

**SINGLE DOSE BIOEQUIVALENCE STUDY OF PENTOXIFYLLINE 400 MG
TABLETS UNDER FED CONDITIONS**

I. STUDY OBJECTIVE

This study compared the relative bioavailability of pentoxifylline following a single oral dose (1 x 400 mg) of pentoxifylline tablets (Pentoxil™) by Upsher-Smith Laboratories, Inc. with that of Trental® by Hoechst-Roussel Pharmaceuticals, Inc. in healthy adult male volunteers under non-fasting conditions. The study also compared the differences in plasma concentrations of pentoxifylline after dosing the test formulation with and without food.

II. INVESTIGATORS AND FACILITIES

Clinical Research Facilities and Investigators:

Same as for Fasting Study

Clinical Laboratory Facilities:

Analytical Facility:

Same as Fasting Study

Statistical Analysis:

Same as Fasting Study

III. STUDY DATES

Dose administration: Period I, 3/16-17/96; Period II, 3/23-24/96; Period III, 3/30-31/96

Analytical completed: Between 4/2-30/96 using _____ method

Between 7/24-8/20/96 using _____ method

IV. EXPERIMENTAL

Same as for fasting study except as noted:

Test Product; Lot No. 15869 (a sub-lot of the manufactured lot #61037, _____ ablets)

Reference Product Lot No. 0780665; Exp. Date 02/97

Design: Randomized, single dose, three-way crossover

Number of Subjects: Eighteen healthy adult men and six alternates initiated the study.

Dosage: 1x400 mg tablet

Fluid and Food Intake:

Breakfast: At 30 minutes before dosing, the appropriate randomized subjects were served a standardized, high fat breakfast:

one buttered English muffin

one fried egg

one slice of American cheese

one slice of Canadian bacon

one serving of hash brown potatoes

180 mL of orange juice

240 mL of whole milk

V. ANALYTICAL

Determination of Pentoxifylline and its Major Metabolites, MI and MV, in Human Plasma Samples by

Method

VI. CLINICAL NOTES

Twenty-four (24) subjects (18 plus 6 alternates) were recruited for this study. All volunteers were healthy adult males and had completed an acceptable medical history, medication history, physical examination, an electrocardiogram, screens for HIV 1 & 2 antibody, hepatitis B surface antigen and drugs of abuse prior to study initiation. Selected routine clinical laboratory measurements were performed during screening. The screening urinalysis values were unremarkable. The urine drug abuse screen was negative for all subjects. Upon completion of the study, the physical examination and selected clinical laboratory measurements were repeated.

On study days 1, 8 and 15, a single oral dose (1 x 400 mg tablet) of test pentoxifylline tablets or reference pentoxifylline tablets (Trental[®]) was administered to volunteers. Each subject was dosed with one of the three regimens given below in a randomized fashion so that each subject was dosed with all regimens upon completion of the study:

1. 1 tablet of test product with _____ of room temperature water 30 minutes after initiation of a standardized, high fat breakfast
2. 1 tablet of test product with _____ of room temperature water without breakfast
3. 1 tablet of reference product with _____ of room temperature water 30 minutes after initiation of a standardized, high fat breakfast

Meals and fluid intake were controlled during each 24 hour post-dose confinement period.

Blood sampling (19 per subject each period) for drug content analysis occurred within one hour prior to dosing (0 hour) and after dose administration at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, and 30 hours. The blood samples were collected in EDTA vacutainers, centrifuged, and the plasma pipetted into polypropylene tubes, frozen and stored until shipment for analysis. All samples were processed under yellow lighting and placed in the freezer within 1 hour of collection. Upon completion of the study, the plasma samples were packed on dry ice for express overnight delivery to the analytical facility, CEDRA Corporation, Inc. for determination of the pentoxifylline, MI, and MV plasma concentrations by a validated analytical procedure.

All twenty-four volunteers successfully completed the study.

There were five deviations from the protocol instructions of no nonprescription medications within 7 days of Period I dosing. These medications were aspirin, Tylenol, vitamin C, and Excedrin. In the opinion of the clinical investigators these deviations should not compromise the validity of the study.

Blood pressure and heart rate were measured prior to dosing, at 12 and 24 hours after each dose, and upon completion of the study. In assessing the subjects and reported values for heart rate and blood pressure, none of the reported changes, though numerically significant at times, were clinically significant. It is the opinion of the investigators, that none of the changes could be directly

attributed to the drug product tested.

Some subjects reported using OTC drugs during the study. In the opinion of the clinical investigators, the problems and medication usage reported were not related to study medication or study participation and should not affect the integrity of the study.

Thirty-three adverse events were reported in thirteen of twenty-four subjects dosed and included the following events (incidence): dysphonia(1- hoarse throat), earache (1), fatigue (1 - tired), fever(2; 1-fever, 1-feverish), headache (12), laceration left hand (1), malaise (1-body aches), nausea (1), pain (1 - left arm sore), pharyngitis (5 - sore throat), purpura (2; 1 - left arm knot, 1 small welt left arm), respiratory disorder(2; 1 - nasal congestion, 1 - stuffy head), rhinitis (2; 1 clogged nose, 1 - runny nose), and sinusitis (1 - sinus congestion). There were no serious adverse events or any events which required terminating any subject from the study.

In general, the clinical laboratory values were unremarkable over the course of the study. Also, the clinical portion of the project was completed without any significant sequelae attributable to the investigational drug. In general, all blood collections were successfully completed as per protocol design. The safety monitoring was completed to the satisfaction of the clinical investigators. The clinical laboratory values were considered unremarkable and none of the values outside of the reference range at study exit were considered directly attributable to the product. In the opinion of the investigators, the clinical portion of the project was successfully completed.

VII. PHARMACOKINETIC STUDY RESULTS

The results of the comparison of the three treatments for the parent compound, MI, and MV are summarized in the following tables. For all pharmacokinetic parameters, comparable food effects were shown for both formulations.

Table 11
Mean Plasma Concentrations of Pentoxifylline 24 Subjects
Following a Single-Dose of Pentoxifylline 400 mg Extended Release
Tablet under Non-Fasting Conditions

| TIME | MEAN1 | SD1 | MEAN2 | SD2 | MEAN3 | SD3 | RMEAN12 | RMEAN13 |
|------|--------|--------|-------|-------|--------|-------|---------|---------|
| 0 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | . | . |
| 0.5 | 19.71 | 19.42 | 58.96 | 23.76 | 12.68 | 10.49 | 0.33 | 1.55 |
| 0.75 | 29.61 | 22.58 | 61.90 | 21.61 | 24.97 | 21.02 | 0.48 | 1.19 |
| 1 | 40.65 | 26.35 | 55.62 | 19.88 | 31.10 | 18.42 | 0.73 | 1.31 |
| 1.5 | 46.59 | 25.40 | 54.63 | 23.03 | 55.13 | 45.84 | 0.85 | 0.85 |
| 2 | 58.65 | 34.95 | 54.00 | 22.37 | 73.98 | 94.13 | 1.09 | 0.79 |
| 2.5 | 60.68 | 45.50 | 47.05 | 25.85 | 67.33 | 67.20 | 1.29 | 0.90 |
| 3 | 67.78 | 52.91 | 39.76 | 23.49 | 73.74 | 78.90 | 1.70 | 0.92 |
| 3.5 | 91.11 | 90.55 | 36.25 | 20.12 | 76.77 | 76.82 | 2.51 | 1.19 |
| 4 | 113.15 | 100.74 | 30.68 | 17.90 | 88.24 | 94.38 | 3.69 | 1.28 |
| 4.5 | 143.85 | 104.50 | 41.27 | 25.29 | 134.55 | 91.86 | 3.32 | 1.07 |
| 5 | 103.10 | 61.63 | 38.58 | 16.00 | 99.75 | 52.47 | 2.67 | 1.03 |
| 6 | 63.80 | 46.02 | 27.58 | 11.00 | 66.73 | 34.77 | 2.31 | 0.96 |
| 8 | 30.68 | 22.04 | 23.47 | 11.69 | 29.35 | 15.02 | 1.31 | 1.05 |
| 10 | 24.73 | 20.65 | 25.45 | 16.05 | 26.29 | 20.73 | 0.97 | 0.94 |
| 12 | 23.78 | 16.65 | 29.31 | 28.46 | 19.66 | 14.87 | 0.81 | 1.21 |
| 16 | 6.50 | 6.64 | 15.70 | 10.46 | 9.13 | 8.65 | 0.41 | 0.71 |
| 24 | 2.55 | 2.73 | 3.59 | 2.59 | 3.02 | 3.01 | 0.71 | 0.84 |
| 30 | 0.00 | 0.00 | 0.76 | 2.02 | 0.00 | 0.00 | 0.00 | . |

UNITS: PLASMA LEVEL=NG/ML TIME=HRS

MEAN1=Test-Fed, MEAN2=Test-Fast, MEAN3=Ref-Fed,
RMEAN12=TestFed/TestFasted, RMEAN13=TestFed/RefFed

Table 12
LSMEANS of Pharmacokinetic Parameters of Pentoxifylline in 24
Subjects Following a Single-Dose of Pentoxifylline 400 mg
Extended Release Tablet under Non-Fasting Conditions

| PARAMETER | LSM1 | LSM2 | LSM3 | RLSM12 | RLSM13 |
|--------------------|--------|--------|--------|--------|--------|
| AUCI | 722.52 | 616.14 | 719.94 | 1.17 | 1.00 |
| AUCT | 687.91 | 568.60 | 689.51 | 1.21 | 1.00 |
| C _{MAX} | 171.55 | 76.40 | 164.70 | 2.25 | 1.04 |
| *LAUCI | 673.75 | 576.85 | 674.63 | 1.17 | 1.00 |
| *LAUCT | 633.91 | 524.40 | 642.68 | 1.21 | 0.99 |
| *LC _{MAX} | 140.53 | 73.61 | 136.92 | 1.91 | 1.03 |

UNITS: AUC=NG HR/ML C_{MAX}=NG/ML T_{MAX}=HR

LSM1=LSMEAN Test-Fed, LSM2=LSMEAN Test-Fast, LSM3=LSMEAN Ref-Fed

RLSMN12=TestFed/TestFasted, RLSMN13=TestFed/RefFed

* These values represent the geometric means (antilog of the means of the logs).

For pentoxifylline the arithmetic mean (\pm SD) T_{max} values (hours) for test-fed, test-fasted and reference-fed treatments are 4.2 \pm 0.9, 1.8 \pm 2.8, and 4.5 \pm 1.5, respectively. The arithmetic mean (\pm SD) T_{1/2} values (hours) for test-fed, test-fasted and reference-fed treatments are 2.9 \pm 1.4, 5.2 \pm 2.8, and 3.1 \pm 2.0, respectively.

Table 13
Mean Plasma Concentrations of MI in 24 Subjects Following a
Single-Dose of Pentoxifylline 400 mg Extended Release Tablet
under Non-Fasting Conditions

| TIME HR | MEAN1 | SD1 | MEAN2 | SD2 | MEAN3 | SD3 | RMEAN12 | RMEAN13 |
|---------|--------|--------|--------|--------|--------|--------|---------|---------|
| 0 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | . | . |
| 0.5 | 24.00 | 19.32 | 94.43 | 35.95 | 16.26 | 13.30 | 0.25 | 1.48 |
| 0.75 | 50.34 | 37.97 | 153.99 | 40.95 | 40.58 | 34.96 | 0.33 | 1.24 |
| 1 | 77.71 | 45.79 | 192.41 | 49.01 | 63.79 | 44.75 | 0.40 | 1.22 |
| 1.5 | 116.28 | 59.93 | 223.29 | 48.43 | 128.76 | 90.38 | 0.52 | 0.90 |
| 2 | 171.38 | 85.35 | 243.08 | 66.32 | 196.24 | 199.54 | 0.71 | 0.87 |
| 2.5 | 196.05 | 89.79 | 252.67 | 93.80 | 219.91 | 201.89 | 0.78 | 0.89 |
| 3 | 235.00 | 139.30 | 245.15 | 111.58 | 250.38 | 216.36 | 0.96 | 0.94 |
| 3.5 | 292.70 | 207.92 | 223.93 | 103.64 | 264.40 | 210.43 | 1.31 | 1.11 |
| 4 | 378.33 | 274.64 | 198.53 | 87.92 | 289.48 | 205.87 | 1.91 | 1.31 |
| 4.5 | 419.67 | 266.91 | 178.18 | 70.68 | 362.80 | 234.71 | 2.36 | 1.16 |
| 5 | 411.25 | 223.31 | 170.89 | 61.86 | 365.17 | 158.94 | 2.41 | 1.13 |
| 6 | 303.79 | 159.14 | 137.75 | 46.81 | 291.17 | 130.83 | 2.21 | 1.04 |
| 8 | 164.94 | 93.53 | 106.08 | 53.10 | 157.76 | 74.40 | 1.55 | 1.05 |
| 10 | 109.89 | 71.13 | 108.23 | 67.34 | 119.94 | 79.61 | 1.02 | 0.92 |
| 12 | 120.68 | 90.49 | 105.18 | 77.94 | 98.71 | 69.83 | 1.15 | 1.22 |
| 16 | 42.58 | 39.13 | 87.55 | 52.72 | 46.69 | 43.93 | 0.49 | 0.91 |
| 24 | 12.24 | 11.77 | 16.84 | 12.27 | 14.99 | 23.63 | 0.73 | 0.82 |
| 30 | 1.15 | 5.65 | 4.40 | 8.93 | 0.65 | 2.20 | 0.26 | 1.79 |

UNIT: PLASMA LEVEL=NG/ML TIME=HRS

MEAN1=Test-Fed, MEAN2=Test-Fast, MEAN3=Ref-Fed,

RMEAN12=TestFed/TestFasted, RMEAN13=TestFed/RefFed

Table 14
LSMEAN Pharmacokinetic Parameters for MI in 24 Subjects Following
a Single-Dose of Pentoxifylline 400 mg Extended Release Tablet
under Non-Fasting Conditions

| PARAMETER | LSM1 | LSM2 | LSM3 | RLSM12 | RLSM13 |
|--------------------|---------|---------|---------|--------|--------|
| AUCI | 3004.68 | 2768.07 | 2836.48 | 1.09 | 1.06 |
| AUCT | 2853.79 | 2616.13 | 2780.08 | 1.09 | 1.03 |
| C _{MAX} | 479.71 | 285.04 | 469.25 | 1.68 | 1.07 |
| *LAUCI | 2836.68 | 2635.07 | 2683.65 | 1.08 | 1.06 |
| *LAUCT | 2666.46 | 2451.16 | 2625.33 | 1.09 | 1.02 |
| *LC _{MAX} | 411.79 | 270.41 | 409.11 | 1.52 | 1.01 |

UNIT: AUC=NG HR/ML C_{MAX}=NG/ML TIME=HR

LSM1=LSMEAN Test-Fed, LSM2=LSMEAN Test-Fast, LSM3=LSMEAN Ref-Fed,
 RLSM12=TestFed/TestFasted, RLSM13=TestFed/RefFed

* These values represent the geometric means (antilog of the means of the logs).

For MI the arithmetic mean (\pm SD) T_{max} values (hours) for test-fed, test-fasted and reference-fed treatments are 4.5 \pm 0.9, 2.8 \pm 1.7, and 5.3 \pm 2.1, respectively. The arithmetic mean (\pm SD) T_{1/2} values (hours) for test-fed, test-fasted and reference-fed treatments are 3.6 \pm 2.5, 5.1 \pm 3.3, and 2.9 \pm 1.0, respectively.

Table 15
Mean Plasma Concentrations of MV in 24 Subjects Following a
Single-Dose of Pentoxifylline 400 mg Extended Release Tablet
under Non-Fasting Conditions

| TIME HR | MEAN1 | SD1 | MEAN2 | SD2 | MEAN3 | SD3 | RMEAN12 | RMEAN13 |
|---------|--------|--------|--------|--------|--------|--------|---------|---------|
| 0 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | . | . |
| 0.5 | 74.17 | 56.76 | 331.46 | 117.79 | 52.44 | 34.80 | 0.22 | 1.41 |
| 0.75 | 152.40 | 105.43 | 478.79 | 116.02 | 115.66 | 69.60 | 0.32 | 1.32 |
| 1 | 224.07 | 130.36 | 554.33 | 119.35 | 173.27 | 85.65 | 0.40 | 1.29 |
| 1.5 | 317.43 | 160.17 | 588.21 | 111.48 | 319.23 | 127.72 | 0.54 | 0.99 |
| 2 | 411.34 | 193.73 | 596.46 | 127.55 | 398.42 | 242.21 | 0.69 | 1.03 |
| 2.5 | 427.13 | 176.09 | 589.13 | 150.89 | 409.25 | 198.16 | 0.73 | 1.04 |
| 3 | 503.29 | 210.20 | 522.29 | 142.75 | 462.04 | 185.01 | 0.96 | 1.09 |
| 3.5 | 599.63 | 308.94 | 476.17 | 151.11 | 481.88 | 189.55 | 1.26 | 1.24 |
| 4 | 711.88 | 348.86 | 408.83 | 126.55 | 525.46 | 187.08 | 1.74 | 1.35 |
| 4.5 | 913.17 | 351.23 | 378.71 | 113.32 | 660.83 | 258.66 | 2.15 | 1.23 |
| 5 | 733.54 | 249.35 | 353.13 | 94.42 | 648.88 | 229.88 | 2.08 | 1.13 |
| 6 | 538.88 | 190.11 | 301.67 | 76.87 | 541.33 | 236.24 | 1.79 | 1.00 |
| 8 | 321.38 | 159.61 | 220.42 | 76.39 | 318.99 | 139.54 | 1.46 | 1.01 |
| 10 | 219.66 | 114.24 | 215.82 | 95.51 | 265.98 | 235.43 | 1.02 | 0.83 |
| 12 | 221.35 | 141.39 | 200.61 | 106.50 | 183.19 | 129.49 | 1.10 | 1.21 |
| 16 | 81.75 | 81.83 | 190.85 | 110.10 | 101.59 | 76.57 | 0.43 | 0.80 |
| 24 | 19.58 | 21.69 | 35.81 | 29.60 | 30.02 | 38.70 | 0.55 | 0.65 |
| 30 | 0.22 | 1.09 | 6.38 | 13.94 | 0.22 | 1.08 | 0.03 | 1.01 |

UNIT: PLASMA LEVEL=NG/ML TIME=HRS

MEAN1=Test-Fed, MEAN2=Test-Fast, MEAN3=Ref-Fed,
 RMEAN12=TestFed/TestFasted, RMEAN13=TestFed/RefFed

Table 16
LSMEAN Pharmacokinetic Parameters for MV in 24 Subjects Following
a Single-Dose of Pentoxifylline 400 mg Extended Release Tablet
under Non-Fasting Conditions

| | LSM1 | LSM2 | LSM3 | RLSM12 | RLSM13 |
|-----------|---------|---------|---------|--------|--------|
| PARAMETER | | | | | |
| AUCI | 5819.15 | 5959.17 | 5639.78 | 0.98 | 1.03 |
| AUCT | 5542.41 | 5782.61 | 5368.42 | 0.96 | 1.03 |
| CMAX | 898.63 | 674.00 | 829.42 | 1.33 | 1.08 |
| LAUCI | 5704.29 | 5836.06 | 5490.89 | 0.93 | 1.04 |
| LAUCT | 5437.14 | 5664.99 | 5257.92 | 0.96 | 1.03 |
| LCMAX | 843.08 | 664.18 | 794.52 | 1.27 | 1.06 |

UNITS: AUC=NG HR/ML CMAX=NG/ML TMAX=HR

LSM1=LSMEAN Test-Fed, LSM2=LSMEAN Test-Fast, LSM3=LSMEAN Ref-Fed

RLSMN12=TestFed/TestFasted, RLSMN13=TestFed/RefFed

* These values represent the geometric means (antilog of the means of the logs).

For MV the arithmetic mean (\pm SD) Tmax values (hours) for test-fed, test-fasted and reference-fed treatments are 4.4 ± 0.9 , 2.0 ± 0.7 , and 4.9 ± 2.4 , respectively. The arithmetic mean (\pm SD) T1/2 values (hours) for test-fed, test-fasted and reference-fed treatments are 3.1 ± 2.1 , 4.6 ± 1.9 , and 3.4 ± 2.7 , respectively.

The plasma concentration - time profiles for the parent drug, MI and MV under fed conditions are shown in Figures 4, 5 and 6, respectively.

MULTIPLE DOSE FASTING BIOEQUIVALENCE STUDY

I. STUDY OBJECTIVE

This study compared the bioavailability of pentoxifylline following multiple oral doses [1 x 400 mg tablet administered every eight (8) hours for ten (10) doses] of pentoxifylline tablets (Pentoxil™) by Upsher-Smith Laboratories, Inc. with that of Trental® by Hoechst-Roussel Pharmaceuticals, Inc. in healthy adult male volunteers under steady-state conditions.

II. INVESTIGATORS AND FACILITIES

III. STUDY DATES

Dose administration: Period I, 3/26-30/96; Period II, 4/5-9/96

Analytical completed: Between 4/29-5/17/96 using _____ method
 Between 7/28-7/31/96 using _____ method

IV. EXPERIMENTAL

Same as for fasting study except as noted:

Study Products:

Test Product - Pentoxil™ (Pentoxifylline) 400 mg Extended Release Tablets
[Upsher-Smith Laboratories, Inc.; Lot No. 15870 (a sub-lot of the manufactured
lot #61037, ablets), Exp. Date not shown]

Reference Product = Trental® 400 mg Extended Release Tablets [Hoechst-Roussel
Pharmaceuticals, Inc; Lot No. 0780665; Exp. Date 02/97]

An oral dose (1 x 400 mg tablet) of test pentoxifylline tablets or reference pentoxifylline
tablets (Trental®) was administered to volunteers every eight hours for a total of ten doses
during each study period.

Blood sampling (20 per subject each period) for drug content analysis occurred within one
hour prior to Dose 1 (0 hour) immediately prior to dose 4 (24 hr), dose 7 (48 hr), and
dose 10 (72 hr), and after Dose 10 administration at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5,
5, 6, 7, 8 hours.

V. ANALYTICAL

Determination of Pentoxifylline and its Major MI and MV, in Human Plasma
Samples by

Method

VI. CLINICAL NOTES

At enrollment, all 26 subjects had an acceptable medical history, medication history, physical examination, sitting blood pressure, heart rate, electrocardiogram, clinical laboratory evaluations, a non-reactive HIV 1 & 2 antibody screen, and negative screens for hepatitis B surface antigen and drugs of abuse within twenty-one days prior to Period I dosing. Upon completion of the study, the physical examination and selected clinical laboratory measurements were repeated.

There were no deviations from the protocol instructions of no prescription medications or nonprescription medications within 14 or 7 days of Period I dosing, respectively.

There were four problems (stuffy nose, sore throat, headache, and back ache) reported in the 14 days prior to Period I dosing. In the opinion of the clinical investigators, the problems should have no impact on the integrity of the study, and subject enrollment was allowed.

Meals and fluid intake were controlled during the 84 hour confinement period following Dose 1 during each period. Twenty-five of twenty-six volunteers successfully completed the study. Subject 26 (MJB) dropped prior to Period II dosing secondary to a schedule conflict.

Thirty-three adverse events were reported in seventeen of twenty-six subjects dosed and included the following events (incidence): back pain(1 - back ache), dehydration (3 - felt dehydrated), dizziness (2 - light-headed), edema(2; 1 - swelling left arm, 1 - swelling right arm), headache (7), leg cramps (1 - leg cramps right leg), myalgia(1 - arms sore), nausea(1), pain (2; 1 - left arm pain, 1 - toe pain, first digit left foot), pharyngitis (2 - sore throat), purpura(4; 1 - bruise left arm, 2 - bruise right arm, 1 - hematoma left arm), respiratory disorder(1 - stuffy head), rhinitis (3; 2 runny nose, 1 - stuffy nose), rigors (2 - chills), and tooth disorder (1 - toothache). There were no serious adverse events or any events which required terminating any subject from the study.

In general, the clinical laboratory values were unremarkable over the course of the study.

VIII. PHARMACOKINETIC STUDY RESULTS

Out of a total of 25 subjects 12 received the formulations in the sequence RT, and 13 received in the sequence TR. Three trough levels were measured at times 24, 48, and 72 hr. The firm reported that there was no significant difference between concentrations at time 48 hr and 72 hr, and thus steady-state was reached at the time when the measurement of $AUC_{0-\tau}$ was started. Concentrations during the dosing interval at steady-state from 72 to 80 hr were used for the calculation of area-under-the-curve at steady-state, $AUC_{0-\tau}$.

The results of the bioequivalence assessment for the parent compound, MI and MV are summarized in Tables 17-27.

The mean fluctuation of the test formulation differed from the mean fluctuation of the reference formulation by no more than 20% for the parent compound and MV. However, the difference for MI was 20.1%.

At the 5% level no sequence effect was noted for any of the bioequivalence metrics for the parent or for the two metabolites.

Table 17
Mean Plasma Concentrations of Pentoxifylline at Steady-State (Day-4) in 25 Subjects After 400 mg of Pentoxifylline ER Tablet Every 8 Hours for 10 Doses

| TIME HR | MEAN1 | SD1 | MEAN2 | SD2 | RMEAN12 |
|---------|--------|-------|-------|-------|---------|
| 72 | 39.80 | 21.17 | 46.05 | 27.80 | 0.86 |
| 72.5 | 96.93 | 46.06 | 95.46 | 60.38 | 1.02 |
| 72.75 | 102.11 | 47.34 | 95.76 | 52.03 | 1.07 |
| 73 | 99.42 | 48.17 | 97.22 | 47.36 | 1.02 |
| 73.5 | 85.52 | 41.65 | 83.58 | 37.89 | 1.02 |
| 74 | 77.99 | 38.66 | 71.64 | 33.48 | 1.09 |
| 74.5 | 68.64 | 33.86 | 64.84 | 27.13 | 1.06 |
| 75 | 61.18 | 29.48 | 59.87 | 25.77 | 1.02 |
| 75.5 | 51.11 | 23.78 | 57.66 | 29.31 | 0.89 |
| 76 | 46.28 | 23.64 | 52.96 | 24.23 | 0.87 |
| 76.5 | 65.18 | 32.33 | 78.96 | 36.66 | 0.83 |
| 77 | 61.18 | 28.21 | 69.13 | 31.21 | 0.88 |
| 78 | 46.02 | 25.80 | 47.73 | 24.46 | 0.96 |
| 79 | 35.08 | 16.76 | 38.27 | 21.98 | 0.92 |
| 80 | 28.57 | 13.33 | 34.39 | 18.86 | 0.83 |

UNIT: PLASMA LEVEL=ng/mL TIME=Hrs
 MEAN1=Test, MEAN2=Reference, RMEAN12=T/R ratio

Table 18
Arithmetic and Geometric Mean For Pentoxifylline Pharmacokinetic Parameters at Steady-State (Day-4) in 25 Subjects After 400 mg of Pentoxifylline ER Tablet Every 8 Hours for 10 Doses

| PARAMETER | MEAN1 | SD1 | MEAN2 | SD2 | RMEAN12 |
|-----------|--------|--------|--------|--------|---------|
| AUCT | 478.33 | 183.43 | 497.50 | 205.51 | 0.96 |
| CAVG | 59.79 | 22.93 | 62.19 | 25.69 | 0.96 |
| CMAX | 123.89 | 51.11 | 118.50 | 60.15 | 1.05 |
| CMIN | 25.85 | 13.56 | 28.16 | 15.56 | 0.92 |
| TMAX | 1.18 | 0.97 | 1.69 | 1.49 | 0.70 |
| FLUC | 1.69 | 0.51 | 1.47 | 0.48 | 1.14 |
| *LAUCT | 444.89 | ---- | 451.63 | ---- | 0.99 |
| *LCAVG | 55.61 | ---- | 56.45 | ---- | 0.99 |
| *LCMAX | 114.53 | ---- | 105.37 | ---- | 1.09 |

UNIT: AUC=ng hr/mL CMAX=ng/mL TMAX=hr
 MEAN1=Test mean, MEAN2=Ref mean, RMEAN12=T/R ratios
 * These values represent the geometric means (antilog of the means of the logs).

Table 19
LSMeans and 90% Confidence Intervals For Pentoxifylline at
Steady-State (Day-4) in 25 Subjects After 400 mg of
Pentoxifylline ER Tablet Every 8 Hours for 10 Doses

| PARAMETER | LSM1 | LSM2 | RLSM12 | LOWCI12 | UPPCI12 |
|--------------------|--------|--------|--------|---------|---------|
| AUCT | 477.30 | 494.81 | 0.96 | 87.45 | 105.47 |
| CAVG | 59.66 | 61.85 | 0.96 | 87.45 | 105.47 |
| C _{MAX} | 123.50 | 117.74 | 1.05 | 92.53 | 117.26 |
| C _{MIN} | 25.81 | 27.99 | 0.92 | --- | --- |
| FLUC | 1.68 | 1.48 | 1.14 | --- | --- |
| *LAUCT | 443.21 | 448.29 | 0.99 | 90.55 | 107.95 |
| *LC _{MAX} | 114.06 | 104.65 | 1.09 | 97.34 | 122.04 |
| *LCAVG | 55.40 | 56.04 | 0.99 | --- | --- |

UNIT: AUC=ng hr/mL C_{MAX}=ng/mL

LSM1=LSMEAN of test, LSM2=LSMEAN ref, RLSM12=T/R ratios. LowCI12=Lower C.I. for T/R, UPPCI12=Upper C.I. for T/R

* These values represent the LS geometric means (antilog of the means of the logs).

AUCT= AUCT₇₂₋₈₀, CAVG=AUCT/8, C_{MIN}=minimum conc from time range 72-80 hours, FLUC=[C_{MAX}-C_{MIN}]/CAVG

For the data on pentoxifylline, the C_{max} values for 10 subjects (#'s 1, 5, 6, 11, 12, 13, 14, 15, 22, and 26) during test and/or reference treatment were the first nonzero concentrations. Therefore, data from these 10 subjects for both treatments were deleted and the statistics were recalculated by the reviewer. The results are presented in Table 20.

Table 20
Statistical Reanalysis on Pentoxifylline in 15 Subjects (Excluding 10 Subjects Whose C_{max}
Was the First Nonzero Concentration) Following Dosing Pentoxifylline 400 mg Extended
Release Tablet Every 8 Hours for 10 Doses

| Parameter | T/R | 90% Confidence Interval |
|-----------------------|-------------------|-------------------------|
| AUC ₇₂₋₈₀ | 1.02 ^a | 93.2-110.8 |
| C _{max} | 0.97 ^a | 93.7-129.3 |
| C _{min} | 0.97 ^a | 80.5-113.0 |
| LAUC ₇₂₋₈₀ | 1.02 ^b | 92.7-111.4 |
| LC _{max} | 1.12 ^a | 94.4-132.2 |
| Flux | 1.14 ^a | --- |

a = Ratio of LSMeans

b = Ratio of Geometric LSMeans

Table 21
Mean Plasma Concentrations of MI at Steady-State (Day-4) in 25
Subjects After 400 mg of Pentoxifylline ER Tablet every 8 hours
for 10 doses

| TIME HR | MEAN1 | SD1 | MEAN2 | SD2 | RMEAN12 |
|---------|--------|--------|--------|--------|---------|
| 172 | 230.19 | 94.40 | 226.85 | 106.33 | 1.01 |
| 172.5 | 288.92 | 99.71 | 285.70 | 136.11 | 1.01 |
| 172.75 | 335.00 | 117.91 | 350.44 | 169.67 | 0.96 |
| 173 | 357.84 | 121.08 | 364.28 | 175.07 | 0.98 |
| 173.5 | 381.32 | 150.92 | 372.84 | 155.77 | 1.02 |
| 174 | 408.24 | 177.87 | 363.80 | 141.02 | 1.12 |
| 174.5 | 385.76 | 146.36 | 352.68 | 141.25 | 1.09 |
| 175 | 350.16 | 139.48 | 339.00 | 138.59 | 1.03 |
| 175.5 | 338.92 | 137.94 | 315.79 | 131.18 | 1.07 |
| 176 | 298.96 | 126.16 | 288.99 | 117.99 | 1.03 |
| 176.5 | 260.72 | 114.61 | 267.78 | 106.17 | 0.97 |
| 177 | 245.16 | 113.44 | 262.60 | 114.55 | 0.93 |
| 178 | 196.04 | 99.81 | 195.14 | 90.37 | 1.00 |
| 179 | 150.44 | 69.95 | 158.10 | 83.93 | 0.95 |
| 180 | 115.44 | 52.27 | 132.87 | 71.21 | 0.87 |

UNIT: PLASMA LEVEL=ng/mL TIME=Hrs
 MEAN1=Test, MEAN2=Reference, RMEAN12=T/R ratio

Table 22
Arithmetic and Geometric Mean for MI Pharmacokinetic Parameters
at Steady-State (Day-4) in 25 Subjects After 400 mg of
Pentoxifylline ER Tablet Every 8 Hours for 10 Doses

| PARAMETER | MEAN1 | SD1 | MEAN2 | SD2 | RMEAN12 |
|-----------|---------|--------|---------|--------|---------|
| AUCT | 2183.95 | 803.02 | 2155.13 | 886.69 | 1.01 |
| CAVG | 272.99 | 100.38 | 269.39 | 110.84 | 1.01 |
| CMAX | 433.24 | 178.01 | 406.52 | 165.97 | 1.07 |
| CMIN | 113.80 | 52.96 | 130.35 | 71.44 | 0.87 |
| TMAX | 2.23 | 0.97 | 1.73 | 0.77 | 1.29 |
| FLUC | 1.16 | 0.26 | 1.05 | 0.29 | 1.11 |
| *LAUCT | 2032.73 | ---- | 1969.31 | ---- | 1.03 |
| *LCAVG | 254.09 | ---- | 246.16 | ---- | 1.03 |
| *LCMAX | 398.94 | ---- | 374.35 | ---- | 1.07 |

UNIT: AUC=ng hr/mL CMAX=ng/mL TMAX=hr
 MEAN1=Test mean, MEAN2=Ref mean, RMEAN12=T/R ratios
 * These values represent the geometric means (antilog of the means of the logs).

Table 23
LSMeans and 90% Conference Intervals For MI at Steady-State (Day 4) in 25 Subjects After 400 mg of Pentoxifylline ER Tablet Every 8 Hours for 10 Doses

| PARAMETER | LSM1 | LSM2 | RLSM12 | LOWCI12 | UPPCI12 |
|-----------|---------|---------|--------|---------|---------|
| AUCT | 2177.53 | 2148.76 | 1.01 | 93.38 | 109.30 |
| CAVG | 272.19 | 268.60 | 1.01 | 93.38 | 109.30 |
| CMAx | 431.74 | 405.21 | 1.07 | --- | --- |
| CMIN | 113.66 | 129.95 | 0.87 | --- | --- |
| FLUC | 1.16 | 1.06 | 1.10 | 101.91 | 118.72 |
| *LAUCT | 2024.24 | 1959.80 | 1.03 | 95.28 | 111.97 |
| *LCAVG | 253.03 | 244.97 | 1.03 | --- | --- |
| *LCMAx | 397.21 | 372.83 | 1.07 | 97.51 | 116.40 |

UNIT: AUC=ng hr/mL CMAx=ng/mL
 LSM1=LSMEAN of test, LSM2=LSMEAN ref, RLSM12=T/R ratios. LowCI12=Lower C.I. for T/R, UPPCI12=Upper C.I. for T/R
 * These values represent the LSMEAN (antilog of the means of the logs).
 AUCT= AUCT₇₂₋₈₀, CAVG=AUCT/8, CMIN=minimum conc. from time range 72-80 hours,
 FLUC=(CMAx-CMIN)/CMAx

Table 24
Mean Plasma Concentrations of MV at Steady-State (Day-4) in 25 Subjects After 400 mg of Pentoxifylline ER Tablet Every 8 Hours for 10 Doses

| TIME HR | MEAN1 | SD1 | MEAN2 | SD2 | RMEAN12 |
|---------|---------|--------|---------|--------|---------|
| 72 | 688.84 | 208.90 | 682.96 | 194.73 | 1.01 |
| 72.5 | 898.36 | 261.31 | 868.08 | 281.89 | 1.03 |
| 72.75 | 1050.80 | 309.33 | 1068.24 | 374.43 | 0.98 |
| 73 | 1098.92 | 281.95 | 1105.69 | 343.33 | 0.99 |
| 73.5 | 1087.20 | 273.41 | 1084.00 | 279.48 | 1.00 |
| 74 | 1082.28 | 266.66 | 1012.84 | 200.76 | 1.07 |
| 74.5 | 989.20 | 247.37 | 943.00 | 203.95 | 1.05 |
| 75 | 893.32 | 249.06 | 891.68 | 212.92 | 1.00 |
| 75.5 | 823.88 | 216.48 | 814.88 | 198.77 | 1.01 |
| 76 | 728.56 | 214.78 | 769.32 | 206.92 | 0.95 |
| 76.5 | 680.64 | 207.55 | 742.36 | 195.26 | 0.92 |
| 77 | 624.16 | 188.74 | 706.72 | 193.07 | 0.88 |
| 78 | 546.40 | 172.72 | 581.16 | 164.28 | 0.94 |
| 79 | 429.52 | 120.82 | 458.92 | 131.95 | 0.94 |
| 80 | 326.72 | 68.10 | 383.20 | 120.79 | 0.85 |

UNIT: PLASMA LEVEL=ng/mL TIME=Hrs
 MEAN1=Test, MEAN2=Reference, RMEAN12=T/R ratio

Table 25
Arithmetic and Geometric Mean for MV Pharmacokinetic Parameters
at Steady-State (Day-4) in 25 Subjects After 400 mg of
Pentoxifylline ER Tablet Every 8 Hours for 10 Doses

| PARAMETER | MEAN1 | SD1 | MEAN2 | SD2 | RMEAN12 |
|--------------------|---------|---------|---------|---------|---------|
| AUCT | 5933.83 | 1262.69 | 6068.73 | 1340.12 | 0.98 |
| CAVG | 741.73 | 157.84 | 758.59 | 167.51 | 0.98 |
| C _{MAX} | 1206.40 | 291.95 | 1180.60 | 348.15 | 1.02 |
| C _{MIN} | 322.52 | 74.18 | 373.36 | 119.92 | 0.86 |
| T _{MAX} | 1.42 | 0.79 | 1.28 | 0.45 | 1.13 |
| FLUC | 1.19 | 0.24 | 1.06 | 0.29 | 1.13 |
| *LAUCT | 5801.22 | 0.22 | 5912.25 | 0.24 | 0.98 |
| *LCAVG | 725.15 | 0.22 | 739.03 | 0.24 | 0.98 |
| *LC _{MAX} | 1175.48 | 0.23 | 1142.13 | 0.25 | 1.03 |

UNIT: AUC=ng hr/mL C_{MAX}=ng/mL T_{MAX}=hr
 MEAN1=Test mean, MEAN2=Ref mean, RMEAN12=T/R ratios.

* These values represent the geometric means (antilog of the means of the logs).

Table 26
LSMeans and 90% Confidence Intervals For MV at Steady-State (Day-
4) in 25 Subjects After 400 mg of Pentoxifylline ER Tablet Every
8 Hours for 10 Doses

| PARAMETER | LSM1 | LSM2 | RLSM12 | LOWCI12 | UPPCI12 |
|--------------------|---------|---------|--------|---------|---------|
| AUCT | 5934.42 | 6053.65 | 0.98 | 91.43 | 104.63 |
| CAVG | 741.80 | 756.71 | 0.98 | 91.43 | 104.63 |
| C _{MAX} | 1207.63 | 1177.74 | 1.03 | 91.69 | 113.39 |
| C _{MIN} | 322.08 | 372.46 | 0.86 | --- | --- |
| FLUC | 1.20 | 1.06 | 1.13 | --- | --- |
| *LAUCT | 5798.20 | 5895.55 | 0.98 | 92.59 | 104.46 |
| *LCAVG | 724.78 | 736.94 | 0.98 | --- | --- |
| *LC _{MAX} | 1176.08 | 1139.67 | 1.03 | 94.62 | 112.54 |

UNIT: AUC=ng hr/mL C_{MAX}=ng/mL
 LSM1=LSMEAN of test, LSM2=LSMEAN ref, RLSM12=T/R ratios. LowCI12=Lower C.I. for T/R,
 UPPCI12=Upper C.I. for T/R

* These values represent the LS geometric means (antilog of the means of the logs).

AUCT= AUCT₇₂₋₈₀, CAVG=AUCT/8, C_{MIN}=minimum conc. from time range 72-80 hours, FLUC=[C_{MAX}-C_{MIN}]/C_{MAX}

For the data on MV, the C_{max} values for 2 subjects (#'s 1, and 6) during the test treatment were the first nonzero concentrations. Therefore, data from these 2 subjects for both treatments were deleted and the statistics were recalculated by the reviewer. The results are presented below in Table 27

Table 27
Statistical Reanalysis on MV in 23 Subjects (Excluding 2 Subjects Whose C_{max} Was the First Nonzero Concentration) Following Dosing Pentoxifylline 400 mg Extended Release Tablet Every 8 Hours for 10 Doses

| Parameter | T/R | 90% Confidence Interval |
|-----------------------|-------------------|-------------------------|
| AUC ₇₂₋₈₀ | 1.00 ^a | 94.1-106.4 |
| C _{max} | 1.06 ^a | 97.1-115.9 |
| C _{min} | 0.87 ^a | ---- |
| LAUC ₇₂₋₈₀ | 1.00 ^b | 94.8-106.1 |
| LC _{max} | 1.05 ^b | 97.3-114.3 |
| Flux | 1.16 ^a | ---- |

a = Ratio of LSMeans

b = Ratio of Geometric LSMeans

The plasma concentration - time profiles for the parent drug, MI and MV under steady state conditions are shown in Figures 7, 8 and 9, respectively.

Upsher-Smith Laboratories' formulation of its drug product, Pentoxifylline 400 mg Extended Release Tablets is summarized in Table #28. The reference listed product, Hoechst-Roussel's Trental® 400 mg Extended Release Tablets contain 400 mg of the active drug (Pentoxifylline) and the following inactive ingredients: benzyl alcohol J&C Red No. 27 aluminum lake or hydroxypropyl methylcellulose USP, magnesium stearate NF, polyethylene glycol NF, povidone USP titanium dioxide USP, and other ingredients in a controlled-release formulation.

Table 28
FORMULATION (NOT FOR RELEASE UNDER FOI)

Quantitative Composition: Lot #61037 (Bio-study Lot) Pentoxil™ 400 mg Tablet

| Component | %W/W | mg/Tablet |
|-----------------------------------|---------------|------------|
| Pentoxifylline | 72.20 | 400 |
| Hydroxypropyl Methylcellulose USP | | |
| Magnesium Stearate, NF | | |
| Povidone, USP | | |
| Silicon Dioxide, NF | | |
| Purified Water, USP - REMOVED | | |
| TOTAL | 100.00 | 554 |