

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number      **20-676****

**STATISTICAL REVIEW(S)**

MAY 23 1995

## Statistical Review and Evaluation

NDA #: 20,499  
 Drug Name: Actron, ketoprofen, 12.5 mg tablets  
 Take 1 or 2 tablets every 4-6 hours up to 6 tablets/day.  
 OTC Indication: Temporarily relief for pain, dysmenorrhea, headache, and fever.  
 Sponsor: Bayer  
 Sponsor's Letter Dated: 7/15/94  
 Documents Reviewed: Vols. 1.1, 1.104, 1.106, 1.110, 1.112, 1.113, 1.116, 1.120, 1.124, 1.129.  
 Date Received: 7/25/94  
 Statistician: Richard A. Stein, PhD  
 Statistical Review Date: May 23, 1995 (13 page review)  
 Primary Medical Reviewer: Christina Fang, MD  
 Consumer Safety Officer: David Morgan

### 1. Introduction

The applicant's statistical results for the over the counter (OTC) indication categories of pain, fever, and dysmenorrhea are given below. Study characteristics and results are interpreted and more completely summarized in the medical officer's review. All studies were placebo controlled. All studies had an active control and included the dose of 12.5 mg ketoprofen. Ketoprofen doses studied ranged across studies from 6.25 to 25 mg.

This review is based on the principles set forward in the public joint Nonprescription Drug and Arthritis Advisory Committee meeting held September 8-9, 1994.

#### Statistical Evidence of Efficacy for 12.5 mg Ketoprofen in Pain

Study	Investigator	Time-to-Onset	Relief from Pain	Time-to-Remedication
90-002	Sunshine	yes (1)	yes	yes
91-008	Mehlisch	yes	yes	yes
92-008	Marrero	yes	yes	yes
92-009	Mehlisch	no (2)	yes	yes

#### Statistical Evidence of Efficacy for 12.5 mg Ketoprofen in Fever

Study	Investigator	Mean Temperature	Maximum Temperature
92-002	McMahon	yes	yes
92-003	Schachtel	yes	yes

(1) yes: p-value  $\leq$  0.05, 2-sided comparison to placebo

(2) no: p-value  $>$  0.05, 2-sided comparison to placebo

**Statistical Evidence of Efficacy for 12.5 mg Ketoprofen in Dysmenorrhea**

Study	Investigator	Relief from Pain
92-001	Fulmer	no (2)
92-004	Nelson	yes (1)
92-012	Kisicki	yes

- (1) yes: p-value  $\leq 0.05$ , 2-sided comparison to placebo  
 (2) no: p-value  $> 0.05$ , 2-sided comparison to placebo

**2. Review by Indication Category**

**A. Pain**

The applicant's statistical methods are considered appropriate for the data at hand. This reviewer has checked the analysis of study 90-002, and has verified the applicant's essential statistical finding that 12.5 mg ketoprofen is effective in reducing pain (2-sided  $p < 0.05$  for drug effect).

Studies 90-002, 91-008, 92-008, and 92-009 were all single investigator studies analyzed for drug main effect using an ANOVA model of the form  $y = \mu + T(i) + y_0(ij) + \text{error}$ . There  $y$  represents Pain Intensity Difference (PID), Pain Relief (PR), and the PRID = PID + PR efficacy variables,  $T$  is a drug main effect term, and  $y_0(ij)$  is a baseline Pain Intensity term for patient  $j$  receiving drug  $i$ .

Time to onset of meaningful pain relief was measured by stopwatch in studies 90-002 and 92-008. These stopwatch times to onset are not clearly comparable to the results based on estimating time to onset as  $[30/\text{mean PRID}]$ . These times are displayed below.

		Time-to-Onset (Minutes)			
		Meaningful		PRID Based	
Drug	Study:	90-002	92-008	90-002	92-008
Ketoprofen 12.5 mg		41	38	17	17
Ibuprofen 200 mg		58	44	33	25
Placebo		67	63	58	44

Time-to-Remedication was analyzed statistically by an adaptation of Fisher's protected LSD procedure to the logrank test.

**B. Fever**

The applicant's statistical methods are considered appropriate for the data at hand. This reviewer has checked the analysis of study 92-003 for natural fever and has verified the applicant's essential statistical finding that 12.5 mg ketoprofen is effective in reducing fever (2-sided  $p < 0.05$  for drug effect).

The applicant submitted two fever studies. Study 92-002 is in induced fever. Study 92-003 is in natural fever. The natural fever study was chosen because it was both placebo controlled and in natural fever. I analyzed average 6-hour, and maximum 6-hour fever reduction using an ANOVA model of the form  $y = \mu + T(i) + C(j) + t_0(ijk) + \text{error}$ . Here  $y$  represents average 6-hour and maximum 6-hour fever reduction,  $\mu$  is an overall mean temperature reduction taken across study drugs,  $T$  is a drug effect term for drug  $i$ ,  $C$  is an investigator-effect and  $t_0(ijk)$  is the baseline fever for subject  $k$  in center  $j$ .

receiving drug *i*. In the Schachtel study 92-003, a 95% confidence interval on the maximum difference in the reduction of induced fever between 12.5 mg ketoprofen and placebo was  $1.2 \pm 0.4$  degrees Fahrenheit and  $1.4 \pm 0.4$  degrees Fahrenheit between 25 mg ketoprofen and placebo (see Contrasts on page 13).

### C. Dysmenorrhea

The applicant's statistical methods are considered appropriate for the data at hand. This reviewer has checked the analysis of dysmenorrhea study 92-004, and has verified the applicant's essential statistical findings (2-sided  $p < 0.05$  for drug effect) that 12.5 mg and 25 mg Ketoprofen are effective in dysmenorrhea.

This trial was planned as a crossover design with 4 periods and 4 treatment groups which I analyzed using an ANOVA model of the form

$y = \mu + T(i) + Cycle(j) + Pt(k) + y_0(jk) + error$ . There *y* represents Pain Intensity Difference (PID), Pain Relief (PR), and the PRID = PID + PR efficacy variables, *T* is a drug main effect term, *Cycle* is a term for menstrual cycle, *Pt*(*k*) is a patient block effect, and  $y_0(jk)$  is a baseline Pain Intensity term for patient *k* in cycle *j*.

### 3. Discussion of the Analysis of Fever Studies

The purpose here is to show that apparently dissimilar analyses by the sponsor can be merged onto one under appropriately defined statistical modeling that I will identify soon.

In fever studies, a patient's body temperature is measured at pre-selected time intervals. For any patient, the baseline or time zero evaluation is the first time that patient's body temperature is measured. Temperature measurements are then commonly taken sequentially at 1/2, 1, 2, 3, 4, 5, and 6 hours after the original baseline temperature was recorded.

In the appendix are found the numerical details and the related computer output of the statistical analyses of study 90-003. The variables analyzed are 6-hour temperature AUC, mean 6-hour fever temperature, 6-hour temperature difference from baseline AUC and mean fever 6-hour temperature difference from baseline. These are described under **a**, **b**, **c**, and **d** below and the calculations in the appendix are based on the statistical model that needs be applied to unify these analyses.

**a.** A commonly encountered efficacy variable is constructed for each patient by computing the area under that patient's temperature curve (AUC). These areas can then be compared across the patient groups assigned to the different drugs in that trial. In evaluating these results, it can be correctly argued that such an analysis does not account for patient baseline temperature. The patients assigned to one drug group could have on average, higher baseline temperatures. Conceivably, this could spoil the comparison of the AUCs for the affected drug groups.

**b.** An apparent remedy for this potential disparity in patient baseline temperatures is to calculate differences from baseline body temperature. These differences from baseline can be used to produce a new time curve; and a corresponding area under the curve can again be computed. These AUCs, now based on difference from baseline temperature, can then be compared in the same way as the AUCs for raw body temperature described in the previous paragraph.

Simple t-tests for drug group differences based on raw AUCs and difference from baseline AUCs are expected to be numerically and possibly inferentially different. In an effort to control for baseline temperature inequities, some trials apply a randomization stratified on baseline body temperature. I believe this is good practice, even though I don't believe failure to stratify is a fatal design flaw.

c. AUCs are not numbers that people interpret easily. However, for any patient, if we were to take the computed raw body temperature AUC and divide it by the length of the observation period, then a mean temperature weighted proportionally to the length of the time segments would be computed patient by patient. This could be analyzed for drug group differences.

d. If, as in c, we were to take the patient AUCs based on difference from baseline temperature as defined in b, and divide by the length of the observation period, then a weighted mean temperature *difference* would be computed for each patient. This could be analyzed for drug group differences.

My point is that if one were to analyze the data, from a, b, c, or d under the framework of an ANOVA statistical model  $y = \mu + T(i) + C(j) + y_0 + \text{error}$  where y is one of the efficacy variables defined under a, b, c, or d,  $\mu$  is a grand mean, T(i) is a drug effect, C(j) is a center effect and  $y_0$  is the baseline value of y, i.e., a model that accounts for treatment, center, and baseline, rather than the more naive model one might assume in a, b, c, or d, then in all important aspects, the statistical results are either identical or quickly and simply derivable one from the other.

#### 4. Conclusions

- A. Studies 90-002, 91-008, 92-008, and 92-009 provide adequate statistical evidence of the effectiveness of Actron for the indication of pain.
- B. Study 92-003 in natural fever and Study 92-002 in induced fever provide adequate statistical evidence of the effectiveness of Actron for the indication of fever.
- C. Studies 92-004 and 92-012 provide adequate statistical evidence of the effectiveness of Actron for the indication of dysmenorrhea.
- D. No studies were conducted in headache by the sponsor. Therefore, there is currently inadequate evidence that Actron is effective for the labeled indication of headache.
- E. In the statistical analyses of fever trials, (1) area under the time-temperature curve, (2) area under the time-temperature difference from baseline curve, and (3) mean temperature difference from baseline are all redundant. They contain no information that can not be easily derived from a statistical analysis of ordinary mean fever temperature of each patient using a statistical ANCOVA model that includes a drug group main effect and baseline temperature as a covariate.

Richard A. Stein, Ph.D.  
Mathematical Statistician

Peer Reviewer:

5/23/95  
Hoi M. Leung, PhD

Original NDA 20-499

CC: HFD-007/Christina Fang, M.D.  
HFD-713/Dr. Dubey  
HFD-007/David Morgan, CSO  
HFD-007/Div. File

# Appendix

Abbreviated JMP output of the analyses of 6-hour temperature AUC, mean 6-hour fever temperature, 6-hour temperature difference from baseline AUC and mean fever 6-hour temperature difference from baseline described under a, b, c, and d follow.

**Table of Appendix Contents (Study 92-003)**

Item	Page
2-Way ANCOVA of 6-hour temperature AUC	6
2-Way ANCOVA of 6-hour mean temperature	8
2-Way ANCOVA of 6-hour baseline temperature difference AUC	10
2-Way ANCOVA of 6-hour mean difference from baseline temperature	12

**Noteworthy Facts:**

1. The (Effect Test p-values for TRT) p-value for drug main effect, which are derived from the F-statistics, are all the same in the four analyses found on pages 6, 8, 10, and 12 based on my proposed 2-way ANCOVA model.
2. The estimates of the difference in drug effects are essentially identical. For instance, let us examine the AUC analyses together and separately the mean 6-hour temperature analyses together to see that the AUC results are essentially the same and the 6-hour mean temperature results are the same. Then we will see that the AUC and the 6-hour mean temperature results are essentially the same because they are directly linked mathematically.

Consider the Ketoprofen 12.5 mg minus placebo AUC contrast. From page 7 of the ANCOVA, this difference equals  $36187.16 - 36605.74 = -419$  for the complete AUC. From page 11, this difference equals  $364.09 - (-54.49) = 419$  for the difference from baseline AUC. These results are essentially the same because they differ by only a change of sign.

Consider the Ketoprofen 12.5 mg minus placebo 6-hour mean temperature contrast. From page 9 of the ANCOVA, this difference equals  $100.52 - 101.68 = -1.2$  °F for 6-hour mean temperature. From page 13, this difference equals  $1.01 - (-0.15) = 1.2$  °F for the 6-hour mean temperature difference from baseline. These results are essentially the same because they differ by only a change of sign.

Finally the AUC Ketoprofen 12.5 mg minus placebo AUC contrast of 419 units and the Ketoprofen 12.5 mg minus placebo 6-hour mean temperature contrast of 1.2 units are mathematically related through the 6-hour time period. Six hours contain 360 minutes. Thus, if we divide the AUC by 360 we have  $419/360 = 1.2$ . This is the difference in adjusted mean temperature based on my proposed 2-way ANCOVA model.

3. The parameter estimates associated with baseline temperature, T0, are respectively 281.32, 0.781, 78.68, and 0.219 based on pages 6, 8, 10, and 12. One way to see the relationship of these parameters is to consider the first 3 parameters 281.32, 0.781, 78.68, and to note that the last parameter is obtained from the first three by making use of only the numbers 1 and 360, i.e.,  $[1-(281.32/360)] = 0.219$ ,  $[1-0.781] = 0.219$ , and  $[78.68/360] = 0.219$ .

**Response: AUCF06 is 6-hour temperature AUC**  
**Summary of Fit**

RSquare 0.623191  
 RSquare Adj 0.581742  
 Root Mean Square Error 260.969  
 Mean of Response 36286.94  
 Observations (or Sum Wgts) 112

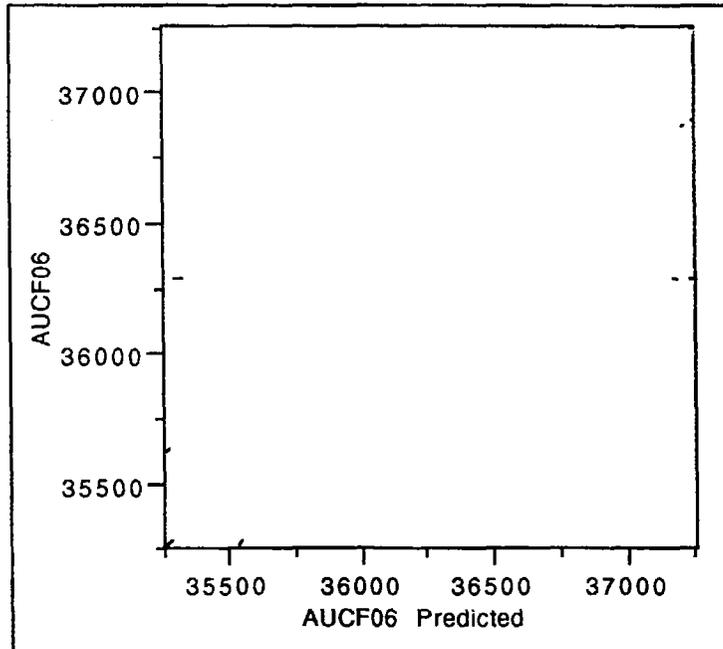
**Parameter Estimates**

Term	Estimate	Std Error	t Ratio	Prob> t
Intercept		3131.714	2.46	0.0157
TRT[ACETAM, PLACEBO]		44.67963	-2.81	0.0060
TRT[KET25, PLACEBO]		43.18869	-1.72	0.0894
TRT[KET12.5, PLACEBO]		43.22839	-3.35	0.0011
Center[1, 8]		70.71402	1.50	0.1358
Center[10, 8]		165.7069	-0.28	0.7838
Center[13, 8]		99.86908	-1.04	0.2997
Center[2, 8]		59.60824	0.32	0.7476
Center[3, 8]		66.39288	0.69	0.4939
Center[5, 8]		99.68436	-0.58	0.5628
Center[6, 8]		52.37807	0.30	0.7674
T0		30.87985	9.11	0.0000

**Effect Test**

Source	Nparm	DF	Sum of Squares	F Ratio	Prob>F
TRT	3	3	4509904.4	22.0733	0.0000
Center	7	7	252718.1	0.5301	0.8099
T0	1	1	5652348.5	82.9948	0.0000

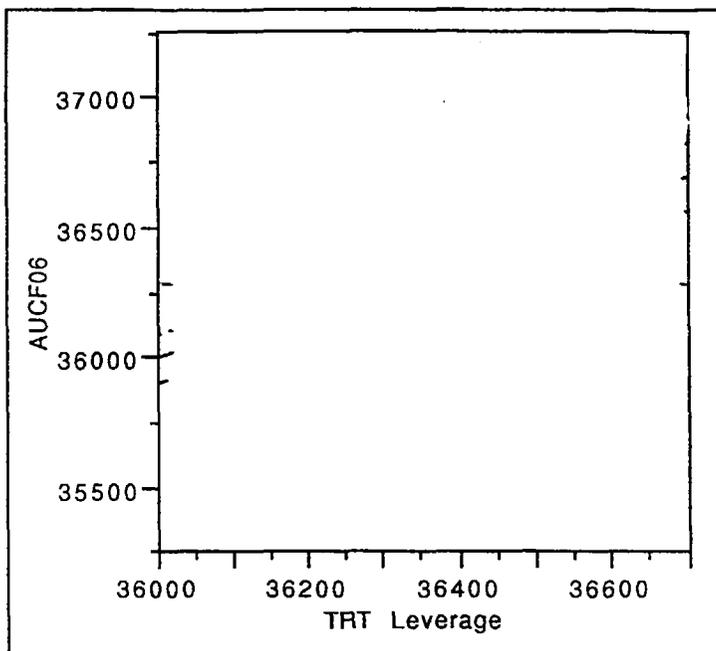
**Whole-Model Test**



**Analysis of Variance**

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	11	11263625	1023966	15.0351
Error	100	6810484	68105	Prob>F
C Total	111	18074109		0.0000

**TRT**



**Effect Test**

Sum of Squares	F Ratio	DF	Prob>F
4509904.4	22.0733	3	0.0000

**Least Squares Means**

Level	Least Sq Mean	Std Error	Mean
ACETAMINOPHEN 650	36135.82067	59.98657163	36202.4
KETOPROFEN 12.5	36187.15717	56.36368352	36151.1
KETOPROFEN 25 MG	36116.20286	55.70165706	36144.9
PLACEBO	36605.73945	53.85722474	36635.6

**Contrast**

ACETAMINOPHEN 650	0	0	1	0	1
KETOPROFEN 12.5	0	1	0	-1	-1
KETOPROFEN 25 MG	1	0	0	1	0
PLACEBO	-1	-1	-1	0	0
Estimate	-489.5	-418.6	-469.9	-70.95	-51.34
Std Error	69.578	69.715	71.682	70.498	71.993
t Ratio	-7.036	-6.004	-6.556	-1.006	-0.713
Prob> t	3e-10	3.1e-8	2.5e-9	0.3166	0.4775
SS	3.37e6	2.46e6	2.93e6	68990	34630
Sum of Squares	4509904.3953			73447.675378	
Numerator DF	3			2	
F Ratio	22.073344068			0.5392251146	
Prob > F	4.758334e-11			0.5848860631	

Response: Tmean6 (= 6-Hour mean temperature)

Summary of Fit

RSquare 0.623191  
 RSquare Adj 0.581742  
 Root Mean Square Error 0.724914  
 Mean of Response 100.7971  
 Observations (or Sum Wgts) 112

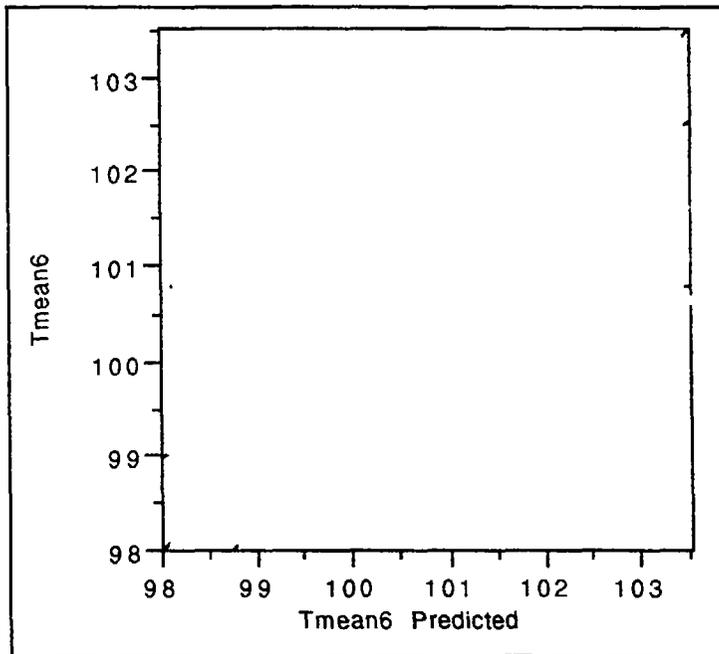
Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob> t
Intercept		8.699205	2.46	0.0157
TRT[ACETAM, PLACEBO]		0.124110	-2.81	0.0060
TRT[KET25, PLACEBO]		0.119969	-1.72	0.0894
TRT[KET12.5, PLACEBO]		0.120079	-3.35	0.0011
Center[1, 8]		0.196428	1.50	0.1358
Center[10, 8]		0.460297	-0.28	0.7838
Center[13, 8]		0.277414	-1.04	0.2997
Center[2, 8]		0.165578	0.32	0.7476
Center[3, 8]		0.184425	0.69	0.4939
Center[5, 8]		0.276901	-0.58	0.5628
Center[6, 8]		0.145495	0.30	0.7674
T0		0.085777	9.11	0.0000

Effect Test

Source	Nparm	DF	Sum of Squares	F Ratio	Prob>F
TRT	3	3	34.798645	22.0733	0.0000
Center	7	7	1.949986	0.5301	0.8099
T0	1	1	43.613800	82.9948	0.0000

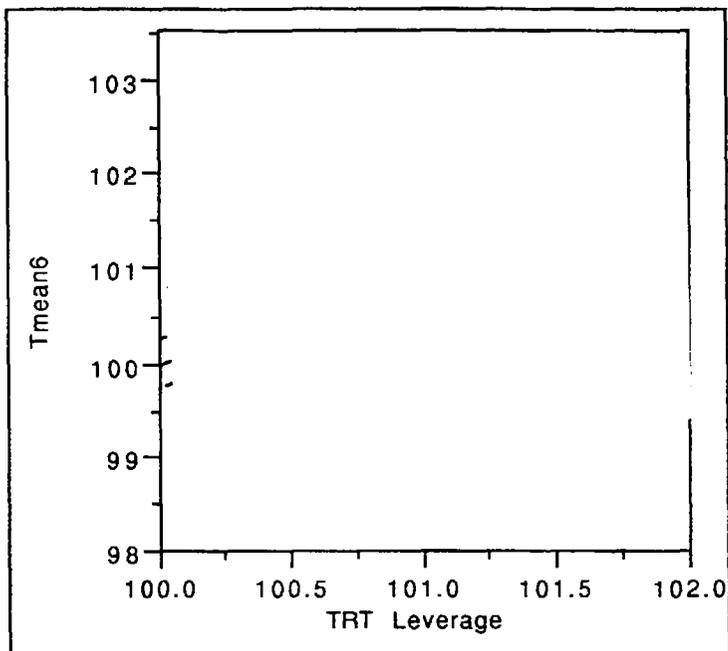
Whole-Model Test



**Analysis of Variance**

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	11	86.91069	7.90097	15.0351
Error	100	52.55003	0.52550	Prob>F
C Total	111	139.46072		0.0000

**TRT**



**Least Squares Means**

Level	Least Sq Mean	Std Error	Mean
ACETAMINOPHEN 650	100.3772796	0.1666293657	100.562
KETOPROFEN 12.5	100.5198810	0.1565657876	100.420
KETOPROFEN 25 MG	100.3227857	0.1547268252	100.403
PLACEBO	101.6826096	0.1496034021	101.766

**Contrast**

ACETAMINOPHEN 650	0	0	1	0	1
KETOPROFEN 12.5	0	1	0	-1	-1
KETOPROFEN 25 MG	1	0	0	1	0
PLACEBO	-1	-1	-1	0	0
Estimate	-1.360	-1.163	-1.305	-0.197	-0.143
Std Error	0.1933	0.1937	0.1991	0.1958	0.2000
t Ratio	-7.036	-6.004	-6.556	-1.006	-0.713
Prob> t	3e-10	3.1e-8	2.5e-9	0.3166	0.4775
SS	26.014	18.944	22.584	0.5323	0.2672
Sum of Squares	34.798645025			0.5667258903	
Numerator DF	3			2	
F Ratio	22.073344068			0.5392251146	
Prob > F	4.758334e-11			0.5848860631	

**Response: AUCFC06 (= 6-Hour difference from baseline AUC)**  
**Summary of Fit**

RSquare 0.437802  
 RSquare Adj 0.375960  
 Root Mean Square Error 260.969  
 Mean of Response 264.308  
 Observations (or Sum Wgts) 112

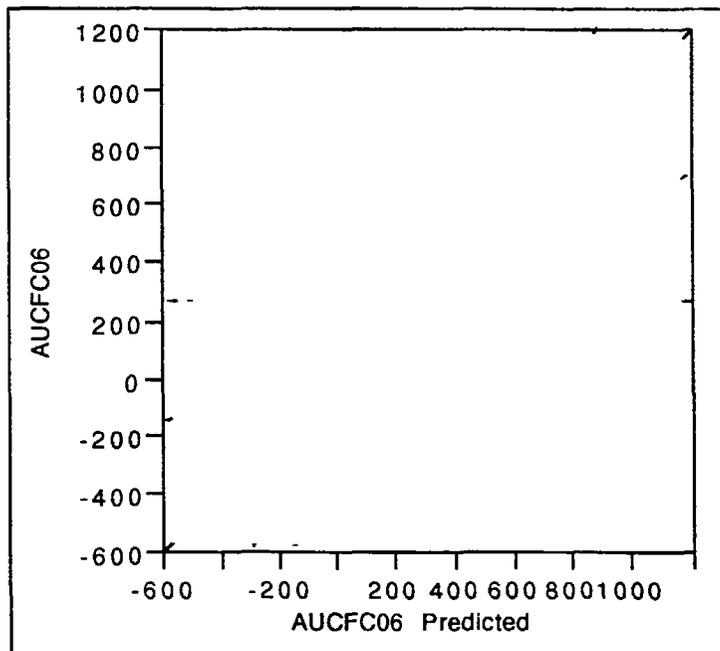
**Parameter Estimates**

Term	Estimate	Std Error	t Ratio	Prob> t
Intercept		3131.714	-2.46	0.0157
TRT{ACETAM, PLACEBO}		44.67963	2.81	0.0060
TRT{KET25, PLACEBO}		43.18869	1.72	0.0894
TRT{KET12.5, PLACEBO}		43.22839	3.35	0.0011
Center[1, 8]		70.71402	-1.50	0.1358
Center[10, 8]		165.7069	0.28	0.7838
Center[13, 8]		99.86908	1.04	0.2997
Center[2, 8]		59.60824	-0.32	0.7476
Center[3, 8]		66.39288	-0.69	0.4939
Center[5, 8]		99.68436	0.58	0.5628
Center[6, 8]		52.37807	-0.30	0.7674
T0		30.87985	2.55	0.0124

**Effect Test**

Source	Nparm	DF	Sum of Squares	F Ratio	Prob>F
TRT	3	3	4509904.4	22.0733	0.0000
Center	7	7	252718.1	0.5301	0.8099
T0	1	1	442135.5	6.4920	0.0124

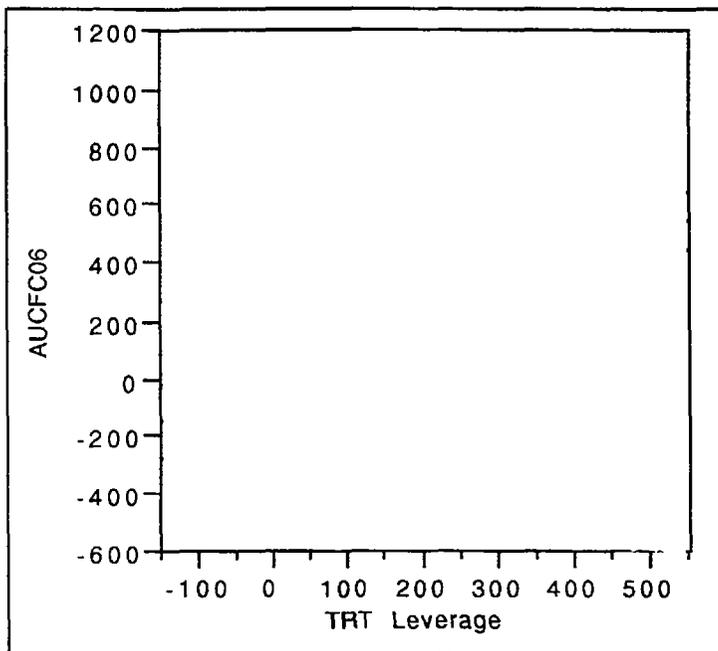
**Whole-Model Test**



**Analysis of Variance**

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	11	5303544	482140	7.0794
Error	100	6810484	68105	Prob>F
C Total	111	12114028		0.0000

**TRT**



**Least Squares Means**

Level	Least Sq Mean	Std Error	Mean
ACETAMINOPHEN 650	415.4293303	59.98657163	405.404
KETOPROFEN 12.5	364.0928338	56.36368352	325.552
KETOPROFEN 25 MG	435.0471361	55.70165706	419.518
PLACEBO	-54.4894489	53.85722474	-73.293

**Contrast**

ACETAMINOPHEN 650	0	0	1	0	1
KETOPROFEN 12.5	0	1	0	-1	-1
KETOPROFEN 25 MG	1	0	0	1	0
PLACEBO	-1	-1	-1	0	0
Estimate	489.54	418.58	469.92	70.954	51.336
Std Error	69.578	69.715	71.682	70.498	71.993
t Ratio	7.0358	6.0042	6.5556	1.0065	0.7131
Prob> t	3e-10	3.1e-8	2.5e-9	0.3166	0.4775
SS	3.37e6	2.46e6	2.93e6	68990	34630
Sum of Squares	4509904.3953			73447.675377	
Numerator DF	3			2	
F Ratio	22.073344068			0.5392251146	
Prob > F	4.758334e-11			0.5848860631	

Response:  $\Delta T_{\text{mean6}}$  (= 6-Hour mean temperature change from Baseline)  
 Summary of Fit

RSquare 0.437802  
 RSquare Adj 0.375960  
 Root Mean Square Error 0.724914  
 Mean of Response 0.734189  
 Observations (or Sum Wgts) 112

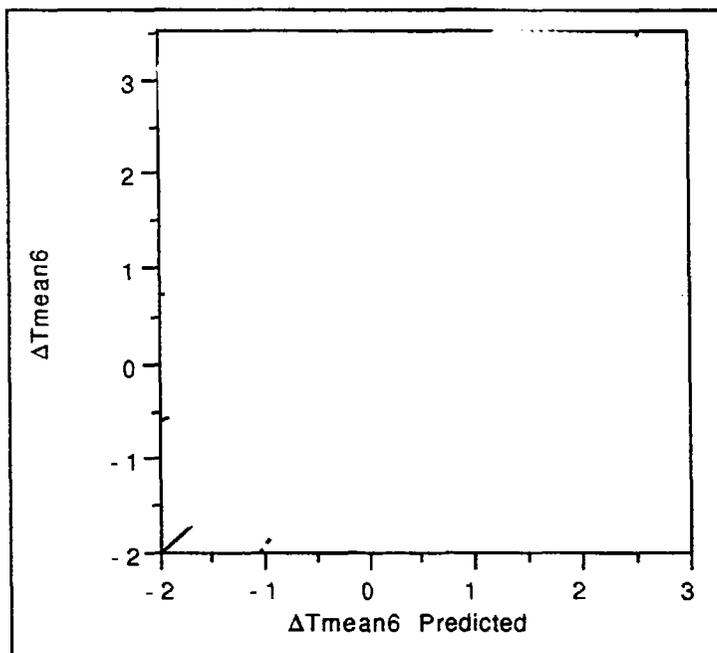
Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob> t
Intercept		8.699205	-2.46	0.0157
TRT[ACETAM, PLACEBO]		0.124110	2.81	0.0060
TRT[KET25, PLACEBO]		0.119969	1.72	0.0894
TRT[KET12.5, PLACEBO]		0.120079	3.35	0.0011
Center[1, 8]		0.196428	-1.50	0.1358
Center[10, 8]		0.460297	0.28	0.7838
Center[13, 8]		0.277414	1.04	0.2997
Center[2, 8]		0.165578	-0.32	0.7476
Center[3, 8]		0.184425	-0.69	0.4939
Center[5, 8]		0.276901	0.58	0.5628
Center[6, 8]		0.145495	-0.30	0.7674
T0		0.085777	2.55	0.0124

Effect Test

Source	Nparm	DF	Sum of Squares	F Ratio	Prob>F
TRT	3	3	34.798645	22.0733	0.0000
Center	7	7	1.949986	0.5301	0.8099
T0	1	1	3.411539	6.4920	0.0124

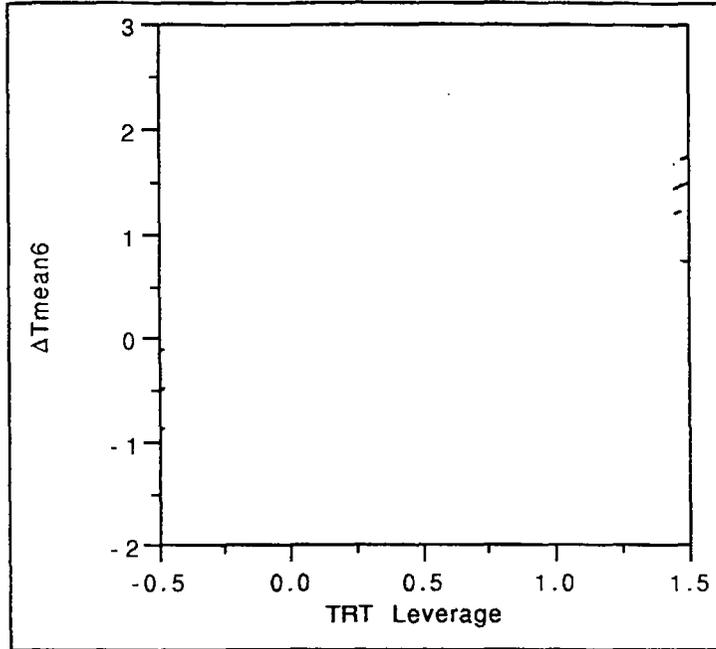
Whole-Model Test



**Analysis of Variance**

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	11	40.922408	3.72022	7.0794
Error	100	52.550027	0.52550	Prob>F
C Total	111	93.472435		0.0000

**TRT**



**Least Squares Means**

Level	Least Sq Mean	Std Error	Mean
ACETAMINOPHEN 650	1.153970362	0.1666293657	1.12612
KETOPROFEN 12.5	1.011368983	0.1565657876	0.90431
KETOPROFEN 25 MG	1.208464267	0.1547268252	1.16533
PLACEBO	-0.151359580	0.1496034021	-0.20359

**Contrast**

ACETAMINOPHEN 650	0	0	1	0	1
KETOPROFEN 12.5	0	1	0	-1	-1
KETOPROFEN 25 MG	1	0	0	1	0
PLACEBO	-1	-1	-1	0	0
Estimate	1.3598	1.1627	1.3053	0.1971	0.1426
Std Error	0.1933	0.1937	0.1991	0.1958	0.2000
t Ratio	7.0358	6.0042	6.5556	1.0065	0.7131
Prob> t	3e-10	3.1e-8	2.5e-9	0.3166	0.4775
SS	26.014	18.944	22.584	0.5323	0.2672
Sum of Squares	34.798645025			0.5667258903	
Numerator DF	3			2	
F Ratio	22.073344068			0.5392251146	
Prob > F	4.758334e-11			0.5848860631	