not take the blinded drug. Two hundred fifty-seven patients completed the study and were considered evaluable for efficacy analysis. Disposition of all screened patients is depicted in the following diagram.

Patient Disposition – Trial 004-02



Most patients who were withdrawn from the trial after receiving treatment were withdrawn because of adverse events. The following table delineates the reasons for withdrawal that were identified by the investigators.

Table 6.2 Discontinued Patients				
Population	**Treatment Group**			
	[redacted] *50%*	[redacted] *100%*	[redacted] *133%*	*MS Contin 100%*
Number completing trial	63	67	60	67
Number discontinuing trial	7	2	9	4
Reason for discontinuation				
Adverse events	2	2	6	2
Lack of efficacy	4		1	
Non-compliance	1		1	1
Unspecified			1	1

From Sponsor's information, Vol. 2.55, pg. 33.

Although several patients deviated from the stabilization requirement in the number of times they dosed with rescue medication, they were subsequently randomized to a treatment group. These patients are listed below:

Table 6.3 Patients Deviating from Stabilization Requirements		
Stabilization Period Deviation	Treatment Group	Patient Numbers
>4 doses rescue med on 3 consecutive days	[redacted] 50%	109-001
>4 doses rescue med on 3 non-consecutive days	[redacted] 133%	133-006
	MS Contin 100%	124-004
>4 doses rescue med on 2 consecutive days	[redacted] 50%	131-009
	[redacted] 100%	126-008
	[redacted] 133%	110-002
	MS Contin 100%	131-013

From Sponsor's in-text Table 10.2-1, Vol. 2.55, pg. 34.

There were also several randomized patients who were considered protocol violations with respect to medication doses, administration and concomitant medications.

- 117-005 (MS Contin 100%) – was not prescribed rescue medication
- 117-006 ([redacted] 100%) – was not prescribed rescue medication
- 117-007 ([redacted] 50%) – was non-compliant with study medication and procedures (took other medication)
- 117-012 (MS Contin 100%) – did not follow double-blind dosing instructions correctly
- 131-008 ([redacted] 133%) – did not take dose of study medication on Day 7
- 133-025 ([redacted] 133%) – took concomitant medication (prednisone 40mg QD) for lupus and asthma when protocol allowed prednisone equivalent at up to 20 mg QD

Patient 117-007 was the only patient excluded from safety, efficacy, and ITT analyses. According to the sponsor, the patient refused to follow instructions for the double-blind portion of the trial, refused to return remainder of study medication and her diary, and would not speak to investigators on the phone during attempted follow-up.

6.1.1.3.2 Demographics/Group Comparability

The number of randomized patients who received trial drug therapy is summarized by age, gender, ethnic origin, Karnofsky Performance[3], and pain history in the following table. There were no statistically significant differences between treatment groups for any of these variables.

Table 6.4
Demographic Variables – Safety Population

Variable	Treatment Group			
	50% *N = 70*	*100%* *N = 69*	*133%* *N = 69*	*MS Contin 100%* *N = 71*
Age				
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				
M/F	32/38	28/41	33/36	33/38
Pain History				
Nonmalignant	58	61	59	60
Malignant	12	8	10	11
Karnofsky Performance				
Mean ± SD	81.21 ± 9.026	80.65 ± 7.372	80.22 ± 8.064	80.49 ± 8.708
Range	70-100	70-90	70-100	70-100
Ethnic Origin				
W/O	60/10	64/5	57/12	64/7

From Sponsor's in-text Table 11.1-1, Vol. 2.55, pg. 36.

A number of patients took over-the-counter and/or prescription medications. The most common medications among all patients were antidepressants (39.4%), antihypertensives (38.4%), benzodiazepines (24%), NSAIDs (20.3%), muscle relaxants (19.7%), antihistamines (16.8%), and proton pump inhibitors (14.7%).

6.1.1.3.3 Unplanned Analyses

The statistical analysis plan called for evaluation of the percent change from baseline in the amount of rescue medication dose and the VAS pain intensity score. However, the protocol called for computation of either change or percent change. Due to a considerable variation of baseline variables between patients, the sponsor considered percent change to be a more accurate measure. Another confounding factor was the existence of many patients who took no rescue medication at baseline. The sponsor calculated percent change by adding "1" to the baseline rescue medication for those

[3] Karnofsky Performance is a physical activity/disability rating scale – see Appendix F

patients. This transformed data showed wide variations and was "difficult to interpret". Therefore, the sponsor chose to use absolute changes in the efficacy parameters in their final analysis.[4]

6.1.1.4 Sponsor's Efficacy Results

Except for median time to drop out and rate of drop out, efficacy was calculated from the last 3 days of the MS Contin stabilization period to the last 3 days of the double-blind period. For most of the efficacy parameters there was apparent worsening after the patients were switched to the double-blinded medication. Therefore, according to the sponsor, a positive dose-response relationship would be manifest as smaller increases ("less worsening") or greater decreases from baseline with increasing doses of [redacted].

6.1.1.4.1 Primary Efficacy Variables

Change or Percent Change in Total Daily Rescue Medication Dose

Of interest, in all four treatment groups, there was an increase in amount of rescue medication required over the baseline requirement once the patient entered the double-blind phase of the trial.

In the Full Analysis population, there was an overall statistically significant (p=0.03) difference among treatment groups in the mean change in amount of rescue medication. The difference in mean change in rescue medication use was 8.2 mg between the [redacted] 133% treated patients and the [redacted] 50% patients and this difference reached statistical significance (p=0.003) reflecting a greater mean change (less rescue) in the total daily rescue medication dose for [redacted] 133% treated patients than for [redacted] 50% patients. The difference in the mean change in rescue medication use for the MS Contin 100% group compared with the [redacted] 50% group, 5.5mg, was also statistically significantly (p=0.045) different reflecting less increase in rescue medication use in the MS Contin 100% group. There were no statistically significant differences for any of the other comparisons ($p \geq 0.096$). The linear trend for dose responsiveness was statistically significant (p = 0.004). Patients with pain of malignant origin in the [redacted] 133% group had the greatest decrease in the mean rescue medication dose. The following table illustrates the changes in rescue medication in the treatment groups and any significant pair-wise comparisons.

[4] Vol. 2.55, pp. 29-30

Table 6.5 Change in Rescue Medication				
Variable	**Treatment Group**			
	[redacted] *50%* *N=67*	[redacted] *100%* *N=67*	[redacted] *133%* *N=69*	*MS Contin 100%* *N=69*
Change in Rescue Med Mean ± S.D. (mg)	11.44 ± 2.79	6.92 ± 1.69	3.17 ± 1.9	5.91 ± 2.19
Overall p value	0.03			
Linear Trend for Dose Response	0.004			
Significant Pair-wise Comparisons	133% < 50% (p=0.003) MSC < 50% (p=0.045)			

From Sponsor's in-text Table 11.3.1-1, Vol. 2.55, pg. 40.

Change in Visual Analog Scale (VAS) Pain Intensity score

In the Full Analysis population, there was an overall statistically significant difference ($p<0.001$) among treatment groups in VAS Pain Score mean change. The difference in the mean change in VAS score was 8.9 mm between the MS Contin 100% group and the [redacted] 50% group, and 4.5 mm between MS Contin and [redacted] 100%. The MS Contin 100% group had the smallest change during the double-blind period and this was statistically significantly less than both the [redacted] 50% ($p<0.001$) and the [redacted] 100% ($p=0.019$) groups. While the MS Contin group had a smaller increase in pain intensity than the [redacted] 133% group, this difference did not reach statistical significance ($p=0.347$). Patients in the [redacted] 133% group had a statistically significantly smaller increase in pain intensity than patients in the [redacted] 50% group ($p<0.001$), a difference of 7 mm. Although patients in the [redacted] 133% group exhibited less increase in pain intensity than those in the [redacted] 100% group, this difference was not statistically significant ($p=0.150$). Similarly, the patients in [redacted] 100% had less increase in pain intensity than the [redacted] 50% patients, but this difference did not reach statistical significance ($p=0.055$). The linear trend for dose responsiveness was statistically significant ($p = 0.001$).

The average VAS pain scores increased slightly from stabilization to the double-blind period for all treatment groups with MS Contin 100% and then [redacted] 133% showing the least amount of increase. The following table illustrates the changes in VAS Pain Intensity scores in the treatment groups and any significant pair-wise comparisons.

Table 6.6 Change in VAS Pain Score				
Variable	**Treatment Group**			
	——— *50%* *N=67*	——— *100%* *N=67*	——— *133%* *N=69*	*MS Contin 100%* *N=69*
Change in VAS score Mean ± s.e.m.	9.08 ± 1.79	4.65 ± 1.51	2.02 ± 1.58	0.15 ± 1.37
Overall p value	<0.001			
Linear Trend for Dose Response	0.001			
Significant Pair-wise Comparisons	133% < 50% (p<0.001) MSC < 50% (p<0.001) MSC < 100% (p=0.019)			

From Sponsor's in-text Table 11.3.1-2, Vol. 2.55, pg. 42.

Change in Pain Descriptor Scale (PDS) score

In the Full Analysis population, there was an overall statistically significant change (p<0.001) among treatment groups in PDS Pain Score. The MS Contin 100% group had the slight improvement in pain descriptor score, while the ——— treated patients had worsened pain descriptor scores. The difference in the change in PDS score for MS Contin 100% was statistically significantly different from both the ——— 50% (p<0.001) and the ——— 100% (p=0.016) groups. Both ——— 133% and ——— 100% groups demonstrated less worsening of PDS scores compared to the ——— 50% group (p<0.001 and p=0.008, respectively). While the MS Contin 110% group demonstrated a slight improvement and the ——— 133% group demonstrated a small degree of worsening, the difference did not reach statistical significance (p=0.318). The difference between the ——— 133% and the ——— 100% groups also did not reach statistical significance (0.148). The linear trend for dose responsiveness was statistically significant (p < 0.001). Patients with pain of malignant origin in the ——— 133% group had the greatest numerical decrease in mean PDS scores. The following table illustrates the changes in PDS scores in the treatment groups and the significant pair-wise comparisons.

Table 6.7 Change in PDS Score				
Variable	**Treatment Group**			
	——— *50%* *N=67*	——— *100%* *N=67*	——— *133%* *N=69*	*MS Contin 100%* *N=69*
Change in PDS score Mean ± s.e.m.	21.94 ± 4.35	8.97 ± 3.07	3.30 ± 3.27	-0.48 ± 2.27
Overall p value	<0.001			
Linear Trend for Dose Response	<0.001			
Significant Pair-wise Comparisons	133% < 50% (p<0.001) 100% < 50% (p=0.008) MSC < 50% (p<0.001) MSC < 100% (p=0.016)			

From Sponsor's in-text Table 11.3.1-3, Vol. 2.55, pg. 44.

6.1.1.4.2 Secondary Efficacy Variables

Number and Adjusted Number of Daily Rescue Medication Doses Required During the 3-day Period From Days 5-7[5]

In the Full Analysis population, there were significant overall changes in number and adjusted number of rescue medication doses ($p<0.001$ for both). The largest difference between any treatment groups in change in mean number of doses and mean change in adjusted number of doses was only approximately 1 dose per day. For change in both number of doses and adjusted number of doses, the increase was greatest in the [redacted] 50% group. The change in the number of doses was least in the [redacted] 133% group (with similar results from MS Contin 100%) while the change in adjusted number of doses was least in the MS Contin 100% (with similar results from [redacted] 133%). The results of the pair-wise comparisons were comparable for both measurements. The 50% [redacted] group required statistically significantly more doses and adjusted doses than each of the other three treatment groups. There were no significant differences in comparisons between MS Contin 100% and [redacted] 133% or [redacted] 100%, nor between [redacted] 100% and [redacted] 133% for either variable. The linear trend for dose responsiveness was statistically significant ($p < 0.001$). The following table illustrates these result.

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[5] Adjusted number of rescue medication doses is defined as total daily dose of rescue medication divided by average dose at baseline; this secondary efficacy variable did not appear in the initial protocol or amendments.

Table 6.8 Change in Number and Adjusted Number of Rescue Medication Doses				
Number of Doses	**Treatment Group**			
	---------- *50%*	———— *100%*	———— *133%*	*MS Contin 100%*
	N=67	*N=67*	*N=69*	*N=69*
Variable				
Change in # Mean ± s.e.m.	1.40 ± 0.22	0.76 ± 0.18	0.40 ± 0.17	0.45 ± 0.16
Overall p value	<0.001			
Linear Trend for Dose Response	<0.001			
Significant Pair-wise Comparisons	133% < 50% (p<0.001) 100% < 50% (p=0.014) MSC < 50% (p<0.001)			
Adjusted Number of Doses	**Treatment Group**			
	———— *50%*	———— *100%*	———— *133%*	*MS Contin 100%*
	N=67	*N=67*	*N=69*	*N=69*
Variable				
Change in Adjusted # Mean ± s.e.m.	1.46 ± 0.22	0.89 ± 0.19	0.51 ± 0.18	0.49 ± 0.16
Overall p value	<0.001			
Linear Trend for Dose Response	<0.001			
Significant Pair-wise Comparisons	133% < 50% (p<0.001) 100% < 50% (p=0.036) MSC < 50% (p<0.001)			

From Sponsor's in-text Table 11.3.1-5, Vol. 2.55, pg. 48.

Change in Quality of Sleep Score

The mean change in quality of sleep score was overall statistically significant (p<0.001) with the greatest increase in the ———— 50% group and the no mean change in the MS Contin 100% group. ———— 100%, ———— 133%, and MS Contin 100% had statistically significantly smaller changes compared with ---------- 50% (p<0.001, all three). The difference in scores between MS Contin 100% and ———— 100%, MS Contin and ———— 133%, and between ———— 133% and ———— 100% did not reach statistical significance (p=0.140, 0.517, and 0.402 respectively). The linear trend for dose responsiveness was statistically significant (p < 0.001). The following table illustrates these results.

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Table 6.9 Change in Quality of Sleep Score				
Variable	**Treatment Group**			
	——— *50%* *N=67*	- - - - *100%* *N=67*	——— *133%* *N=69*	*MS Contin 100%* *N=69*
Change in QOS score Mean ± s.e.m.	1.26 ± 0.20	0.29 ± 0.16	0.10 ± 0.21	-0.00 ± 0.17
Overall p value	<0.001			
Linear Trend for Dose Response	<0.001			
Significant Pair-wise Comparisons	100% < 50% (p<0.001) 133% < 50% (p<0.001) MSC < 50% (p<0.001)			

From Sponsor's in-text Table 11.3.1-6, Vol. 2.55, pg. 50.

Rate of drop out Due to Lack of Efficacy

Only four randomized patients (1.5%) were discontinued due to lack of efficacy. Three of these patients were in the ——— 50% group and one was in the - - - - ———133% group.

Amount of Rescue Medication Dose (mg) Required per Day[6]

In the Full Analysis population, there was an overall statistically significant difference (p=0.03) among treatment groups in the amount of rescue medication used per day. The following table presents these results. Patients in the ———50% group used the greatest amount while patients in the ———133% group used the least. As can be seen, the differences in mean amount of rescue medication used differed by only 5.5 mg between the ——— 133% and ———50% groups and by 3.7 mg between the MS Contin 100% and the ——— 50% groups. These differences reached statistical significance (p=0.003 and p<0.045 respectively). No other comparison reached statistical significance. The linear contrast statement to assess dose response was significant with p=0.004.

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[6] This secondary efficacy measure did not appear in the original protocol or its attached amendments but was added to the final study report.

Table 6.10 Amount of Rescue Medication (mg)				
Variable	Treatment Group 50% N=67	100% N=67	133% N=69	MS Contin 100% N=69
Amount of Rescue Med Mean ± s.e.m.	28.38 ± 4.36	25.92 ± 3.49	22.74 ± 3.15	24.79 ± 4.84
Overall p value	0.03			
Linear Trend for Dose Response	0.004			
Significant Pair-wise Comparisons	133% < 50% (p=0.003) MSC < 50% (p<0.045)			

From Sponsor's in-text Table 11.3.1-4, Vol. 2.55, pg. 46.

6.1.1.4.3 Subgroup Analyses

Age

For patients <65 years of age, there were statistically significant differences in amount of rescue medication between 133% and 50% (p=0.004), and between MS Contin 100% and 50% (p=0.031). For change in VAS score and change in PDS score, there were statistically significant differences between 133% and 50 % (p<0.001, both), MS Contin 100% and 50% (p<0.001, both), 100% vs. 50% (p=0.040 and 0.010, respectively) and MS Contin vs. 100% (p=0.016 and 0.011, respectively).

Same as over-all

Subgroup analyses for change in rescue medication, change in VAS pain intensity score, and change in PDS score for patients ages 65-74 years and patients aged ≥ 75 years did not demonstrate any statistically significant between treatment group comparisons. However, the number of patients in the treatment groups ranged from three to eight for the 65-74 year old group and from four to five for the ≥ 75 year old group (Appendix 7, ISE, Table 02-1.1, Vol. 2.108).

Gender

Subgroup analyses for change in rescue medication and for change in VAS pain intensity score, in male patients, both revealed statistically significant findings between 133% and 50% (p=0.016 and 0.013, respectively). For change in PDS score, there were statistically significant differences in comparisons of 133% and 50% and between MS Contin 100% and 50% (p=0.002 and 0.009, respectively). The lack of statistically significant findings for the other between group comparisons likely represents a loss of statistical power, limiting the value of these analyses and any subsequent interpretations.

In female patients, there were no statistically significant between group comparisons for change in rescue medication. There was less of a difference in mean change in rescue medication between 133% and 50%, 4.33 mg, compared to the

male patients, in which the difference was 11.77 mg. There is no apparent explanation for this difference in between group rescue medication differences based on gender.

For changes in VAS pain intensity score and change in PDS score the analyses in the female patients revealed statistically significant differences between [redacted] 133% and [redacted] 50%, [redacted] 100% and [redacted] 50%, and between MS Contin 100% and [redacted] 50% (p=0.024, 0.026 and <0.001 for VAS score and p=0.008, 0.051 and <0.001 for PDS score). There were also statistically significant differences between MS Contin 100% and [redacted] 100% (p=0.010 for VAS score, p=0.012 PDS score) and between MS Contin 100% and [redacted] 133%, (0.012 for VAS score) all favoring the MS Contin.

The differences in analyses between the two genders may reflect different approaches in how women and men address chronic pain. Overall, the results are not sufficiently different from the total group analyses to warrant further interpretation.

Race

Too few patients were non-Caucasian for meaningful subgroup analyses. There were 19 Hispanic patients, 11 African American patients, one Asian patient, and two patients classified as Other.

Table 6.11
Subgroup Analyses, Pair-Wise Comparisons with p-value ≤0.5

	Subgroup Category				
Outcome measure	<65 years	65-74 years	≥75 years	Female	Male
	N=236	N=18	N=17	N=149	N=123
Change in rescue medication	133[a] vs. 50[b] MSC[c] vs. 50	none[d]	none	none	133 vs. 50
Change in VAS score	133 vs. 50 MSC vs. 50 100[c] vs. 50 MSC vs. 100	none	none	133 vs. 50 100 vs. 50 MSC vs. 50 MSC vs. 100 MSC vs. 133	133 vs. 50
Change in PDS score	133 vs. 50 MSC vs. 50 100 vs. 50 MSC vs. 100	none	none	133 vs. 50 100 vs. 50 MSC vs. 50 MSC vs. 100	133 vs. 50 MSC vs. 50

a. 133 = [redacted] 133% treatment group
b. 50 = [redacted] 50% treatment group
c. MSC = MS Contin 100% treatment group
d. 100 = [redacted] 100% treatment group

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6.1.2 Study TRG004-04: A Double-Blind, Placebo Controlled, Parallel Group Comparison of the Efficacy and Safety of [redacted], MS Contin, and Placebo With an Open Label Extension in the Treatment of Osteoarthritis of the Knee and/or Hip

6.1.2.1 Summary of Findings

This study was a double-blind trial in which patients with moderate to severe osteoarthritis (O/A) of the knee or hip. Patients were randomized into one of four treatment groups: 1) [redacted] 30mg qam, 2) [redacted] 30mg qpm, 3) MS Contin 15mg bid, and 4) placebo. The randomization period lasted for a total of four weeks. The sponsor chose change in WOMAC Index Pain Subscale Score (a compilation of five, 100 mm VAS scales, see Appendix G) and Overall Arthritis Pain Intensity VAS Score (100 mm scale, see Appendix H) as primary efficacy variables.

Change in WOMAC Osteoarthritis Index Pain Subscale Score (See Tables 6.14, 6.15)

Using the change in the WOMAC O/A Pain Subscale, all four treatment arms demonstrated a reduction in pain intensity at Week 1 that increased through Week 3 and persisted to Week 4. The differences between the [redacted] and MS Contin groups compared with placebo demonstrated statistically significantly greater pain reduction at Weeks 1 and 2, for all three active treatments and at Week 3 for the two [redacted] groups. At Week 4, only the [redacted] qam group remained statistically significantly different from placebo. This appears to be related to slight fluctuations in the mean scores in the setting of a relatively robust placebo effect which persists at Week 4. Evaluation of percent change from baseline was also performed and the results were similar to those above.

Overall Arthritis Pain Intensity VAS Score (See Table 6.16)

There were modest improvements in Overall Arthritis Pain Intensity VAS scores for all treatment groups. The smallest improvements were for the placebo group, the largest for the [redacted] qam group. This improvement increased slightly over the 4 week period for the placebo group, and increased to a lesser extent for the two [redacted] groups. Both [redacted] qam and MS Contin demonstrated statistically significantly greater improvement compared with placebo for both absolute change and percent change at Week 1. Only the [redacted] qam group demonstrated statistically significantly differences in comparison with the placebo group for Weeks 2 and 3. The [redacted] qpm group was not statistically significantly better than placebo at any of the measured time points for either analysis.

Post-hoc analyses of the WOMAC Osteoarthritis Index Pain Subscale and Overall Arthritis Pain Intensity VAS scores using difference in use of physical therapy or assistive devices as an additional factor in the analyses were performed by the sponsor. These results demonstrated an improved appearance of efficacy for all active treatment

groups in the results of the WOMAC Osteoarthritis Index Pain Subscale analysis, especially demonstrating persistence of effect that was statistically significantly greater than placebo for all 4 weeks. The results of this post-hoc analysis with the Overall Arthritis Pain Intensity VAS scores demonstrated little difference from the original analysis.

Secondary Efficacy Variables:

The analysis of the WOMAC OA Physical Function Subscale revealed that both of the [redacted] treatment groups were better than placebo for Weeks 1, 2, and 3. There were no consistent effects on sleep. Only [redacted] qpm was found to be statistically significantly better than placebo for patient and physician global assessments. While a greater number of patients receiving placebo withdrew due to lack of efficacy, there were no statistically significant differences.

Conclusion

Based on the outcome measures summarized above, [redacted] qam, [redacted] qpm and MS Contin were superior to placebo in the management of pain associated with osteoarthritis. The effects remained statistically significant for all three treatments for 2 weeks, for the two [redacted] treatments for 3 weeks and just for the [redacted] qam group through week 4 according to the analysis of the WOMAC OA Index Pain Subscale. The results were less robust for the Overall Arthritis Pain Intensity VAS score with only [redacted] qam and MS Contin showing statistically significant improvements compared to placebo at Week 1, and only [redacted] qam continuing to demonstrate statistically significant improvements through Week 3. There was general support for efficacy of [redacted] from the secondary efficacy variables. These findings suggest that [redacted] qam may be somewhat more effective than [redacted] qpm, and may be somewhat more effective than MS Contin, but it is important to recognize that none of the comparisons between active treatment groups demonstrated any statistically significant differences.

These results are difficult to interpret. The sponsor offers the baseline differences in use of physical therapy or assistive devices between treatment groups as a possible influencing factor. When added to the analysis, the statistically significant findings are more sustained for the two [redacted] and MS Contin treatment groups for the WOMAC OA Index Pain Subscale. This post-hoc analysis did not, however, alter the results for the Overall Arthritis Pain Intensity VAS.

The loss of statistical significance for the analyses of results from the later time points may reflect the robust placebo effect, rather than a loss of efficacy of the active treatments or the development of tolerance as these scores were either stable or improved over time. Another possibility is that the underlying disorder, osteoarthritis, is not a pain model with a constant level of pain over time and as such, the improvement in pain scores reflects the natural fluctuations of the condition. If enough patients with a flair of symptoms resulting in adequate pain to enroll in study experienced a reduction of pain

because of the natural history of the osteoarthritis, the results could show a trend for improvement in pain symptoms regardless of therapy, as occurred in the placebo group. This would also be consistent with the finding that the number of patients dropping out due to a lack of efficacy was not statistically significantly different between the active and placebo treatment groups.

6.1.2.2 Study Plan

This study was a multi-center, randomized, double-blind, double-dummy, parallel-group trial study of [redacted] and MS Contin in patients with moderate to severe pain due to osteoarthritis of the knee and/or hip. The study consisted of two periods. During the 2 to 7 day washout phase, all analgesic use was to be discontinued until pain in the index joint was assessed to be ≥40 mm on a visual analog scale. Patients were then to be randomized to receive [redacted] qAM or qPM, MS Contin bid, or placebo. The trial was to be continued for a period of 4 weeks during which time pain relief and safety data were collected.

6.1.2.2.1 Population, Design, and Objectives

Male or female patients 40 years of age and older with osteoarthritis as defined by pre-set criteria, in good health, and with a pain intensity in the index joint of ≥40 mm on a 100 mm Visual Analog Scale (VAS) at baseline were to be enrolled in this study. The patients were to be considered ineligible if they were unable to discontinue NSAIDs and other analgesics during the washout period and throughout the double-blind period, if they had any inflammatory condition contributing to their pain, or if surgical intervention was anticipated within 6 months of screening. The design called for the enrollment of a minimum of 60 patients per treatment arm and a minimum of 240 patients completing the double-blind phase.

The primary objective of the study was to:

- Compare the analgesic efficacy of [redacted] 30mg qam and [redacted] 30mg qpm with placebo in patients with moderate to severe pain due to osteoarthritis

The secondary objectives of the study were to:

- Compare the analgesic efficacy of [redacted] 30mg qam with [redacted] 30mg qpm
- Compare the analgesic efficacy of [redacted] 30mg qam and [redacted] 30mg qpm with MS Contin 15mg q12h.

6.1.2.2.2 Treatment Summary

Washout Phase:

After initial screening, patients were to have begun the washout period in which they were not to take any analgesics (other than [redacted] for 2 to 7 days. An index joint was to have been designated and was to have been used for all subsequent efficacy measurements. Patients were to have continued in the washout phase until pain in the

index joint was ≥40 mm on the VAS scale. If pain did not reach this level, patients were not to have been admitted to the double-blind phase.

Double-Blind Phase

This phase was to have begun with the first dose of study medication and continued for four weeks or until early termination. Patients were to have been randomized into one of four treatment groups:

- Group 1 – [redacted] 30mg qam
- Group 2 [redacted] 30mg qpm
- Group 3 – MS Contin 15mg bid
- Group 4 – Placebo bid

Medications were to have been administered in a double-blind, double-dummy fashion. No dose adjustments were to have been allowed and no rescue medications were to have been provided. The WOMAC Osteoarthritis Index, an Overall Arthritis Pain Intensity VAS, the Physician's and Patient's Global Assessment of Arthritis, Nausea VAS, Drowsiness VAS, a Sleep Questionnaire and the SF-36 Health Survey were to have been completed at screening, baseline and weekly for 4 weeks. This phase of the study was to have continued for a period of 4 weeks at which time patients were to be offered the option to participate in an open-label extension trial of 30mg [redacted] qam or qpm.

6.1.2.2.3 Assessments

According to the protocol, the following assessments were to have been considered primary efficacy measures:

- WOMAC Osteoarthritis Index Pain Subscale Score (See Appendix G)
- Overall Arthritis Pain Intensity VAS Score (See Appendix H)

The following assessments were to have been considered secondary efficacy measures:

- WOMAC Osteoarthritis Index Stiffness Subscale Score (100 mm VAS) (See Appendix G)
- WOMAC Osteoarthritis Index Physical Function Subscale Score (100 mm VAS) (See Appendix G)
- WOMAC Osteoarthritis Composite Index
- Patient's Global Assessment of Osteoarthritis (100 mm VAS, See Appendix I)
- Physician's Global Assessment of Osteoarthritis (100 mm VAS, See Appendix I)
- Incidence of patient withdrawal due to lack of osteoarthritis efficacy
- Impact of pain on sleep (See Appendix J)
- SF-36 Health Survey (Standard Quality of Life Questionnaire)

6.1.2.2.4 Analysis Plan

The sponsor defined three populations for the study:

- Full Analysis Set - those who were randomized to a treatment and took at least one dose of the blinded study medication

- Efficacy Evaluable Population - those who had efficacy data recorded at both baseline and Week 1, or who had baseline information and dropped out before Week 1 due to treatment failure (but not for other reasons)
- Safety Population - those who were randomized and took at least one dose of blinded study medication

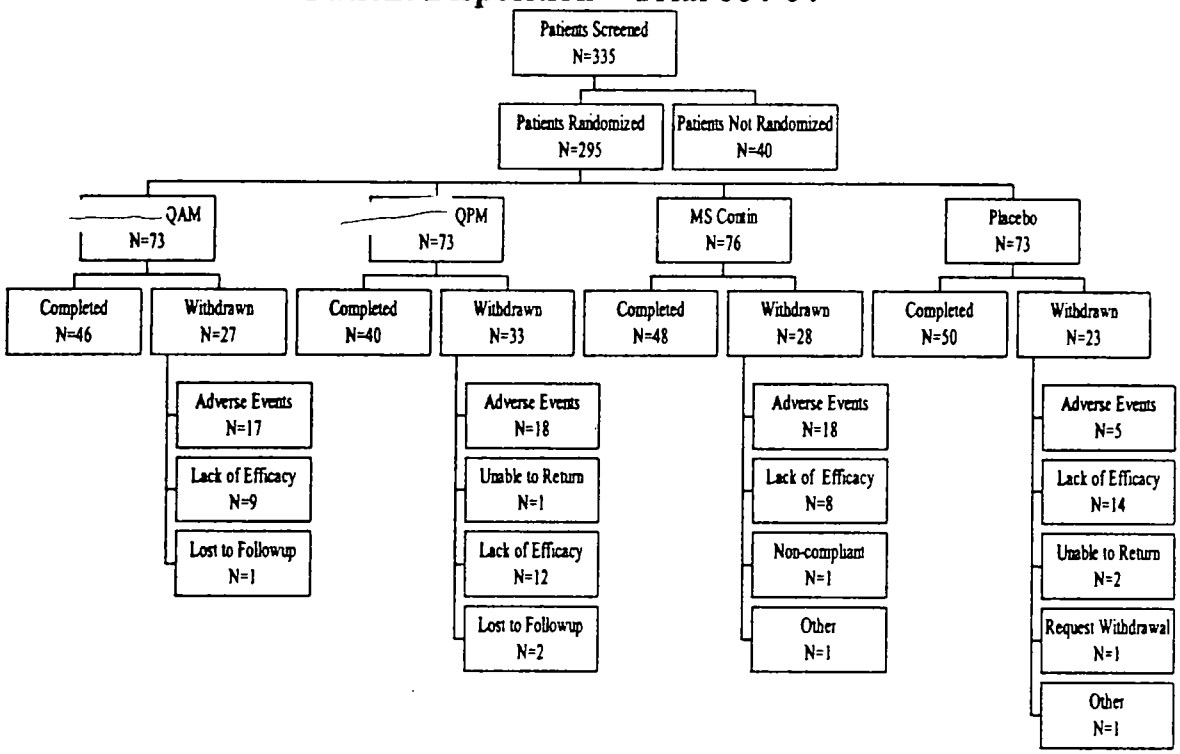
All baseline information was to have been analyzed by Chi-square, Kruskal-Wallis non-parametric analyses or one-way ANOVA to assess degree of balance among randomized treatment groups. The LOCF (last observation carried forward) approach was to have been used for any week during the double-blind period in which efficacy data was missing. Mean of absolute and relative change from baseline to weeks in the double-blind phase was to have been analyzed using a linear model and pair-wise comparisons. The number of days from first dose to withdrawal due to treatment failure was to have been compared among treatment groups using the log-rank test and the rates of withdrawal were to have been compared using the Chi-square or Fisher's Exact test.

6.1.2.3 Study Outcome

6.1.2.3.1 Patient Disposition

A total of 335 patients were screened for the study and 295 of these were randomized into one of the four groups. One hundred eighty-four patients completed the double-blind portion of the study and 111 discontinued prematurely. Most of the patients who did not complete the study experienced either an adverse event (58/111 52%) or withdrew due to lack of efficacy (43/111 38%). Disposition of all screened patients is depicted in the following diagram.

Patient Disposition – Trial 004-04



The most common adverse events leading to withdrawal from the trial and exclusion from the efficacy evaluable population were nausea, vomiting, somnolence, and dizziness. The following table further delineates the reasons for withdrawal that were identified by the investigators.

Table 6.12
Discontinued Patients

Population	Treatment Group				
	Placebo	*MS Contin BID*	*QAM*	*QPM*	*Overall*
Number randomized	73	76	73	73	295
Number completing trial	50	48	46	43	184
Number discontinuing trial	23	28	27	33	111
Reason for discontinuation					
Adverse events	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-compliance	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

From Sponsor's information, Vol. 2.72, pg. 41.

Several patients randomized to study drug, were admitted to the study in violation of the inclusion/exclusion criteria as follows:

- #10S09 (——— qam) – incorrect index joint assessed during the study (left knee rather than right knee)
- #16S04 ——— qam) – index joint was prosthetic
- #16S16 (Placebo) – index joint was prosthetic
- #36S14 (MS Contin) – index joint was prosthetic
- 18S13 ——— qpm) – creatinine 1.9 mg/dL at screening
- #18S09 (MS Contin) – received prednisone one month prior to study entry and continued receiving during study
- #32S11 ——— qpm) - received prednisone one month prior to study entry and continued receiving during study
- #23S34 (MS Contin) – Arthritis Pain Intensity VAS Score was 11 at screening
- #34S09 ——— qpm) - only 39 years old
- #38S06 ——— qam) – only 39 years old

There were also several randomized patients who were considered protocol deviations:

- #21S10 (MS Contin) – prematurely terminated from study for incorrect administration of study medication
- Five Placebo patients, eight MS Contin patients, four ——— qam patients, and six ——— qpm patients used prohibited ——— medications during the trial

6.1.2.3.2 Demographics/Group Comparability

The number of randomized patients who received trial drug therapy is summarized by age, gender, ethnic origin, and osteoarthritis (OA) history in the following table. There were no statistically significant differences between treatment groups for age, gender, ethnic origin, or duration of disease. However, more than twice as many patients identified the knee rather than the hip as the index joint (p=0.02) in all treatment groups and the number of patients undergoing physical therapy or using assistive device was greater in the MS Contin and ——— qpm treatment groups (p=0.04).

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Table 6.13 Demographic Variables – Safety Population				
Variable	**Treatment Group**			
	Placebo *N = 73*	*MS Contin* *N = 76*	*QAM* *N = 73*	*QPM* *N = 73*
Age				
Mean ± SD	61.9 ± 10.68	61.9 ± 10.41	62.6 ± 9.51	63.1 ± 11.14
Range	41-83	42-87	39-82	39-84
Gender				
M/F	22/51	28/48	30/43	31/42
Ethnic Origin				
W/O	58/15	68/8	63/10	60/13
Duration of Disease (yrs)				
Mean ± SD	9.1 ± 7.24	10.5 ± 9.92	10.9 ± 8.92	10.7 ± 10.96
Range[a]	1-29	0-54	0-34	0-55
Index Joint				
Knee/Hip	56/17	64/12	51/22	46/27
Assistive Device and/or PT				
Yes/No	10/63	20/56	9/64	19/54

[a]Range starting at "0" means OA duration of <1 year
From Sponsor's in-text Table 11.1-1, Vol. 2.72, pg. 44; Table 5, Vol. 2.89, pp. 40-42.

All patients had a history of suboptimal responses with acetaminophen and/or NSAID treatment and 42% of the total population used intermittent opioid analgesic therapy. There were no statistically significant differences between treatment groups in baseline drowsiness and sleep assessments, baseline WOMAC OA Index Pain VAS Subscale scores and Overall Arthritis Pain Intensity VAS scores. A statistically significant difference (p=0.03) was observed in baseline nausea assessments with mean nausea VAS scores 7.38, 16.35, 14.66 and 14.52 in the ——— qpm, Placebo, MS Contin, and ——— qam groups, respectively. A number of patients took over-the-counter and/or prescription medications. The most common medications among all patients were antihypertensives (58%), antidepressants (23%), aspirin (16%), antihistamines (12%), and proton pump inhibitors (11%).

6.1.2.3.3 Unplanned Analyses

Because there was a statistically significant difference in the baseline demographics of the treatment groups with respect to undergoing physical therapy or utilizing assistive devices, the sponsor performed additional primary efficacy assessments to account for this variable.

6.1.2.4 Sponsor's Efficacy Results

For each of the stated variables, efficacy was calculated as a change or percent change from baseline. For most of the efficacy parameters, the ———groups were associated with larger change or percent change from baseline than was the placebo group.

6.1.2.4.1 Primary Efficacy Variables

WOMAC Osteoarthritis Index Pain Subscale Score

In the Full Analysis population, the reduction in pain intensity at Week 1 was statistically significantly greater in the [redacted] qam [redacted] qpm, and MS Contin groups than in the placebo group (p=0.009, 0.017, and 0.005). This reduction in pain intensity continued throughout the four-week course of the study. During Week 2, the change from baseline in all three active treatment groups remained statistically significantly greater compared with placebo, and this was also the case at Week 3 for the two [redacted] groups. At Week 4, in spite of sustained improvement in scores, there were no comparisons with placebo that were statistically significant. This appears to be related to slight fluctuations in the mean scores in the setting of a relative robust placebo effect persisting at Week 4. Evaluation of percent change from baseline was also performed and the results were similar to those above. The following table illustrates the changes in pain intensity in the treatment groups and any significant pair-wise comparisons.

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Table 6.14
Change and %Change from Baseline
WOMAC OA Index Pain VAS Subscale Scores

Variable	Treatment Group			
	Placebo N=73	*MS Contin* N=76	*QAM* N=73	*QPM* N=73
Change from Baseline				
Week 1				
Mean ± S.D. (mg)	-12.46±11.64	-61.70±12.70	-56.34±13.97	-56.23±11.68
Overall p value			0.017	
Significant pair wise comparisons			Mam>P (p=0.009) Mpm>P (p=0.017) MSC>P (p=0.005)	
Week 2				
Mean ± S.D. (mg)	-26.93±11.92	-63.43±12.72	-68.70±13.99	-67.34±13.29
Overall p value			0.068	
Significant pair wise comparisons			Mam>P (p=0.017) Mpm>P (p=0.035) MSC>P (p=0.048)	
Week 3				
Mean ± S.D. (mg)	-30.01±13.62	-64.91±12.85	-76.67±13.48	-73.67±14.13
Overall p value			0.054	
Significant pair wise comparisons			Mam>P (p=0.011) Mpm>P (p=0.028)	
Week 4				
Mean ± S.D. (mg)	-34.26±13.05	-65.33±12.64	-74.33±13.04	-71.21±14.05
Overall p value			0.115	
Significant pair wise comparisons			Mam>P (p=0.024)	
	Placebo N=73	*MS Contin* N=76	*QAM* N=73	*QPM* N=73
% Change from Baseline				
Week 1				
Mean ± S.D. (mg)	1.6±5.49	-16.1±4.19	-12.1±5.32	-18.0±3.72
Overall p value			0.017	
Significant pair wise comparisons			Mam>P (p=0.032) Mpm>P (p=0.005) MSC>P (p=0.008)	
Week 2				
Mean ± S.D. (mg)	-4.0±5.34	-18.4±4.24	-15.2±5.79	-21.0±4.0
Overall p value			0.084	
Significant pair wise comparisons			Mpm>P (p=0.018) MSC>P (p=0.039)	
Week 3				
Mean ± S.D. (mg)	-6.3±5.58	-19.64±4.21	-19.3±5.48	-23.1±4.33
Overall p value			0.090	
Significant pair wise comparisons			Mpm>P (p=0.019)	
Week 4				
Mean ± S.D. (mg)	-8.1±5.34	-19.4±4.18	-19.6±5.38	-21.4±4.18
Overall p value			0.204	
Significant pair wise comparisons			none	

Mam=Morphelan qam, Mpm=Morphelan qpm, MSC= MS Contin, P=Placebo
From Sponsor's in-text Tables 11.3.1.1-1 and 11.3.1.1-2, Vol. 2.72, pg. 49.

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A post-hoc analysis of this primary efficacy measurement was performed using the baseline difference in use of physical therapy or assistive devices as a factor in the analysis. As reported earlier, the number of patients undergoing physical therapy or using assistive device was greater in the MS Contin and ——— qpm treatment groups compared to the other two groups.

As demonstrated in the Table 6.15, the change in pain intensity from baseline was statistically significantly greater for the MS Contin and both ——— groups compared to Placebo for Weeks 1, 2 and 3, and for both ——— groups for Week 4. There were no statistically significant treatment differences between administration of ——— vs. MS Contin at any study week nor between the two regimens of ——— administration. The sponsor concludes that, when the analysis is controlled for this demographic difference, the overall treatment effects become more obvious.

Table 6.15
Change from Baseline WOMAC OA Index Pain VAS Subscale Scores
Assistive Devices Added as Factor

Variable	Treatment Group		
	MS Contin	——— QAM	——— QPM
	N=76	N=73	N=73
Change from Baseline	p-Value From Comparison With Placebo		
Week 1	0.004	0.009	0.013
Week 2	0.029	0.017	0.021
Week 3	0.051	0.012	0.020
Week 4	0.068	0.025	0.039

From sponsor's in-text Table 11.3.1.1-4

Overall Arthritis Pain Intensity VAS Score

In the Full Analysis population, there was an overall statistically significant treatment effect in change from baseline at Week 1 (p=0.042) and a trend toward significance at Week 3 (p=0.072). There were modest improvement sin VAS score for all treatment groups. The smallest improvements were for the placebo group, the largest for the ——— qam group. This improvement increased slightly over the 4 week period for the placebo group, and to a lesser extent, the two ——— groups. In the statistical analyses of the Overall Arthritis Pain Intensity VAS Score, the ——— qam group was statistically significantly better than placebo at Weeks 1, 2 , and 3 for both the absolute change in score (p=0.006, 0.042, and p=0.010) and the percent change (P=0.010, 0.031, and 0.007). The ——— qpm group was not statistically significantly better than placebo at any of the measured time points for either analysis. The MS Contin group demonstrated statistically significant improvement over placebo in Week 1 for the absolute change and percent change (p=0.036 and 0.035 respectively) but not for Weeks 2 through 4. These results are presented in Table 6.16.

Table 6.16
Change and %Change from Baseline
Overall Arthritis Pain Intensity VAS Score

Variable	Treatment Group			
	Placebo N=73	*MS Contin* N=76	*QAM* N=73	*QPM* N=73
Change from Baseline				
Week 1				
Mean ± S.D.	-7.96±2.72	-16.30±2.73	-18.30±3.06	-15.64±2.71
Overall p value			0.042	
Significant pair wise comparisons			Mam>P (p=0.006) MSC>P (p=0.036)	
Week 2				
Mean ± S.D.	-10.92±2.97	-17.67±2.89	-18.55±2.88	-16.38±2.64
Overall p value			0.196	
Significant pair wise comparisons			Mam>P (p=0.042)	
Week 3				
Mean ± S.D.	-12.19±3.27	-19.72±2.93	-22.92±2.98	-19.93±3.09
Overall p value			0.072	
Significant pair wise comparisons			Mam>P (p=0.010)	
Week 4				
Mean ± S.D.	-13.65±3.21	-17.67±2.94	-19.66±2.82	-18.32±3.13
Overall p value			0.486	
Significant pair wise comparisons			None	
	Placebo N=73	*MS Contin* N=76	*QAM* N=73	*QPM* N=73
% Change from Baseline				
Week 1				
Mean ± S.D.	-9.3±3.77	-20.6±3.59	-23.0±3.96	-19.80±3.69
Overall p value			0.053	
Significant pair wise comparisons			Mam>P (p=0.010) MSC>P (p=0.035)	
Week 2				
Mean ± S.D.	-12.6±3.90	-22.6±3.79	-24.1±3.96	-20.6±3.45
Overall p value			0.139	
Significant pair wise comparisons			Mam>P (p=0.031)	
Week 3				
Mean ± S.D.	-14.4±4.37	-25.1±3.83	-30.1±3.98	-25.2±4.17
Overall p value			0.052	
Significant pair wise comparisons			Mam>P (p=0.007)	
Week 4				
Mean ± S.D.	-16.7±4.38	-21.9±3.75	-26.1±3.99	-22.5±4.02
Overall p value			0.418	
Significant pair wise comparisons			None	

Mam=Morphelan qam, Mpm=Morphelan qpm, MSC= MS Contin, P=Placebo
From Sponsor's in-text Tables 11.3.1.3-1 and 11.3.1.3-2, Vol. 2.72, pg. 60.

A post-hoc analysis of the change in Overall Arthritis Pain Intensity VAS score was also performed using as an additional factor, patients undergoing physical therapy or using assistive devices. The qam group was significantly better than placebo for Weeks 1-3 but not Week 4 (p=0.007, 0.43, 0.010 and 0.130). The qpm and MS Contin groups were significantly better than placebo at Week 1 only (p=0.047 and p=0.027 respectively). The placebo group also exhibited an improvement in this variable during Weeks 2 through 4. The sponsor concludes that this unexpected placebo response confounds the significant treatment effects between the morphine groups and

that, when the analysis is controlled for this baseline difference (patients undergoing physical therapy or using assistive devices), the overall treatment effects are no different than those exhibited in the uncontrolled analysis.

The sponsor performed additional post-hoc analyses on both primary efficacy variables in an attempt to account for the placebo response seen in Weeks 2 through 4.

Repeated Measures ANCOVA using observed and LOCF data
(Fixed factors – treatment, Week; Covariate – baseline)

1. WOMAC OA Index Pain VAS scores
   - Statistically significant overall treatment effect (p=.047)
   - Statistically significant in reducing pain compared with placebo - [redacted] qam (p=.017), [redacted] qpm (p=0.015), MS Contin (p=0.45)
   - No treatment by time interaction
   - LOCF analysis consistent with these findings

2. Overall Arthritis Pain Intensity VAS Scores
   - No statistically significant overall treatment effects
   - Similar results for both observed and LOCF data

ANCOVA on primary efficacy measures
(Combined [redacted] qam and qpm scores)

1. WOMAC OA Index Pain VAS scores
   - Statistically significant overall treatment effect (change from baseline) at Weeks 1 (p=0.004), 2 (p=0.029), and 3 (p=0.006)
   - Combined [redacted] statistically significantly better at reducing pain than placebo for all 4 weeks (p=0.004, p=0.009, p=0.006, p=0.017)
   - MS Contin was statistically significantly better than placebo for Weeks 1 and 2 (p=0.005, p=0.048)

2. Overall Arthritis Pain Intensity VAS Scores
   - Statistically significant overall treatment effect (change from baseline) at Weeks 1 (p=0.024) and 3 (p=0.044)
   - Statistically significant overall treatment effect (percent change from baseline) at Weeks 1 (p=0.027) and 3 (p=0.031)
   - Combined [redacted] statistically significantly better at reducing pain than placebo for Week 1 (p=0.010) and Week 3 (p=0.036)

6.1.2.4.2 Secondary Efficacy Variables

WOMAC OA Index Physical Function Subscale, WOMAC OA Composite Index

For the WOMAC OA Index Physical Function Subscale, there were no statistically significant overall treatment effects in change from baseline for any of 4 weeks of the study. Both [redacted] treatment groups were significantly better than placebo in the increase of physical function for Weeks 1, 2, and 3 ([redacted] qam: p=0.016, p=0.027, p=0.021; [redacted] qpm: p=0.045, p=0.038, p=0.035)[7]. There were no statistically significant findings in the percent change from baseline.

For the WOMAC OA Composite Index there were no statistically significant findings in change from baseline for overall treatment effects or for individual comparisons. In the percent change from baseline analysis, the only findings were that [redacted] qpm was statistically significantly better than placebo in increasing physical function during Weeks 1 through 3 (p=0.020, p=0.021, p=0.026)[8].

Patient and Physician Global Assessments of Arthritis

No statistically significant effects in either change from baseline or percent change from baseline were noted for overall treatment or for any group comparisons.[9]

Sleep Questionnaire

Several parameters were examined to assess the effect of treatment on sleep:

- Trouble falling asleep – statistically significant overall treatment effects were seen in Week 3 (p=0.005) although there was a trend towards significance in the other weeks. [redacted] qam was significantly better than placebo in all four weeks of the study. Although not statistically significant, when analyzing the difference in means, both [redacted] qam and qpm groups exhibited more trouble falling asleep than placebo between Weeks 3 and 4.[10]
- Need for sleep medication – statistically significant overall treatment effects were seen in Weeks 1, 3, and 4 (p=0.021, p=0.033, p=0.029). However, only [redacted] qpm showed statistically significant results compared with placebo (for weeks 1-4)[11].
- Overall quality of sleep – statistically significant overall treatment effects were seen in Weeks 1, 2, and 4. [redacted] qam and qpm showed statistically significant results compared with placebo for Weeks 1, 2, and 4.[12]
- Number of hours of sleep each night – no statistically significant overall treatment effects for any week of the study. Only [redacted] qam showed statistically significant results compared with placebo for Weeks 1, 2, and 4.[13]

Withdrawal Due to Lack of Efficacy

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[7] From Sponsor's Statistical Table 14.1a, Vol. 2.89, pg. 154.
[8] From Sponsor's Statistical Table 15.2a, Vol. 2.89, pg. 172.
[9] From Sponsor's Statistical Tables 16.1a, 16.2a, 17.1a, 17.1b, Vol. 2.89, pp. 175, 178, 193, 196.
[10] From Sponsor's Statistical Table 18a, Vol. 2.89, pp. 201-202.
[11] From Sponsor's Statistical Table 19a, Vol. 2.89, pp. 208-209.
[12] From Sponsor's Statistical Table 22a, Vol. 2.89, pp. 225-228.
[13] From Sponsor's Statistical Table 23a, Vol. 2.89, pp. 231-233.

There were a slightly greater number of placebo patients who withdrew due to lack of efficacy than in the other treatment groups. However, there were no statistically significant differences between groups in either the rate or the time to dropout.[14]

6.1.2.4.3 Subgroup Analyses

Age

For patients aged <65 years old, an analysis of the change in WOMAC O/A Pain Subscale scores found that [redacted] qpm was statistically significantly different from placebo at all 4 weeks (p=0.019, 0.014, 0.013 and 0.037). No other between treatment group comparisons were statistically significantly different. For the Overall O/A Pain Intensity score, the only statistically significant difference was found at Week 3 for the [redacted] qpm vs. placebo comparison (p=0.015).

For patients ages 65-74, the only statistically significant difference in change in WOMAC O/A Pain Subscale scores was between [redacted] qam and placebo (p=0.032) at Week 1. The placebo group scores for Weeks 2, 3 and 4 were considerably higher than Week 1 and the scores for patients <65 years old (Appendix 7, Table 04DB-1.1), Vol. 2.108). There were no statistically significant differences in the analyses of patients ages 65-74 for the Overall O/A Pain Intensity score.

For patients ≥75 years of age, MS Contin was statistically significantly better than placebo and [redacted] qpm for Weeks 2, 3 and 4 (p= 0.033, 0.009 and 0.003 vs. placebo and p=0.070, 0.011 and 0.009 vs. [redacted] qpm). The differences between the change in WOMAC O/A Pain Subscale scores between MS Contin and [redacted] qam were greater than the difference between MS Contin and [redacted] qpm, but did not reach statistical significance, possibly due to the small number of patients in the [redacted] qam group (n=7). The response measured by the WOMAC O/A Pain Subscale of patients ≥75 years old to MS Contin was considerably larger than the responses of the two younger age groups. For the Overall O/A Pain Intensity score, statistically significant differences occurred at Weeks 3 and 4 for the comparisons of MS Contin vs. placebo (0.003 and 0.042, respectively) and MS Contin vs. [redacted] qpm (p<0.001 andp=0.017, respectively), all favoring MS Contin.

Gender

Analyses by gender for the change in WOMAC O/A Pain Subscale scores found statistically significant differences between [redacted] qpm and placebo at Weeks 2, and 3 for the male patients (p=0.047 and 0.034, respectively). For female patients, there were statistically significant differences between both MS Contin and [redacted] qpm compared to placebo at Week 1 (p=0.022 and 0.039, respectively) and between [redacted] qam and placebo for Weeks 1, 2, 3, and 4 (p=0.013, 0.014, 0.006 and 0.021). The only statistically significant differences in analyses of the Overall O/A Pain Intensity score were for [redacted] qam vs. placebo in women at weeks 1 and 3 (p=0.007 and 0.010, respectively).

[14]From Sponsor's Statistical Table 25.1, Vol. 2.89, pg. 297.

Race
There were too few non-Caucasian patients for meaningful statistical comparisons.

The results of the subgroup analyses by age and gender are sufficiently inconsistent to warrant no further interpretation. The variability may reflect a fault of the small subgroup sizes, as the study was not planned with sufficient enrollment to power statistical evaluations of these subgroups.

Table 6.17
Subgroup Analyses, Pair-Wise Comparisons with p-value ≤0.5

	Subgroup Category				
Outcome measure	<65 years	65-74 years	≥75 years	Female	Male
TRG004-04	N=171	N=81	N=43	N=184	N=111
Change in WOMAC O/A Pain Subscale score	qpm[a] vs. pl[b] W[c]1, 2, 3, 4	qam[d] vs. pl W1	MSC[e] vs. pl W2, 3, 4 MSC vs. qpm W2, 3, 4,	qpm vs. pl W1 MSC vs. pl W1 qam vs. pl W1, 2, 3, 4	qpm vs. pl W2, 3
Overall O/A Pain Intensity score	qpm W3	none	MSC vs. pl W3, 4 MSC vs. qpm W3, 4	qam vs. pl W1, 3	none

a. qpm = ---- 30 mg qpm treatment group
b. pl = placebo treatment group
c. W = Study Week
d. qam = ———-30 mg qam treatment group
e. MSC = MS Contin 15 mg BID treatment group

The following two studies (TRG004-03 and TRG004-04) were open-label extension studies without a comparator and will be presented in an abbreviated format.

6.1.3 Study TRG004-03: A Multicenter, Non-Randomized, Open-Extension Study of ——— in Patients with Chronic, Moderate to Severe Pain Who Have Completed a Prior ——— Clinical Trial

6.1.3.1 Study Design, Population, and Outcome Measures

Patients who completed TRG004-01 (PK study), TRG004-02 (chronic pain trial), TRG004-05 (PK/PD study), or TRG004-06 (PK/PD study) were eligible for enrollment in this open-label, non-comparative study. Patients initially received ——— once a day at a dose closest to the 100% morphine equivalent daily dose that provided stable pain relief during the pre-randomization period of the double-blind studies. Patients without adequate pain relief or with unacceptable adverse events could have upward or downward dosage adjustments. Rescue medication use was also acceptable at a morphine equivalent equal to approximately 10% of the initial daily ——— dose. Safety and efficacy follow-up evaluations were performed every 30 days for one year.

Outcome measures for this study were:

- Pain relief – measured by the Brief Pain Inventory Short Form (scale from 1-10)
- Quality of life – measured by SF-36
- Daily [redacted] dose and number of rescue doses in 24 hours preceding each follow-up evaluation

6.1.3.2 Study Conduct

A total of 118 patients were enrolled in this study. At the time of data cut-off date, 76 patients (64%) were still ongoing. The remainder of the patients (42, 36%) were discontinued for a variety of reasons, the most common being adverse events, lack of efficacy, and request for withdrawal.

The sponsor reported that, for the efficacy variables analyzed, the 42 prematurely discontinued patients had small increases in their [redacted] dose over time. Analysis of all available data, including that from ongoing patients, demonstrated adequate pain control but a worsening of physical and mental state during the course of the trial. However, because 64% of the patients are still ongoing, the available data is not yet adequate to allow substantiation of the sponsor's conclusions.

6.1.4 Study TRG004-04OL: Open-Label, Double-Blind, Placebo Controlled, Parallel Group Comparison of the Efficacy and Safety of [redacted], MS Contin, and Placebo With an Open Label Extension in the Treatment of Osteoarthritis of the Knee and/or Hip

6.1.4.1 Study Design, Population, and Outcome Measures

Patients who completed the 4-week double-blind treatment period of Study TRG04-04 (osteoarthritis of knee or hip) could elect to enter an open-label extension. All patients were randomized to receive once daily [redacted] in the morning or the evening for 26 weeks, regardless of their randomized treatment program during the double-blind phase. The dosage could be increased to provide optimal pain relief with acceptable side effects. Treatment with [redacted] was discontinued at the end of week 30 (includes the 4-week double-blind trial). Efficacy and safety were evaluated at weeks 5, 8, 12, 18, 24, and 30 (after entry into the double-blind phase.

Outcome measures for this study were:

- Arthritis pain, stiffness, and physical function – measured by WOMAC Osteoarthritis Index VAS scales, Overall Arthritis Pain Intensity VAS Scale, physician and patient assessments
- Quality of life – measured by SF-36 and sleeping difficulty VAS Scale

6.1.4.2 Study Conduct

A total of 181 patients were enrolled in this study (95 in [redacted] qam and 86 in [redacted] qpm). At the time of data cut-off date (end of 120-day safety update period),

8 patients (4%) had completed the study and 122 patients (67%) were ongoing in the trial. The remainder of the patients (51, 28%) were discontinued for a variety of reasons, the most common being adverse events and lack of efficacy.

The sponsor reported that, for all efficacy variables analyzed, there were no differences in efficacy between the [redacted] qam and qpm groups and that patients in both groups remained stable throughout this open label extension. This efficacy information is summarized in the following table.

Table 6.16
Efficacy Results

Variable	Start (week 4)		Mid (week 18)		End (week 30)	
	[redacted]		[redacted]		[redacted]	
	am	*pm*	*am*	*pm*	*am*	*pm*
WOMAC						
Mean	1205.3	1293.4	864.9	874.5	1115.8	966.3
(S.D.)	(623.9)	(614.7)	(538.2)	(517.4)	(560.5)	(567.5)
Range	16-2384	61-2376	116-1707	257-1956	213-2084	188-2037
Arthritis Pain Scale						
Mean	57.3	56.3	38.9	38.1	52	51.1
(S.D.)	(28.5)	(28.3)	(27.6)	(23.8)	(27.1)	(25.1)
Range	1-100	3-100	2-78	6-81	10-89	20-92
Patient's Assessment						
Mean	51.3	52.0	34.9	41.2	52.7	49.9
(S.D.)	(28.6)	(25.9)	(19.8)	(20.4)	(24)	(18.8)
Range	0-100	5-100	2-62	9-83	10-90	32-93
Physician's Assessment						
Mean	46.5	49.4	36.7	33.9	50.4	38.4
(S.D.)	(26.9)	(24.3)	(20.8)	(19)	(22.8)	(15.4)
Range	1-93	6-92	2-63	8-77	9-82	12-65
Quality of Sleep						
Mean	47.8	52.8	53.2	56.9	50.9	59.7
(S.D.)	(26)	(26.9)	(25.1)	(27.1)	(23.5)	(16.8)
Range	0-100	0-100	3-94	0-98	2-79	42-92

From Sponsor's Vol. 2.105, Tables 6.4, 7, 8, 9, and 10.5, pp. 33-59.

As can be seen, the measurements of efficacy between the two groups are similar and this similarity remains relatively constant throughout the course of evaluation.

The following studies (TRG004-05, TRG004-06, and TRG004-01) were PK/PD trials with optional entry into trial TRG004-03OL. They will be presented in an abbreviated format.

6.1.5 TRG004-01: Optional entry into TRG004-03 after conclusion

6.1.5.1 Summary

This trial evaluated the pharmacokinetics of [redacted] in patients with chronic moderate to severe pain. Patients received both MS Contin bid and [redacted] qd in the same dose during two periods of study. Frequent blood samples were collected during both periods. This study demonstrated that one-daily administration of [redacted] results in extended

plasma morphine concentrations over 24 hours with lower peak to trough variation for ——— compared to MS Contin.

6.1.6 TRG004-06 and TRG004-05 : Optional entry into TRG004-03 after conclusion

6.1.6.1 Summary

These trials evaluated the pharmacokinetics and pharmacodynamics of ——— in patients with chronic moderate to severe pain of malignant and non-malignant origins. The two-period crossover design was used to establish a PK/PD relationship for once daily ——— and twice daily MS Contin. Frequent blood samples were collected from patients for PK analysis and patients recorded PD measures in a daily diary. Results supported a concentration-effect relationship that was established using VAS scores as the PD endpoint. This relationship was independent of formulation (——— or MS Contin).

7 INTEGRATED REVIEW OF SAFETY

7.1 Summary of Safety Findings

The profile of serious adverse events, discontinuations due to adverse events, and all observed adverse events is consistent with that found with other opioid formulations. There were three deaths in the double-blind trials, all of which were in the cancer population. There were thirteen deaths in the open label trial, all in the chronic use population and all but one in the cancer population.

Only one of the deaths (33%) in the double-blind trials was possibly related to the use of [redacted]. This 78 year old female patient with endometrial cancer developed bowel obstruction and subsequently died. Although this adverse event was most likely a result of metastatic disease, opioids do have a propensity to cause bowel obstruction due to slow intestinal motility. Therefore, it was not possible to exclude [redacted] as a contributing factor.

Four of the deaths (31%) in the open-label trials were possibly related to the use of [redacted]. Although all of these deaths may also be explained by a terminal result of a progressive malignant condition, it was not possible to exclude [redacted]-associated adverse events as contributory to demise.

Safety concerns for [redacted] focus upon the potential increase in typical opioid-related side effects. Information compiled from the submitted safety database gives no information suggesting a deviation from the expected safety profile. Nausea and vomiting, constipation, and somnolence were the most frequent adverse events causing discontinuation from both open-label and double-blind populations and are among the most common adverse events associated with opioid use.

Analysis of laboratory results and vital sign changes from both clinical trial patients and healthy volunteers revealed no trends toward abnormalities that could be attributed to the use of [redacted].

7.2 Adequacy of Exposure and Safety Assessment

A total of 866 subjects were exposed to [redacted] during clinical development, 405 of which were patients in the double-blind trials.[15] Sixty-seven percent (259/389) of these subjects were chronic opioid users. The following table and accompanying chart are a compilation of total [redacted] exposures over time for patients and healthy volunteers (reflecting both active and inactive populations up to the time of the 120-day safety cutoff date.

[15] The safety summary tables use a total of 389 subjects because of double-counting of 16 patients in cross-over trials.

Table 7.1 [redacted]: Exposures – Patients and Healthy Volunteers Active and Inactive Population					
Duration of Therapy (mos)	**Dose (mg)**				
	30-60	*61-200*	*201-400*	*> 400*	*Total*
0-0.5	373	197	87	39	696
0.5-1	170	151	79	35	435
1-2	145	145	77	34	401
2-3	116	131	66	32	345
3-4	103	120	61	29	313
4-5	93	109	57	27	286
5-6	87	103	55	24	269
6-7	61	84	38	20	203
7-8	25	58	24	12	119
8-9	6	39	19	12	76
9-10	3	31	14	11	59
10-11	3	27	12	9	51
11-12	2	17	8	8	35
>12	0	1	1	1	3

From Sponsor's Table 1, pg. 5, Fax 08/29/00.

The sponsor has also provided information on patients who are currently actively enrolled in the trial and had not concluded their course of treatment prior to June 7, 2000, the cutoff date for the safety update report. The following table and accompanying chart represent the actively enrolled patients as of August 9, 2000 who are scheduled to progress through the 12 months duration of therapy.

Table 7.2 [redacted] Exposures Active Population (as of 08/09/00)					
Duration of Therapy (mos)	**Dose (mg)**				
	30-60	*61-200*	*201-400*	*> 400*	*Total*
0-0.5	0	0	0	0	0
0.5-1	0	0	0	0	0
1-2	0	0	0	0	0
2-3	0	0	0	0	0
3-4	0	0	40	0	126
4-5	11	61	37	0	123
5-6	9	56	37	14	116
6-7	8	42	25	10	85
7-8	5	23	14	2	44
8-9	3	15	10	2	30
9-10	1	9	5	0	16
10-11	1	6	4	0	11
11-12	0	1	1	0	2
>12	0	0	0	0	0

From Sponsor's Table 2, pg. 6, Fax 08/29/00.

7.3 Review of the ISS

7.3.1 Methods for Review of Safety

The two double blind trials and open label extensions included in this submission were conducted in different patient populations (i.e. osteoarthritis vs. chronic pain, chronic opioid use vs. opioid naïve). However, the safety data will be pooled and significant differences between the populations will be examined. Data will also be presented for the double-blind population and the combined double-blind and open-label populations.[16] Where appropriate, a separate evaluation of safety information from the healthy volunteer data base will be included. The total number of subjects exposed to ———— was used for the database of all deaths and serious adverse events. Other trial-specific measurements of safety may not include this entire database due to lack of collected information and other intervening circumstances.

The sponsor provided the case report forms (CRFs) for all deaths and withdrawals. Patient summaries for deaths, serious adverse events, withdrawals because of adverse events, and serious adverse events not leading to withdrawal were also provided. Case Report Forms for all deaths and withdrawals were reviewed to determine concordance with summaries and the summaries were found to be consistent with the CRFs.

The term, "adverse event" included any of the following that developed or increased in severity during the course of the study:

- Any signs or symptoms whether thought to be related or unrelated to the study medications
- Any clinically significant laboratory abnormality
- Any abnormality detected during physical examination

The investigator graded signs and symptoms as mild, moderate, or severe based on the following definitions:

- Mild: Causing no limitation of usual activities
- Moderate Causing some limitation of usual activities
- Severe Causing inability to carry out usual activities

Definitions of "serious adverse experience", "life-threatening adverse drug experience", "disability", "unexpected adverse drug experience", and "associated with the use of study agent" are listed below:

- Serious adverse experience – any experience occurring at any dose that results in death, a life-threatening adverse experience, hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, or a congenital anomaly/birth defect
- Life-threatening adverse drug experience – any adverse experience that places patient or subject at immediate risk of death from the adverse experience as it occurred

[16] These analyses include data from both patients and healthy volunteers.

- Disability – a substantial disruption of a person's ability to conduct normal life functions
- Unexpected adverse drug experience – any drug experience with a specificity or severity inconsistent with the investigator brochure

Patients were withdrawn from the osteoarthritis trial if any of the following circumstances occurred:

- Subject decides against further participation
- Investigator may terminate a patient if osteoarthritis symptoms worsen or do not improve
- Investigator may terminate a patient for adverse experiences, intercurrent illness, noncompliance with study, administrative reasons, or to protect the patient's best interests

There were no defined criteria for withdrawal in the chronic pain trial.

7.3.2 Deaths

There were three deaths in the double-blind trials, all of which were in the cancer population. There were thirteen deaths in the open-label trials, all of which were in the chronic opioid use population and all but one of which were cancer patients. Following are individual summaries for each of these patients. (See Appendix K for a table summarizing the demographics, exposure, and cause of death for the sixteen patients)

Double-Blind Studies

TRG004-02, 103-009 (MS Contin 30mg bid)
78 year old female with metastatic endometrial cancer and a previous medical history of hypertension, radiculopathy with progressive back pain, hysterectomy, thyroid cancer s/p thyroidectomy, and depression. She started the stabilization phase with MS Contin 30mg bid and 6 days into this phase was admitted to the hospital with abdominal discomfort, ascites, and altered mental status. During this hospitalization, paracentesis was performed, several units of PRBC's were transfused, and she was treated for oral thrush. She was discharged on the 13th day of the stabilization phase and the following day was randomized into the double-blind phase. She completed this one week phase and the next day was readmitted to the hospital for ascites and possible bowel obstruction, with a planned paracentesis. Eight days later her symptoms had not resolved; she refused further chemotherapy and was discharged to hospice care. She died 16 days after the final dose of study drug. It is this reviewer's assessment that, although the patient's symptoms and ultimate demise were most likely a result of her metastatic endometrial cancer, it is not possible to completely exclude the study drug as a contributory factor to the bowel obstruction because of its propensity to slow intestinal motility.

TRG004-02, 123-004 [redacted] 120mg qd, 100% group)
67 year old female with metastatic bladder cancer and a previous medical history of hypertension, carotid and aortofemoral bypasses, peripheral vascular disease, liver metastases, back pain, and ascites. She was stabilized on MS Contin 60mg bid for 7 days

and was randomized into the double-blind phase. She completed the double-blind phase but did not enter the open-label phase because of progression of her illness. She died at home 5 days after the final dose of study drug from fluid overload and progression of her disease. It is this reviewer's assessment that it is highly unlikely that the study drug was a contributory or causative factor to this patient's demise.

TRG004-02, 138-001 (———— 180mg qd, 100% group)
66 year old male with metastatic non-small cell lung carcinoma s/p chemotherapy and radiation. He had a previous medical history of diabetes, prostatic hypertrophy and peripheral neuropathy. He was stabilized on MS Contin 100mg bid for 6 days and was randomized into the double-blind phase. He began this phase but was discontinued one day after its start due to "continuous and moderate forgetfulness and mild tremors". Twenty-seven days after his last dose of ————, he was admitted to the intensive care unit with neutropenic sepsis and pneumonia. He expired on the following day, 28 days after his last dose of study medication. It is this reviewer's assessment that it is highly unlikely that the study drug was a contributory or causative factor to this patient's demise.

A total of 389 subjects were exposed to ———— during double-blind trials, 80% of who had a history of prior opioid use. All deaths occurred in the chronic pain population with a population-specific incidence of death of 1% (3/326) and a total population incidence of 0.8% (3/389). Two of these deaths were considered by this reviewer to be unrelated to the study drug. The third death was possibly related to the study drug.

Open-Label Studies

TRG004-03, 03-S01 ———— 240mg qd)
42 year old female with metastatic cervical cancer and had participated in protocol TRG004-05 (PK/PD study) prior to entry into this open label study. She began this study with ————240mg qd and was hospitalized 49 days after for gynecological bleeding. The study drug was discontinued at this time, the event resolved, and she was discharged 12 days later. She was again hospitalized 6 days later with increased pain and lymphostasis of legs and abdomen. Seven days after this admission she was discharged to a hospice. The patient expired 30 days after discontinuation of the study drug. It is this reviewer's assessment that it is highly unlikely that the study drug was a contributory or causative factor to this patient's demise.

TRG004-03, 103-002 ————240mg qd)
62 year old male with bronchoalveolar carcinoma of the left lung and a previous medical history of severe COPD, neutropenia, weakness, melanoma, nausea, and edema. The patient participated in protocol TRG004-02 (double-blind study – MS Contin 100% group) prior to entry into this open label study. He began this study with ———— 240mg qd and morphine sulfate immediate release 15mg q4h as needed. He discontinued the study drug on his own two days later because of fever, restlessness, and confusion. Two days later he was hospitalized with a diagnosis of febrile neutropenia and was discharged 3 days later. The patient expired in a hospice 21 days after discontinuation of

the study drug. It is this reviewer's assessment that it is highly unlikely that the study drug was a contributory or causative factor to this patient's demise.

TRG004-03, 103-004 (———— 120mg qd)
78 year old female with metastatic colon cancer and metastases to lung and gallbladder. Previous medical history included mucositis, stomatitis, heart murmur, peripheral edema, chronic diarrhea, necrotic mass protruding through umbilicus, hypertension, and depression. She had participated in protocol TRG004-02 (double-blind study – ———— 100% group) prior to entry into this open label study. She began this study with ————120mg qd and was hospitalized 31 days after for spinal cord compression, mild expressive aphasia, and left facial drooping. She was discharged back to a nursing home 5 days later with orders to continue comfort measures, including the study drug. Seventeen days later she was re-hospitalized for bilateral pneumonia. Study drug was continued for 9 more days until she began to experience dysphagia. She was then switched to continuous IV morphine and expired 6 days later. It is this reviewer's assessment that although this patient's condition was rapidly progressing to a terminal state, it is not possible to completely exclude the study drug as contributing to the dysphagia, possible aspiration, and subsequent severe pneumonia hastening her demise.

TRG004-03, 104-001 (————90mg qd)
59 year old male with metastatic prostate cancer and previous medical history of melena, hematochezia, lymphedema, back pain, dizziness, and diabetes. He had participated in protocol TRG004-02 (double-blind study – MS Contin 100% group) prior to entry into this open label study. He began this study with ———— 60mg qd and was titrated to 90mg qd 3 days later. He withdrew from the study 31 days later because "he had no more pain and did not wish to take the drug". Twenty days after discontinuing the study drug he was hospitalized with infected decubiti and renal failure and expired 2 days later. It is this reviewer's assessment that it is highly unlikely that the study drug was a contributory or causative factor to this patient's demise.

TRG004-03, 110-003 (———— 180mg qd)
61 year old male with local and peripheral metastatic lung cancer and previous medical history of dyspnea, hypertension, nausea, and chest pain. He had participated in protocol TRG004-02 (double-blind study – ———— 50% group) prior to entry into this open label study. He began this study with ———— 60mg qd and was titrated during 49 days to 90mg and subsequently 180mg qd. He was withdrawn from the study when his disease progression required admission to a hospice and he was no longer able to return for evaluation visits. He expired in the hospice 24 days after discontinuing the study drug. It is this reviewer's assessment that it is highly unlikely that the study drug was a contributory or causative factor to this patient's demise.

TRG004-03, 123-001 (———— 60mg qd)
62 year old male with advanced non-small cell lung cancer, consistent with Pancoast tumor, and previous medical history of peptic ulcer disease, severe weight loss, tuberculosis, weakness, and abdominal pain. He had participated in protocol TRG004-02 (double-blind study – MS Contin 100% group) prior to entry into this open label study.

At the end of the double-blind phase (7 days), and coincident with a chemotherapy treatment, he became confused, hypertensive, and severely hypercarbic during a chemotherapy treatment with Taxol. He did not respond to epinephrine treatment and was admitted on the presumption that this was a terminal event. However, he recovered and was discharged after 4 days. During evaluation of this event, the investigator discovered that the patient had erroneously been given an MS Contin dose of 60mg bid rather than his stabilizing dose of 30mg bid. Despite this finding, the investigator concluded that the causative factor for the event was the Taxol infusion and not the doubled dose of MS Contin. Fifteen days after completion of the double-blind portion of the study, he began the open-label portion on his corrected dose of ——— 60mg qd. Eighteen days thereafter he was admitted to the hospital with severe hypercarbia and metabolic acidosis. He subsequently expired 2 days after the last dose of ———— It is this reviewer's assessment that the initial serious adverse event during the double-blind phase could have been due to the incorrect dose of MS Contin being administered. If, as the investigator concluded, Taxol was the cause of this event, the symptoms should have been reversible with the administration of epinephrine (Taxol may cause severe anaphylactic reactions characterized by hypercarbia, angioedema, and bronchospasm). The patient's declining condition was not unexpected for his advanced stage of disease. However, this reviewer cannot conclude that the study drug during either phase did not hasten his demise.

TRG004-03, 103-006 (———— 120mg qd)
61 year old male with widespread metastatic lung cancer and previous medical history of metabolic encephalopathy, COPD, diabetes, depression, and anxiety. He had participated in protocol TRG004-02 (double-blind study ———— 133% group) prior to entry into this open label study. He began this study with ———— 120mg qd and continued on this dose for 341 days. After completion of the trial his pain was treated with another oral morphine equivalent. Eleven days after completing the trial he was admitted to the hospital with mental obtundation and cerebral metastases. He was given palliative care and expired the next day. It is this reviewer's assessment that it is highly unlikely that the study drug was a contributory or causative factor to this patient's demise.

TRG004-03, 103-011 (———— 240mg qd)
78 year old male with pancreatic cancer and previous medical history of necrotizing fasciitis, emphysema, diarrhea, and pain. He had participated in protocol TRG004-02 (double-blind study ———— 133% group) prior to entry into this open label study. He began this study with ———— 120mg qd and was titrated during 223 days to 240mg where his pain was well-controlled. On the 277th day of treatment he was admitted to the hospital with a diagnosis of congestive cardiomyopathy and sepsis. The study drug was discontinued 3 days into this hospitalization and he expired the following day. It is this reviewer's assessment that it is highly unlikely that the study drug was a contributory or causative factor to this patient's demise.

TRG004-03, 106-005 ———— 180mg qd)
44 year old male prostatic cancer and bony metastases and a previous medical history of dyspnea, hypertension, hematuria, weakness, edema, and bone pain. He had participated

in protocol TRG004-02 (double-blind study – [redacted] 133% group) prior to entry into this open label study. He began this study with [redacted] 120mg qd and was titrated during 95 days to 180mg qd. He was admitted to the hospital on day 116 of therapy for workup of possible spinal cord compression. No evidence of this disorder was found although there were indications of disease progression. His chemotherapeutic regimen was changed and he was discharged four days later. He was again hospitalized on the 168th day of treatment for febrile neutropenia. Study drug was continued and he expired 177 days into the treatment program from progression of his disease. It is this reviewer's assessment that it is highly unlikely that the study drug was a contributory or causative factor to this patient's demise.

TRG004-03, 106-006 ([redacted] 150mg qd)
67 year old female with diffuse metastatic adenocarcinoma of the breast and previous medical history of dyspnea, hypertension, edema, anorexia, peripheral neuropathy, nausea, and chest pain. She had participated in protocol TRG004-02 (double-blind study – MS Contin 100% group) prior to entry into this open label study. She began this study with [redacted] 150mg qd. After 9 months of study drug treatment, she had developed encephalopathy, moderate renal failure, and tremors. The study drug regimen was discontinued and palliative care instituted. She expired at home 3 days after discontinuation of the study drug. It is this reviewer's assessment that, although it is more likely that the patient's terminal constellation of symptoms was due to progression of her disease, it is not possible to completely exclude or implicate the study drug as a factor in their occurrence.

TRG004-03, 109-001 ([redacted] 300mg qd)
72 year old male with mixed small cell and squamous cell lung cancer and previous medical history of COPD, coronary artery disease, s/p MI, CHF, and peripheral edema. He had participated in protocol TRG004-02 (double-blind study [redacted] 50% group) prior to entry into this open label study. He began this study with [redacted] 90mg qd and over the course of 3 months was titrated up to 300mg qd. Two weeks into the treatment regimen he developed fever and pneumonia requiring hospitalization that resolved after 2 weeks. After approximately 7 ½ months of study drug treatment, he expired in home hospice care due to "natural course of lung carcinoma". No information was provided by the investigator about intervening events leading up the death and on the admitting physical exam his appearance was described as "normal" with the only change from baseline being shortness of breath and dyspnea. A certificate of death provided by the sponsor lists the cause of death as "Cancer of Lung". During a teleconference with the sponsor on 10-18-00 they confirmed that no other information is available. Therefore, without any additional information, it is not possible to exclude or implicate the study drug as a factor leading to the subject's death.

TRG004-03, 110-001 ([redacted] 180mg qd)
68 year old female with nodular lymphoma and previous medical history of gastrointestinal dysfunction, edema, abdominal pain, pancytopenia, mild hydronephrosis, and recurrent urinary tract infections. She had participated in protocol TRG004-02 (double-blind study [redacted] 100% group) prior to entry into this open label study.

She began this study with ——— 90mg qd and was titrated to 180mg qd over the course of 11 months. After 1 week in this trial she was hospitalized for a urinary tract infection that resolved in 2 days. She expired under home hospice care while receiving trial drug therapy and the cause of death was noted to be "natural progression of her disease". The history, physical exam, and laboratory data that was provided was consistent with this diagnosis. Therefore, it is this reviewer's assessment that it is highly unlikely that the study drug was a contributory or causative factor to this patient's demise.

TRG004-03, 153-002 (——— 90mg qd)

55 year old male with paraplegia secondary to a motor vehicle accident over 20 years ago and previous medical history of blindness, diabetes, aortic rupture, and constipation secondary to narcotic use. He had participated in protocol TRG004-02 (double-blind study – MS Contin 100% group) prior to entry into this open label study. He began this study with ———60mg qd and was titrated to 90mg qd over the course of 1 month. Approximately 5 weeks after beginning the trial, he reported increased constipation and was given a stool softener. Five months later he was admitted to the hospital for increased constipation, was treated with laxatives, and the study drug was discontinued. Sixteen days after discontinuation of the trial therapy, he was washing windows on his car, became unresponsive, and expired. The sponsor listed cause of death as "considered to be a ruptured aneurysm". An autopsy report provided by the sponsor on 10-30-00 confirmed this diagnosis. It is this reviewer's assessment that it is highly unlikely that the study drug was a contributory or causative factor to this patient's demise.

Summary of Mortality Findings

A total of 389 subjects were randomized to ——— in the double-blind trials[17]. The incidence of death in the subjects exposed to ———was 0.5% (2/389) and neither of these deaths was considered by this reviewer to be related to the study drug. A total of 164 subjects were randomized to MS Contin in the double-blind trials and the incidence of death in these subjects was 0.6% (1/164). It is not possible to exclude or implicate use of MS Contin in this death.

A total of 461 subjects were exposed to ——— during open-label trials, 60.7% (280/461) in the chronic opioid use population and 39.3% (181/461) in the osteoarthritis population. All thirteen deaths that occurred were chronic opioid users, with a 4.6% (13/280) population-specific incidence of death and a 2.8% (13/461) incidence in the total population. This reviewer considered nine of these deaths to be unrelated and the remaining four to be possibly related to study drug exposure. There were too few deaths to evaluate if there were effects due to race, age, or other demographic variables.

7.3.3 Non-Fatal Serious Adverse Events

In the double-blind trials, 5 patients had non-fatal serious adverse events during the stabilization phase with MS Contin and 10 patients (2 ———133%, 4 ——— 30mg qpm, 2 MS Contin 100%, 1 MS Contin 15mg bid, 1 placebo) had non-fatal serious

[17] Subjects exposed in double-blind and open-label trials include patients and healthy volunteers.

adverse events during the double-blind phase. This amounted to 6 (1.5%) of treated patients, 3 (1.8%) of MS Contin-treated patients and 1 (1.4%) of placebo-treated patients. These serious adverse events are listed in the following table.

Table 7.3 - Serious Adverse Events
Double Blind Population

Study	*TRG004-02*			*TRG004-04*	
Event	*133%*	*MS Contin 100%*	*Placebo*	*30mg qpm*	*MS Contin 15mg bid*
Chest Pain	X				
Electrolyte Abnormality, Hepatic Failure	X				
Intestinal Obstruction		X			
Pain		X			
Abdominal Pain			X		
Thrombophlebitis				X	
Constipation				X	
Dyspnea				X	
Pneumonia				X	
Liver Function Tests Abnormal					X

From Sponsor's Table 21ABL, Vol. 2-117, pg. 293.

In the open-label trials, 67 patients had non-fatal serious adverse events (54 [redacted] 100%, 6 [redacted] 30mg qam, 8 [redacted] 30mg qpm). The serious adverse events occurring in at least 2% of patients in any treatment group are summarized in Table 7.4. No single adverse event occurred in 2% or more patients, but there were several body systems meeting this criterion. A compilation of the serious adverse events for the combined [redacted] populations were dyspnea (0.7%), vomiting (0.7%), nausea (0.6%), pneumonia (0.6%), and dehydration (0.6%), many of which are known opioid-related side effects. The majority of these events were seen in the [redacted] 100% group. In the combined population this finding is not surprising. Only [redacted] 100%, [redacted] 30mg qpm, and [redacted] 30mg qam patients in the double-blind trial entered the open-label phase trials [redacted] 133%, [redacted] 50%, and MS Contin 100% not entered). Patients were permitted further dose titration within the open-label extensions thus making it more likely that an adverse event would appear as a signal in these larger groups.

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Table 7.4 - Serious Adverse Events Entire Population, 2% or Greater							
Event	*133% N=69*	*100% N=384*	*MS Contin 100% N=904*	*Placebo N=73*	*30mg qam N=164*	*30mg qpm N=163*	*MS Contin 15mg bid N=76*
Any SAE	2.9%	14.1%	2.2%	1.4%	3.7%	7.4%	1.3%
Body as a Whole	1.4%	5.2%	1.1%	1.4%	0.6%	3.1%	0
Cardiovascular System	0	2.6%	0	0	1.8%	0.6%	0
Digestive System	1.4%	2.3%	1.1%	0	1.8%	3.7%	1.1%
Nervous System	0	3.9%	0	0	0	0	0
Respiratory Syst.	0	2/3%	0	0	1.2%	1.4%	0

From Sponsor's Table 21, Vol. BM, 10/299/00, p. 21

The investigator considered one of the events (constipation) in the double blind trials to be treatment-related. Additionally, the investigator considered twelve of the events in the open label trials to be treatment-related. The following table summarizes the information about treatment-related non-fatal events in both populations.

Table 7.5 Treatment-Related, Non-Fatal Serious Adverse Events							
Study # Patient #	*Type of Study*	*Patient Diagnosis*	*Adverse Event*	*Treatment Dose/Day*	*Investigator's Causality Assessment*	*Day of Onset*	*Intensity*
TRG004-04 21-S02	Double blind	Osteoarthritis Knee	Constipation	qpm 30 mg	Possible	8	Severe
TRG004-03 116-015	Open label	Migraines	Drug Dependence	100% 210 mg	Possible	148	Severe
TRG004-03 122-003	Open label	Lumbar Arachnoiditis	Ileus	100% 60 mg	Possible	101	Severe
TRG004-03 123-003	Open label	Metastatic Lung Cancer	Confusion	100% 120 mg	Probable	23	Severe
TRG004-03 126-018	Open label	Osteoarthritis Back	Pneumonia	100% 60 mg	Possible	110	Severe
TRG004-03 133-002	Open label	Chronic pain Knee surgery	Dehydration Nausea	100% 60 mg	Possible	281	Severe
TRG004-03 133-025	Open label	Chronic pain Fibromyalgia	Nausea	100% 150 mg	Possible	43	Moderate
TRG004-03 153-001	Open label	Breast Cancer	Drug Dependence	100% 60 mg	Definite	59	Severe
TRG004-03 153-001	Open label	Breast Cancer	Constipation	100% 60 mg	Possible	205	Moderate
TRG004-04 13-S02	Open label	Osteoarthritis Knee	Enteritis Gastritis	qam 30 mg	Possible	57	Severe
TRG004-04 16-S17	Open label	Osteoarthritis Knee	Nausea, Vomiting Dehydration	qam 30 mg	Possible	45	Moderate
TRG004-04 21-S03	Open label	Osteoarthritis Knee	Constipation	qpm 30 mg	Possible	79	Severe
TRG004-04 28-S01	Open label	Osteoarthritis Knee	Vomiting Dehydration	qpm 30 mg	Possible	133	Moderate

From Sponsor's Table 21ABL, Vol. 2-117, pg. 293; Table 21CDL, Vol. 4-14, pp. 363-367.

With the exception of enteritis/gastritis and pneumonia, all of these treatment-related serious adverse events are known side effects associated with opiate use and did not occur with increased frequency over that which was expected. The patient with gastritis/enteritis had several episodes of nausea and vomiting that were considered non-serious adverse events. These episodes may have contributed to irritation of the gastrointestinal mucosal lining, thus increasing the likelihood of the later development of enteritis. The patient with pneumonia developed this condition after 110 days of ———— treatment. Although not an expected adverse event, progression of a primary respiratory infection to a more severe pneumonic process may have been augmented by opioid-induced hypoventilation. There were too few SAEs to evaluate for effects of race, age, or other demographic variables

7.3.4 Adverse Events Leading to Study Discontinuation

In the double-blind trials, a total of 69 subjects (———— – 44, MS Contin – 21, Placebo – 4) discontinued because of adverse events. Twenty-eight had prior opioid use (defined by the sponsor as "chronic opioid use" or "intermittent opioid use") and 41 were opioid naïve. Fifty-eight of the 69 subjects were in the osteoarthritis population.

Across trials the incidence of discontinuation was similar between patients treated with ———— or MS Contin (chronic pain - 3.1% vs. 3.4%, osteoarthritis - 24.7% vs. 23.7%). In the chronic pain trial, there was no internal trend to suggest a dose-related increase in incidence. Across both trials, the overall incidence of discontinuation in placebo subjects was similar to that seen in the chronic pain population and less than that in the osteoarthritis population. These results are tabulated below.

Table 7.6
Discontinuations Due to Adverse Events (Double Blind Trials) in ≥ 2% of Patients

Event	133% N = 69	100% N = 104	50% N = 86	30mg AM N = 73	30mg PM N = 73	All N = 405	MS Contin 100% N = 88	MS Contin 15mg BID N = 76	MS Contin All N =164	Placebo N = 73
Any Adverse Event	5 (7.2%)	1 (1.0%)	2 (2.3%)	17 (23.3%)	19 (26.0%)	44 (10.9%)	3 (3.4%)	18 (23.7%)	21 (12.8%)	4 (5.5%)
Abd. Pain				1 (1.4%)	1 (1.4%)	2 (0.5%)				2 (2.7%)
Asthenia	1 (1.4%)				2 (2.7%)	3 (0.7%)				
Constipation				7 (9.6%)	5 (6.8%)	12 (3.0%)	1 (1.1%)	5 (6.6%)	6 (3.7%)	
Nausea	2 (2.9%)		1 (1.2%)	5 (6.8%)	10 (13.7%)	18 (4.4%)		6 (7.9%)	6 (3.7%)	
Vomiting	1 (1.4%)		1 (1.2%)	1 (1.4%)	5 (6.8%)	8 (2.0%)		4 (5.3%)	4 (2.4%)	
Dizziness				2 (2.7%)	2 (2.7%)	4 (1.0%)		4 (5.3%)	4 (2.4%)	1 (1.4%)
Somnolence	1 (1.4%)			3 (4.1%)	3 (4.1%)	7 (1.7%)		4 (5.3%)	4 (2.4%)	
Vertigo				2 (2.7%)		2 (0.5%)				
Pruritus				1 (1.4%)	2 (2.7%)	3 (0.7%)		1 (1.3%)	1 (0.6%)	
Dysuria				2 (2.7%)		2 (0.5%)				

From Sponsor's Table 20A, Vol. 2.116, pp. 484-502.

In the open-label trials, as of the 120-day safety cut-off date, a total of 96 subjects (———— 100% - 36, ———— qam – 33, ———— qpm – 27) discontinued because of treatment-emergent adverse events. Thirty-six from the chronic pain

population and 60 were from the osteoarthritis population, with an equal distribution between the AM and PM groups.

The treatment emergent adverse events leading to withdrawal from the double blind and combined populations in at least 0.5% of patients are tabulated in Appendix M. The discontinuation-related adverse event data indicates that [redacted] and MS Contin have similar causation profiles and that no single or group of events occurs with greater frequency in one of the two groups. Additionally, there are no unexpected differences in profiles from the active treatment groups profiles compared to that from the placebo group.

The population distribution for discontinuations due to adverse events is not surprising. The majority of discontinuations in both double-blind (84%) and open-label (63%) groups were in the osteoarthritis population even though overall, they were receiving lower doses of morphine and no additional opiates were available as rescue medication. This was true regardless of whether they received [redacted] or MS Contin. Fifty-nine percent of the discontinuations entering the double blind portion of the trials were opioid-naïve, as would be expected in osteoarthritis patients. It would be expected, and is confirmed by these results, that patients who are either opioid-naïve or are members of a population requiring minimal amounts of opioids to control their pain would have less tolerance to and would be more likely to develop unacceptable adverse events than would a population requiring fairly significant amounts of opioids prior to entry into the study.

7.3.5 Overall Evaluation of Adverse Events

7.3.5.1 Approach to Eliciting Adverse Events in the Development Program

No specific definition was given of an "adverse event" for any of the trials. Only definitions of serious adverse events, unexpected adverse events, and adverse events associated with the use of the medication were included in the final protocols. In all trials, the investigator or a designated evaluator collected adverse event information from the onset of the trial up to a protocol-established post-treatment endpoint. Spontaneously reported events were also recorded.

7.3.5.2 Appropriateness of Adverse Event Categorization and Preferred Terms

Adverse events were coded using the COSTART system and were analyzed in several ways:

- Number of patients reporting at least one episode of a specific adverse event
- Total number of episodes for each event
- Severity of each episode
- Relationship to study medication
- Number of patients discontinuing trial due to adverse events

In a number of instances the investigator's choice of terminology was too general or too specific to be accurately reflected by a COSTART term, leading to a possible underestimation or overestimation of a specific event. In the combined open label and

double blind populations, terms such as "bundle branch block" may be interchangeable "heart block". Likewise "electrocardiogram abnormal", "myocardial infarction", and "substernal chest pain" may be different entities or may all refer to the same condition. In most cases, the error will be one of underestimation than of overestimation.

No events were re-coded during analysis by this reviewer. In most instances, the inappropriate classifications did not change the adverse event profile. Typically, reclassification of the most common events did not result in a change in the incidence of opioid-related events.

7.3.5.3 Selection of Adverse Events for Characterizing the Overall Profile

7.3.5.3.1 Patient Data

The adverse event profiles are characterized in the studied populations by separately analyzing data from the double blind trials and also by analyzing the combined data from the double blind and open label trials. Most of the adverse effects identified have a known association with the use of opiates.

In the chronic pain trial, the overall incidence of adverse events was similar between the [redacted] 133%, [redacted] 100%, and [redacted] 50% (58.0%, 55.8%, and 51.2%, respectively). However, these incidences were considerably higher than in the 42% observed in the MS Contin 100% group. As expected, placebo-treated patients demonstrated the lowest incidence of adverse events, 38.4%.

When compared in a post-hoc statistical analysis performed for this reviewer, the difference between [redacted] 100% and MS Contin 100% approached significance (p=0.058) and the difference between [redacted] 133% and MS Contin 100% was significant (p=0.048). These are an unexpected finding. Given the MS Contin demonstrated efficacy similar to [redacted] 133%, a similar adverse event frequency would be expected. Similarly, in the osteoarthritis trial, patients treated with [redacted] 30mg experienced a greater incidence of adverse events (80.1%) compared with MS Contin 15 mg BID (67.1%) and this difference was also statistically significant (p=0.032). A review of the CRT line listings for Incidence of Treatment Emergent Adverse Events By Summary Population and Treatment Group, Double-Blind Population, (Table 14A, Vol. 2.112, p262) did not reveal any particular adverse event or cluster of related events contributing disproportionately to the overall adverse event frequencies.

In the chronic pain trial, the overall incidence of [redacted]-related adverse events was lower than that seen in the osteoarthritis trial (55% vs. 80%). This difference in adverse event occurrence is most likely due to population differences between the two trials, as explained below. The incidence of events in the chronic pain MS Contin 100% group was lower than that in the osteoarthritis MS Contin 15mg bid group (42% vs. 67.1%). Again, this finding is most likely due to differences in the study population. These two comparisons support the previously advanced theory that patients who are not chronic opioid users (as in the osteoarthritis population) may be less tolerant of opioid-related

side effects than patients who have had chronic exposure to opioids (as in the chronic pain population).

The following table summarizes adverse events occurring in ≥5% of patients in any treatment group from the double blind trials.

Table 7.7
Incidence of Adverse Events in ≥5% Patients (Double Blind Trials)

Adverse Event	Number (%) of Patients						
	133% (N = 69)	*100% (N = 104)*	*50% (N = 86)*	*30 mg* (N = 146)*	*MS Contin 100% (N = 88)*	*MS Contin 15mg bid (N = 76)*	*Placebo (N = 73)*
Any Event	40 (58.0%)	58 (55.8%)	44 (51.2%)	117 (80.1%)	37 (42.0%)	51 (67.1%)	28 (38.4%)
Constipation	5 (7.2%)	6 (5.8%)	5 (5.8%)	65 (44.5%)	4 (4.5%)	22 (28.9%)	3 (4.1%)
Dizziness	5 (7.2%)	2 (1.9%)	2 (2.3%)	14 (9.6%)	4 (4.5%)	9 (11.8%)	1 (1.4%)
Nausea	7 (10.1%)	7 (6.7%)	5 (5.8%)	38 (26.0%)	5 (5.7%)	20 (26.3%)	7 (9.6%)
Pruritus	6 (8.7%)	2 (1.9%)	3 (3.5%)	11 (7.5%)	0 (0%)	2 (2.6%)	0 (0%)
Somnolence	3 (4.3%)	7 (6.7%)	4 (4.7%)	21 (14.4%)	3 (3.4%)	9 (11.8%)	0 (0%)
Vomiting	6 (8.7%)	2 (1.9%)	4 (4.7%)	16 (11.0%)	5 (5.7%)	6 (7.9%)	1 (1.4%)
Abd. Pain	0 (0%)	7 (6.7%)	4 (4.7%)	3 (2.1%)	1 (1.1%)	0 (0%)	2 (2.7%)
Asthenia	4 (5.8%)	4 (3.8%)	4 (4.7%)	5 (3.4%)	1 (1.1%)	7 (9.2%)	0 (0%)
Diarrhea	0 (0%)	2 (1.9%)	3 (3.5%)	3 (2.1%)	1 (1.1%)	1 (1.3%)	4 (5.5%)
Headache	7 (10.1%)	7 (6.7%)	2 (2.3%)	7 (4.8%)	6 (6.8%)	5 (6.6%)	4 (5.5%)
Pain	1 (1.4%)	5 (4.8%)	1 (1.2%)	5 (3.4%)	2 (2.3%)	4 (5.3%)	1 (1.4%)
Sweating	1 (1.4%)	5 (4.8%)	7 (8.1%)	4 (2.7%)	1 (1.1%)	2 (2.6%)	1 (1.4%)

*Highlighted rows are common opioid-related side effects
•————30mg qam and————30mg qpm are combined into a single group - ———— 30mg
From Sponsor's in-text Table 5-3, vol. 2.109, pg. 22.

In the combined populations for the double blind and open label trials, the adverse event profile was similar to that from the double blind population. The most frequently reported events were those commonly associated with opiate use (constipation, nausea, somnolence, dizziness). As was found in the double blind population, the osteoarthritis patients in the combined population had a higher incidence of adverse events than did the chronic pain patients.

A summary of the adverse events occurring in ≥5% of patients in any treatment group from the combined populations is tabulated in Appendix N.

7.3.5.3.2 Subgroup Analysis, Adverse Events

There were overall more frequent adverse events in patients aged 65-74 than less than 65, a finding not unexpected. The number of patients in some of the subgroups was quite small limiting the value of these comparisons. The few number of patients over the age of 75 does not permit adequate comparison. These findings are summarized in Table 7.8.

There were slightly more adverse events reported in female patients. The differences were small.

There were too few non-Caucasian patients to evaluate the differences in adverse event frequency between races.

There were too few patients with pain due to malignancy for a meaningful comparison with patients with non-malignant pain.

Table 7.8
Incidence of All Adverse Events for Patient Subgroups Double-Blind Studies

Subgroup	Number Patients with AE/Number in Subgroup (% with AE)				
	133%, 100%,50% N=259	*30 mg N=144*	*MS Contin 100% N=88*	*MS Contin 15 mg BID N=76*	*Placebo N=73*
Age (years)					
<65	119/226 (52.7 %)	59/79 (74.7 %)	32/77 (41.6 %)	30/46 (65.2 %)	18/46 (39.1 %)
65-74	13/18 (72.2 %)	40/45 (88.8 %)	3/5(60.0 %)	14/20 (70.0 %)	5/16 (31.3 %)
≥75	10/15 (66.7 %)	18/22 (81.8 %)	2/6(33.3 %)	7/10 (70.0 %)	5/11 (45.5 %)
Gender					
Male	60/113 (53.1 %)	46/61 (75.4 %)	14/40 (35.0 %)	18/28 (64.3 %)	7/22 (31.8 %)
Female	82/146 (56.2 %)	71/85 (83.5 %)	23/48 (47.9 %)	33/48 (68.8 %)	21/51 (41.2 %)
Race					
Caucasian	130/229 (56.7 %)	98/123 (79.7 %)	35/80 (43.8 %)	46/68 (67.6 %)	20/58 (34.5 %)
Black	3/11 (27.3 %)	14/18 (77.8 %)	0/3	5/8 (62.5 %)	8/14 (57.1 %)
Hispanic	6/15 (40.0 %)	2/2 (100.0 %)	2/4 (50.0 %)	-	-
Asian	1/1 (100.0 %)	1/2 (50.0 %)			
Other	2/3 (66.7 %)	1/1 (100.0 %)	1/1 (100.0 %)		
Malignancy Status					
Non-malignant	122/226 (54.0 %)	117/146 (80.1 %)	33/75 (44.0 %)	51176 (67.1 %)	28/73 (38.4 %)
Malignant	20/33 (60.6 %)	-	4/13 (30.8 %)	-	-

Source: Sponsor's Table 5-4, Vol. 2.109, p. 23

7.3.5.3.3 Healthy Volunteer Data

One hundred and forty-one healthy volunteers were introduced to varying concentrations and formulations of [redacted] Several studies had crossover designs, exposing each participant to several concentrations and vehicles of delivery. Therefore, the numerical tabulations of adverse events in this population are based upon a total of 372 exposures. Several adverse events may have been listed for a single volunteer and the total number of adverse events (389) reflects this plurality. The majority of exposures were to the 60 mg dose, delivered in various formulations and from various manufacturing sites and, as such, the majority of reported adverse events were also in this exposure group. The following table lists the total number and incidence of adverse events relative to specific exposure group.

Table 7.9 Incidence of Adverse Events in Healthy Volunteers – N (%)						
	Dosage (Formulation)					
	30 mg	*60 mg*	*60 mg (Sprinkle)*	*90 mg*	*120 mg*	*Total (All Groups)*
Total Exposures	30	252	30	30	30	372
All Adverse Events	9	308	47	5	21	389
Specific Adverse Events						
Headache	1 (3.3)	51 (20.2)	9 (30.0)			61 (16.4)
Nausea	1 (3.3)	38 (15.1)	2 (6.7)	1 (3.3)	4 (13.3)	45 (12.1)
Dizziness	2 (6.7)	29 (11.5)	9 (30.0)	2 (6.7)	2 (6.7)	42 (11.3)
Asthenia	1 (3.3)	31 (12.3)	4 (13.3)	1 (3.3)	2 (6.7)	39 (10.5)
Pruritis		31 (12.3)	4 (13.3)			35 (9.4)
Vomiting	2 (6.7)	16 (6.3)	4 (13.3)		2 (6.7)	24 (6.5)
Abd. Pain		11 (4.4)	4 (6.7)		2 (6.7)	14 (3.8)
Pharyngitis		7 (2.8)	4 (13.3)			11 (3.0)
Somnolence		7 (2.8)				7 (1.9)
Constipation		5 (2.0)				5 (1.3)
Diarrhea					2 (6.7)	2 (0.5)

From Sponsor's information – Fax 12-20-00.
*Highlighted rows are adverse events most commonly reported in double-blind patient trials
*Number of adverse events may be greater than number of exposures; incidence calculated on total exposure data.

7.3.5.3.4 Summary of Adverse Event Data

The adverse event profiles of common opioid adverse events (nausea, dizziness, pruritis, vomiting, somnolence, constipation) were analyzed in the double-blind patient trials, combined double-blind and open-label patient trials, and healthy volunteer trials.

In both of the double-blind pivotal trials, patients receiving ——— experienced a greater incidence of adverse events than patients receiving MS Contin. This was true for all ——— treatment groups: 133%, 100%, 50%, 30mg qam and 30mg qpm. Another view is that this finding was true for opioid tolerant patients in the chronic pain study, and opioid non-tolerant patients in the osteoarthritis. In the chronic pain study, patients receiving ———133% and to a large extent those receiving ——— 100% experienced comparable efficacy as patients receiving MS Contin. There is no ready explanation for this finding. There was no focused increase in any particular adverse event or group of adverse events.

The osteoarthritis population had a greater incidence of adverse events than did the chronic pain population, regardless of their randomization group. This finding supports the theory that opioid-naïve patients, as were most osteoarthritis patients, tended to experience or report more adverse events than did patients with chronic opioid use, as in the chronic pain population. The chronic pain population may have developed tolerance

to these events or may have been more cognizant of the risk/benefit ratio associated with opioid use.

In the healthy volunteer studies, the 60mg dosage groups had the highest incidence of opioid-related adverse events. This finding could be explained by the fact that 76% (282/372) of all exposures were to this formulation. An equal or increased incidence in the other groups may have been undetected given the small number of exposures to these formulations. The incidence of nausea and vomiting greater in the healthy volunteer population and the osteoarthritis patients than the chronic pain patients. Pruritis was most common among healthy volunteers. The incidence of constipation and somnolence was greater in the combined patient population. These findings could be explained by the theory that constipation and somnolence are more commonly associated with the multiple dosing and the higher doses of opioids used during the trials with patients, rather than the single doses in studies using healthy volunteers. However, the incidence of nausea and vomiting and pruritus may not be related to chronic use or single use but rather is an intrinsic effect seen with any opioid exposure.

7.3.6 Additional Analyses and Explorations

7.3.6.1 Laboratory Findings

7.3.6.1.1 Extent of Laboratory Testing in the Development Program

A standard battery of testing (hematology, electrolytes, renal and hepatic function, and urinalysis) was conducted at screening, baseline, and weeks 1, 2, 3, and 4 in the double blind trials. This testing was continued in the open label extensions for weeks 5, 8, 12, 18, 24, 30, and 31. The testing was also conducted in the event of early termination in any trial.

7.3.6.1.2 Selection of Studies and Analyses for Overall Drug-Control Comparisons

Analysis of laboratory data was conducted separately on each trial, on the pooled results of the double-blind trials, and on the pooled results of the open-label trials. This analysis included a comparison of abnormalities between treatment groups and between dosage groups. For each laboratory test, the mean changes from baseline to each time interval were analyzed. In some cases, the mean percent change from baseline was also analyzed.

7.3.6.1.3 Analyses and Explorations of Data

In the healthy volunteers, analysis of the primary data from all formulation and dosage groups revealed no trends toward [redacted] associated or induced abnormalities. The mean changes of laboratory testing from baseline, as analyzed from the primary data, were small and not statistically significant.

In the patient population, for all treatment groups and dosage groups, the mean changes of laboratory testing from baseline, as analyzed from the primary data, were small and not statistically significant. However, due to a variety of factors, some of which are listed below, there were inconsistencies in definition and analysis of this data across study sites.

- Some were recorded as adverse events although not all sites used the same guidelines for reporting
- Many abnormalities were present at baseline or were attributable to concomitant medication
- Some were explained on the laboratory reports (hyperkalemia in a hemolyzed specimen)
- The study physician incorrectly interpreted the results (mild hypocalcemia in patient with hypoalbuminemia

There were a total of 20 patients in the double-blind and open-label studies who had laboratory abnormalities listed as adverse events. For a description of these patients and their associated abnormalities, see Appendix O)

7.3.6.1.4 Discontinuations for Laboratory Abnormalities

Three patients were discontinued from the trials because of laboratory abnormalities. One of these patients was in the double blind osteoarthritis pain trial, totaling 1.3% (one of 76). This osteoarthritis patients was treated with MS Contin was discontinued due to increased LFT's. The LFT's of Patient 36-S15 increased as follows: ALT 26 to 233 U/L, AST 33 to 367 U/L, LDH 172 to 550. One week following study discontinuation, the AST and LDH values were within normal limits, and the ALT was 82 U/L. The remaining two patients were in the open label trials, both of which were in the osteoarthritis continuation trial and were exposed to ——— (0.43% of the total ——— exposure group and 1.1% of the osteoarthritis ——— group). One of these patients was discontinued because of elevated liver function tests. Patient 23-S02 was discontinued from the open-label extension of TRG004-004, due to the following LFT's: ALT 175 U/L, AST 282 U/L and alkaline phosphatase 87 U/L. These values returned to normal following discontinuation of study drug. The other patient, Patient 12-S01, also in the open label extension for TRG004-04, was discontinued from the study for an unspecified coagulation disorder. No laboratory values reflecting this coagulation disorder were provided.

7.3.6.1.5 Summary of Laboratory Analysis

Analysis of laboratory results from the healthy volunteer and clinical trials did not reveal any trends toward abnormality that could be attributed to the use of ———. Although four ——— patients in the clinical trials had abnormal liver function tests, one of these patients had a malignancy that could have led to the abnormality and one had elevated levels at baseline. The remaining two patients, an extremely small percentage of those exposed to ———, cannot be considered to reflect a signal for treatment-related liver function abnormalities.

Leukopenia was noted in six ———exposed patients. However, all of these patients were from the cancer population. Leukopenia is associated with several malignant disorders and may also be the result of chemotherapeutic or irradiation treatments. In addition, leukopenia was present in all of these patients prior to ——— exposure.

Therefore, it is highly unlikely that treatment with ——— contributes to the development of this abnormality.

7.3.6.2 Vital Signs

7.3.6.2.1 Extent of Vital Sign Screening in the Development Program

Vital signs were recorded at screening, at baseline, at protocol-specific interval time points, and at the end of the study in all trials. These measurements included blood pressure (systolic and diastolic), heart rate, and respiratory rate. A clinically relevant decrease in blood pressure was defined as a decrease from the baseline value in either systolic or diastolic blood pressure of ≥10mm Hg.

7.3.6.2.2 Selection of Studies and Analyses for Overall Drug-Control Comparisons

An analysis of vital signs was conducted separately on each double-blind trial, on pooled results of the double-blind trials, and on the pooled results of the open-label trials. A comparison between treatment groups and dosage groups was performed. In the open-label studies, patients were also classified according to their prior use of opioids. Mean change from baseline to each time point was analyzed.

7.3.6.2.3 Analyses and Exploration of Data

In the healthy volunteers, analysis of the primary vital sign data from all formulation and dosage groups revealed no trends toward ——— associated or induced abnormalities. The changes and mean changes from baseline of blood pressure, heart rate, and respiratory rate were neither clinically nor statistically significant.

For all treatment groups in the double-blind trials, the mean changes in systolic and diastolic pressure were neither statistically nor clinically significant. In addition, there was no evidence that blood pressure changes were dose-related. The percentage of patients in the opioid-naïve population (osteoarthritis Trial 004-04) exposed to both ——— and MS Contin had blood pressure changes that were slightly greater than for patients in the chronic use population (Trial 004-02). The following table illustrates these results.

Table 7.10
Patients with ≥ 10mm Hg Decrease in Blood Pressure
(Double-Blind Trials)

Blood Pressure Number (%)	Treatment Group						
	——— *133%*	——— *100%*	*50%*	*30mg*	*MS Contin 100%*	*MS Contin bid*	*Placebo*
Systolic	17 (24.6)	14 (20.6)	19 (27.5)	53 (37.7)	10 (14.5)	37 (48.7)	25 (34.2)
Diastolic	17 (24.6)	12 (17.6)	9 (13.0)	28 (19.2)	11 (15.9)	23 (30.3)	15 (20.5)

From Sponsor's in-text Table 5-15, Vol. 2.109, p. 38.

See APPENDIX P for a more detailed summary of population-specific changes in blood pressure.

In the double-blind trials, mean changes in heart rate and respiratory rate were similar between patient populations and treatment groups and were not statistically or clinically significant. Vital sign changes, categorized by dose and treatment groups, that were classified as adverse events are tabulated below.

Table 7.11
Number (%) of Patients with Vital Sign Abnormalities Reported as Adverse Events (Double-Blind Trials)

Vital Sign	Treatment Group								
	30-60	*61-200*	*201-400*	*>400*	*MS Contin 30-60*	*MS Contin 61-200*	*MS Contin 201-400*	*MS Contin >400*	*Placebo*
↑ BP	1 (0.4%)								2 (2.8%)
↓ BP	1 (0.4%)								
↑ HR	1 (0.4%)								1 (0.4%)
↓ HR						1 (2.0%)			
↑ RR	3 (1.8%)	2 (2.0%)	1 (2.8%)		2 (2.0%)				
↓ RR			1 (2.8%)						

From Sponsor's Table 18B (1), Vol. 2.116, pp. 1-227.

In the combined double-blind and open-label trials, there was a tendency for opioid-naïve patients to have greater mean changes in heart rate, blood pressure, and respiratory rate than chronic use patients. However, these changes were statistically and clinically insignificant. Heart rate, blood pressure, and respiratory rate changes, categorized by dose and treatment groups, that were classified as adverse events are tabulated below.

Table 7.12
Number (%) of Patients with Vital Sign Abnormalities Reported as Adverse Events (Combined Double-Blind and Open-Label Trials)

Vital Sign	Treatment Group							
	133%	*100%*	*50%*	*30mg am*	*30mg pm*	*MS Contin 100%*	*MS Contin 15mg bid*	*Placebo*
↑ BP		5 (1.3%)		4 (2.4%)	3 (1.8%)			2 (2.7%)
↓ BP		2 (0.5%)		2 (1.2%)	1 (0.6%)			
↑ HR				1 (0.6%)	2 (1.2%)			1 (1.4%)
↓ HR		2 (0.5%)		1 (0.6%)		1 (1.1%)		
↑ RR	1 (1.4%)	14 (3.6%)	2 (2.3%)	2 (1.2%)	4 (2.5%)	1 (1.1%)	1 (1.3%)	2 (1.2%)
↓ RR	1 (1.4%)	1 (0.3%)						

From Sponsor's 11-01-00 submission, Attachment 1, Table 14, pp. 1-15.

7.3.6.2.4 Discontinuations for Vital Sign Abnormalities

There were only two patients in the double-blind trials that were discontinued for vital sign abnormalities. Both of these patients were in the osteoarthritis [redacted] 30mg