CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 020707

STATISTICAL REVIEWS

Statistical Review and Evaluation

JAN 17 1997

NDA#: 20-707/Class 3S

Applicant: Sanofi Winthrop, Inc.

Name of Drug: Skelid® (tiludronate disodium) tablet

Indication: Paget's disease (osteitis deformans)

Documents Reviewed: Vols. 1.1, 1.238-1.267
Submission dated February 28, 1996

Medical Reviewer: Sam Dutta, M.D., Ph.D.

Background:

Paget's disease, also called osteitis deformans, is an idiopathic, progressive disease marked by increased bone resorption and excessive attempts at repair, resulting in weakened, deformed bones of increased mass. Both urine hydroxyproline (a measure of bone resorption) and serum alkaline phosphatase (SAP, a measure of bone formation) are increased in Paget's disease; these biochemicals are thus useful markers of metabolic activity and therapeutic response. SAP, therefore, has been chosen as the primary efficacy parameter for the clinical studies.

Controlled Clinical Studies:

The submission included two randomized, double-blind, placebo-controlled studies (P1845 & P1619) and one active-controlled study (P1552). Etidronate, an orally administered bisphosphonate approved for Paget's disease, is the comparator for the active-controlled study. The placebo-controlled studies had a 12-week treatment period followed by a 12-week off treatment period.

Study P 1619

This was a 16-center, randomized, placebo controlled, double blind, dose ranging study of tiludronate in Paget's disease. The study was conducted in the UK from April 1991 to September 1992. The duration of the study was 24 weeks with a 12-week active treatment phase and a 12-week off treatment follow-up phase. The objective of this trial was to compare 3 doses of tiludronate for 12 weeks in patients with Paget's disease to determine the optimal dose of tiludronate in treating the disease. From an open study using the tablet formulation (P1036), the effective dosage with the tablet appeared to be 400 mg/day. The purpose of Study P 1619 was to confirm this assumption.

The study included patients of either sex aged 18 years and over

with a diagnosis of Paget's bone disease. The lesions were confirmed by radiography and/or scintigraphy. The total serum alkaline phosphatase level had to be twice the maximum normal value of the local laboratory carrying out the determination.

Estimated from a previous study, P1036, the 400 mg/day tiludronate had a success rate of 57% after 12 weeks. With 25 patients per group, a power of 80% and a 2-sided alpha of 0.05, one can detect a true difference of 40% in success rates between two groups of 57% and 17%.

Treatment Allocation

Patients in each center were randomized to one of 4 treatment groups of placebo, 200 mg/day, 400 mg/day and 600 mg/day. All patients received 3 tablets daily according to the following scheme:

Treatment Group	# of tiludronate Tablet	# of placebo Tablet
Placebo	0	3
200 mg/day	1	2
400 mg/day	2	1
600 mg/day	3	0

All 3 tablets were taken at the same time with water in the morning at least 2 hours before, or at least 2 hours after, taking food.

The 6 visits included the baseline, week 2, 4, 8, 12 and a final visit at week 24 (or 12 weeks after stopping treatment).

Statistical Analysis

Differences in the number of patients who show a 50% reduction in alkaline phosphatase were compared between placebo and the pooled tiludronate groups and between each of the tiludronate groups. Alkaline phosphatase levels were also compared (using a one way analysis of covariance) between the tiludronate groups and placebo adjusting p-values by Dunnett's multiple comparison method.

The comparison of the number of patients who show a 50% reduction in alkaline phosphatase was carried out on both the efficacy population (patients reached 12 weeks in study) and an `intent-to-treat' population (failure for withdrawals before 12 weeks).

Patient Population

A total of 113 patients were randomized and 112 were treated with study medication. The following table displays the status of patients:

Table I. Patient Status of Study 1619

Number of Patients	Placebo	200 mg	400 mg	600 mg	Total
Randomized	26	29	30	28	113
Treated	26	29	29	28	112
Evaluable at 12 weeks	23	25	27	25	100
Evaluable at follow-up*	23	26	28	27	104
Withdrawals					
ADEs	1	3	1	2	7
Death	0	2	0	0	2
Other	5	1	1	2	9

*4 patients entered 24-week follow-up though not evaluable at week 12.

Demographic and Baseline Information

Table II. is a summary of demographics and baseline data.

Table II. Summary of Demographics and Baseline

	Placebo n=26	200 mg n=29	400 mg n=29	600 mg n=28
# of Male	12	12	18	18
# of Females	14	17	11	10
	Mean [range]			
Age (years)	69 [47 - 87]	70 [52 - 82]	72 [55 - 81]	68 [51 - 81]
Duration (years) of Diagnosis of Paget's Disease	8.5 [0 - 26]	7.1 [0 - 36]	11.1 [0 - 36]	5.5 [0 - 34]
	Geometric Mean (minimum - maximum)			
Serum alkaline phosphatase (IU/l) (normal range 25-115)	387.5 (139-1611)	397.4 (174-1795)	434.5 (197-1614)	436.1 (131-1268)

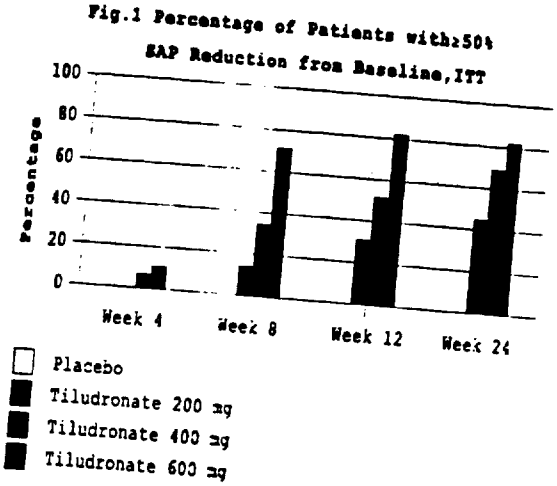
All patients were Caucasian except for one patient in the 600 mg

group who was black. The mean duration of Paget's disease was longer in the tiludronate 400 mg group (11.1 years) than other treatment groups (5.5-8.5 years). Serum alkaline phosphatase levels were similar in each of the treatment groups at entry.

Efficacy Results

Responder Analysis (50% reduction from Baseline)

Table III. & Fig. 1 display the proportion of patients with at least 50% reduction of SAP in the intent-to-treat population.



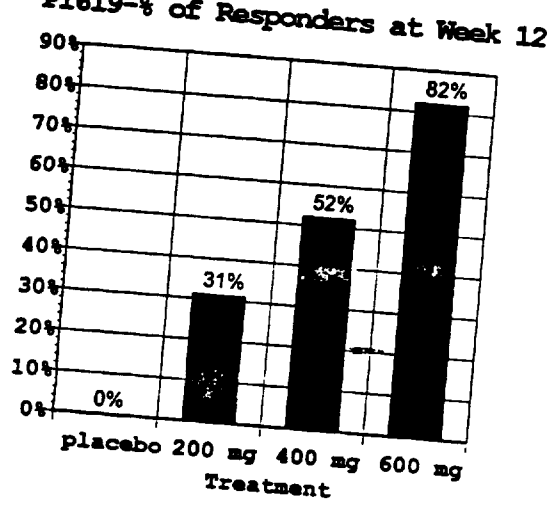


Table III. Number (percentage) of responders at 3 & 6 months

	Treatment			
	Placebo	Tiludronate 200 mg[1]	Tiludronate 400 mg[1]	Tiludronate 600 mg[1]
Week 12 ITT	0/26(0%)	9/29(31%)	15/29(51.7%)	23/28(82.1%)[2]
Efficacy	0/21(0%)	9/24(37.5%)	15/26(57.7%)	22/24(91.7%)[2]
Week 24 ITT	0/26(0%)	13/29(44.8%)	20/29(69%)	23/28(82.1%)[2]
Efficacy	0/21(0%)	14/23(60.9%)	20/26(76.9%)	22/23(95.7%)

p-values are adjusted by Sidak procedure

[1] $p \leq 0.01$ compared with placebo

[2] $p \leq 0.001$ at week 12 and $p=0.0334$ at week 24 compared with 200 mg tiludronate

There were no responders in the placebo group. After adjusting p values by the Sidak procedure, all tiludronate groups significantly outperformed placebo at both week 12 and week 24. The 600 mg group at week 12 is significantly better than the 200

mg group but the 400 mg is not statistically different from the 200 mg group. The percentage of patients whose alkaline phosphatase levels normalized (≤115 IU/l) at weeks 12 and 24 are displayed in Table IV.

Table IV. Percentage of normalized SAP (≤115IU/l) at 3 & 6 months

	Treatment			
	Placebo	Tiludronate 200 mg	Tiludronate 400 mg	Tiludronate 600 mg
Week 12 ITT Efficacy	0/23(0%) 0/21(0%)	3/25(12.0%) 2/24(8.3%)	4/27(14.8%) 3/26(11.5%)	9/25(36.0%)[1] 8/24(33.3%)[1]
Week 24 ITT Efficacy	0/23(0%) 0/21(0%)	8/26(30.8%)[1] 6/23(26.1%)	11/28(39.3%)[1] 10/26(38.5%)[1]	12/27(44.4%)[1] 10/23(43.5%)[1]

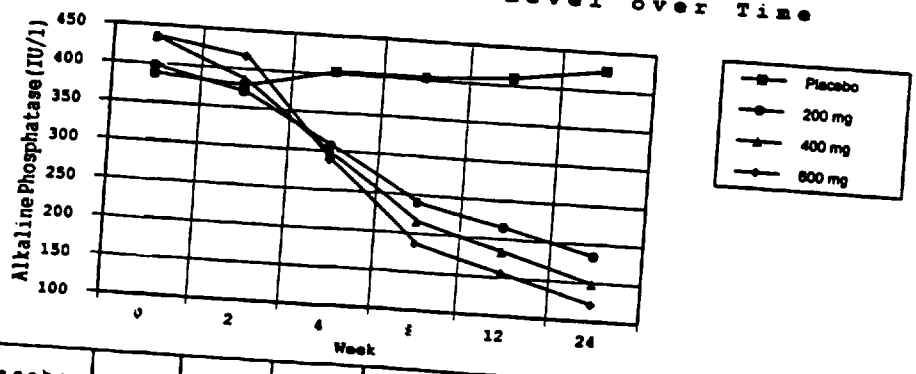
p-values are adjusted by Sidak procedure
[1] $p<0.05$ compared with placebo

At week 12, the 600 mg group had significantly greater number of patients with normalized SAP than placebo. But, the 200 mg and 400 mg groups are not significantly different from placebo.

In the analysis of variance, in order to meet the underlying assumptions the natural log transformation was used. The results were in terms of adjusted geometric means and adjusted geometric mean ratios. It was concluded that the tiludronate groups had a significantly greater reduction in SAP level than placebo. Also, there was strong statistical evidence to suggest that SAP was reduced more by tiludronate 600 mg compared with 200 mg.

The SAP value over time is in the following figure.

P1619-Geometric Mean SAP Level over Time



Placebo	387	379	403	413	410	426
200 mg	347	371	307	243	215	184
400 mg	434	387	297	215	183	149
600 mg	416	417	289	185	155	122

Pain assessment

There is no statistical difference between the treatment groups for number of patients complaining of Pagetic pain nor the median of VAS scores (Huskisson Visual Analogue Scale).

Adverse Events

The adverse event rate in the placebo group was 53.8% compared to 65.5%, 79.3% and 82.1% in the 200 mg, 400 mg, and 600 mg tiludronate groups. The most common adverse events reported were GI. Diarrhea occurred significantly more frequently on tiludronate (14/86, 16%) than placebo (0/26) which is statistically significant at p=0.037 (Fisher's exact test).

Conclusion:

For the primary efficacy outcome, the number of responders (≥50% reduction of SAP), study P 1619 showed tiludronate 200 mg, 400 mg and 600 mg all had a greater proportion of patients with 50% or more reduction of SAP at week 12 than placebo which had no responders. The percentages of patients with 50% or more reduction were 0%, 31%, 52%, 82% at week 12 for placebo, 200 mg, 400 mg, and 600 mg, respectively. In addition, the 600 mg was statistically significantly better than the 200 mg in the responder analysis. The 400 mg dose is considered optimal because of the increased GI intolerance at the 600 mg dose.

Study P 1552

This was a double-blind, randomized, multicenter, European study (France, Belgium, The Netherlands, Germany, Spain, Italy) to compare Tiludronate to Etidronate.

Patients included were men and women over 18 years of age who suffered from symptomatic Paget's disease with lesions that have been confirmed by radiography or scanning and present a total alkaline phosphatase serum level twice that of the maximum normal values of the laboratory carrying out the assay.

The main objective of this study is to demonstrate that 400 mg/day of Tiludronate is more effective than 400 mg/day of Etidronate in the treatment of Paget's disease in 3 months. The secondary objective is to compare at 6 months 3 groups of patients, one group of patients treated with Tiludronate will have the treatment suspended after 3 months (placebo treatment), two other groups of patients treated with either Tiludronate or Etidronate will have treatment continued for 6 months.

The treatment length and dosage for each treatment group is as follows:

month	0	3	6
T 400 mg/d 3 months	two 200 mg T tablets two placebo capsules	two placebo tablets two placebo capsules	
T 400 mg/d 6 months	two 200 mg T tablets, two placebo capsules		
E 400 mg/d 6 months	two 200 mg E capsules, two placebo tablets		

Efficacy Evaluation

The efficacy was analyzed in terms of success/failure. Success was defined as at least a 50 % reduction of alkaline phosphatase serum level in international units per liter.

A missing value was considered a failure in the intent-to-treat analysis. The second analysis on the efficacy population includes patients with documented efficacy data.

The secondary efficacy criteria was the painful phenomena evaluated using HUSKISSON's Visual Analog Scale and phosphocalcic metabolism.

The primary analysis of the efficacy criterion was the success rate after three months. Fisher's exact two-tail test was used to compare the Etidronate group and the two Tiludronate groups.

After six months, both Tiludronate groups were considered separately and a chi-square test of the ratio of probability was performed.

A qualitative comparison of the therapeutic groups (two to three months and three to six months) was carried out by means of an analysis of covariance of the alkaline phosphatase levels. A multiple comparison procedure was used to detect possible groupings of adjusted means.

Deviations from Protocol

There were a number of violations in patient assignment. In ten centers, the numbering order for the patients was not always chronological. A random block size of 6 was used to balance treatment assignment. The randomization list was not always followed. The blocks were shared by several centers in Belgium, Germany, Italy, Spain. A total of 290 patients were selected in 97 centers and 234 were included in 85 centers.

Twenty-eight patients had violations of inclusion/exclusion criteria (10 excluded from efficacy analysis). Sixty-two (62) patients deviated from the procedure called for by the protocol and were all excluded from the efficacy analysis. Thirty-three (33) of the 62 had an assessment date deviation and 29 had a baseline serum alkaline phosphatase concentration deviation (4 missing values). Some patients deviated from the protocol for more than one reason.

Study Population

Eighty-five centers in 6 countries enrolled 234 patients in the study with 78 patients in the tiludronate 3 month treatment group, 77 in the tiludronate 6 month treatment group and 79 in the etidronate treatment group. Thirty patients discontinued before completing 6 months as called for in the protocol with 14, 11 and 5, respectively for tiludronate 3 month, tiludronate 6 month and etidronate. Those patients may have observations due at the next scheduled visit performed before leaving the study. They are excluded from the efficacy analysis, but included in the ITT analysis. Table V. displays the number of patients for whom bone metabolism or pain data are available by treatment and Table VI. displays the number of patients excluded from the efficacy analysis.

Table V. Number of patients with available data

Visit	Treatment			
	Tiludronate 3	Tiludronate 6	Etidronate	All groups
baseline	78	77	79	234
Visit 2	78	76	78	232
Visit 3	70	73	76	219

Table VI. Number of patients excluded from the efficacy analysis

Visit	Treatment			
	Tiludronate 3	Tiludronate 6	Etidronate	All groups
Visit 2	25	19	15	59
Visit 3	27	22	17	66

Patient Demographic Characteristics

Table VII. Patient demographic characteristics

	Treatment			
	Tiludronate 3	Tiludronate 6	Etidronate	p-value
Male/Female	52/26	49/28	38/41	0.04
Mean age(range) yrs	68.4(41.3-85.1)	70.2(42.7-89.6)	67.8(43.7-85.2)	0.30
Mean weight(range)kg	72.0(51.0-105.0)	71.7(50.0-107.0)	67.3(50.0-104)	0.02
Height(range) cm	165(145-185)	166(145-190)	163(143-180)	0.04
Race: Caucasian Negroid Other	75(96%) 3(4%) 0(0%)	76(99%) 0(0%) 1(1%)	78(99%) 1(1%) 0(0%)	0.24

The two tiludronate groups had more men than women compared to the more evenly balanced etidronate group. The differences in weight and height is related to the gender differences. When gender was incorporated into the model there is no statistical difference (p=0.16, 0.14, weight, height).

Baseline characteristics of disease

Disease history

The median duration of Paget's disease was 5 years. The majority of patients had more than one site of disease. The most common were the pelvis (182 patients) the lumbar spine (101) and the skull (88).

Out of the 234 patients 167 (71%) had been previously treated for Paget's disease and 64 (27%) were receiving analgesia. One hundred twenty-two (52%) patients had previously received bisphosphonate treatment for Paget's disease.

Baseline pain

One hundred seventy-two (74%) patients had bone pain at baseline. In the tiludronate 6 months group, the proportion is higher (83%) than in the etidronate group (66%), (p=0.017). The pain in the dorsal spine was significantly more common in the tiludronate 6 months group (12%) than in the tiludronate 3 months (6%) or etidronate (5%). Global pain severity as assessed by VAS score was comparable between the three treatment groups (mean scores 33.1 tiludronate 3 months; 41.8 tiludronate 6 months; etidronate 38.0; p=0.14).

Phosphocalcic metabolism

There was no significant difference between treatment groups in the SAP or urinary hydroxyproline concentrations or in the urinary hydroxyproline/creatinine ratio. Table VIII. displays mean values of baseline concentrations of these 3 factors.

Table VIII. Baseline means ± sem (range) of serum alkaline phosphatase, urinary hydroxyproline, and urinary hydroxyproline/creatinine ratio.

	Treatment			
	Tiludronate 3	Tiludronate 6	Etidronate	p-value
SAP IU/L	504.1±51.4 (174.0-2259.0)	475.4±36.6 (122.0-1901.0)	451.4±45.1 (124.0-2460.0)	0.50
Urinary hydroxyproline	376.0±60.2 (11.0-3153.0)	360.0±45.3 (13.0-1864.0)	502.4±98.3 (15.9-6180.0)	0.66
Hydroxyproline/ creatinine ratio	0.084±0.02 (0.001-1.417)	0.060±0.006 (0.000-0.397)	0.081±0.014 (0.001-0.814)	0.73

Efficacy Results

Primary efficacy analysis

A treatment success rate of at least a 50% reduction in the alkaline phosphatase level from baseline to 3 months in the ITT population was designated as the primary efficacy analysis. Patients with missing data were considered to be failures.

Results of ITT and efficacy analyses for the two treatment groups are shown in the following table:

Table IX Number (percentage) of responders at 3 months

≥50% reduction	Treatment		p-value
	Tiludronate	Etidronate	
ITT	89/155(**57.4**%)	11/79(**13.9**%)	<0.001
Efficacy	73/107(**67.6**%)	10/62(**16.1**%)	<0.001

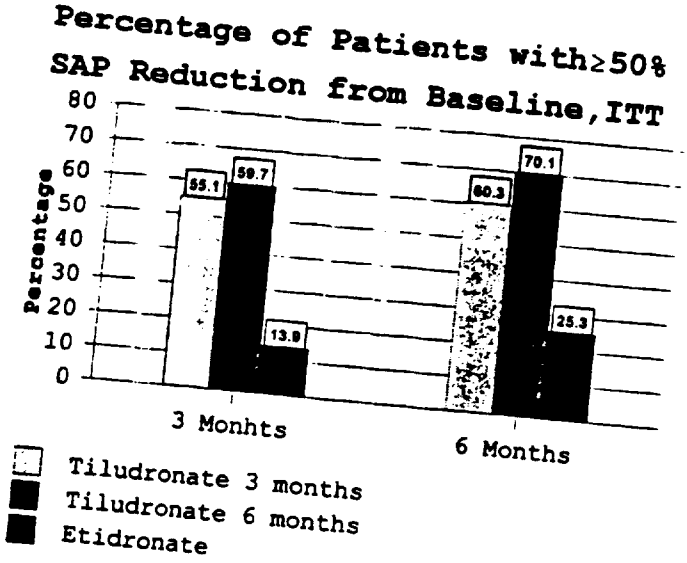
The proportion of patients with a 50% or more reduction from baseline in SAP was statistically significantly greater in Tiludronate than in Etidronate for ITT (57.4% vs. 13.9%) and efficacy analyses (67.6% vs. 16.1%) with $p<0.001$.

The 6 months result is in the following table.

Table X. Number (percentage) of responders at 6 months

	Treatment					
	Tiludronate 3		Tiludronate 6		Etidronate	
	3 months	6 months	3 months	6 months	3 months	6 months
ITT	n=78 43(55.1%)	47(60.3%)	n=77 46(59.7%)	54(70.1%)	n=79 11(13.9%)	20(25.3%)
Efficacy	n=49 33(67.4%)	40(81.6%)	n=50 33(66.0%)	42(84.0%)	n=60 10(16.7%)	18(30.0%)

The percentage of responders are higher with Tiludronate 3 months and Tiludronate 6 months than with Etidronate with $p<0.001$. There is no statistical difference between the two Tiludronate groups at month 6 (ITT, $p=0.24$, Efficacy, $p=0.80$).



Pain Assessment

a) Bone Pain

At baseline, a higher portion of patients in the tiludronate 6 months group (83%) reported bone pain (including non-Pagetic sites) than in the etidronate group (66%), (p=0.017).

At 3 months and 6 months, the investigator reported patient's bone pain in relation to Paget's disease. The number (percentage) of patients with bone pain at baseline, month 3 and 6 is displayed in Table XI.

Table XI Number (percentage) of Bone pain

	Treatment		
	Tiludronate 3	Tiludronate 6	Etidronate
baseline	56/78 (71.8%)	64/77 (83.1%)*	52/79 (65.8%)
3 months	47/77 (61.0%)	54/75 (72.0%)	46/77 (59.7%)
6 months	38/70 (54.3%)	43/73 (58.9%)	40/76 (52.6%)

* significant at p=0.017 vs. Etidronate

Severity of bone pain at rest and change in bone pain at rest were analyzed by each of the 10 anatomical sites studied. There was no statistically significant difference between the three treatment groups at any of the 10 sites.

Other Analysis

1. Normalized SAP

The analysis of patients with normalized SAP was not designated in the protocol but is of interest as an outcome variable. A normalized patient is a patient with a SAP level below the upper limit of the central laboratory's normal range (≤105 IU/l). Percentages of patients with normalized SAP levels at 3 months and 6 months are displayed in Table XII.

Table XII. Number (percentage) of normalized SAP at 3 and 6 months, ITT

	Treatment		
	Tiludronate 3 months	Tiludronate 6 months	Etidronate
3 months	12/78 (15.4%)	10/77 (13.0%)	4/79 (5.1%)
6 months	19/78 (24.4%)	21/77 (27.3%)	9/79 (11.4%)

At 6 months, the two Tiludronate groups had a greater proportion of normalized patients than the etidronate group. P-values were 0.039 and 0.015, respectively.

At 3 months the combined tiludronate group had 22/155 (14.2%) patients with normalized SAP compared to 4/79 (5.1%) of the etidronate group. This was statistically significant with p=0.046 (Fisher's exact test).

2. Geometric means of SAP

The natural log transformation was applied to SAP data in order to meet the assumptions underlying the analysis of variance. The geometric means at baseline, 3 months, and 6 months are displayed in Tables XIII and XIV for the ITT population.

Table XIII. Baseline adjusted geometric means of SAP at 3 months

	Treatment		Ratio [CI] Tilu/Etid	p value
	Tiludronate	Etidronate		
Baseline	401.58	359.07		
3 months	182.37	264.41	0.626 [0.559, 0.701]	<0.0001

Table XIV. Baseline adjusted geometric means of SAP at 6 months

	Treatment		
	Tiludronate 3 months	Tiludronate 6 months	Etidronate
Baseline	391.97	401.45	362.52
6 months	146.14	140.08	233.70
Ratio [CI] to Etidronate	0.590* [0.506, 0.689]	0.556* [0.476, 0.649]	

* Statistically significant ($p<0.05$) when compared to Etidronate

The ratio of Tiludronate 6 month to tiludronate 3 month is 0.942 [0.803, 1.104] which is not statistically significant.

Conclusion

Study P 1552 showed that after 3 months treatment of either Tiludronate 400 mg/day or Etidronate 400 mg/day there was statistically significant greater percentage of patients with 50% or more reduction in the Tiludronate (57%) than the Etidronate (14%) group. At month 6, the responder rate for 3-month tiludronate followed by 3-month placebo treatment was 60%; for tiludronate 6-month treatment group the rate was 70% and for the etidronate 6-month treatment group it was 25%. Both the tiludronate groups are significantly better than etidronate but the two tiludronate groups (3-month and 6-month) were not different.

Study P 1845

This was a randomized, double-blind, placebo-controlled, dose ranging trial to investigate the effects of a 200 mg and 400 mg dose of the tablet formulation of tiludronate in patients with Paget's disease of the bone.

The primary efficacy variable was the change from baseline in total serum alkaline phosphatase (SAP) at Week 12. Analysis of variance models were to be used to compare the treatment groups. Nonparametric methods were to be considered if the normal assumption for change in SAP was not justified.

One of the secondary efficacy variables was the incidence rate of patients who have demonstrated at least a 50% reduction in SAP from baseline.

The study included male or female patients 35 years of age or older with location of the Pagetic bone lesions based on an isotopic total body scan performed within the two years prior to study entry, and the total serum alkaline phosphatase level (central laboratory) at least twice the upper normal value.

A radiologic survey of the Pagetic bones was to be performed at the baseline visit to confirm Paget's disease and to identify those patients who have skull osteoporosis circumscripta or advancing wedge/flamed shaped segments of resorption in the long bones. Those patients so identified were to have follow-up radiologic surveys of those lesions performed at the Week 12 and Week 24 visits. The Week 24 surveys were to be compared to the baseline and Week 12 surveys by a central blinded reader.

All patients who qualify and volunteer for a bone biopsy of a non-Pagetic iliac crest, were to have the procedure performed, as an additional safety assessment, at only the Week 24 visit.

At the screening visit, patients were ascertained to meet the inclusion and exclusion criteria. If a patient was qualified after all laboratory and bone scan tests, if needed, a baseline visit was to be scheduled within 30 days of the screening visit.

At the baseline visit patients had a plasma specimen obtained for drug analysis, and underwent a radiologic survey of their Pagetic bones. The purpose of the radiologic survey was to confirm Paget's disease, and identify those patients having skull osteoporosis circumscripta or advancing wedge/flamed shaped segments of resorption in the long bones. Those patients so identified had the originals of those X-rays sent to a blinded

central reader.

At the baseline visit patients were randomized into one of the three treatment groups of placebo, 200 mg tiludronate and 400 mg tiludronate. Placebo patients were to take two placebo tablets nightly, the 200 mg tiludronate patients, one active 200 mg tiludronate tablet and one placebo tablet nightly, and the 400 mg tiludronate patients, two active 200 mg tiludronate tablets nightly.

The treatment phase visits were at weeks 2, 4, 8, and 12. The observation phase visits were at weeks 16, 20, and 24. Those patients identified at the baseline visit as having osteoporosis circumscripta or advancing wedge/flamed shaped segments of resorption in the long bones were to undergo a radiologic survey of those areas during the week 24 visit. The originals of these X-rays were to be sent to the blinded central reader, and the findings of this survey were to be compared to those observed at the week 12 visit, to determine the effect of treatment discontinuation, if any, upon those areas.

A minimum of 35 patients per dose group (a total of 105) were to be randomized at 20 study centers. This sample size was to provide a power of greater than 0.9 to detect a 40% difference in response rates of treatment success in the active and placebo groups with an alpha level of 0.05.

Study Results

Patient Disposition

A total of 140 subjects were randomized at 20 study sites. One of the 400 mg patients withdrew before the first dose of study medication; therefore, there were 139 patients in the intent-to-treat population. One hundred thirty-seven (137) patients completed the Treatment Phase of the study (Week 12) and 134 completed the Treatment and Observation Phases of the study (Week 24). Patients who completed the Week 24 visit were assumed to have completed the Week 12 visit. Patients who did not complete the entire study (through Week 24) were considered to have completed through Week 12 if the duration of treatment was at least 77 days (11 weeks), where duration of treatment was defined to be the number of days from treatment start to the most recent date tablets were returned. Six patients were discontinued from the study and/or study drug. One placebo patient (010-0012) who stopped study drug due to an adverse event, but completed all study visits was included among both the 134 patients who

completed all study visits, and among the 6 subjects who permanently discontinued study drug.

There were 125 evaluable patients, all of whom completed the Treatment and Observation Phases of the study.

The Clinical Investigator's Agreement with Dr. Kantor and Dr. Chausmer (Center 15) was terminated. Consequently, the 3 patients from this site (one patient in each treatment group) were among those excluded from the evaluable population.

Table XV. Patient Status

		Skelid		
	Placebo	200 mg	400 mg	Total
Patients randomized	48	45	47	140
Intent-to-treat	48	45	46	139
Completed 12 weeks	46	45	46	137
Completed 24 weeks	45	44	45	134
Permanent discontinuation	4*	1	1	6
adverse event discontinuation	3	-	-	3
Evaluable for efficacy	39	42	44	125
Completed 12 weeks	39	42	44	125
Completed 24 weeks	39	42	44	125
Not evaluable for efficacy	9	3	2	14
Completed 12 weeks	7	3	2	12
Completed 24 weeks	6	2	1	9

* One placebo patient (010-0012) who permanently discontinued study drug also completed all study visits.

Four placebo patients, one 200 mg patient and one 400 mg patient permanently stopped study drug and/or discontinued from the study.

Reasons for permanently stopping study drug and/or the study are displayed in Table XVI.

Table XVI. Study Drug Discontinuation

Reasons	Placebo	Skelid		Total
		200 mg	400 mg	
Adverse event				
Diarrhea, micturition frequency abnormal	1[a]	-	-	1
Arrhythmia	1[a]	-	-	1
Dyspepsia	1[b]	-	-	1
Personal	1[a]	-	-	1
Site closed by sponsor	-	1[c]	1[c]	2

[a] Permanently stopped study drug and permanently discontinued from the study.
[b] Permanently stopped study drug but completed all study visits.
[c] Completed study drug, but permanently discontinued from the study during the follow-up phase.

Protocol Deviations

Eight patients in each of the 3 treatment groups (total 24) had one or more protocol deviations. The most common protocol deviations were as follows: nine patients had a laboratory test result at study entry that was significantly different from normal (as evaluated by the investigator), and six patients had an SAP level at study entry that was not at least twice the upper normal value. All protocol deviations were considered by the sponsor to be minor and these patients were evaluable for efficacy. Three of the patients who had protocol deviations were considered not evaluable for efficacy, but for reasons other than the protocol deviations.

Demographics

There were no statistically significant differences among the three treatment groups in demographic characteristics. Ninety-one of the 139 ITT patients (65%) were male and 48 (35%) were female. The majority of patients were Caucasian (126/139, 91%). The mean age was 69.5 years, the mean weight was 78.2 kg, and the mean height was 166.8 cm.

Medical History and Diagnoses

There were no clinically meaningful differences among the three treatment groups at baseline with respect to medical histories. All patients had Paget's disease of the bone, as determined by an isotopic total body scan performed within two years before study entry or at the screening visit. Paget's disease was radiographically confirmed at the baseline visit for all patients, with the exception of one 200 mg Skelid patient (003-0011) who had a radiographic assessment performed before study entry. One patient in the 200 mg group (010-0001) was diagnosed with Paget's disease on November, 1, 1980 which was recorded incorrectly as the patient's birth date (June 1, 1930).

Baseline Data

There were no statistically significant differences among the three treatment groups in baseline efficacy data, including SAP, urinary hydroxyproline/creatinine, Pagetic pain scores, alkaline phosphatase bone isoenzyme, and urinary pyridinoline cross links/creatinine ($p \geq 0.106$).

Baseline efficacy data by treatment group are displayed in Table XVII.

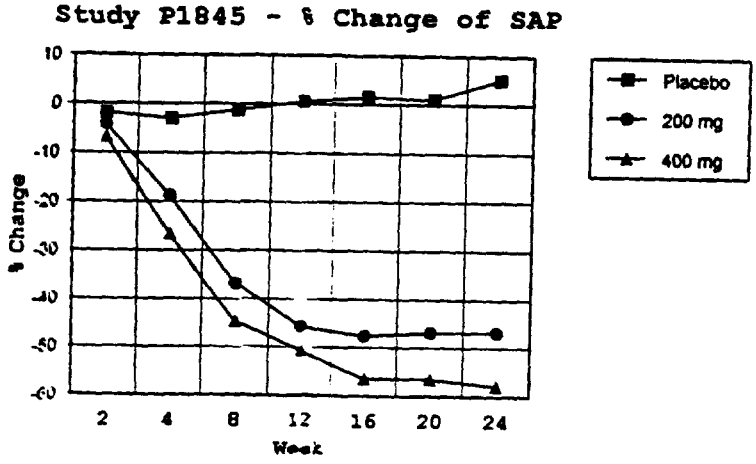
Table XVII. Patient Baseline Summary

	Placebo	Skelid 200 mg	Skelid 400 mg	Total
SAP (IU/L)				
N	48	45	46	139
Mean (sd)	611.8(627.0)	542.4(429.9)	418.6(237.4)	525.4(466.6)
Median	394.5	404	324.5	372
Range	210-4004	205-2476	199-1237	199-4004
Urinary hydroxyproline/creatinine (mmol/mol)				
N	48	45	46	139
Mean (sd)	114.9(85.7)	127.7(176.1)	86.1(50.2)	109.5(116.2)
Median	88	88.8	77.4	82.3
Range	15.3-507	38.9-1195.5	14.7-218.5	14.7-1195.5
Pagetic pain score (cm)				
N	48	45	46	139
Mean (sd)	3.3(2.9)	4(3.2)	3.2(2.8)	3.5(3.0)
Median	2.9	3.4	2.6	3.2
Range	0 - 10	0 - 10	0 - 9.3	0 - 10

	Placebo	Skelid		Total
		200 mg	400 mg	
Alkaline phosphatase bone isoenzyme (IU/L)				
N	47	45	46	138
Mean (sd)	464(539.1)	464.4(388.3)	351(212.6)	426.5(404.
Median	299	321	266.5	298
Range	31-3585	143-2195	155-1098	31-3585
Urinary pyrodinoline cross links/creatinine (pmol/µmol)				
N	46	42	44	132
Mean (sd)	831.4(625.2)	647.4(424.0)	540.7(455.1)	675.9(522.
Median	631.5	507	414.5	484
Range	98-2449	166-2123	89-2655	89-2655

Sponsor's Primary Efficacy Analysis (Intent-to-Treat)

The primary efficacy outcome was the percent change from baseline in SAP at week 12. At week 12 there was a significant difference with regard to the overall comparison ($p<0.001$). Pairwise comparisons showed significant differences between the placebo group and each of the two active treatment groups ($p<0.05$). No statistically significant difference was detected between the 200 and 400 mg groups. The mean percent change in SAP from baseline at week 12 was 1%, -46%, and -51% in the placebo, 200 mg, and 400 mg groups, respectively. At week 24, the means were 5%, -47%, and -58% in the placebo, 200 and 400 mg groups, respectively. At week 24, the pairwise comparisons showed significant differences between the placebo group and each of the active treatment groups and there was a significant difference between the 200 and 400 mg groups ($p<0.05$). Mean percent change from baseline in SAP over time is displayed in the following figure.



The week 12 and week 24 mean, median, and percent change in SAP are displayed in Table XVIII.

Table XVIII. Mean, Median, and Percent Change of SAP - ITT

SAP (U/L)	Placebo	Skelid 200 mg	Skelid 400 mg
Week 12			
Mean (sd)/median	45 774.5(744.5)/452.5	45 279.7(232.3)/241	46 198.2(115.8)/162
%Change "	0.5(11.6)/0.1	-45.8(15.3)/-48.9	-50.8(15.6)/-53.
Week 24			
Mean (sd)/median	45 684.1(777.9)/455	44 275.9(250.7)/207	45 157.1(76.0)/139
%Change "	5.1(15.0)/1.9	-46.8(22.3)/-51.9	-57.9(16.8)/-61.2

No statistically significant interaction between treatment and gender, treatment and age (<65, or ≥65), or treatment and body weight were detected at week 12 or week 24. The majority of patients were Caucasian (91%), therefore, no conclusions were made with respect to treatment-by race interactions.

Sponsor's Secondary Outcomes Analysis

1. Treatment Success

Treatment success was defined as the percentage of subjects who had at least a 50% decrease from baseline in SAP.

At week 12, the rate of treatment success in the 3 treatment groups of placebo, 200 mg and 400 mg skelid was 0%, 42% and 61%, respectively. The overall comparison was significant at $p<0.001$. Pairwise comparisons showed significant differences between the placebo group and each of the two active treatment groups ($p<0.001$). The difference between the 200 and 400 mg groups was not significant (X^2 test, $p=0.075$) at $\alpha=0.05$.

At week 24, the rate was 0%, 51% and 72% in the placebo, 200 mg and 400 mg groups, respectively. Statistical conclusions at week 24 were similar to those at week 12, except that a significant difference was detected between 200 and 400 mg groups (X^2 test, $p=0.043$).

2. Patients Whose SAP Returned to Within the Reference Range

The following table displays the number (%) of patients whose SAP returned to within the reference range at week 12 and week 24.

Table XIX. Number (Percent) of Patients with Normalized SAP

Visit	Placebo n=48	Skelid 200 mg n=45	Skelid 400 mg n=46
Week 12	0	3(7%)	9(20%)
Week 24	0	3(7%)	16(35%)

At week 12, the overall comparison was significant at p=0.003 (X^2 test). Pairwise comparisons showed a significant difference between placebo and 400 mg. The differences between the placebo and 200 mg groups, and between the 200 and 400 mg groups, approached significance (p=0.069 & p=0.078).

Reviewer's Analysis

The Fisher's exact test was applied because of no incidence in the placebo group. At week 12, there were no significant differences between the placebo and 200 mg groups (p=0.242) and between the 200 mg and 400 mg groups (p=0.119).

3. Pagetic Pain Scores

At week 12, the mean changes from baseline in Pagetic pain scores were -0.3, -1.2, and -0.3 in the placebo, 200 mg, and 400 mg groups, respectively. There were no significant differences among the 3 treatment groups in the mean change from baseline in Pagetic pain scores at any visit. (P≥0.106).

4. Skull and Long Bone X-Ray Findings

Thirty patients were identified at baseline X-ray to have skull osteoporosis circumscripta or advancing wedge/flamed shaped segments of resorption in the long bones. Of the 30 patients, 9 were from the placebo group, 10 from the 200 mg group and 11 from the 400 mg group. Twenty of the 30 patients had scintigraphic information: 13 patients were provided with screening whole body bone scintigrams and 7 had scintigraphy reports available. Ten of the 30 patients had neither scintigrams nor scintigraphy reports available.

One of the skull lesions (10 009, 400 mg) showed no abnormal uptake on scintigraphy and was excluded from all subsequent analyses. Twelve-week radiographs were not available for patients 06 010 (placebo) and 07 011 (200 mg).

The following table shows radiographic changes of all 30 patients at weeks 12 and 24.

Table XX. Change of Radiography at Weeks 12 & 24

	Week 12	Week 24	Placebo	200 mg	400 mg
Improvement	I	II		01007 06003	01021 08008 19001
	I	I		**07011** 08017	01015 18002 18006
No Improvement	NC	NC	06014 **06020** 09002 10017 **12007** 14006 16003	03003 **03011** 07004 14001	**07003** **10009** **18013**
	NC	P		08006 18011	**06007** 08007
	P	P	18008		
	P	PP	06006		
	Total n=30		n=9	n=10	n=11

I: improvement, NC: no change, P: progression
II,PP: improvement or progression at 24 weeks in excess of that seen at 12 weeks
Bold: patients excluded from week 12
Underline: patients excluded from week 24
10009, no evidence of Paget's disease in the bone that was radiographed, 06020 and 07011, week 12 radiographs were not available, 03011, 07003, 12007, 18006, & 18013, the level of confidence of assessment was poor, 06007, a femoral prosthesis may have simulated bone turnover.

The week 12 radiographic response is displayed in Table XXI.

Table XXI. Radiographic Response at Week 12

Radiographic Improvement	Placebo	200 mg	400 mg	Total
Week 12*				
No	7(100%)	5(62%)	1(14%)	13
Yes	0(0%)	3(38%)	6(86%)	9
Total	7	8	7	22
Week 24**				
No	8(100%)	5(56%)	3(37%)	16
Yes	0(0%)	4(44%)	5(63%)	9
Total	8	9	8	25

*p=0.004, **p=0.029, Fisher's Exact Test

Reviewer's Analysis

All 30 patients were included in the analysis. The independence of treatment and responses of the 3 treatments and 3 responses table were tested using Jonckhere-Terpstra test. The exact p-value is 0.005 at week 12 and 0.067 at week 24.

The week 12 radiographic response is displayed in Table XXII.

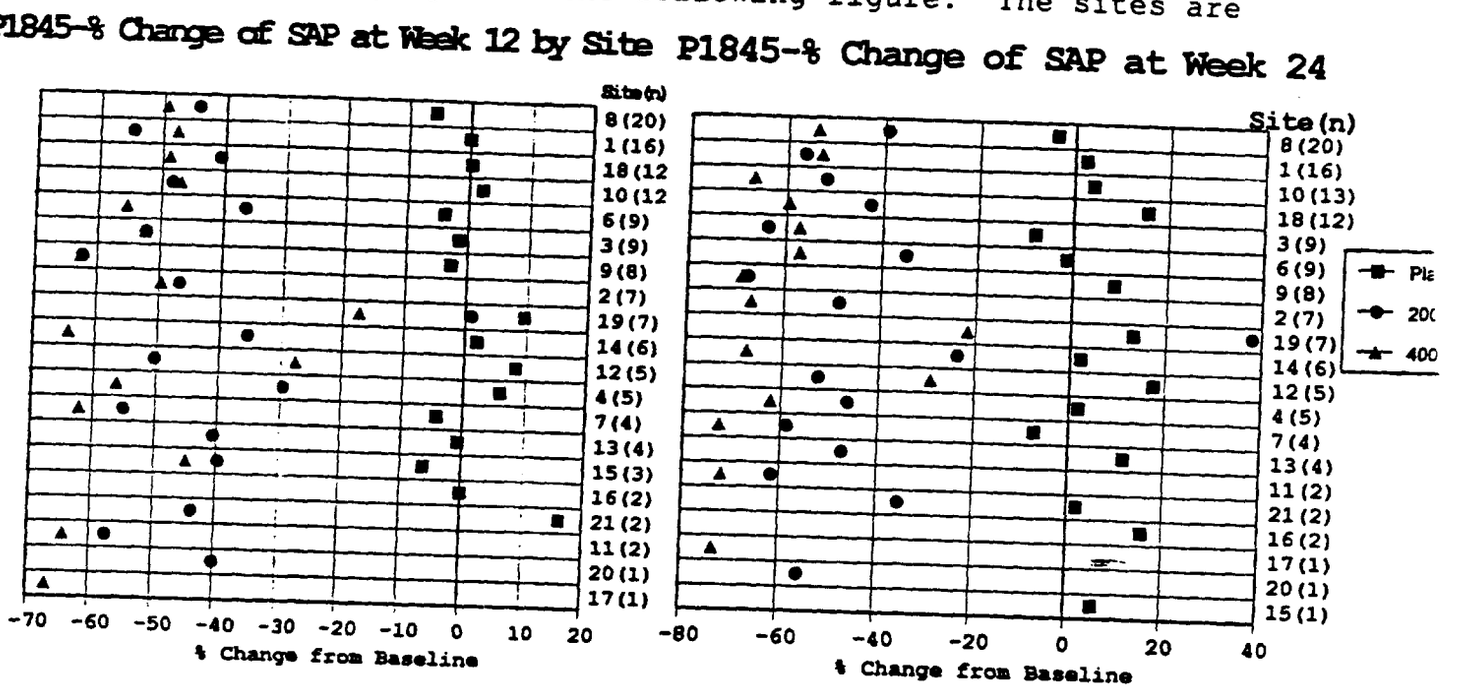
Table XXII. Radiographic Response at Weeks 12 & 24

Radiographic response	Placebo	200 mg	400 mg	Total
Week 12*				
Improvement	0(0%)	4(40%)	6(55%)	10
No Change	7(78%)	6(60%)	5(45%)	18
Progression	2(22%)	0(0%)	0	2
Total	9	10	11	30
Week 24**				
Improvement	0(0%)	4(40%)	6(55%)	10
No Change	7(78%)	4(40%)	3(27%)	14
Progression	2(22%)	2(20%)	2(18%)	6
Total	9	10	11	30

*p=0.0047, **p=0.067, Jonckheere-Terpstra test

Reviewer's Analysis

The percent change from baseline of SAP at week 12 and week 24 by center is displayed in the following figure. The sites are



sorted by the descending number(n) of patients in that site.

The graph indicated that patients in the placebo group (square) had limited decrease or increase in percent change of SAP. Only one center (19) had a mean increase in the 200 mg group.

Conclusion

The primary efficacy outcome is the percent change in SAP from baseline at week 12. At week 12 the placebo group had an increase of 0.5% and the 200 mg skelid group had a reduction of 45.8% and the 400 mg skelid group had a 50.8% reduction in SAP from baseline. The two active treatment groups are statistically significantly different from placebo. For the treatment success outcome, the percentage of patients with at least a 50% reduction in SAP from baseline were 0%, 42% and 61% for the placebo, 200 mg skelid and 400 mg skelid treatment groups, respectively, at week 12. The X-ray analysis of long bone also showed a significant difference between skelid and placebo in the improvement, no change, and progression of the disease. With 30 patients in the X-ray analysis, the percent with improvement for skelid was

40%(4/10) and 66%(6/11) for the 200 mg and 400 mg groups and none of the 9 patients in the placebo group improved. Two out of the 9 (22%) placebo patients had a disease progression and none of the skelid patients progressed.

Overall Conclusion:

Based on the percentage of patients with 50% Serum Alkaline Phosphatase (SAP) reduction, the two placebo-controlled studies with 12 weeks of treatment duration showed statistically significant reduction in SAP in the tiludronate treatment groups as compared to placebo. Both the 200 mg and 400 mg tiludronate groups are efficacious compared with placebo. The 600 mg group in Study P1619 had a higher incidence of diarrhea. In the active-controlled trial, tiludronate was better than etidronate in SAP reduction. In the 400 mg tiludronate group the 12 week result of the intent-to-treat analysis on responders (≥50% of SAP) showed 51%, 52% and 57%, respectively, for the two placebo-controlled studies (P1845, P1619) and the active-controlled study (P1552). In the active-controlled study 400 mg tiludronate showed a significantly greater reduction than the 400 mg Etidronate group which had a 14% responder rate at 3 months. At 6 months, in comparing patients who took 400 mg tiludronate 6 month and patients who took 400 mg tiludronate for 3 months then placebo for 3 months there was no statistical significant difference. The responder rates were 70% and 60%, respectively, for tiludronate 6 months and tiludronate 3 months.

Lee-Ping Pian

Lee-Ping Pian, Ph.D.
Mathematical Statistician

Concur: Mr. Marticello Dan Marticello 1/17/97

Dr. Nevius 1/17/97

cc: Arch NDA 20-707
HFD-510
HFD-510/SSobel, GTroendle
HFD-510/SDutta
HFD-510/RHedin
HFD-715/Chron., Division file, DMarticello, LPian

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This review contains 26 pages

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 020707

CLINCIAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEWS

DEC 20 1996

Clinical Pharmacology & Biopharmaceutics Review

NDA: 20-707	**SUBMISSION DATE: February 28, 1996** **September 18, 1996** **October 03, 1996** **October 17, 1996**
BRAND NAME:	**SKELID®**
GENERIC NAME:	**Tiludronate disodium 240 mg tablet equivalent to 200 mg tiludronic acid**
REVIEWER:	**Carolyn D. Jones, Ph.D.** **Robert M. Shore, Pharm.D.**
SPONSOR:	**Sanofi Winthrop, Inc.** **Malvern, PA 19355**
Type of Submission:	**Original NDA (NME)** **Code: 1S**

SYNOPSIS:

SKELID® (tiludronate disodium) is a bisphosphonate compound characterized by Phosphorus-Carbon-Phosphorus (P-C-P) bonds. This compound's structure differs from other bisphosphonates by a (4-chlorophenylthio) chain attached to the basic P-C-P structure. The drug is recommended for the treatment of Paget's disease which is marked by a progressive increased bone resorption and formation, resulting in weakened, deformed bones of increased mass. Its mechanism of action is to inhibit the osteoclast activity through a probable reduction in enzymatic and transport processes which lead to the characteristic bone resorption. SKELID® will be marketed as a 200 mg tablet, with a proposed dose of 400 mg (2 x 200 mg tablets) once daily orally for twelve weeks.

A number of different formulations

Tiludronate is a highly water soluble drug with low intestinal permeability. The mean absolute oral bioavailability is 6% under fasting conditions. It is absorbed with a $T_{max} < 3$ hours; however, the intra-subject coefficients of variation for C_{max} and AUC ranged from 40% to 45% after a single dose. When administered orally, C_{max}, AUC and urinary excretion (Ae) increased more than proportionally with doses ranging from 200 mg to 800 mg, although renal clearance was similar between doses. This non-linearity was more evident between the 600 mg and 800 mg doses, both of which are larger than the dose recommended for the treatment of Paget's disease (400 mg). The absorption of tiludronate was significantly (90%) reduced by food.

Tiludronic acid has a high affinity for bone and its elimination from this tissue is very slow. After IV administration of tiludronic acid, 50% to 60% of the dose was eliminated in urine, with the remainder of the dose appearing to be distributed in tissues, including bone. Thirteen days after administration of tiludronate urinary excretion was not complete. Tiludronic acid is significantly bound to serum proteins (90% to 92%). *In vitro* protein binding studies demonstrate that 91% of circulating tiludronic acid is bound to serum albumin. Only salicylic acid resulted in a significant displacement (7%) of tiludronic acid from its binding sites.

The half-life for elimination of tiludronic acid from human bone has not been assessed; however, in studies in animals, it has been determined to be as long as 300 days. Estimates of the plasma elimination half-life of tiludronic acid, from plasma and urine in healthy volunteers after a single dose, are approximately 40-60 hours and 60-80 hours, respectively. In Pagetic patients after repeated administration, the plasma elimination half-life is approximately 150 hours. These estimates do not fully take into account the slow elimination from bone.

In vitro studies with human hepatocytes and human liver microsomes have confirmed the lack of metabolism of tiludronic acid that was demonstrated in *in vivo* animal studies.

The sponsor reports no statistically significant differences in any pharmacokinetic parameters between elderly males, elderly females and young males , although the mean AUC and C_{max} in

elderly females was approximately 1.5 times greater than those of young and elderly male subjects. Weight-normalization of the pharmacokinetic parameters did not change these results. However, the weaknesses in study design (small sample size, protocol violations, different batches of tablets used, elderly and young were not studied at the same time) make the interpretation of results difficult and the utility of the study questionable. Results of sub-group analyses from one pivotal study (P1845) suggest that neither age nor gender impacted on clinical outcomes. Tiludronate pharmacokinetics have not been evaluated in patients less than 18 years of age. Since tiludronate is unmetabolized and only excreted in urine, no studies have been conducted in subjects with hepatic insufficiency. Differences in pharmacokinetics were observed in renally impaired subjects; whether these differences are significant cannot be ascertained due to the small sample size and lack of parallel healthy controls in this study.

Specific drug interaction studies have been conducted with a number of nonsteroidal anti-inflammatory drugs, Maalox®, and digoxin. No significant alteration in systemic exposure to tiludronic acid were observed after administration with diclofenac. Aspirin may decrease the bioavailability of tiludronate. Indomethacin appeared to increase the bioavailability of tiludronate. Maalox decreased the bioavailability of tiludronate when given 1 hour prior to administration of tiludronate; however, no effect was observed when Maalox is given 2 hours after tiludronate. Tiludronate did not produce any significant change in digoxin pharmacokinetic parameters.

Tiludronate reduced baseline alkaline phosphatase levels 47% and 58% in the 200 mg and 400 mg groups, respectively. A dose-response relationship is evident.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II has reviewed NDA 20-707 submitted February 28, September 18, October 03, and October 17, 1996. The to-be-marketed formulation and the clinical trial formulation are bioinequivalent; the to-be-marketed formulation is approximately 15% to 30% more bioavailable. However, therapeutic equivalence was demonstrated between the two formulations as evidenced by an equipotency study which was a side-by-side comparison of safety and efficacy of the two formulations, as well as safety and efficacy comparisons of the two clinical studies, each one using a different formulation. The medical officer informed OCPB that the safety and efficacy profiles are comparable between the two formulations.

Although the design of a number of the pharmacokinetic studies was less than desirable (small sample size, improper sample handling, poor study design, lack of suitable statistics), the overall Human Pharmacokinetic Section is acceptable to OCPB and general comments (p.42) and labeling comments (p.43) should be sent to the sponsor as appropriate.

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Appendix 1-4
Study Summaries
Proposed Label

(Appendices and Attachment available from DPE-II upon request)

BACKGROUND:

Paget's disease is an idiopathic, progressive disease marked by increased bone resorption and formation resulting in weakened, deformed bones of increased mass. The disease in most patients is asymptomatic. However, both urine hydroxyproline (a measure of bone resorption) and serum alkaline phosphatase (SAP, a measure of bone formation) are increased in Paget's disease. SAP is the standard diagnostic tool, measure of disease activity and therapeutic response, and therefore the primary efficacy parameter.

SKELID® was initially submitted to the agency by Sanofi Pharmaceuticals as IND ..1 1991. It was transferred to Sterling Drug, Inc. and Sanofi Winthrop, Inc. in 1994. Three pivotal trials were conducted in support of this application. P1845 was conducted in the United States and P1619 and P1552 were conducted in Europe. As of December 31, 1995, SKELID® has been approved for marketing in eight countries for Paget's disease.

SKELID® ($C_7H_7ClNa_20_6P_2S$) anhydrous form, M.W. 362.6 is a white to off-white powder with pKa's 10.85, 6.90, 2.95 and 1.30. Its partition coefficient is log P < -3.8 and it shows no signs of hygroscopicity. Tiludronate is used to refer to the administered compound and tiludronic acid is used to refer to plasma concentrations and pharmacokinetic parameters. Doses of tiludronate are expressed as tiludronic acid (240 mg tiludronate disodium = 200 mg tiludronic acid).

Unlike other bisphosphonates, tiludronic acid can be quantified in plasma at therapeutic doses, and therefore, the pharmacokinetics of tiludronic acid have been evaluated extensively during the course of clinical development. Tiludronic acid concentrations have been quantified in plasma, urine and bone using high performance liquid chromatographic techniques with ultraviolet detection (265-280 nm). The limits of quantitation were 0.01-0.07 mg/L in plasma, 0.025-0.2 mg/L in urine and 2.5 mg/kg in bone.

Protocol Number	Title	Page
1616	Comparison of the bioavailability of SR41319B in healthy volunteers at the dose of 20 mg by the IV route and 400 mg by the oral route (Study Report RS0045930421/01). Sanofi Recherche. 25 May 1993	15
1676	Bioequivalence of two oral formulations of SR41319B in healthy subjects (Study Report RS0045920206/01). Sanofi Recherche. 09 April 1992.	17
	Population pharmacokinetic analysis of tiludronate bioavailability in normal subjects (Study Report 2130). Sanofi Research Division. 19 May 1995.	18
2084	Multicenter open, parallel-group study of the bioequipotence of two tablet formulations of oral tiludronate in Paget's Disease of bone (Study Report RS0045950817/02). Sanofi Recherche. 18 October 1995.	19
1836	Evaluation of the intra-individual variability of the pharmacokinetic profile of SR41319B after a single dose administration of 400 mg in healthy volunteers (Study Report RS0045920206/02). Sanofi Recherche. 15 April 1992.	22
1270	Bone concentrations of SR41319, 24 hours after single and repeated administrations of 400 mg SR41319B in tablet form (Study Report RS0045930511/02). Sanofi Recherche. 15 July 1993.	23
1615	Comparison of the pharmacokinetics of SR41319B in healthy subjects and patients with Paget's Disease (Study Report RS0045930507/01). Sanofi Recherche. 30 July 1993.	23

1586	Effect of food intake on the pharmacokinetic profile of SR41319B after a single dose administration of 400 mg in healthy volunteers, influence of time and nature of food. (Study Report RS0045920225/01). Sanofi Recherche. 15 September 1990.	26
	Tiludronate metabolism by human hepatic microsomal fractions and human hepatocytes in primary cultures (RS0005951002/01) 30 November 1995	28
1011	Tolerance and pharmacokinetics of tiludronate after multiple dose administration of 200, 400, 600 and 800 mg to healthy volunteers (Study Report RS060910527/SA1). Sanofi Recherche. 26 October 1991.	28
1646	SR41319B pharmacokinetics after single dose oral administration in patients with chronic severe renal failure (Study Report RS0045930517/01). Sanofi Recherche. 23 July 1993.	30
859.87	The influence of age on the pharmacokinetics of SR41319B after oral administration of 400 mg in the form of 200 mg tablets (Study Report RS0045920730/01). Sanofi Recherche. 03 March 1993.	30
	In vitro study of the blood fixation of SR41319B-drug interactions (RS850870511/CF1)	33
1782	Evaluation of the influence of SR41319B on plasma concentrations of digoxin after repeated administration (Study Report RS0045930615/01). Sanofi Recherche. 26 July 1993.	33
702.86	SR41319B associated with non-steroid anti-inflammatory agents—clinical tolerability and laboratory safety (Study Report RS060900510/SA1). Sanofi Recherche. 10 May 1990.	34
1660	A study of the interaction between tiludronate (SR41319B) and aspirin (Study Report RS0045921028/01). Sanofi Recherche. 09 February 1993.	35
1597	Influence of hydroxide of aluminum and magnesium (Maalox®) intake on the pharmacokinetic profile of SR41319B administered by oral route, single dose (400 mg) (Study Report RS060911022/SA1). Sanofi Recherche. 22 October 1991.	35
1613	Pharmacokinetic study of the interaction between diclofenac and SR41319B after single administration to healthy volunteers (Study Report RS0045930428/01). Sanofi Recherche. 02 June 1993.	36

1659	A study of the interaction between tiludronate (SR41319B) and indomethacin. Sanofi Recherche. 03 February 1993.	37
1845	A phase 3 placebo-controlled efficacy study of tiludronate disodium for the treatment of Paget's disease of the bone (Study Report 1373)	38
1619	A multicenter, randomized, placebo controlled, double-blind, dose ranging study of tiludronate in Paget's disease (Study Report 1748, addendum 1, addendum 2)	40

DRUG FORMULATION:

Several formulations were used in the drug development process including: a sachet, an injection, a capsule, tablets. The 9O1 tablet (to-be-marketed formulation) was used in the pivotal P1845 placebo-controlled efficacy trial and the 3C1 clinical trial formulation was used in two pivotal studies: P1619 placebo-controlled efficacy trial and P1552 positive-controlled trial with etidronate. Twelve uncontrolled clinical trials were conducted, three of which used the 9O1 formulation. All of the drug product batches used in the pivotal safety and efficacy studies were manufactured at a pilot plant facility. The commercial formulation will be manufactured at one facility in France.

The sponsor initially developed a method (3C1 tablets) for the production of tiludronate disodium tablets. However, difficulties were experienced during scale-up and the company decided to switch to a method for the commercial product (9O1 tablets). Formulations of the 3C1 and 9O1 tablet are presented in Table 1. Figure 1 is the structure of tiludronate. A comparative table of the various development formulations is included in the Appendix.

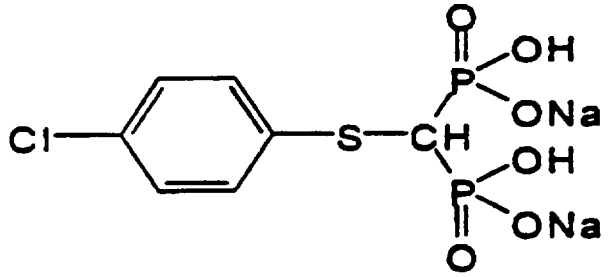

Figure 1: The chemical structure of tiludronate disodium (SKELID®).

Table 1 : SKELID® Composition (UNIT FORMULA)		
Ingredient	**9O1 Tablet Quantity, mg**	**3C1 Tablet Quantity, mg**
Tiludronate disodium[a] (as Tiludronic acid)	200[b]	200
Lactose Monohydrate, NF		
Sodium Lauryl Sulfate, NF		
Crospovidone, NF		
Hydroxypropyl Methylcellulose 2910, USP		
Magnesium Stearate, NF		
Purified Water, USP[d]		
TOTAL WEIGHT		

[a]Tiludronate disodium is the hydrated hemihydrate of the disodium salt of tiludronic acid. The tablet dose is expressed as tiludronic acid.
[b]The equivalent amount of the hydrated salt is approximately 240 mg.
[c]Amount of lactose for a nominal of tiludronate disodium.
[d]Not included in the finished product.

DISSOLUTION:

All dissolution media were adequate as evidenced by the ability to achieve sink conditions (Table 2).

Table 2. The Solubility of Tiludronate Disodium in Various Aqueous Media	
Medium	**Solubility at Saturation Point (mg/ml)**
0.1 N Hydrochloric Acid	111
Purified Water (pH 4.7)	136
pH 1.2 (dissolution medium)	137
pH 7.4	445

The sponsor conducted an analysis to compare the dissolution profiles of 3 batches of the 3C1 tablet to 3 batches of the 9O1 tablet using a pH range from with USP Apparatus at rpms. To determine similarity the sponsor used the following formula:

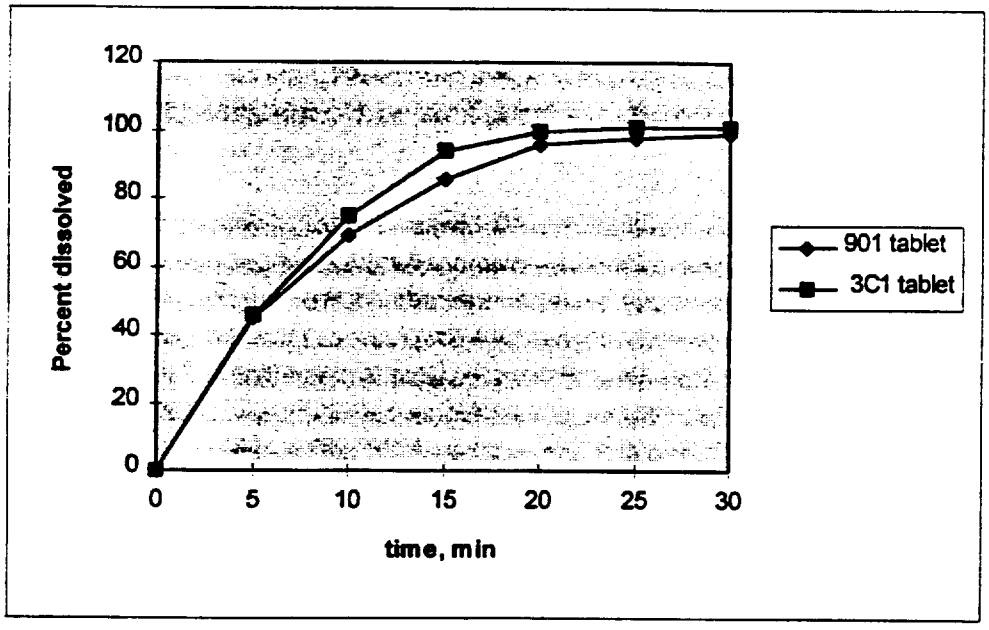

Figure 2: Comparison of 3C1 and 9O1 200 mg tiludronate disodium tablets in pH media (Each curve is average of 3 batches).

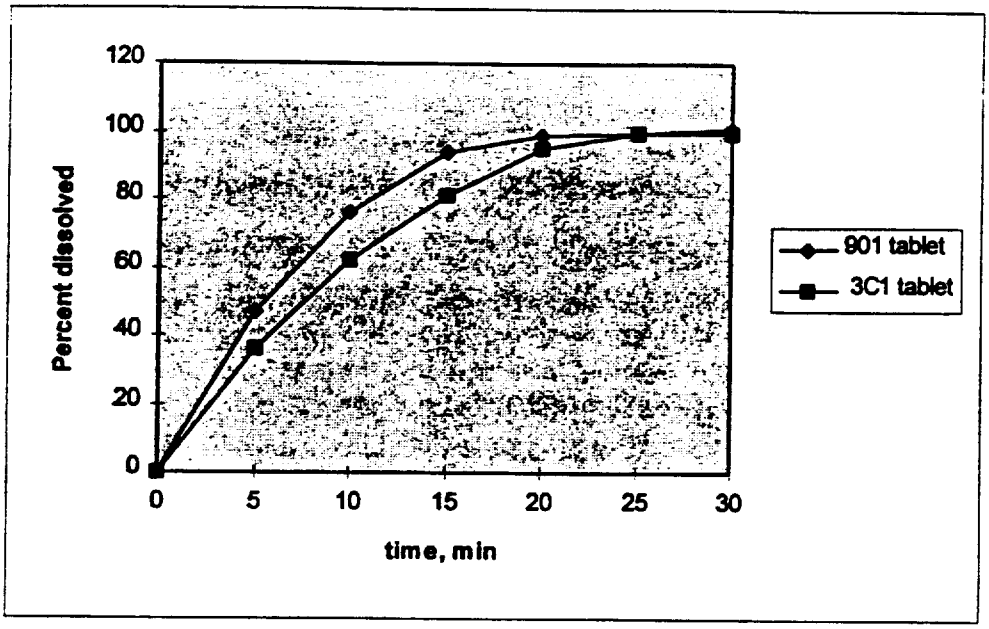

Figure 3: Comparison of 3C1 and 9O1 200 mg tiludronate disodium tablets in pH media

Apparent from Figures 2 and 3 is the 'flip-flop' that the 3C1 and 9O1 dissolution profiles have, depending on the pH. Although these graphs are averages of a few batches, a separate analysis, by batch, showed a consistently faster dissolution, at early time points, of the 9O1 formulation as compared to the 3C1 formulation at the profiles were more variable. However, figure 4 demonstrates the similarity of the dissolution profile for the 9O1 formulation at various pHs. Dissolution profiles of the 3C1 formulation, at various pHs, did not show the same degree of likeness (data not shown).

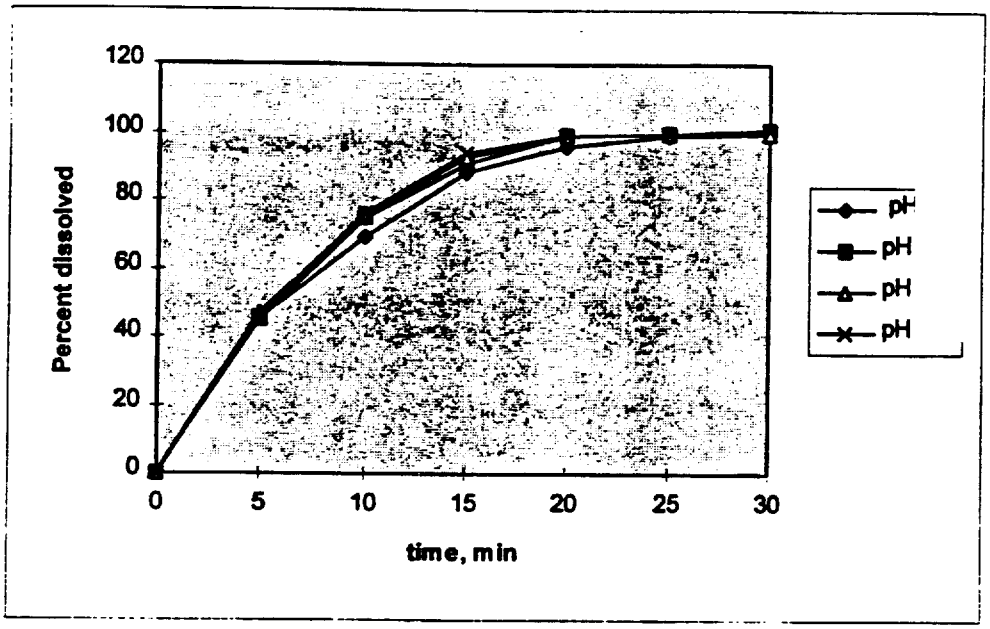

Figure 4: 9O1 200 mg tiludronate disodium tablet evaluated at 4 different pHs (Curves are averages of batches).

The firm has not provided dissolution data for small 3C1 batches used in many of the PK biostudies. The intended commercial batch size is tablets and many of the 3C1 batches used in the pharmacokinetic clinical studies were less than tablets, including: P1011 Dose proportionality, P1276 Pharmacokinetics in Paget's patients, PCL859.87 Influence of age, and P1597 Maalox® drug-drug interaction study. The 9O1 batch used in the P1676 Bioequivalence study was tablets. The two pivotal clinical studies used tablets from commercial batch sizes of approximately for the 3C1 tablets and for the 9O1 tablets. Available data allows for some assurance that scale-up production does not adversely affect dissolution or clinical outcome. This is demonstrated by the similar efficacy and safety, seen in the pivotal studies, between commercial size 9O1 batches and commercial size 3C1 batches, which were scaled-up from the smaller 3C1 batches used in most pharmacokinetic clinical studies. Additionally, Figure 5 presents the dissolution profiles at pH (the only pH data available) of commercial size 3C1 batches and both small and commercial size 9O1 batches. Notice the trend of a faster dissolution profile with the 3C1 formulation at his pH, as well as the similarity between the two 9O1 formulations profiles.

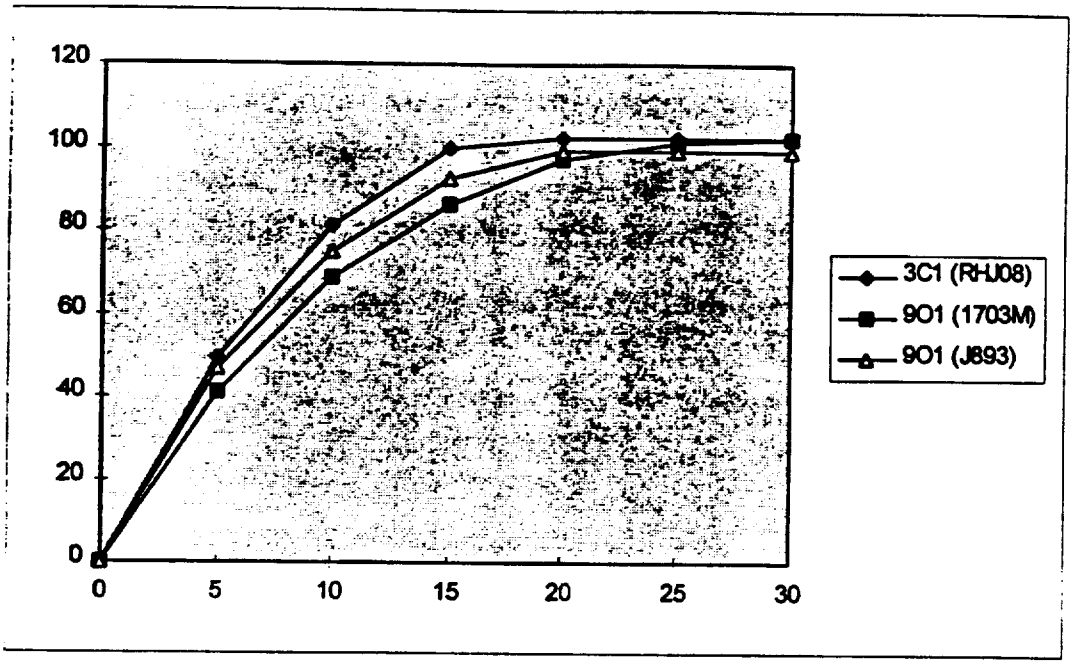

Figure 5: Comparison of three lots of tiludronate disodium tablets in pH 1.2 media. 3C1 Batch RHJ08 (size) used in pivotal trial P1619, 9O1 Batch 1703M (size) used in bioequivalence study P1676, 9O1 Batch J893 (size) used in bioequipotency study P2084.

The sponsor suggested the following dissolution method and specification: USP Apparatus at rpms rotation speed and Q= at 30 minutes at pH media. An acceptable agency standard method calls for a paddle speed of rpms and an alternate speed of rpms. However, USP alternate speed can be either rpms. The sponsor compared the dissolution at the three speeds, with similar results obtained beyond approximately 20 minutes (Figure 6).

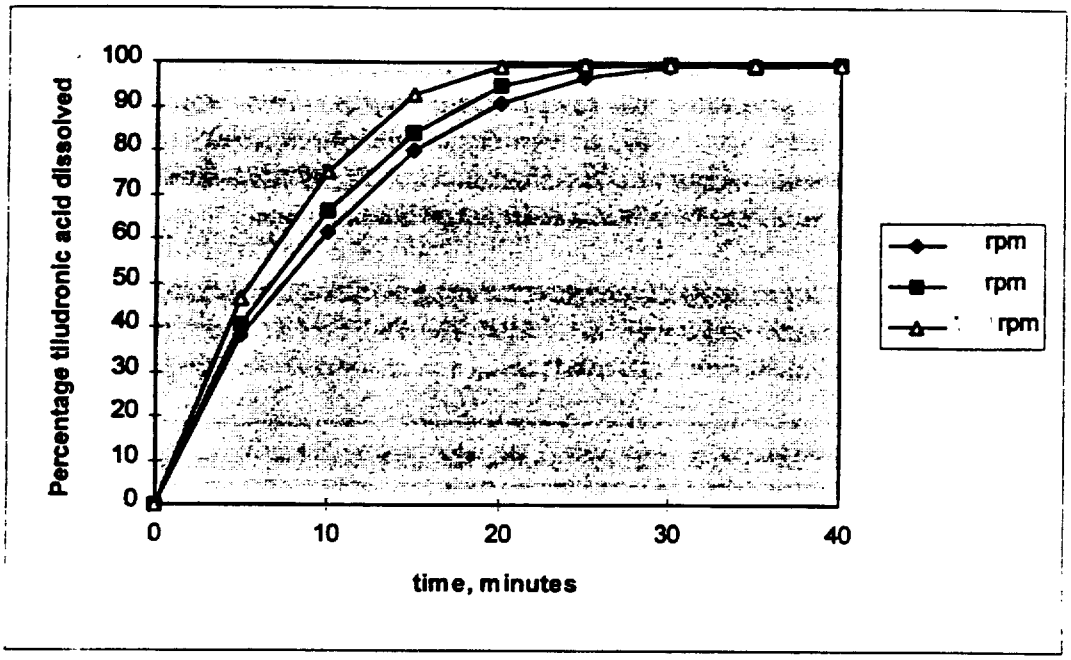

Figure 6: 9O1 200 mg tiludronate disodium tablet evaluated at 3 different rpms.

Although it is the company's desire to keep the speed at rpms, the agency does not accept this rotation speed. Therefore, the company should develop a dissolution method using rpms, or rpms as an alternate. After close examination of individual tablet dissolution data, a more discerning specification of Q= at 20 minutes is recommended.

ANALYTICAL METHODOLOGY:

Four different laboratories were used to conduct tiludronate assays: Collegeville, PA was used to analyze plasma during a 1995 timeframe; Belgium was used in 1991 and 1992 to analyze both plasma and urine; Netherlands analyzed urine during a 1993 time-frame; and Manchester, England was where many of the plasma and urine pharmacokinetic samples were analyzed. Independently, the laboratories provided assay validation data, but no cross validation of these laboratories was performed.

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TABLE 4. Analytical Methods Used in the Analysis of Tiludronate in Urine Samples

HUMAN PHARMACOKINETICS AND BIOAVAILABILITY STUDIES:

I. Bioavailability/Bioequivalence

A. Absolute Bioavailability

The mean absolute bioavailability of the 3C1 tablet formulation and the pharmacokinetic parameters after IV dosing were studied in 12 healthy male volunteers (P1616). Each subject

received, in a randomized crossover design with a 3-week washout period between doses, 400 mg as an oral dose (2 tablets, fasting) or 20 mg as a 2-hour intravenous infusion. The absolute bioavailability determined from plasma and urinary data was approximately 6% (Table 5, Figure 7). This value also corresponded to the fraction of the dose absorbed. A wide inter-individual variability in absolute bioavailability was observed (range:).

About 60% of the IV dose was recovered in urine during the first 96 hours postdose, and approximately 40% of the injected dose was considered bound to bone tissue. Tiludronic acid was still excreted in urine 13 days after dosing. Renal clearance (0.5 L/h, i.e., 8 mL/min) was constant over time and was in the same range for both routes of administration.

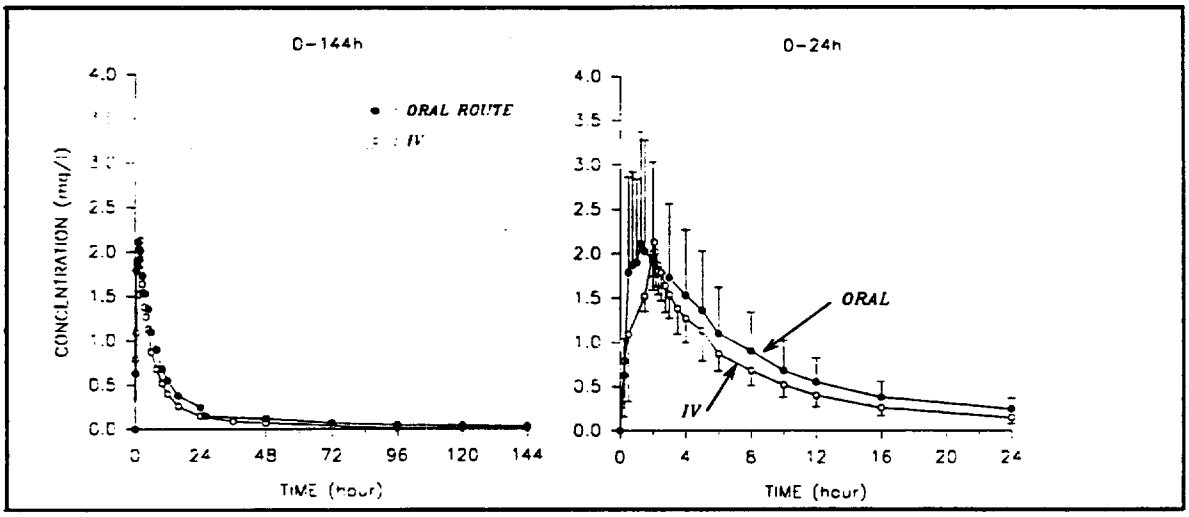

FIGURE 7: Mean tiludronic acid plasma levels versus time after oral administration of 400 mg and IV administration of 20 mg (2-hour infusion) to 12 healthy volunteers .

TABLE 5
Mean Pharmacokinetic Parameters (SD) of Tiludronic Acid After Oral (400 mg, 3C1 Tablet) and IV (20 mg, 2-hour infusion) Administration to 12 Healthy Volunteers

Parameters	Oral	IV
Plasma Data		
C_{inf} (mg/L)	n.a.	2.01 (0.42)
C_{max} (mg/L)	2.31 (1.25)	2.20 (0.44)
t_{max} (h)	1.2 (0.7)	1.9 (0.5)
AUC_{0-24h} (mg·h/L)	18.65 (9.14)	14.53 (3.17)
AUC_{0-tobs} (mg·h/L)	27.51 (14.81)	18.50 (6.69)
t½p (h)	56.73 (30.84)[a]	48.81 (66.08)[c]
Urinary data		
Ae_{0-96h} (mg)	11.94 (4.55)[b]	11.16 (1.49)[c]
Ae_{0-tobs} (mg)	11.85 (5.76)[c]	11.84 (1.48)[c]
Fe_{0-96h} (%)	3.0 (1.1)[b]	55.8 (7.5)[c]
Fe_{0-tobs}(%)	3.0 (1.4)[c]	59.2 (7.4)[c]
t½u (h)	83 (23)[a]	66 (16)[a]
$Cl_{R\ 0-tobs}$ (p) (L/h)	0.48 (0.08)[d]	0.54 (0.09)

[a] n=8
[b] n=9
[c] n=10
[d] n=11
n.a. not applicable

B. Bioequivalence

Because many of the pharmacokinetic studies submitted in the Human Pharmacokinetic Section, as well as one of the two pivotal studies were conducted with the 3C1 tablet formulation, while the second pivotal study was conducted with the to-be-marketed 9O1 formulation, the issue of bioequivalence (BE) between the 3C1 and 9O1 formulations is an important one.

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The primary efficacy endpoint evaluated in P1619 and P1845 was change in baseline serum alkaline phosphatase (SAP) concentrations at Week 12, with a secondary endpoint of SAP changes at 24 weeks. Table 7 shows the percent change from baseline values at the 200 mg and 400 mg dose levels.

TABLE 7
Mean Percent Change from Baseline in SAP

Week	Number of subjects/mean percent change					
	Placebo		Total Daily Dose of Tiludronate			
			200 mg		400 mg	
	P1845 (9O1)	P1619 (3C1)	P1845	P1619	P1845	P1619
12	44/0.5	23/4.3	45/-46	25/-46	46/-51	27/-54
24	45/5.1	23/13.1	44/-47	26/-50	45/-58	28/-60

The two tablet formulations gave comparable therapeutic and similar statistical ($p>0.05$) responses at both dose levels and at both times of analysis. Safety parameters were also similar between studies.

After the pre-NDA meeting with the Firm, the Division (DMEDP and OCPB) met internally and discussed the BE issue. It was determined to accept the two formulations (3C1 and 9O1) as therapeutically equivalent, and allow Sanofi Winthrop to use the studies (P1845-9O1 and P1619-3C1) as the two pivotal studies for an NDA submission.

Therefore, the Division has determined that the two formulations are to be accepted as therapeutically equivalent, although strict pharmacokinetic bioequivalence has not been demonstrated.

In further discussions with Dr. Dutta (MO), it has been ascertained that there is more supportive data (at least 5 uncontrolled trials with a total of about 700 patients) for efficacy and safety. Essentially, although strict pharmacokinetic equivalence between the 3C1 and 9O1 formulations has not been demonstrated, the clinical impression is that there is no significant difference seen in patients.

An open label, parallel group multicenter Phase 3 trial comparing the bioequipotency of the 9O1 and 3C1 tablet formulations of tiludronate was conducted (P2084). Eighty-eight Pagetic patients were included in this study (39 in the 3C1 group and 49 in the 9O1 group). Tiludronate was administered

for 3 months as 400 mg qD dosed in the morning with no food being taken within 2 hours of drug administration. Plasma samples were obtained prior to drug administration and at 0, 1, 2, 3 and 4 hours after tiludronate administration at Months 1, 2, and 3. Pharmacokinetic parameters are given in Table 8.

TABLE 8
Mean (SD) Pharmacokinetic Parameters After Oral Administration of 400 mg qD Tiludronic Acid as 3C1 or 9O1 Tablets to Pagetic Patients

Parameters	3C1 Tablet			9O1 tablet		
	Month 1 (n=30)	Month 2 (n=31)	Month 3 (n=30)	Month 1 (n=38)	Month 2 (n=40)	Month 3 (n=40)
C_{max} (mg/L)	2.74 (1.36)	3.10 (1.34)	2.97 (1.36)	3.27 (1.76)	3.28 (1.43)	3.57 (1.94)
t_{max} (h)	1.80 (0.80)	2.16 (0.93)	2.18 (0.91)	2.04 (0.81)	1.88 (1.03)	1.97 (1.00)
Median (h)	1.92	1.92	1.92	1.92	1.83	1.92
C_{min} (mg/L)	0.63 (0.37)[a]	0.64 (0.35)	0.73 (0.38)	0.66 (0.38)	0.71 (0.37)[b]	0.91 (0.45)

[a] n=29
[b] n=39

C_{max} and C_{min} did not differ between formulations. Gender analysis indicated that female subjects (n=40) had higher C_{max} and C_{min} concentrations ($p<0.001$) with both formulations.

Based on the above data, 90% confidence intervals for the ratios of C_{max} and C_{min} for both formulations were determined at Months 1, 2 and 3 and for all 3 months combined. These intervals are given in Table 9.

TABLE 9
90% Confidence Intervals
for the Ratio of Geometric Means (9O1/3C1)
for C_{max} and C_{min} for All Pagetic Patients

	All 3 Months	Month 1	Month 2	Month 3
		C_{max}		
All Patients	1.03-1.17	0.96-1.46	0.89-1.26	0.97-1.41
		C_{min}		
All Patients	0.99-1.14	0.79-1.40	0.87-1.35	0.94-1.55

As in other studies, the data suggest that the bioavailability of the 9O1 tablet is greater than that of the 3C1 tablet. The confidence intervals at each month did not fall within normal acceptance limits (0.8-1.25) for bioequivalence. However, when the data for all 3 months were pooled, the confidence intervals for both C_{max} and C_{min} were consistent with bioequivalence (0.8-1.25) of the two tablet formulations. As tiludronic acid plasma concentrations were only measured to 4 hours postdose, AUC was not calculated by the Firm.

The primary bioequipotency measure was the logarithm of the ratio of baseline-normalized SAP after 3 months (D_{84}) of therapy. The 90%CI for this parameter, as well as after 1 (D_{28}) and 2 (D_{56}) months of therapy, is shown in Table 10.

TABLE 10
90% CI for Ratio (3C1/9O1) of Baseline normalized SAP

Day of Treatment	Number of Pts. Included (3C1/9O1)	90% CI
D_{28}/D_0	36/45	0.89-1.05
D_{56}/D_0	35/45	0.82-1.03
D_{84}/D_0	33/45	0.80-1.06

The two formulations appear to be of similar potency after 3 months of therapy. The median decrease in SAP after 3 months of therapy, for the 3C1 and 9O1 tablets, was 64% and 63%, respectively. This is comparable to the decreases seen in the two pivotal studies. Safety parameters were similar between the two formulations, with mild/moderate gastrointestinal ADRs (diarrhea,

dyspepsia, nausea and vomiting) being the most frequently reported.

C. Intra-individual Variability

[Study P1836, "Evaluation of the Intra-individual Variability of the Pharmacokinetic Profile of Tiludronate After a Single Dose Administration of 400mg in Healthy Volunteers", had been previously reviewed by Dr. TM Chen under the IND.]

The wide inter-individual variability and the low absorption of bisphosphonates suggest a wide intra-individual variability. A specific study using replicate design (P1836) was conducted to define the intra-individual variability of various pharmacokinetic parameters. Nine healthy volunteers received, under fasting conditions, 400 mg tiludronate (3C1 formulation) on three occasions (P1, P2, P3) with a washout period of 14 days between administrations. Mean (CV%) values of the pharmacokinetic parameters are shown in Table 11.

TABLE 11
Measures of Intra/Inter-Subject Variability for C_{max} and AUC Values of Tiludronic Acid After Three Oral Doses of 400 mg Tiludronate (3C1 Tablet) to the Same Healthy Volunteer (n=9)

Parameter	P1	P2	P3	Mean Intra-Individual CV%
C_{max} (mg/L)	2.61 (61%)	3.31 (38%)	2.49 (40%)	40%
$AUC_{0\text{-}obs}$ (mg·h/L)	24.80 (62%)	29.76 (39%)	25.10 (43%)	40%
90% CI	"REF"	100 - 188%	65 - 177%	--

No statistically significant period effect was observed, but a significant (p=0.03) subject effect was detected for $AUC_{0\text{-}obs}$. The intra-individual variabilities for AUC and C_{max} ranged from 18% to 71% and 8% to 69%, respectively. The 90% confidence intervals for the log AUC ratios for all period comparisons did not fall within the normally accepted bioequivalence limits (0.8-1.25) (same formulation/batch used in all three periods).

II. Pharmacokinetics

A. Single vs. Multiple Dose Administration

An open label parallel design study (P1270) was conducted in 12 male subjects with osteoarthrosis of the hip to evaluate concentrations of tiludronate in bone. They were divided into four groups of three and administered tiludronate orally in the morning according to the following scheme: 1) single dose of 400 mg tiludronate given once, 2) 400 mg of tiludronate given daily for 5 days, 3) 400 mg given daily for 15 days, and 4) 400 mg given daily for 30 days. The concentration of tiludronic acid in bone increased with increasing length of administration and did not show signs of reaching steady state after 30 days. The concentrations of 4, 9, 16, and 30 mg tiludronate/kg bone corresponded to the four treatment arms outlined above, respectively, while plasma concentrations did not show a consistent trend to increase with repeated administration (Figure 8a, 8b). Figure 8c demonstrates the increasing trend of the ratio of bone concentrations/plasma concentrations as a function of the duration of tiludronate treatment.

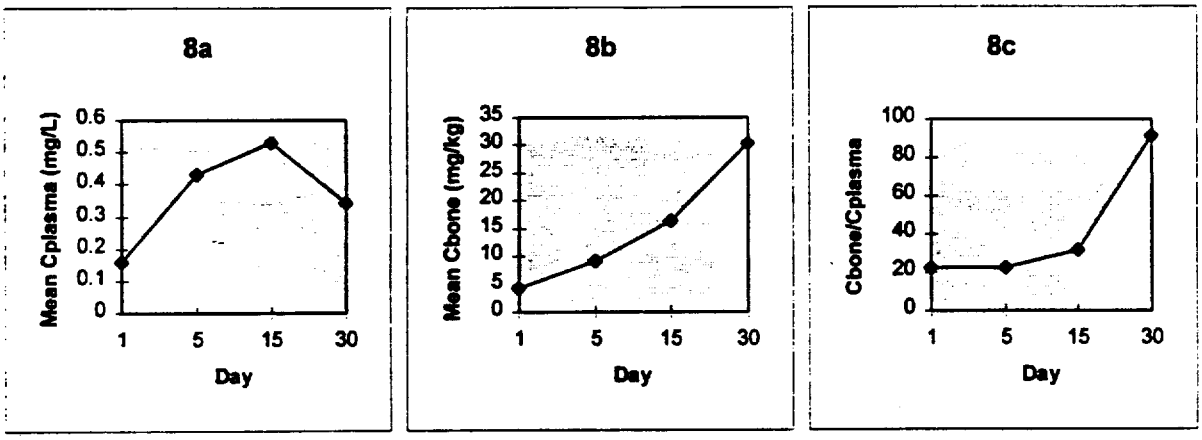

Figure 8(a-c): Mean plasma (a), bone (b) and ratio of bone/plasma © concentrations of tiludronate as a function of the length of treatment.

The above described study was not well characterized due to the following reasons:

1) Small sample sizes (3 persons per group). Statistical analyses were not conducted.

2) It could not be adequately determined whether the plasma concentrations had achieved steady-state. Both the plasma and bone assays were acceptable; however, the bone assay was more variable for precision compared to plasma assay (~19%).

B. Healthy volunteers vs. Pagetic patients

An open-label multiple dose study (P1615) was conducted in 8 patients with Paget's disease (7M/1F)

and in 12 healthy male volunteers ranging in age from 52-76. Study participants were given tiludronate 400 mg daily, without food, in the morning for 12 days. There were no significant differences in C_{max}, AUC, T_{max}, C_{min} or $t_{1/2}$ p between the two groups (Table 12), although mean $AUC_{(0-24)}$ was 20% greater in Pagetic patients. A wide intra-subject variability in absorption was observed in both groups.

The Ae_{0-t} was significantly lower in the Pagetic patients (Table 13) . Urinary excretion was not completed 14 days after the last administration. The Clr_{0-192h} weight normalized was also significantly different between groups, but there was no real correlation between renal clearance and creatinine clearance although creatinine was also lower in Pagetic patients. A noteworthy finding in this study was that diastolic blood pressure significantly increased in Pagetic patients and significantly decreased in healthy volunteers.

TABLE 12
Plasma Pharmacokinetic Parameters of Tiludronic Acid in Healthy Volunteers and Subjects with Paget's Disease After 12 Days of Administration of Tiludronate (3C1 Tablets, 400 mg/day)

Parameters	Pagetic Patients (n = 8) Mean Values (SD)	Healthy Volunteers (n = 12) Mean Values (SD)
C_{max} (D12) (mg/L)	4.62 (1.04)	3.75 (0.94)
t_{max} (D12) (h)	2.2 (0.9)	1.9 (0.8)
C_{min} (D12) (mg/L)	0.99 (0.64)	0.8 (0.26)
AUC_{0-24h} (D12) (mg·h/L)	49.26 (22.06)	40.71 (12.85)
C_{max}-C_{min} (D12) (mg/L)	3.63 (0.68)	2.95 (0.8)
t½p (h)	149[a] (64)	137[b] (50)

[a] n = 7
[b] n = 11

TABLE 13
Urinary Pharmacokinetic Parameters of Tiludronic Acid in Healthy Volunteers and Subjects with Paget's Disease After 12 Days of Administration of Tiludronate (3C1 Tablet, 400 mg/day)

Parameters	Pagetic Patients (n = 8) Mean Values (SD)	Healthy Volunteers (n = 12) Mean Values (SD)
Ae (D1 to D26) (mg)	212 (76)	314 (75)
Fe (D1 to D26) (%)	4.4 (1.6)	6.5 (1.6)
$Ae_{0\text{-}24h}$ (D12) (mg)	20 (10)	25 (9)
$Fe_{0\text{-}24h}$ (D12) (%)	5.0 (2.6)	6.3 (2.1)
$Cl_{R\ 0\text{-}24h}$ (D12) (mL/min/kg)	0.11 (0.05)	0.14 (0.07)
$Cl_{R\ 0\text{-}192h}$ (D12) (mL/min/kg)	0.09 (0.03)	0.14 (0.04)

Wide intra-patient variability in daily urinary excretion of tiludronate is shown in Figure 9.

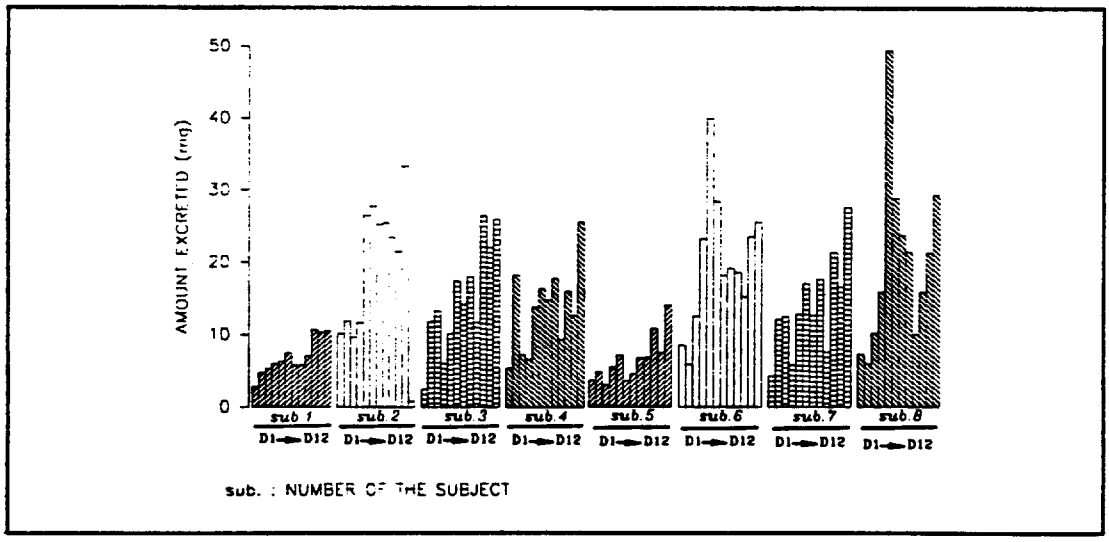

FIGURE 9: Daily urinary excretion of tiludronic acid during the treatment period (12 days) in eight Paget's patients.

This study was flawed for reasons which include the following:

1) According to the protocol, the volunteers were to be matched to the Pagetic patients. However, a significant difference in age, body weight and creatinine clearance was observed.

2) The study was designed as a parallel study, but the healthy subjects were studied from

05/31/91-10/01/91 and the Pagetic patients were studied from 09/13/91-09/19/92.

3) No pre-study (blank) urine samples were taken. These samples were taken at the conclusion of the study.

4) According to the protocol, plasma samples were to be collected prior to the daily administration of tiludronate; however, in several situations the samples were taken after the dose.

C. Food Effects

The influence of food on the oral absorption of tiludronate was studied with the 1A1 capsule formulation, the 3C1 tablet formulation and a tablet formulation prepared in Japan. Only the data obtained with the 3C1 tablet will be presented.

The influence of a normal or hypocalcic breakfast during or 2 hours before the administration of 3C1 tiludronate tablets was evaluated in a five-way crossover study in 10 healthy male volunteers (P1586). These results confirmed that absorption is decreased when tiludronate is given with or 2 hours after breakfast when compared to the results obtained under fasting conditions. Absorption is decreased by 90% when tiludronate is given with or 2 hours after a normal breakfast and by 80% when given with or 2 hours after a hypocalcic breakfast. However, there were no differences associated with the type of breakfast eaten or time of administration (with or 2 hours after a meal). Three adverse events were reported. Two episodes (nausea and vomiting) occurred in the same subject. The third incident was a headache. There was no correlation between fasted and non-fasted in the incidence of adverse events in this study. The results are summarized in Table 14 and Figure 10. In both pivotal safety and efficacy trials (P1619 and P1845), patients were instructed not to take tiludronate within 2 hours of a meal.

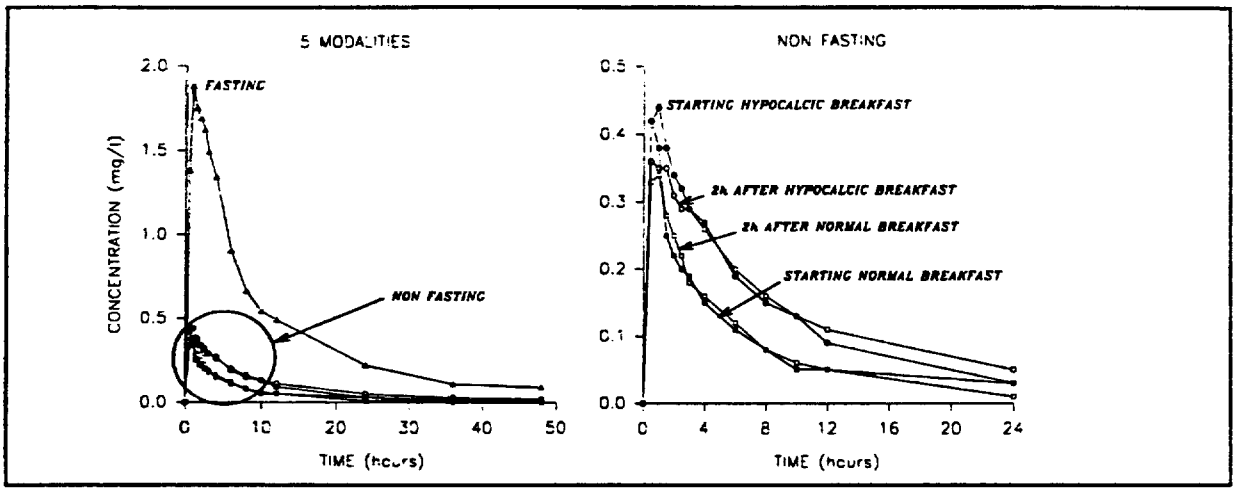

FIGURE 10: Mean tiludronic acid plasma levels after administration of tiludronate (3C1 tablet) under fasting and nonfasting conditions (with or 2 hours after a normal or hypocalcic breakfast) to 10 healthy volunteers.

TABLE 14
Mean (SD) Pharmacokinetic Parameters of Tiludronic Acid After Administration of Tiludronate (3C1 Tablet) Under Fasting and Nonfasting Conditions (With or 2 hours after a Normal or Hypocalcic Breakfast) to 10 Healthy Volunteers

Parameters	Modality				
	A	B	C	D	E
C_{max} (mg/L)	1.99 (0.95)	0.48 (0.37)	0.42 (0.32)	0.42 (0.14)	0.38 (0.34)
t_{max} (h)	1.25 (0.54)	1.15 (1.05)	1.35 (1.08)	0.51 (0.01)	0.67 (0.25)
AUC_{0-tobs} (mg·h/L)	19.38 (9.94)	3.55 (3.48)	4.02 (3.20)	2.12 (1.34)	2.01 (2.20)

A Fasting
B With hypocalcic breakfast
C 2 hours after hypocalcic breakfast
D With normal breakfast
E 2 hours after normal breakfast

Pooled data from 3 studies of the pharmacokinetics of the 3C1 tablet (400 mg) administered 2 hours after breakfast were compared to the 3C1 tablet studied primarily after administration of single doses under fasting conditions. The results, shown in Table 15, confirmed that breakfast 2 hours before dosing decreased the absorption of tiludronic acid, and dairy products further reduced bioavailability.

TABLE 15
Pooled Pharmacokinetic Parameters of Tiludronic Acid For 400 mg Tiludronate (3C1 Tablet) Administered Fasting or 2 hours After Breakfast

Parameters	Fasting	Nonfasting
C_{max} (mg/L)	2.66±1.22 (n=151)	0.89±0.90 (n=36)
$AUC_{0\text{-}tobs}$ (mg·hr/L)	26.68±12.99 (n=151)	8.45±9.84(n=36)
$Ae_{0\text{-}tobs}$ (mg)	17.89±9.40 (n=60)	5.30±7.19 (n=32)
$Fe_{0\text{-}tobs}$	4.5±2.3 (n=60)	1.3±1.8 (n=32)

III. Metabolism

Since tiludronate is readily distributed to bone and eliminated very slowly from this tissue, the sponsor claimed it was not possible to study the metabolism of tiludronate in humans with radiolabeled drug. Its metabolism, however, was evaluated *in vitro* using both human hepatocyte and microsomal preparations. In both of these human liver preparations, no metabolism of tiludronate was detected. However, 3% of the dose was excreted unchanged in the urine after oral administration and 59% was excreted unchanged after a 20 mg IV infusion. The sponsor claimed the balance was probably bound to bone tissue.

IV. Dose and Dosage Form Proportionality

[Study P1011, "Tolerance and Pharmacokinetics of Tiludronate After Multiple Dose Administration of 200, 2x200, 3x200, and 4x200 mg to Healthy Volunteers", has been previously reviewed by Dr. TM Chen under the IND. However, the NDA submission included more data and allowed for weight-normalized analysis to be conducted.]

Tiludronate (or placebo) was administered to a total of 40 healthy male volunteers in a multiple-dose, double-blind, parallel groups study (P1011). Subjects (n=8 in each group) received a daily dose of 0 (placebo), 200, 400, 600 or 800 mg tiludronate (3C1 tablet) for 12 days. The treatment was taken in the morning with a glass of mineral water after 10 hours of fasting, with lunch served 2 hours after dosing. The mean pharmacokinetic parameters of tiludronic acid determined on Day 12 are shown in Table 16.

TABLE 16
Mean (SD) Pharmacokinetic Parameters of Tiludronic Acid After Repeated Administration (3C1 Tablet) for 12 Days to Healthy Male Volunteers

Parameters	1x200 mg	2x200 mg	3x200 mg	4x200 mg
C_{max} (mg/L)[a]	1.23 (0.54)	1.29 (0.63)	1.78 (0.41)	1.95 (0.31)
AUC_{0-24h} (mg·h/L)[a]	11.20 (4.50)	13.83 (5.95)	17.72 (4.08)	20.08 (3.19)
Ae_{0-24h} (mg)[a]	8.84 (4.32)	12.28 (5.41)	14.24 (3.16)	14.59 (1.83)
$T_{1/2}$ (h)[d]	ND	77.58 (17.83)	65.00 (6.56)	72.48 (10.06)
CLr_{0-24h} (L/h)[b]	0.84 (0.22)	0.99 (0.15)	0.93 (0.07)	0.75 (0.12)
fe_{0-24h} (%)[c]	4.03 (1.78)	5.55 (2.22)	6.26 (1.66)	7.26 (1.22)

[a] Normalized to 200mg and 70kg.
[b] Renal Clearance; Ae_{0-24}/AUC_{0-24} at SS; Normalized to 70kg.
[c] Ae_{0-24}/dose·100 at SS (NB: Not as generally defined by IV dosing; Since compound is poorly absorbed and primarily undergoes renal elimination, this parameter maybe more reflective of F_{abs}).
[d] $Ln(2)/K_{el}$, from log-linear regression of terminal portion of plasma conc.-time curve.
ND Not Determined (many data ≤ LOQ).

$T_{1/2}$ did not differ between doses. fe differed between 200 and 800 mg. C_{max} for the 200 and 400 mg doses differed from that of the 800 mg dose. AUC for the 200 mg dose differed from the 600 and 800 mg doses, and the 400 mg dose differed from the 800 mg dose. Ae for the 200 mg dose differed from the 600 and 800 mg doses. CLr for the 800 mg dose was less than the 400 mg dose, although similar linear relationships between average plasma concentrations and urinary excretion rates were seen, with no differences between slopes (reflective of CLr) for the dose groups.

Most of the pharmacokinetic parameters exhibited a more than proportional increase with increasing dose. A few possible explanations for this non-linearity have been explored:

1) An increase in absorption; Fecal blood loss was examined, as a marker of GI damage by this compound, which might increase GI permeability. Although there appeared to be a slight but consistent trend toward increased fecal blood loss after dosing in each dose group, this trend was not significant and was seen in the placebo group as well.

2) Saturation of elimination; Because renal clearance and $T_{1/2}$ were reasonably constant versus dose, saturation of the elimination process is unlikely.

3) Saturation of binding to bone or plasma proteins, resulting in increased tiludronate plasma concentrations and decreased apparent Vd; The consistency of CLr and $T_{1/2}$ indicate a constant Vd at the terminal phase, and tiludronate protein binding has been shown to be linear from 1 to 10 mg/L.

A definitive reason for the observed non-linearity in tiludronate pharmacokinetic parameters remains elusive. However, given the recommended dosing scheme (400 mg qD), this will probably have limited clinical consequences.

V. Special Populations

Renal

The pharmacokinetics of tiludronic acid were studied in 9 subjects suffering from renal disease (creatinine clearances between 10 and 30 mL/minute) who received 400 mg of tiludronate under fasting conditions (P1646). One person vomited shortly after drug administration and was not included in the pharmacokinetic analysis. Table 17 shows pharmacokinetic parameters.

TABLE 17
Pharmacokinetic Parameters of Tiludronic Acid After Single 400 mg Oral Dose of Tiludronate (3C1 tablet) to Eight Subjects with Renal Disease

Parameter	Mean Values (SD)
C_{max} (mg/L)	3.45 (2.98)
t_{max} (h)	1.91 (1.37)
$AUC_{0\text{-}tobs}$ (mg·h/L)	86.97 (49.39)
t½ (h)	205 (52)[a]

[a] n=6

The sponsor reported that after single doses, C_{max} values were in the range observed in healthy volunteers (Mean: 2.66 mg/L, n = 151); conversely, $AUC_{0\text{-}tobs}$ were approximately three times higher (Mean: 26 mg·h/L, n = 151). A longer elimination half-life was observed in subjects with renal disease (approximately four times longer after single doses). The systemic exposure of tiludronic acid was approximately three times higher than in healthy volunteers after single doses.

The study was so poorly designed that no real inferences could be made about the performance of tiludronate in renally impaired subjects. Problems with the study are as follows:

1) The study sample size was small (8 subjects) and no healthy control group was used.
2) The sponsor conducted a cross-study comparison of the renally impaired subjects to healthy subjects.
3) No statistical analysis of PK parameters was conducted.

The company has not adequately evaluated tiludronate in this patient population.

Age

The pharmacokinetics of tiludronic acid were studied in 12 elderly subjects (6M/6F) 70 years or older and compared to 6 healthy young male volunteers 40 years or younger (PCL 859.87). Additionally, gender differences between elderly males and females were investigated. Each subject

received a single oral dose of 2x200 mg tiludronate after an overnight fast. The results are presented in Table 18.

TABLE 18
Mean (SD) Pharmacokinetic Parameters of Tiludronic Acid After Administration of 400 mg of Tiludronate (3C1 Tablets) to Young and Elderly Subjects (n=6 per group)

Parameter	Young Males	All Elderly	Elderly Males	Elderly Females
C_{max} (mg/L)	2.19 (0.67)	2.66 (1.72)	2.04 (1.02)	3.27 (2.13)
C_{max} (mg/L/70kg)	2.29 (0.57)	2.20 (1.21)	1.93 (1.03)	2.47 (1.42)
t_{max} (h)[c]	1.33	1.50	1.50	2.25
$AUC_{0\text{-}obs}$ (mg·h/L)	27.31 (21.93)	35.23 (19.84)	26.70 (12.19)	43.76 (23.30)
$AUC_{0\text{-}obs}$ (mg·h/L/70kg)	27.56 (20.64)	29.99 (17.34)	25.38 (12.82)	34.59 (21.12)
$Ae_{0\text{-}obs}$ (mg)	7.41 (3.26)	8.59 (6.30)[d]	9.92[a] (6.64)	ND
Fe (%)[b]	1.85 (0.81)	2.15 (1.58)[d]	2.48[a] (1.66)	ND

ND: Not determined (urine collection for 2 subjects only)
[a] n = 5
[b] $Ae_{0\text{-}obs}$/ dose x 100 (= F_{abs})
[c] Median
[d] n = 7

No statistically significant differences ($p>0.1$) between the young vs all elderly, young vs. elderly males, and elderly males vs. females were found with regard to the pharmacokinetic parameters (actual and weight-normalized). However, mean C_{max} and $AUC_{0\text{-}obs}$, as well as median T_{max}, tended to be higher in elderly females than young or elderly males.

This study was extremely flawed for reasons which include the following:

1) According to protocol inclusion criteria, elderly subjects could not have renal clearance less than 70 mL/min, yet each elderly subject with a baseline serum creatinine (n=10) had a calculated renal clearance below 70 mL/min (a protocol violation), with a median (range) of 47 mL/min (21-63), including 2 subjects below 30 mL/min. However, the inclusion criteria may have been unrealistic. The actual sample may be more reflective of the creatinine clearance seen in this population and have more clinical relevance.

2) This study used 3 different batches of tablets, one of which had only 1000 manufactured tablets and was used for all young subjects,

3) Subjects were not studied at the same time - young subjects were studied between 04/22/87 and 07/15/87, while the elderly started 07/11/88 (more than a year after the young subjects) and did not finish until 11/05/90 due to recruitment problems,

4) Two young subjects donated 300 mL of blood 15 days prior to the study (a protocol

violation),

5) One elderly subject continued on acetylsalicylic acid, but a protocol amendment states that no subject may be taking salicylic acid,

6) One elderly subject was diabetic (a protocol violation),

7) No young females were studied,

8) Urine samples were missing and deviation of collection times exceeded 10% in many cases.

These weaknesses, along with the small number of subjects studied, make interpretation of these results difficult and the usefulness of this study for labeling purposes limited, at best.

An analysis of plasma concentrations versus various demographic characteristics was also conducted in P1845, the North American pivotal study, using the 9O1 formulation tablet. The results indicated that age had a statistically significant association at both the 200 mg and the 400 mg doses. For the 400 mg dose, subjects ≥65 years of age had higher mean steady-state concentrations (approximately 2 to 3 fold difference in trough values) than younger subjects. However, SAP reductions (efficacy) and adverse drug events (safety) were not influenced by age.

Gender

No studies were conducted to specifically investigate gender. Based on the age study, the sponsor concluded that no statistically significant gender differences were observed between elderly male and elderly female subjects given a single 400 mg dose of tiludronate. However, results from the age study are tenuous.

Analysis of plasma concentration data obtained in the North American pivotal safety and efficacy trial in Paget's disease (P1845) did not demonstrate a statistically significant gender effect.

A gender analysis from P2084 Bioequipotency Study indicated that female subjects had higher C_{max} and C_{min} concentrations ($p<0.001$) with both formulations, but clinical differences between genders were not detected.

Pediatric

The sponsor did not investigate tiludronate in populations under 18 years of age.

VI. Drug Interactions

A. In vitro

In vitro studies were carried out to assess the protein-binding interaction between NSAIDS, aspirin and tiludronate. The results are shown in Table 19. The main interaction occurs with salicylic acid and phenylbutazone.

TABLE 19
Interaction with NSAIDS and Salicylic Acid on the Serum Protein-Binding of Tiludronic Acid

Drug	Change in Serum Protein-Binding of Tiludronic Acid
Salicylic acid	Reduced (7%)
Phenylbutazone	Reduced (4%)
Diclofenac	Reduced (1-2%)
Ibuprofen	Reduced (1-2%)
Oxyphenbutazone	Reduced (1-2%)
Piroxicam	Reduced (1-2%)
Valproic acid	Reduced (3%)
Paracetamol	No modification
Furosemide	No modification
Sulfa methoxasole	No modification
Tolbutamide	Reduced (1-2%)

Tiludronate did not displace the serum protein-binding of salicylic acid or warfarin.

In vitro studies demonstrated that 91% of circulating tiludronic acid in plasma was bound to serum protein and specifically to serum albumin (92% on isolated human serum albumin). Binding to red blood cells represented less than 5% of the total concentration. Binding to human serum was constant over the 1 - 10 mg/L range.

B. In vivo

Because both tiludronate and digoxin are eliminated via the kidney and digoxin has a small therapeutic index, the possible interaction between digoxin and tiludronate, at steady-state, was

investigated in 12 healthy volunteers (P1782). All subjects received digoxin 0.25 mg per day for 24 days, with tiludronate (3x200 mg per day for 2 days as a loading dose, followed by 2x200 mg daily) during the last 12 days. Digoxin pharmacokinetics were evaluated on day 12 (digoxin alone) and compared to those from day 24 (digoxin + tiludronate). Tiludronate pharmacokinetics were determined on day 24 only.

The geometric mean C_{max} for digoxin alone decreased by 18% vs. administration with tiludronate (1.61 ng/mL vs. 1.32 ng/mL, p=0.008) while AUC_{0-24} decreased by only 10% (12.19 ng·h/mL vs. 10.96 ng·h/mL, p=0.006).

Based on the 90% confidence interval of the $AUC_{0-24h}$and C_{max} ratios for digoxin, tiludronate had only a slight impact on the bioavailability of digoxin (Table 20). However, C_{max} values for digoxin tended to be lower (about 18%) in the presence of tiludronate. The arithmetic mean of t_{max} for digoxin (1.04±0.55 h) and digoxin+tiludronate (1.19±0.63 h) were comparable. It was concluded that tiludronate does not produce any clinically significant changes in digoxin pharmacokinetics.

TABLE 20
LSRatio and 90% CI for Digoxin Pharmacokinetic Parameters at Steady-State after Administration of Digoxin Alone (Ref.) and with Tiludronic Acid (Test; 3C1 Tablet)

Pharmacokinetic Parameter of Digoxin	LSRatio (T/R)	90% CI
AUC_{0-24h}	89.9	84.9-95.2
C_{max}	82.3	73.9-91.7
PTF	89.0	75.3-105.3
PAF	91.4	79.9-104.5

PTF=percent peak/trough fluctuation
PAF=percent AUC fluctuation

Tiludronate steady-state pharmacokinetics were examined on day 24. Values (arithmetic mean±SD) for C_{max} (2.82±1.24 mg/L), T_{max} (1.67±0.44 hr), AUC_{0-24h} (28.72±12.73 mg·h/L), and Ae_{0-24h} (22.02±9.5 mg) were comparable with single-dose study results when 10 hour pre-dose and at least 2 hour post-dose fasts were implemented.

A study (PCL 702.86) was conducted to assess any interaction between tiludronate and 3 NSAIDs (aspirin, indomethacin, and diclofenac). However, the results of this study are dubious for reasons which include:

1) No information was submitted on the tiludronate assay,
2) A 200 mg dose of a different (capsule) formulation, with lower bioavailability than either

the 3C1 or 9O1 formulations, was used,

3) AUC was calculated to only 4 hours post-dose,

4) small sample size (n=6 for each NSAID).

Three separate studies (reviewed below) further assessed these drug interactions.

Of notable interest is that one pivotal study (P1845) excluded subjects on "gastrotoxic drugs (i.e. aspirin, NSAIDs)." Thus, the co-administration, under controlled conditions, of aspirin/NSAIDs with tiludronate, has not been fully evaluated. The following OCPB drug-drug interaction study reviews do not imply that this co-administration is safe; they only evaluate pharmacokinetic interactions.

The effect of aspirin (600 mg) on the pharmacokinetics of tiludronate was investigated (P1660) in 12 healthy Caucasian, male volunteers. Tiludronate pharmacokinetics were evaluated alone and when a single dose of aspirin was administered 2 hrs before, simultaneously with, and 2 hrs after a single 2x200 mg dose of tiludronate. The results are presented in Table 21.

Non-significant ($p>0.1$) reductions in geometric mean $Ae_{0\text{-}obs}$ of 54% (from 5.23 mg to 2.42 mg) with simultaneous aspirin administration, and C_{max} of 38% (from 0.85 mg/L to 0.53 mg/L), $AUC_{0\text{-}obs}$ of 47% (7.85 mg·h/L to 4.17 mg·h/L), and $Ae_{0\text{-}obs}$ of 58% (from 5.23 mg to 2.19 mg) with 2 hour post-dose aspirin administration, for tiludronate were observed. Through discussion with the Medical Division, it has been ascertained that this decrease in bioavailability of tiludronate (up to about 50%) when administered with, or two hours before aspirin, may be of clinical importance.

TABLE 21
LSRatio (90% CI) for Pharmacokinetic Parameters of Tiludronic Acid 400 mg Alone (Ref., 3C1 Tablet) and with Aspirin 600 mg (Test)

Pharmacokinetic Parameter	Tiludronate 8am Aspirin 6am	Tiludronate 8am Aspirin 8am	Tiludronate 8am Aspirin 10am
C_{max}	0.99 (0.66-1.49)	0.75 (0.50-1.13)	0.62 (0.41-0.94)
$AUC_{0\text{-}obs}$	0.98 (0.60-1.61)	0.76 (0.46-1.25)	0.53 (0.32-0.87)
$Ae_{0\text{-}obs}$	0.70[a] (0.36-1.35)	0.46[a] (0.24-0.89)	0.42[b] (0.22-0.81)

[a] n=11
[b] n=10

The effect of Maalox® tablets on the pharmacokinetics of tiludronate 2x200 mg was investigated

(P1597) in 12 healthy male, Caucasian volunteers. Maalox® was administered at 8am and 8pm during the two days preceding the administration of tiludronate, and then, on the third day, at 1 hour before or 2 hours after the single tiludronate dose. The results are presented in Table 22.

TABLE 22
LSRatio (90% CI) of Pharmacokinetic Parameters of Tiludronic Acid After Administration of 400 mg of Tiludronate Alone (Ref., 3C1 Tablet), 1 hour after Maalox® (Test1) and 2 hours before Maalox® (Test2) to 12 Healthy Volunteers

Pharmacokinetic Parameter	Tiludronate 1 hr after Maalox®	Tiludronate 2 hrs before Maalox®
C_{max}	0.37 (0.27-0.51)	0.86 (0.62-1.19)
AUC_{0-48h}	0.40[a] (0.30-0.55)	0.96 (0.70-1.31)

[a] For two subjects AUC was computed up to 36 hours for Test1

When administered alone, tiludronic acid mean pharmacokinetic values for C_{max} and AUC_{0-48} were significantly greater vs. administration 1 hour after Maalox (3.35 mg/L vs. 1.59 mg/L, p=0.0002; 27.2 mg·h/L vs. 13.8 mg·h/L, p=0.0004) but no significant differences were found with administration 2 hr before Maalox (2.90 mg/L, p>0.2; 25.9 mg·h/L, p>0.6). Maalox® intake 1 hour before tiludronate administration decreases the bioavailability of tiludronate, whereas Maalox® taken 2 hours after tiludronate does not significantly affect bioavailability. It is therefore recommended that, if Maalox® is required, it should be taken at least 2 hours after tiludronate. This data does not determine the length of time, after Maalox administration, that should elapse so that tiludronate bioavailability is not affected.

The effect of diclofenac on the pharmacokinetics of tiludronate was investigated (P1613) in 12 healthy male, Caucasian, volunteers. Diclofenac 50 mg was administered 2 hours before, simultaneously with, and 2 hours after a single 2x200 mg dose of tiludronate. The results are presented in Table 23.

TABLE 23
LSRatio (90% CI) for Pharmacokinetic Parameters of Tiludronic Acid 400 mg Alone (Ref., 3C1 Tablet) and with Diclofenac 50 mg (Test)

Pharmacokinetic Parameter	Tiludronate 10am Diclofenac 8am	Tiludronate 10am Diclofenac 10am	Tiludronate 10am Diclofenac 12pm
C_{max}	1.26 (0.90-1.76)	0.98 (0.70-1.37)	1.28 (0.98-1.78)
$AUC_{0\text{-}obs}$	1.40 (0.90-2.16)	1.16 (0.75-1.80)	1.56 (1.01-2.43)
$Ae_{0\text{-}obs}$	1.22 (0.79-1.87)	1.06[a] (0.68-1.66)	1.37 (0.89-2.11)

[a] n=11

No significant pharmacokinetic differences were found, between tiludronate alone vs. diclofenac administered 2 hrs before, with, and 2 hrs after tiludronate, for geometric mean Cmax (0.64 mg/L vs. 0.81 mg/L, 0.63 mg/L, and 0.82 mg/L, respectively; overall p>0.36), $AUC_{0\text{-}obs}$ (4.53 mg·h/L vs. 6.32 mg·h/L, 5.25 mg·h/L, and 7.09 mg·h/L; overall p>0.33), $Ae_{0\text{-}obs}$ (3.21 mg vs. 3.91 mg, 3.53 mg, and 4.41 mg; overall p>0.60), or median T_{max} (2.25 h vs. 1.50 h, 1.75 h, and 2.00 h; overall p>0.60).

Although there was a slight trend toward increased tiludronate bioavailability with the administration of diclofenac 2 hours before and 2 hours after the administration of tiludronate, there does not seem to be strong evidence that diclofenac affects tiludronate pharmacokinetics in a clinically important manner.

The effect of a single indomethacin 50 mg dose on the pharmacokinetics of tiludronate was investigated (study P1659) in 12 healthy male volunteers. Indomethacin was administered 2 hours before, with, and 2 hours after a single 2x200 mg dose of tiludronate. The results are presented in Table 24.

TABLE 24
LSRatio (90% CI) of Pharmacokinetic Parameters of Tiludronic Acid After Administration of 400 mg Tiludronic Acid Alone (Ref., 3C1 Tablet) or with 50 mg Indomethacin (Test) to 12 Healthy Volunteers

Pharmacokinetic Parameter	Tiludronate 10am Indomethacin 8am	Tiludronate 10am Indomethacin 10am	Tiludronate 10am Indomethacin 12pm
C_{max}	1.67 (1.03-2.71)	2.19 (1.34-3.55)	1.32 (0.81-2.15)
$AUC_{0\text{-}obs}$	1.82 (0.90-3.67)	2.68 (1.33-5.40)	1.23 (0.61-2.48)
$Ae_{0\text{-}obs}$	2.47[a] (1.08-5.67)	3.55[b] (1.67-7.56)	2.39[a] (1.05-5.43)

[a] n=8
[b] n=9

The geometric mean C_{max} and $Ae_{0\text{-}obs}$ for tiludronate alone (0.36 mg/L and 1.25 mg, respectively) and simultaneously with indomethacin (0.80 mg/L and 4.44 mg) differed (p=0.03 for both). No other pharmacokinetic values were significantly different between tiludronate alone vs. any other treatment.

Even with consideration for the wide intrasubject variability of tiludronate pharmacokinetics, there is a consistent trend toward increased tiludronate bioavailability with administration before, after, and especially with indomethacin.

VII. Pharmacokinetic/Pharmacodynamic Relationships

The relationship between tiludronate plasma concentration as a function of dose and changes in mean percent reduction in baseline SAP, for intent-to-treat subjects, is presented in Figure 11. Blood levels were obtained throughout the 12 week clinical efficacy and safety trial (P1845) which used the 9O1 tiludronate tablet formulation. Blood concentrations were determined at 2, 4, 8, 12 and 16 weeks after administration of the drug. The hysteresis plot demonstrates a time displacement between reduction in SAP and tiludronate plasma concentrations. Nearly maximal reductions in SAP levels were maintained following cessation of drug administration even though plasma concentrations of tiludronate were at or below assay quantitation levels (Figure 12).

Significant differences in SAP reduction were observed for the 200 and 400 mg groups compared to placebo at Week 12. At the Week 24 visit, the mean percent changes from baseline in SAP were 5%, -47%, and -58% in the placebo, 200 mg, and 400 mg groups, respectively (Table 25). However at Week 24, a significant difference ($P<0.05$) was also detected between the 200 and 400 mg groups.

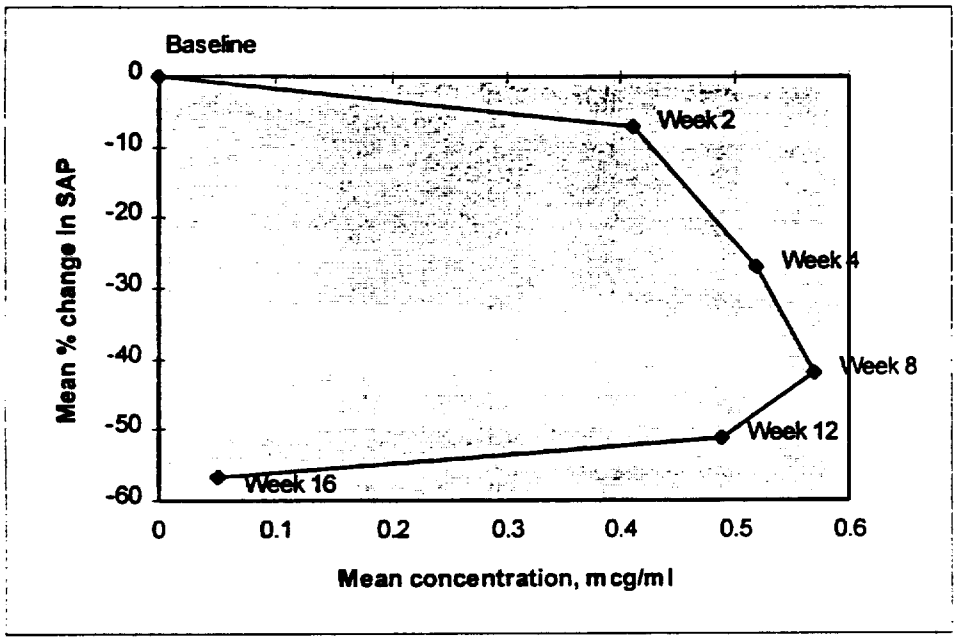

Figure 11: Relationship between Tiludronic Acid Plasma Concentration (400 mg) and Mean Changes in SAP Using the 9O1 Tablet (n≈40 at each week; weeks 2, 4, and 8 are concentrations at 10 to 14 hrs after dosing, while week 12 is last dose trough concentration).

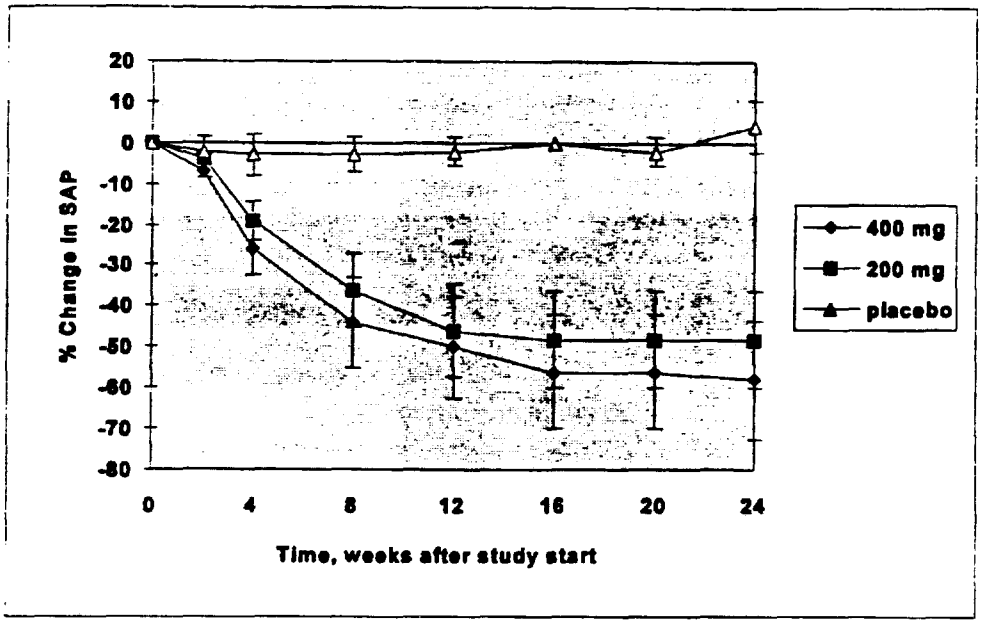

Figure 12: Relationship between Weeks after Study Start and Mean Changes in SAP Due to the 9O1 Tablet.

Table 25
Mean Percent Changes from Baseline in SAP (IU/L) in Intent-to-Treat Subjects (9O1 Tablet)

Treatment Group/Visit	% Change in SAP	
	Time, in Weeks	
	Week 12 (N)	Week 24 (N)
Placebo	0.5 (44)	5.1 (45)
200 mg SKELID®	-45.8 (45)	-46.8 (44)
400 mg SKELID®	-50.8 (46)	-57.9 (45)

A randomized placebo controlled, double-blind, dose ranging study (N=112, treated) using the 3C1 tablet formulation was also conducted (P1619). Single daily doses of 200, 400 or 600 mg qD were given orally. Plasma levels of tiludronic acid before, and 1 hour after drug administration at Week 12 were measured at two centers (N=6). Tiludronate reduced alkaline phosphatase levels and a dose response was apparent. Alkaline phosphatase responded to tiludronate within 2 weeks, with the most dramatic reduction occurring between weeks 2 and 4. A plateau still had not been reached after 24

weeks (Figure 13). An increase in the reporting of adverse events, mostly gastro-intestinal, occurred with increasing dose.

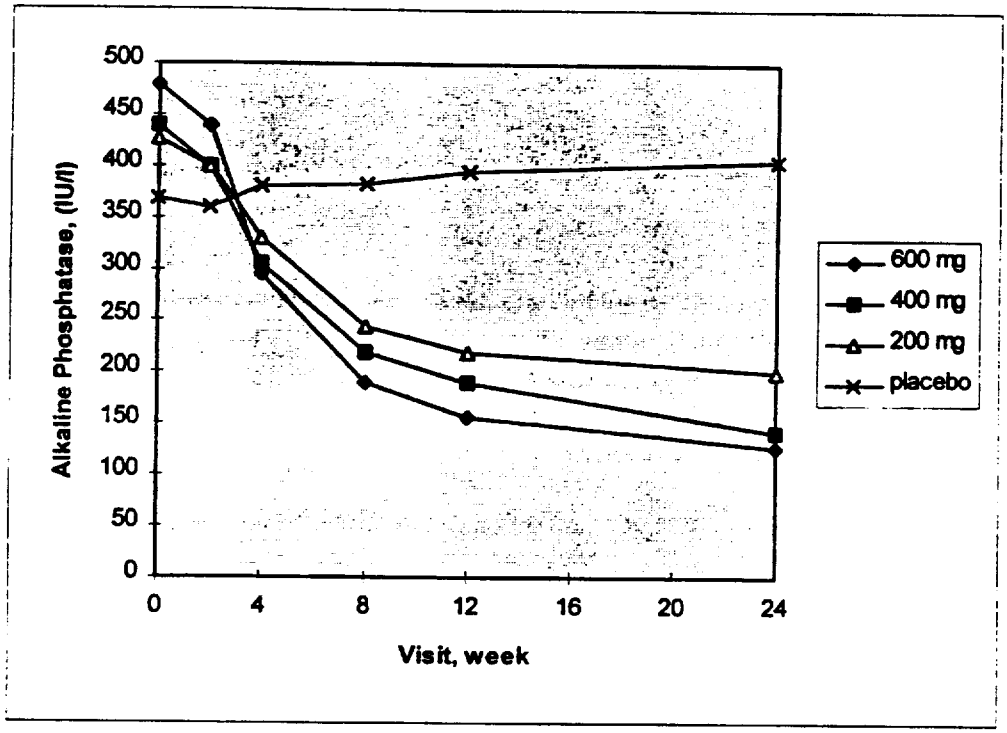

Figure 13: Changes in Geometric Mean Serum Alkaline Phosphatase Levels over Time Using the 3C1 Tablet.

COMMENTS TO BE SENT TO THE FIRM:

1. Although similar results were obtained using a speed of compared to and the agency does not accept because it is generally less discriminating . The agency recommends the following dissolution method and specification: USP Apparatus at speed and Q= at 20 minutes in pH

2. The sample size used in some of the studies was less than desirable, including: P1836 (n=9); P1270 (n=3/arm); P1615 (n=8 Pagetic patients); P1586 (n=10); P1011 (n=8/arm); P1646 (n=8 evaluable); PCL859.87 (n=6/arm). Results from such studies are only suggestive, not conclusive.

3. The sponsor should use only one batch of a given tablet formulation per study. For example, in the age study, three different 3C1 batches were used which added variability to the results.

4. The age study (PCL859.87) is severely flawed for the following reasons:

1) According to protocol inclusion criteria, elderly subjects could not have renal clearance less than 70 mL/min, yet each elderly subject with a baseline serum creatinine (n=10) had a calculated renal clearance below 70 mL/min (a protocol violation), with a median (range) of 47 mL/min (21-63), including 2 subjects below 30 mL/min. However, the inclusion criteria may have been unrealistic. The actual sample may be more reflective of the creatinine clearance seen in this population and have more clinical relevance.

2) This study used 3 different batches of tablets, one of which had only 1000 manufactured tablets and was used for all young subjects,

3) Subjects were not studied at the same time - young subjects were studied between 04/22/87 and 07/15/87, while the elderly started 07/11/88 (more than a year after the young subjects) and did not finish until 11/05/90 due to recruitment problems,

4) Two young subjects donated 300 mL of blood 15 days prior to the study (a protocol violation),

5) One elderly subject continued on acetylsalicylic acid, but a protocol amendment states that no subject may be taking salicylic acid,

6) One elderly subject was diabetic (a protocol violation),

7) No young females were studied,

8) Urine samples were missing and deviation of collection times exceeded 10% in many cases.

5. 3C1 batch sizes used in many pharmacokinetic clinical studies tended to be small. SUPAC Guidance recommends pilot batches be at least 10% of commercial production batches or 100,000 tablets, whichever is greater. Although SUPAC is intended for post-approval scale-up, it seems rational to apply them generally. With a proposed commercial production size of tablets, some clinical study batches were of a size substantially less than tablets. Dissolution data for these small clinical batches would have been helpful in making comparisons to commercial size batches.

5. When conducting drug interaction studies, the drug interaction should be studied in both

directions i.e., the effect of the reference compound on the test drug's pharmacokinetics and the effect of the test drug on the reference drug's pharmacokinetics.

6. Some of the parallel design studies submitted as part of this NDA were of inferior design. Recruitment and evaluation of subjects, in the different treatment groups, was sometimes more than 1-1.5 years apart. This can add considerable variability when comparing the groups.

7. In the design of pharmacokinetic studies the sponsor should, whenever possible, conduct side-by-side comparisons (use a control group) and avoid cross-study comparisons, which can add variability.

8. (P.3) In the proposed package insert, the second paragraph under Absorption currently reads "...with peak plasma concentrations of approximately 3 mg/L occurring...".

The studies referenced, P1228, P1616, and P1676, had mean peak plasma concentrations of 2.08, 2.31, and 2.75 mg/L, respectively, with a mean of 2.4 mg/L (approximately 2.5 mg/L, not 3 mg/L). However, on p.6, under Summary of Pharmacokinetic Parameters in the Normal Population, the maximum plasma concentration after a single 400 mg dose is stated to be 2.66 mg/L (approximately 3 mg/L). Page 6 references more studies, and includes those referenced on p.3. For consistency, it is recommended that the reference on p.3 be changed to include all studies referenced on p.6.

LABELING COMMENTS:

1. (P.3) The first paragraph under Distribution should read "...equivalent to 400 mg/day tiludronic acid to **non-Pagetic patients with osteoarthrosis**, the steady...".

The study referenced, P1270, enrolled male patients undergoing surgery for osteoarthrosis, not healthy volunteers.

2. (p. 5) The following statements should be added to the end of the Renal Insufficiency paragraph: **"These values were obtained in a cross-study comparison between healthy volunteers and Pagetic patients."**

The sponsor did not conduct a side-by-side comparison of renal patients with healthy volunteers or Pagetic patients. Therefore, the fact that a cross-study comparison is being made should be noted.

3. (P.6) The Drug-Drug Interaction section should read, "The pharmacokinetics of SKELID are not significantly altered by coadministration of diclofenac[56]. Aspirin may decrease the bioavailability of SKELID by 50%[55]. The bioavailability of SKELID is decreased 80% by calcium[57], 60% by some antacids[58], and increased 2-4 fold by indomethacin[59]. The pharmacokinetic parameters of digoxin are not significantly modified by SKELID coadministration.[60] *In vitro* studies show that tiludronate disodium does not displace warfarin from its binding site on protein.[61]

These changes are based on the actual data reviewed and give an indication of the extent to which tiludronate pharmacokinetics is affected.

4. (P.10) The second paragraph on this page should read "...Pagetic patients' baseline SAP level, gender, or age in the population...".

5. (p. 11) Information for Patients, comment 1 should be changed to, "Take SKELID® with 6 to 8 ounces of plain water **only**, at least 2 hours before or after eating, **preferably in the morning, and remain in an upright position and/or engage in light physical activity for the first hour after administration.**

These changes are being suggested to address: 1) the 90% drop in bioavailability that is observed when tiludronate is taken with food and 2) concerns regarding the development of gastric lesions that are associated with other bisphosphonates that are currently on the market due to patients obtaining a supine position immediately after consuming the tablets.

Comment 3 should read, **"Refrain from taking indomethacin within 2 hours of taking SKELID.[110]"**

Comment 4 should be added, and read, **"Calcium supplements[108] and antacids[109] should be taken at least 2 hours after taking tiludronate."**

This change is being recommended because available data suggest that tiludronate bioavailability is not affected if it is taken 2 hour before Maalox (i.e. divalent cations), but that tiludronate bioavailability is significantly decreased if taken 1 hour after Maalox (e.g. 'How long to wait before taking tiludronate after Maalox' has not been determined).

6. (P.11) The Drug Interactions section should read, "The pharmacokinetics of SKELID are not significantly altered by coadministration of diclofenac[112]. Aspirin may decrease the bioavailability of SKELID by 50%[111]. The bioavailability of SKELID is decreased 80% by calcium[113] , 60% by some antacids[114], and increased 2-4 fold by indomethacin[115]. The pharmacokinetic parameters of digoxin are not significantly modified by SKELID coadministration.[116] *In vitro* studies show that tiludronate disodium does not displace warfarin from its binding site on protein.[117]

7. (P.16) In the Overdose section, the sentence,

' should be removed.

8. (P.17) In the Dosage and Administration section, the last paragraph should read, "SKELID should be taken at least 2 hours before mineral supplements, calcium supplements,[143] or antacids containing aluminum or magnesium.[146] SKELID should not be taken within 2 hours of indomethacin or food.[145]

The changes are being recommended to maintain consistency with other labeling recommendation, based on data reviewed.

Carolyn D. Jones
Robert M. Shore

Carolyn D. Jones, Ph.D.
Robert M. Shore, Pharm.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics
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RD initialed by Hae-Young Ahn, Ph.D., Team Leader 11/18/96

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FT initialed by Hae-Young Ahn, Ph.D., Team Leader 12/20/96

cc: NDA 20-707 (1 copy), HFD-510(Dutta, Hedin, Barbehenn), HFD-340 (Vishwanathan), HFD-870(Ahn, Jones, Shore, M. Chen), HFD-870(Drug file, Chron. file, Reviewer).