OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA	20-560 (b) (4) 038: BB: BB
Submission Dates	January 31, 2003; April 24, 2003; July 2, 2003
Brand Name	FOSAMAX®
Generic Name	alendronate sodium
Reviewer	S.W. Johnny Lau
Team Leader	Hae-Young Ahn
OCPB Division	DPE II (HFD-870)
ORM division	Metabolic and Endocrine (HFD-510)
Sponsor	Merck Research Laboratories
Relevant IND(s)	(b) (4)
Submission Type; Code	pediatric study report for exclusivity; priority
Formulation; Strength(s)	5, 10, 35, and 70 mg oral tablets (b) (4)
Indication	(b) (4)

1 Executive Summary

Alendronate sodium, a bisphosphonate, is approved to treat and prevent osteoporosis in postmenopausal women, treat osteoporosis in men, treat glucocorticoid-induced osteoporosis, and treat Padget's disease. The sponsor submitted supplemental NDA 20-560 in response to the Food and Drug Administration's October 27, 2000 pediatric study Written Request and its March 8, 2002 amendment to seek the following for alendronate sodium:

- pediatric 6-month exclusivity
- (b) (4)
- (b) (4)
- (b) (4)

The sponsor conducted 2 clinical studies to satisfy the pediatric study Written Request and submitted the results in supplemental NDA 20-560. Briefly, the 2 studies are:

1. an efficacy and safety study (P135) to compare the effects of alendronate (5 or 10 mg daily) versus placebo, on pediatric patients aged 4 through 18 years with severe OI for: (1) change in mean lumbar spine (L1 to L4) bone mineral density at Month 12 and (2) safety and tolerability.
2. an absolute oral bioavailability study (P172) for the 35 and 70 mg alendronate oral tablets as compare to an 125 µg alendronate intravenous injection (2.5 mg/mL) in OI pediatric patients.

Per Study P172, the mean alendronate oral bioavailability (95% CI) with respect to a 125 µg intravenous dose was 0.43% (0.28%, 0.64%) for OI pediatric patients weighing < 40 kg who received 35 mg oral dose and was 0.56% (0.36%, 0.87%) for OI pediatric patients weighing ≥ 40 kg who received 70 mg oral dose. The alendronate oral bioavailability is similar between OI patients and adults (historical data).

See medical officer's review for Study P135.

1.1. Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed the Human Pharmacokinetics and Bioavailability section for supplemental NDA 20-560 and finds it acceptable. The sponsor should receive the labeling comments below (addition is underscored and deletion appears as strikethrough):

CLINICAL PHARMACOLOGY

Special Populations

Pediatric: (b) (4)

[redacted]

S.W. Johnny Lau, R.Ph., Ph.D.
OCPB/DPEII

An Optional Intra-Division Clinical Pharmacology and Biopharmaceutics Briefing for supplemental NDA 20-560 was conducted on June 26, 2003; participants included H. Malinowski, J. Hunt, H. Ahn, and J. Lau.

FT signed by Hae-Young Ahn, Ph.D., Team Leader 6/ /03

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3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

The sponsor conducted Study P172 for alendronate to:

- determine the oral BA with respect to an intravenous dose in OI pediatric patients
- compare the oral BA results in OI pediatric patients to those for the historical adult data.

This study is part of the requirement to satisfy the pediatric study Written Request issued by the Office of Drug Evaluation II, Center of Drug Evaluation and Research, Food and Drug Administration on October 27, 2000.

Study P172 was a 2-period, randomized, single-dose, crossover, pharmacokinetic study conducted in 24 OI pediatric patients. Patients < 40 kg body weight received 2 single alendronate doses: a 35 mg oral tablet and a 125 μg intravenous dose. Patients ≥ 40 kg body weight also received 2 single alendronate doses: a 70 mg oral tablet and a 125 μg intravenous dose. The washout period was at least 2 weeks. All alendronate administration was after an overnight fast. Urine samples were collected for 24 hours postdose for alendronate concentration determination.

The mean alendronate oral bioavailability (95% CI) with respect to a 125 μg intravenous dose was 0.43% (0.28%, 0.64%) for OI pediatric patients weighing < 40 kg who received 35 mg oral dose and was 0.56% (0.36%, 0.87%) for OI pediatric patients weighing ≥ 40 kg who received 70 mg oral dose.

In comparison, the mean oral bioavailability (95% CI) in the prespecified adult historical control group was 0.65% (0.54%, 0.77%). The geometric mean ratio (GMR) of bioavailability for OI pediatric patients weighing < 40 kg compared to the adult historical controls was 0.63, with a 95% CI of (0.39, 1.04). The GMR of bioavailability for OI pediatric patients weighing ≥ 40 kg compared with the adult historical controls was 0.86, with a 95% CI of (0.52, 1.41). The alendronate oral bioavailability was similar between OI pediatric patients and adults (historical data).

The sponsor also conducted Study P135 (efficacy and safety study) to satisfy the pediatric study Written request. See medical officer's review for Study P135.

4 Question-Based Review

4.1 Background

Osteogenesis imperfecta (OI) or "brittle bone disease" is a group of hereditary disorders of Type I collagen, characterized by osteoporosis and extreme bone fragility, which leads to fractures, chronic unremitting bone pain, severe skeletal deformities, short stature, and functional limitation. Alendronate sodium, marketed as FOSAMAX®, is a bisphosphonate that acts as a specific inhibitor of osteoclast-mediated bone resorption to treat and prevent osteoporosis. The sponsor primarily seeks alendronate sodium's pediatric exclusivity (b) (4)

The sponsor conducted a human absolute oral bioavailability study (P172) and a clinical safety and efficacy study (P135) in OI pediatric patients. Study P172 used the 35 mg oral alendronate single dose for patients < 40 kg body weight and 70 mg oral alendronate single dose for patients ≥ 40 kg body weight. Whereas, Study P135 used the 5 mg oral alendronate daily dose for patients < 40 kg body weight and 10 mg oral alendronate daily dose for patients ≥ 40 kg body weight. Alendronate doses differed between the 2 studies because the sponsor was requested to switch patients on 5 and 10 mg once-daily dosing to 35 mg and 70 mg once-weekly dosing, respectively, during Year 2 per the Written Request.

4.2 General Clinical Pharmacology

Alendronate clinical pharmacology information is available in:

- product labeling
- A.G. Porras et al. Pharmacokinetics of alendronate. *Clin Pharmacokinet* **36**:315-28 (1999).
- J.H. Lin. Bisphosphonates: a review of their pharmacokinetic properties. *Bone* **18**:75-85 (1996).

4.3 Bioanalytical

Are the bioanalytical methods for alendronate properly validated?

Yes. Briefly, the alendronate bioanalytical method in human urine samples had 3 steps:

(1) isolation, via precipitation and solid phase extraction of the analyte from urine,
(2) automated pre-column derivatization to form fluorescent products of the analytes, and
(3) high pressure liquid chromatography (HPLC) separation and fluorescence detection of the resulting derivatives.

Validation for the alendronate bioanalytical method in human urine samples follows:

	Alendronate
Method	HPLC - fluorescent quantification
LLOQ, ng/mL	1 ng/mL, > 15% below LLOQ = not quantifiable
Recovery, %	not available
Linearity, ng/mL	1 – 25 ng/mL
Accuracy	
intraday	97.2 – 106.0%
interday	93.6 – 113.5%
Precision, % CV	
intraday	3.0 - 7.5%
interday	5.4 - 9.3%

LLOQ = lower limit of quantitation

4.4 Biopharmaceutics

1. Were the formulation tested in Studies P172 and P135 identical to the marketed formulation?

Yes. The formulations of the 35 and 70 mg alendronate oral tablets tested in Study P172 were the same as those to the marketed tablets. The formulation of the IV alendronate solution tested in Study P172 was the same as those tested under IND [redacted] (b) (4) to determine alendronate oral bioavailability (BA). The formulation of the 5 and 10 mg alendronate tablets tested in Study P135 were the same as those to the marketed tablets.

2. Did the sponsor adequately assess the alendronate absolute BA in OI patients?

Yes. Briefly, Study P172 was an open-label, 2-period, randomized, single-dose, crossover, pharmacokinetic study conducted in 24 OI pediatric patients, 12 patients each for the < 40 kg and ≥ 40 kg body weight groups. Patients < 40 kg body weight received 2 single alendronate doses: a 35 mg oral tablet and a 125 µg intravenous dose. Patients ≥ 40 kg body weight received 2 single alendronate doses: a 70 mg oral tablet and a 125 µg intravenous dose. The washout period was at least 2 weeks. An 11-hour overnight fast preceded all alendronate dosing, which was administered with 180 mL tap water. Patients received a standardized meal 2 hours after dosing. Alendronate was intravenously infused over 2 hours. Urine samples were collected for 24 hours postdose for alendronate concentration determination. Absolute oral alendronate BA was assessed as the total urinary excretion over 24 hours following the 35 or 70 mg tablet relative to the 125 µg IV administration. The urinary excretion data was normalized to 1 mg dose for both oral and IV administration.

The sponsor's absolute alendronate oral BA assessment follows:

- 0.43% with 95% CI (0.28% - 0.64%) for < 40 kg OI patients administered 35 mg oral dose vs. 125 µg IV dose
- 0.56% with 95% CI (0.36% - 0.87%) for ≥ 40 kg OI patients administered 70 mg oral dose vs. 125 µg IV dose

This reviewer repeated the analyses and observed the same results as the sponsor's assessment above (see Attachment).

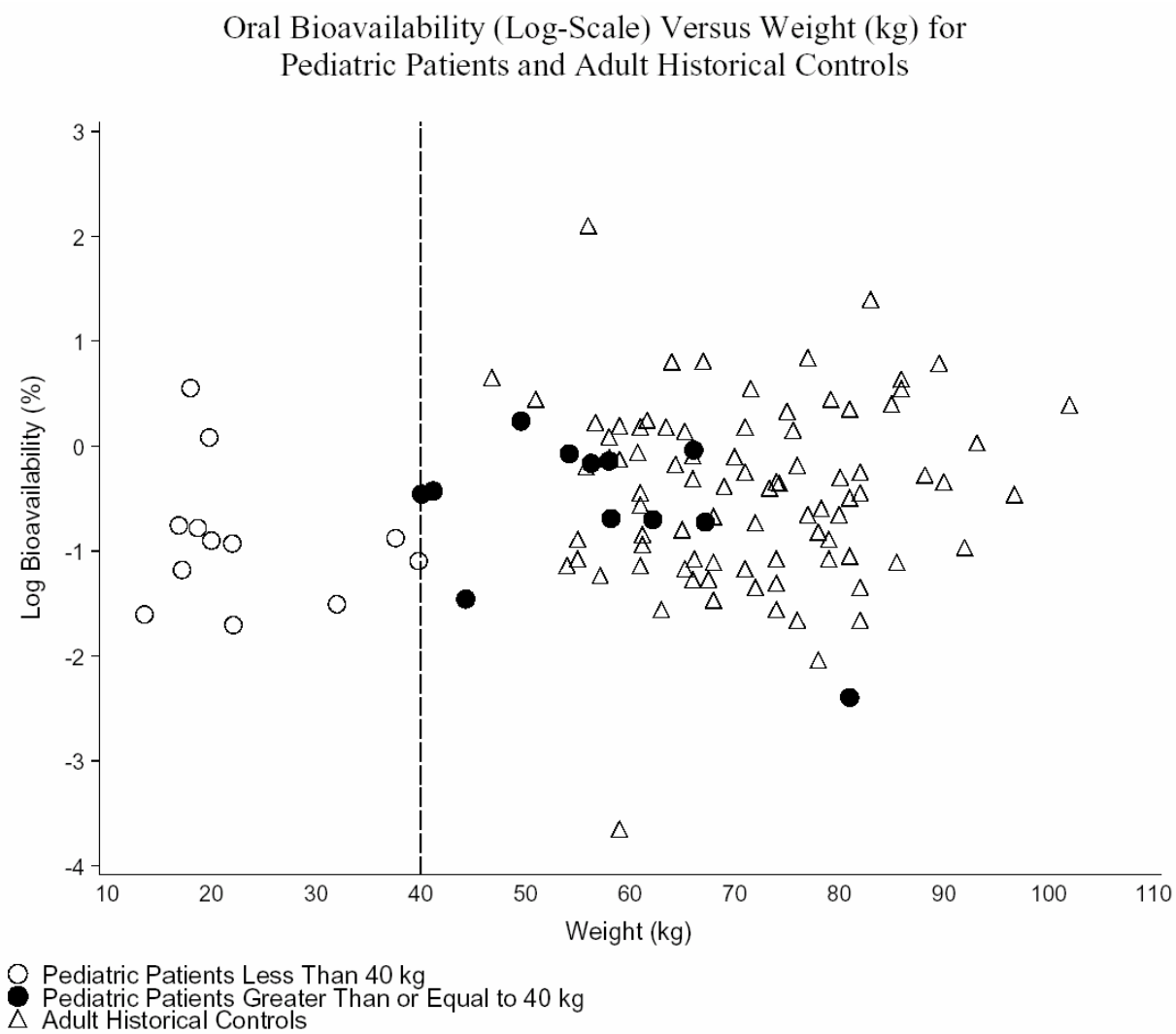
Summary Statistics for Bioavailability (%) of Alendronate
for Adult and Pediatric Patients

Population	N	LS Mean (%)	Median (%)	Min (%)	Max (%)	Standard Deviation (%)	GMR to Adult	95% CI for GMR
<40 kg	12	0.41	0.40	0.18	1.74	0.45	0.63	(0.39, 1.04)
≥40 kg	12	0.56	0.64	0.09	1.27	0.33	0.86	(0.52, 1.41)
Adult	86	0.65	0.68	0.03	8.17	1.02		
RMSE=0.810								
Pooled Pediatric	24	0.48	0.48	0.09	1.74	0.39	0.74	(0.51, 1.07)
Adult	86	0.65	0.68	0.03	8.17	1.02		
RMSE=0.809								

LS = Least-squares (back-transformed from the log scale).
GMR = Geometric mean ratio.
CI = Confidence interval.
RMSE = Root Mean Square Error from the analysis of variance model.

Data Source: [2.1]

The overall geometric mean (95% CI) BA for adult patients in the preselected 4 historical studies was 0.65% (0.54%, 0.77%) (See table above). The participants in these 4 studies (65, 69, 74, and 144) represented female and male from the age range of 21 to 76. Per the table above, the geometric mean ratio (GMR) of BA in OI pediatric patients weighing < 40 kg, relative to the adult population, was 0.63, with a 95% CI of (0.39, 1.04). The GMR of BA in pediatric patients weighing ≥ 40 kg, relative to the adult population, was 0.86, with a 95% CI of (0.52, 1.41). The GMR of BA in the pooled OI pediatric patient population relative to the adult population, was 0.74, with a 95% CI of (0.51, 1.07). The log BA versus body weight figure below graphically demonstrates the similarity of BA between OI patients and adults (historical data).



The GMR with 95% CI of the total alendronate urinary excretion after the oral administration to intravenous administration in the 2 dose groups of OI patients and the GMR with 95% CI of the total alendronate urinary excretion of pooled OI pediatric patients to adults were all identical to the corresponding BA assessment as shown above. The dose-adjusted GMR of total urinary excretion after IV dosing for pediatric patients weighing < 40 kg, relative to the adult population, was 1.09, with a 95% CI of (0.92, 1.29) (see table below). The dose-adjusted GMR of total urinary excretion after IV dosing for pediatric patients weighing ≥ 40 kg, relative to the adult population, was 1.08, with a 95% CI of (0.91, 1.28). The GMR ratio of total urinary excretion after IV dosing for the pooled pediatric patient population, relative to the adult population, was 1.09, with a 95% CI of (0.96, 1.23). This is consistent that the total alendronate urinary excretion data upon intravenous administration is similar between OI pediatric patients and adults (historical data).

Summary Statistics for Total Urinary Excretion of Alendronate (µg)
for Adult and Pediatric Patients After an IV Dose (Dose-Adjusted to 1 mg)

Population	N	LS Mean (µg)	Median (µg)	Min (µg)	Max (µg)	GMR to Adult	95% CI for GMR
<40 kg	12	442.0	459.5	313.4	518.9	1.09	(0.92, 1.29)
≥40 kg	12	438.5	440.5	336.6	572.9	1.08	(0.91, 1.28)
Adult	86	405.3	420.3	158.6	803.3		
RMSE =0.281							
Pooled Pediatric	24	440.2	459.5	313.4	572.9	1.09	(0.96, 1.23)
Adult	86	405.3	420.3	158.6	803.3		
RMSE[ll]=0.280							

LS = Least-squares.
GMR = Geometric mean ratio.
CI = Confidence interval.
RMSE = Root Mean Square Error from the analysis of variance model.

Data Source: [2.1]

5 Labeling Comments

CLINICAL PHARMACOLOGY

Special Populations

Pediatric: (b) (4)

[redacted]

See the added (underscored) and deleted (strikethrough) statements above.

(b) (4)

[redacted]

Attachment

SAS code for assessing alendronate absolute BA in < 40 kg OI patients:

```
data fosamax;
infile 'C:\510 review\osteo\bisphosphonate\NDA\20560\u120560.txt';
input sub per seq trt $ amt amtpermg;
lnamtpermg=log(amtpermg);
proc sort data = fosamax;
by trt;

proc means data = fosamax;
by trt;

proc glm data = fosamax;
 class sub per seq trt;
 model lnamtpermg = seq sub(seq) per trt;
 test h = seq e = sub(seq);
 estimate 'ORAL1 vs. IV1' trt -1 1;
lsmeans trt / pdiff cl alpha=0.05;
 proc print data = fosamax;
 run;
```

SAS Output for assessing alendronate absolute BA in < 40 kg OI patients:

```
The SAS System        17:44 Thursday, June 19, 2003   1

------------------------------------------- trt=IV1 ------------------------------
--------------

                                      The MEANS Procedure

        Variable        N             Mean         Std Dev         Minimum
Maximum

ffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffff
        sub            12        7.2500000       3.9571569       1.0000000
13.0000000
        per            12        1.4166667       0.5149287       1.0000000
2.0000000
        seq            12        1.5833333       0.5149287       1.0000000
2.0000000
        amt            12       47.0116667       5.4314234      33.4700000
55.2600000
        amtpermg       12      445.5846667      56.0215671     313.3895000
518.9437000
        lnamtpermg     12        6.0913502       0.1361541       5.7474468
6.2517954

ffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffff


------------------------------------------ trt=ORAL1 -----------------------------
--------------
```

Variable	N	Mean	Std Dev	Minimum	Maximum
sub	12	7.2500000	3.9571569	1.0000000	13.0000000
per	12	1.5833333	0.5149287	1.0000000	2.0000000
seq	12	1.5833333	0.5149287	1.0000000	2.0000000
amt	12	78.4650000	62.9086046	24.2200000	245.9800000
amtpermg	12	2.2482808	1.8025389	0.6939830	7.0481380
lnamtpermg	12	0.5936822	0.6514070	-0.3653078	1.9527635

The GLM Procedure

Class Level Information

Class	Levels	Values
sub	12	1 2 3 5 6 7 8 9 10 11 12 13
per	2	1 2
seq	2	1 2
trt	2	IV1 ORAL1

Number of observations 24

The GLM Procedure

Dependent Variable: lnamtpermg

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	13	184.2504476	14.1731114	72.05	<.0001
Error	10	1.9672379	0.1967238		
Corrected Total	23	186.2176855			

R-Square	Coeff Var	Root MSE	lnamtpermg Mean
0.989436	13.26951	0.443536	3.342516

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.3918587	0.3918587	1.99	0.1885
sub(seq)	10	2.1081539	0.2108154	1.07	0.4575
per	1	8.2447840	8.2447840	41.91	<.0001
trt	1	173.5056510	173.5056510	881.98	<.0001

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.3918587	0.3918587	1.99	0.1885
sub(seq)	10	2.1081539	0.2108154	1.07	0.4575
per	1	0.4043091	0.4043091	2.06	0.1822
trt	1	173.5056510	173.5056510	881.98	<.0001

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.39185872	0.39185872	1.86	0.2027

Parameter	Estimate	Standard Error	t Value	Pr > |t|
ORAL1 vs. IV1	-5.45379005	0.18364117	-29.70	<.0001

The GLM Procedure
Least Squares Means

trt	lnamtpermg LSMEAN	H0:LSMean1= LSMean2 Pr > |t|

IV1	6.09100979	<.0001
ORAL1	0.63721974	

trt	lnamtpermg LSMEAN	95% Confidence Limits	
IV1	6.091010	5.801677	6.380342
ORAL1	0.637220	0.347887	0.926552

Least Squares Means for Effect trt

i	j	Difference Between Means	95% Confidence Limits for LSMean(i)-LSMean(j)	
1	2	5.453790	5.044612	5.862968

Obs	sub	per	seq	trt	amt	amtpermg	lnamtpermg
1	1	1	2	IV1	33.47	313.390	5.74745
2	2	2	1	IV1	43.75	414.692	6.02754
3	3	1	2	IV1	55.26	512.141	6.23860
4	5	2	1	IV1	50.56	472.965	6.15902
5	6	1	2	IV1	48.92	455.918	6.12231
6	7	1	2	IV1	48.56	476.078	6.16558
7	8	2	1	IV1	49.42	451.324	6.11219
8	9	1	2	IV1	49.74	463.129	6.13800
9	10	2	1	IV1	50.60	464.220	6.14036
10	11	2	1	IV1	44.47	405.748	6.00573
11	12	1	2	IV1	45.20	518.944	6.25180
12	13	1	2	IV1	44.19	398.467	5.98762
13	1	2	2	ORAL1	24.22	0.694	-0.36531
14	2	1	1	ORAL1	157.02	4.499	1.50389
15	3	2	2	ORAL1	35.87	1.028	0.02741
16	5	1	1	ORAL1	29.95	0.858	-0.15296
17	6	2	2	ORAL1	48.88	1.401	0.33688
18	7	2	2	ORAL1	69.06	1.979	0.68249
19	8	1	1	ORAL1	52.61	1.507	0.41042
20	9	2	2	ORAL1	73.97	2.119	0.75117
21	10	1	1	ORAL1	75.99	2.177	0.77811
22	11	1	1	ORAL1	245.98	7.048	1.95276
23	12	2	2	ORAL1	71.55	2.050	0.71791
24	13	2	2	ORAL1	56.48	1.618	0.48140

SAS code for assessing alendronate absolute BA in ≥ 40 kg OI patients:

```
data fosamax;
infile 'C:\510 review\osteo\bisphosphonate\NDA\20560\u220560.txt';
input sub per seq trt $ amt amtpermg;
lnamtpermg=log(amtpermg);
proc sort data = fosamax;
```

```
by trt;

proc means data = fosamax;
by trt;

proc glm data = fosamax;
 class sub per seq trt;
 model lnamtpermg = seq sub(seq) per trt;
 test h = seq e = sub(seq);
 estimate 'ORAL2 vs. IV2' trt -1 1;
lsmeans trt / pdiff cl alpha=0.05;
 proc print data = fosamax;
 run;
```

SAS Output for assessing alendronate absolute BA in ≥ 40 kg OI patients:

```
The SAS System        17:51 Thursday, June 19, 2003   1

------------------------------------------ trt=IV2 ------------------------------
--------------

                                     The MEANS Procedure

        Variable       N            Mean         Std Dev         Minimum
Maximum

ffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffff
        sub           12      22.5000000       3.6055513      17.0000000
28.0000000
        per           12       1.5000000       0.5222330       1.0000000
2.0000000
        seq           12       1.5000000       0.5222330       1.0000000
2.0000000
        amt           12      48.3983333      10.1204589      35.6500000
62.7900000
        amtpermg      12     446.5684833      88.7606363     336.6383000
572.9015000
        lnamtpermg    12       6.0832550       0.2006009       5.8190091
6.3507138

ffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffff


----------------------------------------- trt=ORAL2 -----------------------------
--------------

        Variable       N            Mean         Std Dev         Minimum
Maximum

ffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffff
        sub           12      22.5000000       3.6055513      17.0000000
28.0000000
        per           12       1.5000000       0.5222330       1.0000000
2.0000000
        seq           12       1.5000000       0.5222330       1.0000000
2.0000000
```

```
        amt            12     195.4283333      86.4450071      36.3100000
313.8400000
        amtpermg       12       2.8078783       1.2420259       0.5216950
4.5091950
        lnamtpermg     12       0.8925867       0.6311750      -0.6506722
1.5061186

ffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffffff
                                         The SAS System        17:51 Thursday,
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                                       The GLM Procedure

                                    Class Level Information

                  Class         Levels    Values

                  sub               12    17 18 19 20 21 22 23 24 25 26 27 28

                  per                2    1 2

                  seq                2    1 2

                  trt                2    IV2 ORAL2


                                  Number of observations    24
                                         The SAS System        17:51 Thursday,
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                                       The GLM Procedure

Dependent Variable: lnamtpermg

                                                    Sum of
      Source                      DF          Squares     Mean Square    F Value
Pr > F

      Model                       13      164.0930221      12.6225402      52.81
<.0001

      Error                       10        2.3900516       0.2390052

      Corrected Total             23      166.4830737


                    R-Square     Coeff Var      Root MSE    lnamtpermg Mean

                    0.985644      14.01642      0.488882           3.487921


      Source                      DF        Type I SS     Mean Square    F Value
Pr > F

      seq                          1        0.2866738       0.2866738       1.20
0.2991
```

```
      sub(seq)                  10       1.6660625       0.1666062       0.70
0.7106
      per                        1       0.4820603       0.4820603       2.02
0.1860
      trt                        1     161.6582256     161.6582256     676.38
<.0001


      Source                    DF     Type III SS     Mean Square    F Value
Pr > F

      seq                        1       0.2866738       0.2866738       1.20
0.2991
      sub(seq)                  10       1.6660625       0.1666062       0.70
0.7106
      per                        1       0.4820603       0.4820603       2.02
0.1860
      trt                        1     161.6582256     161.6582256     676.38
<.0001


           Tests of Hypotheses Using the Type III MS for sub(seq) as an Error
Term

      Source                    DF     Type III SS     Mean Square    F Value
Pr > F

      seq                        1      0.28667375      0.28667375       1.72
0.2189


                                                        Standard
          Parameter                   Estimate             Error    t Value    Pr >
|t|

          ORAL2 vs. IV2            -5.19066832      0.19958505     -26.01
<.0001
                                      The SAS System        17:51 Thursday,
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                                   The GLM Procedure
                                  Least Squares Means

                                                          H0:LSMean1=
                                     lnamtpermg             LSMean2
                              trt         LSMEAN          Pr > |t|

                              IV2      6.08325500             <.0001
                              ORAL2    0.89258668


                                     lnamtpermg
                              trt         LSMEAN      95% Confidence Limits

                              IV2       6.083255       5.768802     6.397708
                              ORAL2     0.892587       0.578134     1.207039
```

Least Squares Means for Effect trt

i	j	Difference Between Means	95% Confidence Limits for LSMean(i)-LSMean(j)	
1	2	5.190668	4.745965	5.635372

Obs	sub	per	seq	trt	amt	amtpermg	lnamtpermg
1	17	2	1	IV2	62.79	572.902	6.35071
2	18	1	2	IV2	51.89	484.501	6.18312
3	19	2	1	IV2	60.66	551.956	6.31347
4	20	1	2	IV2	58.37	543.482	6.29800
5	21	1	2	IV2	35.65	336.638	5.81901
6	22	2	1	IV2	37.90	355.869	5.87456
7	23	2	1	IV2	51.84	478.670	6.17101
8	24	1	2	IV2	37.07	341.974	5.83474
9	25	1	2	IV2	40.08	368.044	5.90820
10	26	2	1	IV2	43.85	398.274	5.98714
11	27	1	2	IV2	58.92	524.199	6.26187
12	28	2	1	IV2	41.76	402.312	5.99723
13	17	1	1	ORAL2	36.31	0.522	-0.65067
14	18	2	2	ORAL2	313.84	4.509	1.50612
15	19	1	1	ORAL2	243.50	3.499	1.25235
16	20	2	2	ORAL2	189.98	2.730	1.00415
17	21	2	2	ORAL2	297.53	4.275	1.45275
18	22	1	1	ORAL2	215.04	3.090	1.12806
19	23	1	1	ORAL2	77.53	1.114	0.10790
20	24	2	2	ORAL2	201.94	2.901	1.06521
21	25	2	2	ORAL2	127.19	1.827	0.60292
22	26	1	1	ORAL2	134.23	1.929	0.65679
23	27	2	2	ORAL2	238.23	3.423	1.23047
24	28	1	1	ORAL2	269.82	3.877	1.35499

20 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

S.W. Johnny Lau
7/7/03 06:23:48 PM
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Hae-Young Ahn
7/9/03 02:49:17 PM
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