

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 020707

MEDICAL OFFICER REVIEWS

1/10/97

1. Title and General Information

1.1 Title/Heading- Medical Officer's Review

1.1.1 NDA # 20-707

1.1.2 Date of submission: February 28, 1996.

1.1.3 Filing date : April 28, 1996

1.1.4 Review completed: Nov.15,1996.

1.2 Drug name

1.2.1 Generic name : Tiludronate disodium

1.2.2 Proposed trade name: Skelid

1.2.3 Chemical name: [[[4-chlorophenyl] thio] methylene]bis[phosphonic acid]. disodium salt.

1.3 Sponsor: Sanofi Winthrop, Inc.
9 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355

1.4 Pharmacologic Category: It is a bisphosphonate with antiresorptive action on bone.

1.5 Proposed Indication: Skelid is indicated for treatment of Paget's disease of bone (osteitis deformans).

1.6 Dosage Form(s) and Routes of Administration:

1.7 NDA Drug Classification: .1 S.

1.8 Important Related Drugs:

Approved bisphosphonates for the treatment of Paget's disease of bone:

-Etidronate disodium (Didronel/ Procter and Gamble)

-Alendronate sodium (Fosamax /Merck Res. Lab.)

-Pamidronate disodium (Aredia/ Ciba-Geigy)

Investigational bisphosphonates for Paget's disease of bone:

1.9 Related reviews

- Biopharm . Rev.
- Statistical Rev.
- Pharmacology Rev.
- Chemistry Rev.

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3. **Material reviewed:** This NDA consists of a total 324 volumes. Specific volumes that

are included in the following table are shown in Table 1

Review Subject	NDA Vol. #
Nonclinical Pharm. Toxicol.	1.9, 1.13, 1.17
Nonclinical ADME	1.54, 1.59
Human pK Data/Conclusion	1.60, 1.99, 1.103-1.114
Clinical Data	1.116-1.177
Clinical Trials	1.178-1.227
Published Literature	1.228-1.237
<u>CRF</u>	1.273-1.324

4. **Chemistry/Manufacturing Controls:** See Chemistry review for relevant information.
5. **Animal Pharmacology/Toxicology:** This reviewer has only summarized the pharmacology data. For detailed information and comments, see Pharmacology review.

5.1 Mechanism of action- The mechanism of action of tiludronate was tested in four studies using *in vivo* animal (rat) models. Increased bone resorption was induced in thyroid parathyroidectomized (TPTX) rats by treating them with retinoid derivatives. The results of these studies were reported to indicate complete inhibition of retinoid-induced bone resorption at doses of 50-100 mg/kg/day given orally, or 5 mg/kg/day given by s.c. injection. At these doses, tiludronate did not influence food intake or renal function.

Compared to the effects of pamidronate and etidronate, tiludronate was reported to be more potent in inhibiting bone resorption. However, the exact relative potency of these compounds were not determined. In another dose-ranging study (in rats), the minimum effective dose of tiludronate (in terms of inhibiting retinoid-induced bone resorption) was reported to be 12.5 mg/kg/day given orally.

The *in vitro* studies using fetal mouse calvaria demonstrated that tiludronate was more potent than etidronate in inhibiting the release of radio-labeled calcium by various resorptive agents (e.g., PTH, prostaglandin E₂, IL-1, 1, 25 (OH)₂ D₃, etc). In these

studies, sponsor also investigated the cellular basis of the antiresorptive action of tiludronate. (**Comments:** This reviewer feels that additional studies are warranted in order to clearly define its cellular basis of action). The inhibitory effect of tiludronate on bone resorption was reported to be not due to "inhibition of recruitment of the osteoclast precursors." The suggested molecular mechanisms of action of tiludronate are: i) disruption of the active ring of "polarized osteoclasts (probably due to inhibition of tyrosine phosphatase), and ii) inhibition of the proton pump of the osteoclasts.

5.1.1 Effect of tiludronate on bone formation and mineralization- Sponsor states that four *in vivo* and three *in vitro* studies were carried out to study the effect of tiludronate on bone matrix formation and mineralization. The effect of tiludronate was tested on formation of calcified plaque (probably simulates hydroxyapatite crystal deposition) following s.c. injection of saturated solution of pot. permanganate in rats. The drug did not interfere with the formation of the calcified plaque and prevented spontaneous dissolution of plaques at a dose equal to or two-fold higher than the dose for inhibition of bone resorption.

The results of an *in vitro* study (using isolated osteoblast cells from mouse calvaria) showed no effect of tiludronate (over a wide range of concentrations) on "incorporation of proline into collagen." Sponsor has concluded that tiludronate at "maximally effective antiresorptive doses does not interfere with "bone mineralization or osteoblastic activity."**(Comments:** Sponsor should have performed the so-called Schenk assay and compare the effect of tiludronate, etidronate and alendronate on bone resorption and mineralization in growing rats).

5.1.2 Effect of tiludronate on calcium and phosphorus balance and bone mass-

These studies were carried out in normal and TPTX rats and non-rodents. The sponsor has drawn the following conclusions from these studies:

- i) Increased intestinal absorption of calcium in a dose-dependent fashion. Urinary excretion of calcium did not show any change.
- ii) Tiludronate seems to "uncouple bone resorption from bone formation" temporarily, and that leads to a positive calcium balance.
- iii) Increased intestinal absorption of calcium was mediated by increased production of $1,25(\text{OH})_2 \text{D}_3$.
- iv) Tiludronate treatment also leads to a positive phosphorus balance in normal and TPTX rats by increasing renal tubular resorption of phosphorus (mechanism not clear but reported to be PTH-independent).

v) Positive effects of tiludronate on calcium and phosphorus balance probably contribute to the prevention of bone mass loss in estrogen-deficient rodent and several non-rodent models.

The results of these studies seem to indicate that tiludronate at least partially contributes toward preservation of bone mass in estrogen-deficient modeling (rats) and remodeling species (ewes).

5.1.3 Bone tolerance- Long-term toxicity of tiludronate on skeleton was studied in rats, baboons and mice. Potential toxicity was analyzed by various techniques, such as radiography, microradiography, histomorphometry of bone biopsy materials, bone density measurement, biomechanical tests, and biochemical markers of bone turnover.

Rats- Animals were treated with tiludronate in doses up to 200 mg/kg/day (approx. 25 x the human dose) for 3 to 6 months. Sponsor states that microradiography and histological evaluation of femurs revealed "tiludronate induced no bone abnormality in the bone structure and no increase in osteoid borders" at the highest dose. Even at a dose of 160 mg/kg/day for 3 months and followed by 3 months of recovery, tiludronate showed no deleterious effects on structure as assessed by histology. Other rat studies with 3-month treatment with tiludronate (50 mg/kg/day) also showed no change in bone mineral density and strength compared to controls.

Baboons- Growing baboons were treated with tiludronate at a dose of 80 mg/kg/day for 6 months). Sponsor claims that radiographic and histomorphological evaluations revealed "no signs of osteomalacia." However, there was marked " **reduction in bone turnover.**" In one-year toxicity study, there was also a "low incidence of fractures" in animal treated with tiludronate at a dose of 40 mg/kg/day, but difference in the incidence of fractures was not statistically significant compared to control animals. These fractures were reported to be healed normally in both treated and untreated groups. Biomechanical testing of strength of radius of treated (at above-mentioned dose) animals did not show any decrease in bone strength. In contrast, the results of torsional tests with long bones indicated dose-dependent increase in "mechanical resistance" of long bones to fractures. Changes in mechanical strength were correlated with increased bone mineral density (BMD).

Dogs- In a dog study, a dose of 10 mg/kg/day of tiludronate was reported to show no evidence of "frozen bone" after one year of treatment. At a dose of 5 mg/kg/day (equivalent to proposed dose for the Paget's disease of bone), tiludronate treatment did not affect the repair of bone lesion induced by osteotomy.

Sponsor's overall conclusion on the quality of bone formed during long-term treatment with tiludronate is that the drug has no "negative effect on bone quality."

Comments: Both rat and baboon studies were not carried out for optimum duration that is required in our current Osteo-Guidelines. Since these studies were carried out at doses which were 7 to 25 times the human dose, one would expect considerable accumulation of the drug in skeletal tissue within a short time. Beside the dose and duration of exposure to tiludronate, the kinetic properties of the drug also play important role in the assessment of toxicity on bone quality. Tiludronate at a dose of 80 mg/kg/day was reported to cause marked decrease in bone turnover and slight increase in the incidence of fractures (though not statistically significant). The sponsor should provide additional evidence (from preclinical and/or clinical studies) in support of its conclusion that tiludronate has no negative effect on bone quality.

5.2 Secondary pharmacology - Studies were carried out in mouse, rats, guinea pigs, and dogs to determine its effects on major physiological systems.

CNS- Tested in mice. At a very high dose (800 mg/kg/day), tiludronate caused slight sedation and moderate hypothermia.

Resp. system- No significant adverse effects were reported in guinea pigs and dogs.

Cardiovasc. system- Cardiovascular effects were reported to be dependent upon the route of administration and the state of consciousness (anesthetized or non-anesthetized) of the animals. In anesthetized dogs, intra duodenal administration of tiludronate (at doses above 5 mg/kg) caused hypotension and decreased contractility of the heart. Rapid iv infusion of the drug (at a dose of 10 mg/kg in 10 minutes) caused depression of myocardial contractility and cardiac output, and hypotension. If the same dose is administered over a 2-hour period, those changes are not seen. The sponsor has suggested that acute effects were due to formation of calcium complex with tiludronate, resulting in lowering of circulating calcium level. In unanesthetized dogs, administration of tiludronate at a dose of 40 mg/kg/day for one month did not affect cardiovascular parameters.

G-I system- In rats, tiludronate at very high doses (100-200 mg/kg p.o.) caused delayed emptying of stomach. Tiludronate was not seen to affect gastric secretion and intestinal transit time in rats. Occasional vomiting was noted with tiludronate, during chronic administration of the drug at a dose of 40 mg/kg.

Urinary system- Acute oral or iv administration of tiludronate was not reported to alter urinary excretion of electrolytes.

Immune system- Tiludronate tested in *in vitro* lymphocyte proliferation assays and *in vivo* (mice) study showed no effect on the immune system. The drug showed no "photo toxic or photo allergic" effect in guinea pigs.

Anti-inflammatory and antiarthritic activity - The results were inconclusive in *in vivo rat models*. However, sponsor claimed some antidegenerative effect of tiludronate in an *in vitro* system.

5.3. Toxicology studies

Acute toxicity- LD50s of tiludronate (p.o. and i.v. routes) were determined in rats and mice.

Repeated-dose oral toxicity- These studies were carried out in mice, rats and baboons. In fasted mice, a 13-week administration of drug (at doses of 83 mg/kg or greater in 10% w/w/ gum arabic or distilled water) resulted in renal toxicity. The max. tolerated dose of tiludronate in mice was reported to be 42 mg/kg.

In 6-month studies, rats given tiludronate at doses of 60 and 160 mg/kg/day and greater resulted in kidney and stomach toxicity (See Pharm. review for the nature of adverse effects). From results of these studies the sponsor estimated that the max. tolerated dose of tiludronate in fasted rats would be 50 mg/kg/day. In repeated dose comparative studies, tiludronate, etidronate and pamidronate were reported to be equitoxic when given to nonfasted rats, at a dose of 50 mg/kg/day (in gum arabic) for 3 months.

In baboons, reversible gastric and renal lesions were reported at a dose of 80 mg/kg/day for longer period. At a dose of 40 mg/kg/day for 12 months there were no stomach or kidney lesions.

The sponsor concluded that tiludronate-induced skeletal lesions (inhibition of bone modeling) generally occurred at doses lower than those which affected kidney or stomach.

Repeated intravenous dosing (up to one month duration)- These studies were carried out in rats, dogs and baboons. Intravenous tiludronate-induced gastric and kidney lesions were similar to those reported with oral administration. Treatment related mortality was reported at doses of 20 mg/kg in dogs, 40 mg/kg in baboons, and 50 mg/kg/day in rats. The non-toxic doses were 3 mg/kg/day for baboons. ECG changes and slight nephrotoxicity were reported in rats and baboons at 5-6 and 10-12 mg/kg/day, respectively.

Carcinogenicity -These studies carried out in rats and mice for 80 weeks to 2 years at doses up to 25-50 mg/kg/day revealed no "treatment-related effect on the incidence of tumor types or on proliferative and preneoplastic lesions suggestive of carcinogenic potential for tiludronate." (Comments: The Pharmacology review will address the carcinogenic potential of tiludronate in more details).

Special tox. studies (performed with impurities and intermediates of synthesis)- These

had no mutagenic effect in the Ames test. The sponsor has discussed the relative maximum nontoxic doses of these impurities and synthesis intermediates in male and female rats.

Interaction studies - Studies were carried out with single or repeated concomitant administrations of NSAIDs and tiludronate. Multiple administration of piroxicam and tiludronate (at a dose of 160 mg/kg/day) was reported to "increase gastric lesions." Tiludronate at all doses tested, showed increased gastric lesions when administered with aspirin.

Reproductive studies - Sponsor states that tiludronate at a dose up to 75 mg/kg/day showed no adverse effect on male or female fertility or pre- or postnatal development of rats. In rats, mice and rabbits, no teratogenic effect of tiludronate was noted at doses up to 200-375 mg/kg/day (given in gum arabic or distilled water). However, at these doses there was "slight maternal toxicity" (decrease in body weight gain). At a dose of 375 mg/kg/day, tiludronate showed "slight embryotoxic effect" in association with maternal toxicity in mouse.

Mutagenicity studies - In mammalian or nonmammalian *in vitro* cell systems, tiludronate showed no "mutagenic or clastogenic" activity. Similarly, *in vivo* studies showed no evidence of mutagenicity even at very high dose (833 mg/kg).

5.4 Preclinical pharmacokinetics

5.4.1 Absorption and bioavailability- The results are summarized in Table 2.

Table 2. Absorption/bioavailability of tiludronate* in rats, mice, dogs, and baboons.

Animal Species	% Of An Oral Dose Absorbed
Baboon and Mice	15-16
Rats	11
Dogs	6
Rabbits	1

* Tiludronate was dissolved in dist. water and administered in fasted animals.

5.4.2 Plasma levels and pK parameters after a single oral dose of tiludronate.
The results are summarized in Table 3.

Table 3. Some kinetic parameters of tiludronate after a single oral dose (50 mg/kg).

Animal Sp.	Cmax (mg/L)	t max (Hours)	AUC (mg·h/L)
Mouse	10-16	0.5-1	17
Rat	"	"	31
Dog	"	"	108
Baboon	"	4.5	143
Rabbit	3.5	0.5-1	15

The apparent terminal plasma concentrations ranged between 60 and 365 hours across species.

Nonlinearity in AUC and C max was reported at higher doses of tiludronate in mice and rats. Plasma concentrations of tiludronate (from day to day and across studies and in all species) varied widely due to "inter-individual and nutrition-state variabilities".

Sponsor states that limited data are available on plasma concentrations of tiludronate following repeated administrations. See Pharmacology review for details. The results of per oral multiple-studies in baboons showed marked inter-individual variability in plasma levels. At higher dose (≈ 80 mg/kg), tiludronic acid was reported to be present in the plasma at 8 months after stopping drug administration. In short-term (1 month) iv studies with lower doses (< 12 mg/kg/day), a linear relationship between plasma concentrations and doses was reported. A dose-response pattern was reported in daily urinary excretion of the drug.

5.4.3 Distribution

Tiludronate was reported to be 80% serum protein bound in baboons. Approx. 50% of an iv dose remains "in the body" for 70-144 hours in all species tested. The overall tissue distribution pattern of tiludronate in wide dosage range was similar in mice and rats. Bone and cartilaginous tissues showed highest affinity for the drug. Radioactive drug did not appear to penetrate the brain, spinal cord and pancreas.

Bone - A nonhomogeneous distribution of tiludronate was reported in bone; proximal and distal parts of long bones had greater concentration of the drug than the mid shaft. Longer studies (3-6 months) resulted in "supraproportional" increase of drug levels in these tissues. At higher doses, the binding sites in bone

appeared to be saturated.

5.4.4 Metabolism

Tiludronate was not found to be metabolized in several species of animals (rodents and higher species).

5.4.5 Tiludronate is mostly excreted in the urine. Less than 2% of an administered dose is excreted in the bile. Following an oral dose, presence of marked radioactivity in the feces, represents incomplete absorption of the drug from the gut. Most of the urinary excretion of the drug seems to occur within 24 hours and the remainder is excreted over a long period of time. Coadministration of tiludronate and acetylsalicylic acid was reported to increase the urinary excretion of tiludronate.

5.4.6. Sponsor's conclusion on pharmacology and toxicology- Sponsor has concluded that results of preclinical *in vitro* and *in vivo* studies have demonstrated that tiludronate acts primarily by inhibiting increased bone resorption/turnover without adversely affecting the bone formation at doses tested. The principal target organs for its toxicity were the stomach and kidney. The preclinical profile of tiludronate is safe for its use in the treatment of Paget's disease of bone.

5.4.7 Reviewer's comments: Preclinical studies to determine the mechanism of action of the drug appear to be adequate and the results showed its primary action is the inhibition of increased bone turnover. Thus, its demonstrated mechanism of action justifies its use in the treatment of Paget's disease of bone. With regard to its long-term toxicity, the data seem to be inadequate about the species of animals tested and the duration of treatment. Pharmacology reviewer's comments and recommendations are very **relevant and important** in this respect..

6. Clinical Background

6.1 Relevant human experiences

This NDA is for the treatment of Paget's disease of bone, characterized by increased bone resorption and formation, which results in bone pain, deformity, abnormal bone histology, and increased incidence of fractures.

Currently, the following drugs are approved for the treatment of Paget's disease of bone:

- Calcitonin (salmon and human)
- Didronel (etidronate disodium)
- Aredia (pamidronate disodium for injection)

- Fosamax (alendronate sodium)

6.2 Important information from related INDs and NDAs

Currently, a number of newer bisphosphonates are being investigated for the treatment of Paget's disease of bone. Additional information and clinical experiences with newer investigational agents are needed to determine optimal therapeutic regimens and the possibility of permanent or prolonged suppression of abnormal bone turnover with minimal adverse experiences.

Toxicities of other approved bisphosphonates (i.e., Didronel, Aredia, and Fosamax) are well documented in their package inserts

6.3 Foreign experience

As of 1995, Skelid is approved for the treatment of Paget's disease of bone in the following countries: Belgium, Finland, Luxembourg, Netherlands, Peru, Sweden, and Switzerland.

6.4 Human Pharmacology, Pharmacokinetics, Pharmacodynamics

Human pharmacology- Data on human pharmacology/pharmacodynamics were primarily obtained from clinical trials with Skelid in Paget's disease of bone and other metabolic bone diseases. Sponsor states that no pharmacodynamic studies were carried out with tiludronate disodium except for 4 tolerance studies (one with single oral doses and 3 with repeated oral doses).

i) Single rising-dose safety study: This study was carried out in normal healthy volunteers. Tiludronate (capsule formulation) was used in a dose range of 100 to 1600 mg/day. Each subject received placebo on Day 1 and tiludronate on Day 2 after 10 hours of fasting. Each subject was observed for 21 days for clinical adverse events (AEs) and laboratory abnormalities.. The report indicated no serious AEs or treatment-related discontinuation from the study. The most common AEs reported in this study included headache, feeling of faintness and diarrhea. Diarrhea was considered to be tiludronate-related and lasted for 2-4 days. There were no significant abnormalities in hematology, blood chemistry or U/A tests.

ii) Repeated-dose safety study- This is a double-blind, placebo-controlled study to determine the safety of repeated doses of tiludronate (100 mg/day for 4 days) in small groups of healthy male volunteers. Subjects were monitored for intolerance and laboratory abnormalities over a period of 18 days. The report indicated no serious AEs or laboratory abnormalities due to tiludronate. Only one subject developed papular non-pruritic skin rash that lasted for about 12 hours

iii) Repeated-dose safety study- This is a single-blind study to determine the safety of tiludronate in normal healthy male volunteers. Tiludronate was administered at doses of 100 or 200 mg/day for 5 days. No serious tiludronate-related AEs and laboratory abnormalities were noted in tiludronate treated subjects. In relation to lymphocyte function tests, possible "immune-mediated" reversible decrease in lymphocyte subpopulation (LEU1, LEU3) was noted in tiludronate treated subjects. Clinical significance of this effect is not clear.

iv) Repeated-dose safety study- This is a double-blind, placebo controlled study to determine the safety of tiludronate, 800 and 1000 mg/day (400 and 500 mg B.I.D.) for 7 days in normal healthy male volunteers. Three headaches occurred in the tiludronate (1000 mg) group as opposed to one migraine headache in the placebo group. No significant changes occurred in ECG, hematology, blood chemistry, and U/A.

Human pK studies- This reviewer will discuss only the summary of pK data and overall conclusions: For details see biopharm. review.

At therapeutic dose level, plasma concentration of tiludronic acid can be determined. The limits of quantitation of tiludronic acid by HPLC technique with UV detection (265-285 nm) are: a) 0.01-0.07 mg/L for plasma, b) 0.025-0.2 mg/L for urine and c) 2.5 mg/kg for bone.

Absorption -The mean absolute bioavailability of 400 mg tiludronate (2 x 200 mg tablets) was reported to be 6% (range) under fasting condition. The t_{max} is < 3 hours. However, after a single dose there is wide inter-subject variations for C_{max} and AUC in the range of 40-45%.

Dose proportionality- C_{max} and AUC of tiludronic acid were reported to be dose proportional after an iv infusion (over 0.5 hour) of 10, 20 and 30 mg. However, after oral administration of 200, 400, 600, and 800 mg of tiludronic acid (tablet formulation) for 12 days, there was a non-linear relationship between plasma levels and increase in dose. Sponsor states that this non-linearity is mainly due to increased absorption of the drug, but saturation of skeletal sites could not be excluded. This phenomenon was more evident at doses between 600 and 800 mg of tiludronic acid. Proposed dose of tiludronate for Paget's disease of bone is 400

excluded. This phenomenon was more evident at doses between 600 and 800 mg of tiludronic acid. Proposed dose of tiludronate for Paget's disease of bone is 400 mg/day.

Absorption of tiludronate (capsule formulation) from intestine is markedly decreased by the presence of food. Its absorption is reduced (2 to 3 fold) if "administered with or 2 hours after a hypocalcic breakfast," or if administered with "dairy-based" breakfast. Its absorption is not affected if administered with "acidified water." Absorption of tiludronate tablets is more affected (relative to fasting condition) by the timings in relation to breakfast as discussed above. Absorption of some tablet formulation of tiludronate is decreased by approx. 90% if "administered with or 2 hours after a normal breakfast." If administered 0.5 to 1 hour before meals, its absorption is less affected.

Bioequivalency of different formulations of tiludronate- Addition of sodium lauryl sulfate (SLS) to tiludronate tablets resulted in enhanced absorption of tiludronic acid.

The two pivotal efficacy and safety studies were carried out using two different tablet formulations (using dry and wet granulation). The equivalency of these two tablet formulations was studied in a small group of subjects (N=24). Based on AUC and C_{max} data, bioavailability of the tablet formulation with wet granulation was found to be approx. 15% greater than tablets with dry granulation. **Sponsor states that confidence intervals for this difference did not meet Agency's bioequivalency criteria (0.8-1.25).**

Comments: Because of differences in bioequivalency of two different tablets of tiludronate in PK studies, sponsor stressed the importance of therapeutic equivalency based on the results of the clinical trials. Based on changes in the primary efficacy endpoint (serum alk. phosphatase), sponsor claimed that two tablet formulations were therapeutically equivalent at "both 200-mg and 400-mg doses at 12 weeks and 24 weeks after the beginning of tiludronate administration."

Absorption and elimination: These studies were carried out mostly in pagetic patients and in a small group of normal healthy volunteers. Results showed higher plasma levels of tiludronic acid in pagetic patients compared to normal healthy volunteers. Pagetic patients were also reported to manifest lower clearance of tiludronic acid compared to normal subjects. At both dose levels (200 and 400 mg/day), plasma levels of tiludronic acid were greater after 12 weeks of treatment in subjects older than 65 years of age compared to younger patients.. There were no differences in plasma levels of tiludronic acid in respect to gender, weight.

Distribution: After an iv administration of a single dose of tiludronate, 50% to 60% of it was excreted in the urine during 0-96 hours, and the remainder was bound to bone. In patients with osteoarthritis, the bone concentration of tiludronic acid was reported to be **approx. 30 mg/kg**, after about 30 days of its administration at a dose of 400 mg/day.

Tiludronic acid was reported to be bound to serum protein to the extent of 90% to 92%), mostly to albumin. The drug was reported to be displaced significantly (about 7%) from its binding site by **salicylic acid**. Analgesics and anti-inflammatory drugs (names not mentioned) did not affect protein binding of tiludronic acid. Warfarin had no effect on its binding to serum albumin.

Metabolism: There are no *in vitro* or *in vivo* data to suggest metabolism of tiludronic acid.

Elimination: Kidney is the primary organ responsible for its elimination from the body. The elimination half-life of tiludronic acid from bone has not been determined. In animal studies, it has been determined to be as long as 300 days. Elimination half-life of tiludronic acid (after a single dose in healthy volunteers) from plasma and urine was reported to be 40-60 and 60-80 hours, respectively. In pagetic patients, elimination half-life (not taking into account of its release from bone) was about 150 hours. Renal clearance of tiludronic acid ranged between 0.5 and 0.9 L/hour. It was reported to be constant over time and not influenced by the dose.

pK profile of tiludronic acid in special populations : pK profiles of tiludronic acid were determined in elderly female (age 77 ± 4 years) and compared to young male (age 26 ± 1 years) subjects. There were no statistically significant differences between these groups for any pK parameters, except for AUC in elderly female subjects was found to be about 1.5 times that of young and elderly male subjects. In the North American pivotal efficacy study in Paget's disease of bone, a significant difference was noted in the plasma levels of tiludronic acid (about 2-fold difference in trough concentrations after a single 400 mg dose between subjects under and over 65 years of age). However, such a difference in plasma levels of tiludronic acid was not associated with clinically relevant effects.

Pediatric subjects: Tiludronate was not evaluated in subjects less than 18 years of age.

Gender difference : There was no difference with respect to the effects of tiludronate.

Racial difference : Racial differences in pK parameter were not studied.

Racial difference : Racial differences in pK parameter were not studied.

Renal insufficiency : Impairment of renal function could alter the elimination of tiludronic acid. In one study involving patients with severe impairment of renal function (creatinine clearance between 10-30 mL/min), administration of a single 400 mg dose of tiludronate resulted in increase of AUC (about 3-fold) and prolonged (up to 205 hours) elimination half-life, compared to normal healthy volunteers.

Hepatic insufficiency: Tiludronate was not evaluated in patients with hepatic insufficiency.

Drug Interaction: Sponsor has performed drug interaction studies with the following drugs:

- Maalox
- Digoxin
- Anti-inflammatory drugs (aspirin, diclofenac, and indomethacin)

Absorption of tiludronate was reported to decrease if taken within one hour of Maalox administration. If Maalox was given 2 hours after tiludronate, there was no effect on the absorption. Tiludronate did not show any effect on plasma levels of digoxin or its urinary excretion. Aspirin or diclofenac given 2 hours before or after tiludronate did not alter the "systemic exposure" ("exposure" is probably an error and it should be absorption) to tiludronate. Indomethacin given as pretreatment for 5 days before tiludronate or given together, resulted in increased absorption of tiludronate.

Sponsor's conclusion: The following pK properties of tiludronate have been highlighted:

- Low and variable absorption of tiludronate from the intestine.
- The drug was not metabolized in the body.
- Large part of a dose was taken up by the bone and eliminated very slowly from bone.
- The drug was primarily excreted in the urine.
- Primarily bound to serum proteins, mainly to albumin.
- Foods and Maalox decreased and indomethacin increased absorption of tiludronate.

- Renal clearance of tiludronate was markedly decreased in patients with severe impairment of renal clearance.

Reviewer's Comments: The overall kinetic profile of tiludronate disodium appears to be similar to that of other bisphosphonates (including alendronate). Bisphosphonates are poorly absorbed from the intestine. Absorption of bisphosphonates are markedly decreased if they are administered with meals, particularly in the presence of calcium and iron (due to formation of non-absorbable salts).

A large part (up to 60 %) of absorbed bisphosphonates is rapidly taken up by the bone and the remainder is excreted in the urine. There is no evidence so far that bisphosphonates are metabolized in humans.

The overall pK profile of tiludronic acid is similar to that of alendronate sodium (Fosamax). Patients with severe renal impairment (creatinine clearance of 10-30mL/min) may retain more tiludronic acid in the skeletal sites.

6.5 Relevant background information (meetings, commitments) : The following interactions took place between the Agency and the sponsor regarding developing Skelid for Paget's disease and other indications

- Pre-IND meeting - July 11, 1991.

Open-label continuation of treatment of Pagetic patients after completion of initial 12-week controlled trial was discussed. Agency agreed to the proposal of continuing Skelid treatment at a dose of 400 mg daily for additional 12 weeks.

- Sponsor had several discussions with the representative(s) of the Biopharm. Div. regarding change in formulation of Skelid for use in clinical trials.
- Sponsor had several discussions with the pharmacologist regarding preclinical carcinogenicity and reproductive tox. studies.
- IND submission -August 1, 1991.

Protocol submission for Paget's disease of bone.

- Protocol revisions and submission of a revised protocol-November 13, 1992.

- Sponsor agreed to provide additional data on the stability of drug products.
- Agency agreed that sponsor has conducted two adequate and well - controlled pivotal studies. Sponsor made it known that two studies were carried out using two different tablet formulations of the drug.
- The two formulations were different with respect to AUC and C_{max} , as such did not meet standard regulatory bioequivalency criteria.
- The results of pivotal clinical trials were to provide evidence for therapeutic equivalence of two tablet formulations in the target population.
- Agency agreed that efficacy and safety of Skelid in two studies were equivalent.
- Sponsor was informed by the Pharm. reviewer (Dr. McNerney) that Carcinogenicity Assessment Committee's recommendations would be considered for NDA filability.

6.6 Directions for use:

Proposed Information for Patients: " Patients receiving Skelid should be instructed to:

1. Take Skelid with 6 to 8 ounces of plain water at least 2 hours before or after eating.
2. Maintain adequate calcium and vitamin D intake.
3. Refrain from taking calcium supplements, antacids, or indomethacin within 2 hours of taking Skelid.

Reviewer's Comments : This section may require further revisions after completion of all reviews.

7. Description of Clinical Data Sources:

7.1 Study Type and Design/Patient Enumeration, Demographics, Extent of Exposure:

The following studies were listed to support the efficacy and safety of Skelid for the treatment of Paget's disease of bone:

- **Three controlled studies with 9O1 or 3C1 formulation..**
- **Uncontrolled pagetic studies with the 9O1 or 3C1 formulation (12 studies)**
- **Additional studies were carried out in pagetic and osteoporotic patients in the U.S., Europe and Japan.**

Three controlled clinical trials were to provide substantial evidence of safety and efficacy for Skelid in the treatment of Paget's disease of bone.

The relevant information on study type and design, population size, demographics, and extent of exposure are summarized in Table 4.

Table 4. Study design, patient population, demographics, and treatment duration of controlled Pagetic studies

Protocol No./Study Design	No. of Subjects	Dose of Skelid/Etidronate	Duration of Tx.
P 1845/D-B, R, Pl.-C..	139	200 or 400 mg/day*	12 Weeks + 12 F/U
P 1619/D-B,R,Pl.-C	112	200,400, or 600 mg/day**	12 Weeks +12 F/U
P 1552/D-B,R,A-C τ	234	400mg/day Skelid or 400 mg/day etidronate	1-3 Mo Skelid*** 4-6 Mo Placebo

* Skelid tablet formulation (9O1); ** Skelid tablet formulation 3C1; *** Skelid tablet formulation (3C1); τ three treatment groups: a) Skelid 3 mo + placebo 3mo, b) Skelid 6 mo, and c) etidronate 6 months.

Uncontrolled clinical studies: Twelve uncontrolled, open-label studies were listed. One international, one US/ Canada, and the rest were conducted in Belgium, France and Spain. In 10 of 12 studies, the tablet formulation (3C1) was used in a dose range of 400- 1200 mg/day for 1 day to 6 months. Higher doses (600-1200mg/day) of Skelid were used only in two of the 12 studies. Four of these studies included a small number of patients. All 12 studies were considered for safety purpose. Only five of the 12 studies were considered for efficacy of Skelid in the treatment of Paget's disease of bone.

Additional studies: These studies included healthy subjects, pagetic patients and with different formulations of Skelid. The results of these studies are primarily presented for safety of Skelid therapy.

7.2 Postmarketing experience: Sponsor states that the drug has been approved in recent years in other countries. There are not enough postmarketing clinical data to report.

7.3 Literature:

The sponsor has submitted literature reports on both Skelid and other antipagetic drugs (bisphosphonates and non-bisphosphonates) related to their use in the treatment of Paget's disease of bone. The reports on agents other than Skelid are summarized, and reports on Skelid are reviewed individually.

Adamson et. al. (Lancet 1993;342: 1459-60), reported mineralization defects (histomorphometric findings) in pagetic patients treated with iv pamidronate. Authors suggest a short course of pamidronate with caution.

Alexander et. al. (Metab. Bone Dis. & Rel. Dis. 1981: 4&5: 309-16), reported the effects of ethane hydroxy disphosphonate (EHDP) on quantitative bone histology in a group of pagetic patients. The new bone formed during EHDP treatment revealed normal lamellar texture. EHDP therapy also resulted in decreased marrow fibrosis and osteoclast count.

Altman, R.D. (Am J. Med. 1985; 79: 583-590), reported the results of a long-term follow-up of pagetic patients treated with intermittent EHDP. The author has discussed the types of responses expected in patients treated with a single course of EHDP and retreatment following recurrence. Large percentage of patients with relatively mild disease showed biochemical improvement as a result of a single course of treatment. Patients with a modest disease (based on baseline SAP and U/OHP values) required retreatment "less often than once a year." A small percentage of patients with severe disease clinically developed resistance to EHDP (5 mg/kg/day). In another follow-up study, Altman and Collins (Journal not cited) reported that about 40 percent of pagetic patients required a single course of EHDP, 34% required frequent retreatment and 26% of patients required infrequent retreatment.

Amor et. al. (The 21st Eur.Symp. Calcif. Tissue, March 1989), reported the preliminary results of a study with a new bisphosphonate (Skelid) in the treatment Paget's disease of bone (n= 77). Patients were treated with Skelid at a dose of 400 mg/day (5.9 ± 1 mg/kg/day) for 3 to 6 months. The results showed marked decrease in baseline SAP and U/OHP/Cr ratio, 3 and 6 months after treatment.

Biochemical improvement was associated with improvement in bone pain. The authors suggested that further studies are needed to determine the optimum dosage regimen.

Anderson et. al. (Seminars in Arthritis and Rheumatism 1994; 23: 273-75), reported the results of 4 clinical trials with iv pamidronate in the treatment of Paget's disease of bone. (**Comments:** Intravenous pamidronate is an approved drug for the treatment of Paget's disease of bone). The report suggests that some patients may require higher doses of pamidronate for eradication (radiographic) of most of pagetic sites in the body.

Arboleya et. al. (Rev. Clin. Esp 1993; 193:467-71), compared the biochemical effects and safety of iv infusions of pamidronate (30 mg/day for 3 days) and clodronate (300 mg/day for 3 days) in a small group of patients with Paget's disease of bone. Both drugs caused significant decrease in SAP and U/OHP. Both drugs were reported to be safe and effective for the treatment of patients with marked biochemical activity or resistant to conventional therapy. Side effects included slight fever. One patient treated with pamidronate developed thrombocytopenia (self limiting) 6 months after treatment.

Aldrin et. al. (The 21st Eur. Symp. Calcif. Tissue, Jerusalem, March 1989), in this report presented histomorphometric changes in bone biopsy materials obtained from 3 patients treated with Skelid for 6 months. Skelid therapy resulted in marked decrease in osteoclast activity (number of osteoclasts/mm²). Study of dynamic histomorphometric parameters showed no evidence of mineralization defects due to Skelid treatment.

Aldrin et. al. (Clin. Rheumatoll. 1989;1: 71-79): In an open non-randomized study, a group of patients (n=35) with Paget's disease of bone were treated with Skelid at doses of 5 or 11 mg/kg/day for 2-6 months. All of these patients had elevated SAP and U/OHP values at baseline. Eighty percent of patients experienced baseline bone pain. All patients had undergone bone scanning (Technetium ^{99m}m).

Skelid treatment resulted in an improvement of bone pain in about 70% of patients. Skelid treatment at two different doses resulted in significant decreases in both SAP and U/OHP/Cr ratio. About 11% and 40% of patients experienced normalization of SAP and U/OHP/Cr ratio respectively, after treatment. Patient who were refractory to previous treatment with EHDP and/or calcitonin were reported to respond well to Skelid. All patients were reported to show decrease in scintigraphic bone scan scores. Significant biochemical improvement was reported to last 3 months after stopping therapy. Other than mild abdominal discomfort (in 2 patients) for 2 hours after taking the medication, no other side

effects of Skelid were reported. (**Comments:** The study was not aimed to determine the ideal dose and duration of treatment of pagetic patients with Skelid).

Aldrin et. al. (11th Eur. Congr. Rheumatology Athens, Greece, June 1987), in this report presented the results of a 2- month treatment with Skelid (at dose of 200, 400 and 800 mg/day, p.o.) in a small group (n=22) of pagetic patients. The results indicated decrease in SAP and U/OHP/Cr ratio 2 months after Skelid therapy. The group of patients treated with 800 mg/day of Skelid (n=14) showed 54% and 20% reductions in SAP and U/OHP/Cr values respectively, 3 months after therapy. The study reported no side effects of Skelid treatment.

Aldrin and his associates reported therapeutic benefits of Skelid in several other brief reports. In one report (First Int. Symp. Paget's Dis. of Bone, Manchester, UK, August 1992), a group (n=5) of pagetic patients with radiological evidence of involvement of the skull was treated with Skelid (400 mg/day) for 6 months (one patient received treatment for 2 months). Three of 5 patients had typical osteoporosis circumscripta lesion of the skull and 2 had mixed lesions of resorption and formation. Skelid therapy was reported to cause improvement of skull lesions (i.e., increased radiodensity with moderate advance of the resorption front, improvement in "mottled" appearance, disappearance of parietal resorption areas, remineralization of pagetic lesions, and regression of osteoporosis circumscripta).

Bijvoet et. al. (Acta Orthop. Scand. 1974; 45: 926-34), reported delayed periarticular radiological appearance of ossification following treatment with EHDP in patients with total hip replacement. (**Comments:** EHDP is approved for the treatment of heterotopic ossification).

Body et. al. (3rd Int. Symp. Osteoporosis, Denmark, October 1990), tried Skelid therapy in the treatment of hypercalcemia of malignancy. The results were equivocal and the authors commented that Skelid was "not potent enough for treating cancer hypercalcemia and its potential nephrotoxicity will limit its intravenous use.."

Bounameaux et. al. (Lancet 1983; p.471), reported three cases of renal failure associated with iv bisphosphonates and report recommended slow infusion of bisphosphonate "in daily doses of no more than 1 g and renal function should be monitored."

Boyce et. al., (Lancet 1984; 821-24): A small group of pagetic patients were treated with EHDP. (**Comments:** This report has no direct bearing on the safety and efficacy of Skelid for the treatment of Paget's disease of bone).

Burckhardt, P. (Sem. Arthritis Rheumatol. 1994; 23: 237-39), discussed the role of biochemical markers and bone scintigraphy in the long-term assessment of response to therapy in patients with Paget's disease of bone.

Canfield et. al. (JCE & M 1977; 44: 96-106), reported a study with EHDP in the treatment of Paget's disease of bone. This report has no direct relation to safety and efficacy of Skelid.

Chappard et. al. (JBMR 1995; 10: 112-18): This is a prospective, randomized, placebo-controlled study of the effects of Skelid on bone loss in a small group of paraplegic patients. Patients with posttraumatic medullary lesion of the spinal cord (between C5 and T12) were recruited. They were randomly assigned to three treatment groups (200 and 400 mg/day Skelid and a placebo group). Patients with serum creatinine > 130 microm/L; proteinuria > 0.5 g/day; leukopenia ,3000 WBC/microL; Hgb < 80 g/L; thrombocytopenia 100,000/ microL; 5' nucleotidase > 20UI/L were excluded. Skelid was administered at doses of 200 and 400 mg/day. All patients received treatment for 3 months. Transiliac bone biopsies were performed before and after treatment. The results showed an insignificant decrease in bone volume in the placebo and 200 mg/day groups. Skelid 400mg/day group showed slight increase in bone volume. In all three treatment groups, osteoid parameters showed no significant changes. The number of osteoclast cells increased in the placebo group, decreased in both Skelid groups. Authors have commented that Skelid by virtue of its antiresorptive action could be effective in reducing bone loss in paraplegic patients. (Comments: This report has no direct bearing on the safety and efficacy of Skelid for the treatment of Paget's disease of bone).

Combe et. al. (Sanofi report): This report presented the results of Skelid therapy in a small open study involving 23 patients with Paget's disease of bone. Twenty of 23 patients were treated with EHDP and calcitonin prior to Skelid therapy. Patients were treated with Skelid at a dose of 400 mg (200mg B.I.D.) daily for 6 months. Changes in bone pain and biochemical parameters were evaluated after 3 and 6 months.

The results showed improvement in pain index and scores (on Huskisson scale) after 3 months of treatment. In 20 patients, SAP and U/OHP were reported to decrease 72% and 52% respectively, after 3 months of treatment. Nine of these patients who completed 6 months of treatment, showed further decrease in SAP and U/HOP. Two patients were reported to show no response to Skelid therapy. One patient was dropped from the study because of epigastric pain. Two additional patients were reported to discontinue the study due to recurrent conditions not related to Skelid. Biochemical effects observed after 3 months of treatment with Skelid (6 mg/kg/day) were similar to those reported in the

literature with EHDP at doses of 5 to 7 mg/kg /day.

Devogelaer et. al. (Calcif. Tissue Int. 1984; 44 (suppl), S: 104): In an open study, 20 patients with Paget's disease of bone were treated with Skelid 400 mg/day for 6 months. After 3 months of treatment, SAP decreased significantly from baseline (with 4.5 times the upper limit of normal). SAP further decreased (51% of the initial value) with continuation of therapy for 6 months, and remained at reduced level 6 months after discontinuation of Skelid therapy. Urinary OHP/Cr ratio dropped significantly during the course of treatment. Skelid was reported to be well tolerated in this study.

Devogelaer et. al. (Bone and Mineral 1994; 25: S 82): This is a double-blind active controlled study conducted in 12 patients with Paget's disease of bone. Baseline SAP was at least 2 times the upper limit of normal and all had radiological evidence of active disease. All patients received either EHDP or Skelid 400 mg/day orally for 6 months.

Both treatment groups showed similar decrease in SAP from baseline. X-ray films were examined in a blinded manner before and 6 months after treatment. The report indicates concordance between x-ray film reviewers with respect to changes in skeletal lesions. About "19 bones" were evaluated and prior to treatment, 3 had predominant lytic lesions, 4 had mixed (lytic and condensing) lesions, 9 had predominant condensing lesions, and 3 had "pure" condensing lesions. After 6 months of treatment with EHDP or Skelid, 7 bones were reported to appear denser, 5 showed questionable increase in density, 2 with questionable increased resorption and 2 with "frank resorption," and 3 bones showed no change. All of the negative "evolutions" were reported to be in patients of the EHDP group, and "all the positive evolutions" were in the Skelid group. One patient in the EHDP group experienced "symptomatic microfissures" of pagetic tibia.

Dewis et. al. (Ann.Rheumatic Dis. 1985; 44: 34-38): In an open trial the effects of EHDP (tablets, 20 mg/kg/day) and pamidronate (liquid dosage form, 4.5 mg/kg/day) treatment (for 3 months) of patients with Paget's disease of bone were compared. The results indicated improvement of bone pain, decrease in SAP and U/OHP as a result of treatment with either drug. The remission was reported to last for about 12 months. The purpose of this report was to suggest that a short course of EHDP at the above dose was more effective than a longer treatment with low dose. The study showed no significant advantages of pamidronate over EHDP.

Dodd et. al. (Br. J. Radiol. 1987; 60: 849-60): Serial x-ray films with 57 lytic pagetic bones (from 54 patients treated with EHDP) and 20 lesions from 20

patients treated with pamidronate were examined to assess the treatment effects. Mainly the skull and tibial lesions were evaluated because accurate positioning of these sites was easily achieved.

In the EHDP treated group, both healing and deterioration of lytic lesions were reported. Of 26 total lytic lesions of the skull, 13 lesions showed deterioration, 5 showed healing, and 8 lesions showed no change. Ten of 18 tibial lesions showed deterioration and only 5 showed healing. The overall results showed deterioration in slightly more than 50% of all lesions.

In the pamidronate treated group, 17 of 20 patients showed partial or complete healing of lytic lesions. The lytic wedges were healed by different ways; either by "filling in," or by changing the direction of progression of lesions. In one patient there was definite deterioration of lytic tibial lesion.

The report suggests that changes in biochemical indices to therapy may not always reflect changes in skeletal lesions. There are also discrepancies between scintigraphic and radiological changes to antipagetic therapy.

Dumon et. al. (Bone and Mineral 1991; 15: 257-66): This is a dose-ranging study of iv tiludronate in a group of patients with hypercalcemia of malignancy. The authors of this report suggest that compared to pamidronate, "tiludronate is not indicated for treatment of tumor-associated hypercalcemia because of the need for high iv doses which are potentially nephrotoxic."

Reviewer's comments on literature reports:

Tiludronate (Skelid) is a new bisphosphonate. In recent years, the drug has been approved for either in the treatment of Paget's disease of bone or postmenopausal osteoporosis in some countries. Therefore, the overall clinical experience with this drug is limited.

Most of literature reports on the use of bisphosphonates for the treatment of Paget's disease of bone dealt with etidronate, clodronate, and pamidronate. Based on the results of preclinical studies with tiludronate, and clinical experiences with approved bisphosphonates, one can reasonably predict the probable therapeutic benefits of tiludronate for the treatment of Paget's disease of bone. Qualitatively its effects on biochemical indices of Paget's disease of bone appear to be similar to those of approved bisphosphonates (e.g., etidronate, pamidronate, and alendronate), but it may differ from those drugs with respect to potency and adverse effects.

Open trials of Aldrin and his associates and controlled trial by Devogelaer et.

al., with tiludronate are relevant to this NDA. The results of open trials showed biochemical, clinical (bone pain), scintigraphic, radiological, and histomorphometric improvements in pagetic patients with mild to moderate severity. In these studies Skelid was administered in a dose range of 200-400 mg/day (5-11 mg/kg/day) for 2-6 months. When the treatment was stopped, biochemical improvement was reported to be sustained for 6-18 months in some patients.

In the controlled study (Devogelaer et. al.), 12 patients with mild to moderate Paget's disease of bone were treated with EHDP (400 mg/day) or tiludronate (400 mg/day) for 6 months. When the effects of study drugs on biochemical indices and skeletal lesions were compared, biochemical improvement was reported to be similar in both treatment groups with respect to serum calcium, SAP, and U/Ca/Cr ratio. After 6 months of treatment with tiludronate, skeletal lesions showed "positive evolutions." Whereas, patients treated with EHDP were reported to show "clear-cut worsening" of bone lesions. One patient in this group developed symptomatic microfissure of the tibia.

Data presented in these small studies with tiludronate need to be confirmed by adequate well-controlled trials.

8. Clinical Studies

8.1 Trial # 1 (Protocol # P 1845 /Study report 1373)

8.1.1 Objective and rationale: Primary objective was to determine the efficacy (in terms of biochemical improvement) and safety of Skelid for the treatment of patients with Paget's disease of bone.

Skelid belongs to the same class of compounds known as bisphosphonates. These drugs are known to inhibit bone resorption in vitro and in vivo tests. Bisphosphonates, like etidronate (po), pamidronate (iv) and alendronate (po) are approved for the treatment of patients with Paget's disease of bone. Investigational bisphosphonates (including Skelid) by virtue of their antiresorptive action, are likely to be clinically effective in diseases with increased bone resorption, especially Paget's disease of bone.

8.1.2 Design: Multicenter, randomized, double-blind, placebo-controlled study.

8.1.3 Protocol

8.1.3.1 Investigators: There were 22 investigators of this

controlled study; all but one were located in the United States. One investigator (Dr. Sturtridge) was from Ontario, Canada. Michael R. McClung, M.D., of Center for Metabolic Bone Disorders was listed as the principal investigator of this study. All the investigators were qualified.

8.1.3.2 Population, procedure: One hundred forty Pagetic patients with scintigraphic demonstration of skeletal lesions and elevated levels of SAP (at least twice the upper normal value) were included in this study. The demographic characteristics of the patient population are summarized in Table 5.

Table 5. Demographic characteristics

Characteristics	Placebo N (%)	SKELID		Total
		200mg	400mg	
Gender				
Male	28 (58.3)	31 (68.9)	32 (69.6)	91 (65.5)
Female	20 (41.7)	14 (31.1)	14 (30.4)	48 (34.5)
Race				
Caucasian	41 (85.4)	41 (91.1)	44 (95.7)	126 (90.6)
Other	7 (14.6)	4 (8.9)	2 (4.3)	
Age	N=48	N=45		139*
Range	42-82	32-84	43-85	32-85

* One patient in the 400mg Skelid group withdrew before initiation of treatment.

Sponsor has listed the exclusion criteria that were followed in conducting this trial. **Comments:** Exclusion criteria were appropriate and satisfactory.

Patients were randomly assigned to one of three treatment groups according to a computer-generated randomization code.

Formulation 901 for Skelid tablets was used in this study. Placebo tablets were matched to Skelid formulation.

Skelid was administered at doses of 200 and 400 mg tablets. Treatment groups and dosing schedule for Skelid and placebo are shown Table 6.

Table 6. Treatment groups and dosing schedule.

Groups	Treatment	Procedure
Gr. 1	Placebo	Two placebo tablets at night
Gr.2	Skelid 200 mg	One 200mg Skelid tab. and one placebo tab. at night
Gr. 3	Skelid 400 mg	Two 200 mg Skelid tab. at night

Skelid doses (200 or 400 mg/day) were selected on the basis of the results of preliminary open and controlled studies earlier reviewed in this document All patients received study drugs for 12 weeks.

The study drugs (Skelid or Placebo) were taken with at least 8 ounces of water, fruit juice (without calcium supplementation), or black coffee, at least 2 hours after taking any food and at least one-half hour before retiring. Calcium intake (i.e., milk, yogurt, cheese, fruit juice with calcium supplementation, antacids) was avoided during the time periods of study drug administration.

If a patient received a drug with significant effects on skeletal metabolism (e.g., another bisphosphonate, calcitonin, gallium nitrate, and glucocorticoids) during treatment phase of the study, that subject was discontinued from the study. Patients were advised to maintain a constant dose of pain medications during the treatment phase, if it was allowed by the protocol.

Screening and baseline investigations included medical history, PE, blood and urine chemistries, hematology, fecal occult blood, bone scan (only during screening), radiologic survey, pain scale (using visual analog scale of Huskisson), and **optional** assessment of hearing, cardiac output, skin temperature over long pagetic bones, upper G-I endoscopy, and neural deficits.

Baseline Visits occurred within 30 days after screening.
The study was divided into Treatment Phase (Visits/Week

2, 4, 8, and 12) and Observation Phase (Visits/Week 16, 20 and 24).

8.1.3.3 Endpoints

Efficacy- Primary efficacy endpoint of the study was the percent change (from baseline) in SAP at the end of treatment phase (Week 12). **Secondary** efficacy endpoints of the study were :

- Percent of patients with 50% reduction in elevated baseline SAP as a result of therapy.
- Percent of patients with normalization of SAP.
- Percent change (from baseline) in U/OHP/Cr ratio as a result of treatment.
- Percent of patients who required intervention with other antipagetic agent(s).
- Improvement in pagetic pain (assessed by using visual analog scale and by the requirement of analgesics).
- Radiological improvement of pagetic bone (skull and long bones) lesions.

Reviewer's comments on the appropriateness of the endpoints:

It is known that Paget's disease of bone is characterized by localized increased bone resorption (osteoclast-mediated) and compensatory increased bone formation. Increased bone turnover leads to formation of disorganized new bone.

Clinical laboratory abnormalities were reported to correlate well with the extent of skeletal involvement. In pagetic patients, both SAP and U/OHP are markedly increased. The primary objective of pharmacologic management of Paget's disease of bone is to reduce these elevated markers of bone turnover to normal or near normal. Biochemical remission of the disease process is associated with relief of symptoms in a majority of patients. Suppression of elevated indices of bone turnover to within normal range for approved bisphosphonates like pamidronate and alendronate was shown to revert abnormal histomorphometric parameters of bone remodeling to normal.

Suppression of elevated biochemical indices (i.e., SAP and U/OHP) of bone turnover was the primary/secondary endpoints of clinical trials for all antipagetic agents (salmon and human

calcitonin, and the bisphosphonates like etidronate, pamidronate, and alendronate) previously approved by this Agency.

The proposed primary and secondary efficacy endpoints of this study are appropriate. IND protocol for this study was previously reviewed and deemed appropriate.

Safety parameters- Safety of SKELID therapy was evaluated by monitoring the following parameters:

- Medical history
- Adverse events
- Vital signs
- Clinical laboratory data
- Bone biopsy in "qualified" subjects
- Fecal occult blood
- Endoscopic examination of upper G-I tract

Pharmacokinetic parameters- Additionally, in this study the sponsor has collected blood samples at baseline and at Visits 2, 4, 8, 12, 16, 20, and 24 for analysis of plasma levels of tiludronate.

8.1.3.4 Statistical considerations: For description of various statistical models utilized in the data analyses see statistical review. All efficacy and safety analyses were performed using Intent-to-treat and evaluable patient populations.

Sample size of 35 patients per treatment group was calculated to provide a power > 0.90 at a significance level of 0.05 to detect a 40% difference (between active and placebo groups) in response rates of treatment success.

Statistical analyses were performed with respect to:

- Demographic differences between two treatment groups
- Primary efficacy endpoints (SAP)- 12-week data and data with "last observation carried forward." Treatment- by- center interaction and overall treatment comparisons.
- Secondary efficacy endpoints- Incidence of treatment success, subjects with at least 50% decrease from baseline in SAP. Number of subjects with normalization of SAP as a result of therapy.

Treatment effects on U/OHP, pagetic pain, changes in the requirement of pain medication, and radiographic improvement in skeletal lesions.

· Exploratory efficacy endpoints - Exploratory efficacy endpoints included bone specific SAP and urinary pyridinoline cross links /Cr ratio. Same statistical methods were used to analyze these variables.

Safety variables - All safety variables, e.g., adverse events, clinical lab. values, vital signs were subjected to routine statistical methods. Histomorphometric data from iliac crest bone biopsy of non-pagetic sites were similarly analyzed.

8.1.4 RESULTS

Efficacy results

8.1.4.1 Patient disposition and comparability

Of a total 140 subjects randomized to three treatment groups. 139 subjects were included in ITT analysis. One subject in 400 mg Skelid group withdrew from the study prior to initiation of therapy. Of 139 patients, 137 patients (98%) were reported to complete the treatment phase of the study. A total of 134 patients (96%) completed both treatment and follow-up phases of the study. Patient disposition is summarized in Table 7.

Table 7. Summary of patient disposition

Subjects	Placebo N (%)	SKELID		Total
		200mg	400mg	
ITT	48*	45 (100)*	47 (100)*	140 (100)*
Completed 12 weeks Tx Phase	46 (96)	"	46 (98)	137 (99)
Completed 24 Wk.	45 (94)	44(98)	45 (96)	134 (96)
Evaluable Pt.	39 (81)	42 (93)	44 (94)	125 (89)
Completed 12 weeks Tx Phase	39(81)	42 (93)	44 (94)	125 (89)
Completed 24 Wk.	39 (89)	"	"	125 (89)
Not Evaluable**	9 (19)	3 (2)	2 (4)	14 (10)

* These patients were actually randomized to receive the study drugs. Total number of patients for the ITT group was 139.

** Some of these patients completed 12-week treatment and 12-week observation phase.

Four patients in the placebo and one each in 200 and 400 mg Skelid groups were discontinued from the study. Only 3 patients in the placebo group were discontinued from the study due to an adverse event.

Protocol deviations: Eight subjects (17% to 18%) in each treatment group were reported to have one or more protocol deviations. The common protocol deviation was abnormal laboratory values at entry into the study. Six subjects entered into the study with SAP level not at least twice the upper limit of normal. Few subject in

each group had protocol deviations relative to exclusion criteria (lab. values deviated significantly from the reference range or subjects receiving "gastrotoxic medications" or with a history of drug-related allergy). Three subjects (2 in the placebo group and 1 in the 400 mg Skelid group) were considered nonevaluable for efficacy; in the placebo group, one patient had baseline serum calcium value of 11.6 mg/dL and the other received less than 80% of the study drug. The patient in the Skelid group had low baseline serum calcium (8.3 mg/dL)

Reviewer's comments: There was no consistent pattern for protocol deviations in any treatment group that could have influenced the outcome of active treatment regimen. In ITT analysis, all but three patients were included.

Permanent stoppage of study drug therapy and/or the study: Four patients in the placebo group were permanently dropped from the study; three due to adverse events and one due to personal reason. The adverse events included diarrhea, arrhythmia and dyspepsia. One of three patients stopped the study drug, but completed all 24 study Visits. Two patients in the Skelid group completed the study drug, but were discontinued from the study during the follow-up phase. The investigational sites at which these two patients were enrolled were closed by the sponsor.

Prior medical histories and diagnoses : These are summarized in Table 8.

Table 8. Prior medical histories and diagnoses of study population.

Med. Hist. and Diagnoses	No. of Pt.*	Percent of Pt.
Musculoskeletal	105/139	76
Gastrointestinal	87/139	63
Ear/eye/nose/throat	72/139	52
C.V. System	72/139	52
Sensitivity to Med.	41/139	29
One or More Fractures	61/136	44
Abnormal Phys. Findings		
Musc.-Sk. Syst.	61/137	45
Rectum	11/34	32
Eyes	41/136	30
Ear/Nose/Throat	34/137	25
Skin	33/136	24
CVSyst.	21/137	15
Common Sites of Sk.Lesions		
Pelvis	107/108	91
Spine (Lumbar)	50/82	61
Skull	48/79	61
Rt. Lower Limb	44/75	59
Lt. Lower Limb	42/73	58
Lt. Upper Limb	22/57	39
Spine (Thoracic)	39/72	54

Sponsor states that there was no clinically significant differences between three treatment groups with respect to prior medical histories/diagnoses (Appendices 2.4.1 through 2.4.10 of this submission vol. 194, pp.326-349). **More than 50% of enrolled patients had polyostotic Paget's disease of bone.** No attempt was made to stratify patients according to number of pagetic lesions.

Prior medications: Review of the list of medications used before baseline showed no clinically significant differences between three treatment groups. Similar percentages (85% to 96%) of patients in the placebo and active treatment groups used medications prior to baseline.

Baseline efficacy data: Baseline efficacy measurements included SAP, U/OHP/Cr, pagetic pain score, SAP (bone isoenzyme), and U/pyridinoline cross links. Table 9 summaries the baseline efficacy values.

Table 9. Baseline efficacy measurements for all patients.

Parameters	Placebo	SKELID(mg)		Total
		200	400	
SAP (IU/L)	N=48	N=45	N=46	N=139
Median	394.5	404	324.5	372
Mean (SD)	611.8 (627)	542.4(429.9)	418.6	525.4 (466.6)
Range	210-4004	205-2476	(237.4) 199-1237	199-4004
U/OHP/Cr (mmol/mol)	N=48	N=45	N=46	N=139
Median	88	88.8	77.4	82.3
Mean (SD)	114.9(85.7)	127.7(176.1)	86.1	109.5(116.2)
Range	15.3-507	38.9- 1195.5	14.7- 218.5	14.5-1195.5
Pagetic Pain Scores	N=48	N=45	N=46	N=139
Median	2.9	3.4	2.6	3.2
Mean (SD)	3.3 (2.9)	4 (3.2)	3.2(2.8)	3.5 (3.0)
Range	0.10	0-10	0-9.3	0-10
SAP Bone Isoenz (IU/L)	N=47	N=45	N=46	N=138
Median	299	321	266.6	298
Mean(SD)	464 (539.1)	464.6(388.3)	351	426.5(404.7)
Range	31-3585	143-2195	(212.6) 155- 1098	31-3585
U.Pyridinoline/Cr Ratio (pmol/ μ mol)	N=46	N=42	N=44	N=132
Median	631.5	507	414.5	484
Mean (SD)	831.4(625.2)	647.4(424.0)	540.7(455.1)	675.9(522.9))
Range	98-2449	166-2123	89-2655	89-2655

Compliance : Based on the number of tablets consumed, compliance was to the extent of 95% and 99%, in the placebo and Skelid groups, respectively.

Intent-to-Treat analysis of data (ITT)

A total number of 139 randomized patients were included in the ITT analysis. Ninety-two percent, 98% and 100% of patients completed 1-12 weeks of treatment in the placebo, 200 and 400 mg Skelid doses, respectively. Between 90% and 96% of treated patients took 81-84 doses of the study drugs (placebo or Skelid).

Concomitant medications: Ninety-eight to 100% of patients in three treatment groups received one or more concomitant medications during the course of the study. The use of concomitant medications was distributed evenly among three treatment groups, except for the following: lipid lowering drugs, antibiotics, and chemotherapeutics, dermatologics, and cold and cough medications. "Alimentary tract and metabolism preparations" were the most common drugs used by both treatment groups (75% of patients).

8.1.4.2 Primary efficacy endpoint (ITT analysis):

Serum alkaline phosphatase (SAP)

The mean and median percentage changes in SAP are presented in Table 10.

Table 10. Mean and Median percent changes from base line in SAP (IU/L).

Treatment group	Number of Patients	% change	
		Mean (SD)	Median
Placebo	48	NA	
Baseline			
Week 12	44	0.5 (11.6)	0.1
Week 24	45	5.1 (15.0)	1.9
Skelid 200 mg			
Week 12	45	-45 (15.3)*	-48.2
Week 24	44	-46 (22.3)*	-51.9
Skelid 400			
Week 12	46	-50.8 (15.6)*	-53.2
Week 24	46	-57.9 (16.8)**	-61.2

* $p < 0.001$. Pairwise comparison with the placebo group showed significant differences ($p < 0.05$) between the placebo and each of two treatment groups.

In both active treatment groups there were significant decreases from baseline in SAP at Weeks 12 and 24. However, between two active groups there were no significant difference in the decreases in SAP.

With respect to significance of decrease in SAP at Visits 2 through 24, the p value for the overall treatment comparison from Week 4 through 24 was, 0.001. With respect to pairwise comparison (placebo vs 200 mg, placebo vs 400 mg, and 200 vs 400 mg (the p value was < 0.05 from Week through Week 24). Compared to 200 mg dose, 400 mg dose caused greater percent decreases in mean SAP at Weeks 4, 8, 16, and 20. ($p < 0.05$). See Fig. 8.2.5.1A (NDA vol.1.194, p. 82)

There was no significant treatment-by-center interaction at baseline for the actual SAP values or changes in SAP at any other Visits.

Further, data were analyzed for missing data at Week 12. With the last value carried over method, the results were similar to those

without replacement.

Study of the relationship (displacement) between the plasma levels of tiludronate (as a function of dose) and mean percent decrease in SAP showed a temporal relationship. However, changes in baseline SAP were noted over relatively wide range of plasma tiludronate, and maximum decrease in SAP was maintained after treatment at plasma levels near or below assay limit.

Treatment-by-demographic characteristics interaction- Mean percent changes from baseline in SAP were further analyzed with respect to gender, race, age, weight, BSA (body surface area), and BMI. There was no difference between male and female with respect to response to Skelid therapy on SAP changes from baseline. For all other demographic characteristics, there were no statistically significant treatment interactions.

8.1.4.3 Secondary endpoints ITT analyses

Distribution of response and treatment success (at least a 50% decrease from baseline in SAP) - The incidence of treatment success is presented in Table 11.

Table 11. The incidence of treatment success for ITT subjects.

Visits	Skelid 200 mg N=45	Skelid 400mg N=46(%)	p-Values
Week 12	19 (42)	28 (61)	<0.001
Week 24	23 (51)	33 (72)	<0.001

Statistically significant percent of patients showed 50%- \geq 75% decreases from baseline in SAP at 200 and 400 Skelid doses at Week 12. At Week 24, the treatment successes were 51% and 72% of patients at 200 and 400 mg doses, respectively with similar statistical significance. At Week 12, the difference between two doses was not statistically significant ($p=0.075$). However, at Week 24, the difference between two treatment doses with respect to the incidence of treatment success was statistically significant ($p=$

0.043). At Week 4, there was no statistically significant difference in the overall incidence of treatment success in any of three groups. See table 8.2.6.1C, vol. 1.194, p.92. Significant differences were observed at Weeks 8, 16, and 20 in the overall comparison. The differences between 200 and 400 mg doses of Skelid were variable at same visits.

Number of subjects with SAP returned within the reference range as a result of Skelid treatment-

Reference values for SAP:

Sex	Age Range	Reference Range (IU/L)
Female and Male	20-999	31-115

At Week 12, in 7% and 20% of patients with elevated SAP returned to within reference range at 200 and 400 mg doses, respectively. At Week 24, a larger percentage of patients (35%) at 400 mg dose achieved the same response. Compared to the placebo, the 400 mg group showed a significant difference ($p=0.001$). The differences between placebo and 200 mg group and between 200 and 400 mg groups were not statistically significant at Week 12. Up until Week 8, no subject showed return of elevated SAP levels to within the reference range.

Urinary hydroxyproline/creatinine ratio (U/OHP/Cr)- Reference range 6.02-18.05 mmol/mol for all ages).

The results are summarized in Table 12.

Table 12. Mean percent changes from baseline in U/OHP/Cr ratio in ITT subjects (See also sponsor's Table 8.2.6.3A, vol.1.194, p. 95)

Treat.Gr./Visits	No. of Subjects	Mean % Change (SD) /Median	p-Value
Skelid 200 mg			
Week 12*	44	-37.6 (28.5)/-39.9	< 0.001
Week 24*	44	-30.9 (48.2)/-43.9	<0.001
Skelid 400 mg			
Week 12**	46	-52.6 (22.9)/-57.2	<0.001
Week 24**	45	-40.4 (41.1)/-53.8	<0.001

*Baseline mean (SD) =126.9 (178.0) mmol/mol at Week 12

Baseline mean (SD) = 129.7 (177.6) mmol/mol at Week 24

** Baseline mean (SD) at Week 12= 86.1 (50.2) at Week 12

Baseline mean (SD) at Week 24= 84.0 (48.6) at Week 24

Skelid therapy at doses of 200 and 400 mg/day for 12 weeks resulted in significant decreases in the urinary excretion of hydroxyproline (a marker of bone resorption). Both overall (changes from baseline) and pairwise comparisons (between placebo and each of two treatment groups) were statistically significant. The onset of decrease in U/OHP excretion was seen at Week 2 ($p < 0.005$) and significant decrease in U/OHP excretion was maintained during the entire course of observation over 24 weeks. There were no significant differences between 200 and 400 mg groups with respect to decrease in U/OHP excretion as a result of Skelid therapy for 12 weeks (See also Table 8.2.6.3B, vol. 1.194, p. 96 for p values).

Treatment intervention- No treatment intervention by other agents or therapies was reported during the course of the study.

Changes in Pagetic pain scores- There were no significant differences between the placebo and two Skelid groups with respect to the mean changes from baseline in Pagetic pain scores at any Visits. However, the placebo and Skelid treatment groups showed some difference with respect to the percentages of patients with "improved" or "worsened" pain scores (Table 13).

Table 13. Percent of patients with improved or worsened Pagetic pain scores.

Treatment Gr./Visits	No.(%) of Pt. Improved	No. (%) of Pt. Worsened
Placebo		
Week 12	24 (53)	17 (38)
Week 24	15 (33)	26 (58)
Skelid 200 mg		
Week 12	29 (64)	11 (24)
Week 24	27 (61)	12 (27)*
Skelid 400 mg		
Week 12	26 (58)	15 (33)
Week 24	24 (55)	17 (39)*

* P=0.01 for overall comparison; For pairwise comparison, p=0.004 for patients in 200 mg Skelid group.

Approximately, 7% to 11% of patients in all three treatment groups showed no change in pagetic pain to trial drugs. At 200 mg dose, Skelid seems to cause improvement in pagetic pain in significant proportion of patients over the study period.

Changes in demands for pain medication- Analgesics were the most frequently demanded drugs for pain and there were no statistically significant differences between three groups with regard to demand for analgesic drugs. In the placebo, 200 and 400 mg Skelid groups, 25% -30% of patients demanded pain medications.

Skull and long bone X-ray findings- Scintigraphy was performed in about 20 of 30 subjects who had predrug x-rays. In those 20 subjects, a total of 110 pagetic foci were detected, with an average 6 lesions per subject. The most commonly affected sites with pagetic involvements included pelvis (21%), spine (19%), femur (7%), humerus (11%), tibia (9%), skull (9%), scapula (7%), and other sites (less than 3%).

Of the 30 subjects who had x-rays, 29 (9 placebo, and 10 each in two Skelid groups) patients had radiological evidence of Paget's disease of bone. One patient had neither radiographic nor scintigraphic evidence of Paget's disease of bone. Radiographs were obtained in each subject at baseline, Weeks 12 and 24. In two subjects (one in placebo and one in Skelid group), radiographs for Week 12 were not available. All the radiographs were evaluated in a blinded manner. Filling in of "intracortical clefts or of the resorption" were considered as an evidence of healing. Extension of osteolytic lesions was considered as a sign of disease progression. The results are summarized in Table 14.

Table 14. Summary of radiographic changes to placebo and Skelid therapy.

Treatment Gr./Visits	No. of Pt.	% of Pt. Improved	% of Pt. With No Change	% of Pt With Progression
Placebo	8			
Week 12		None	75 (N=6)	25 (N=2)
Week 24		None	88 (N=7)	12 (N=1)
Skelid 200 mg or 400mg	19			
Week 12		47 (N=9)	53 (N=10)	None
Week 24		56 (N=5)*	60 (N=6)**	40 (N=4)

* Five of nine patients who showed improvement at Week 12 continued to improve over the observation period.

** Six of 10 patients with no change at Week 12 continued to show

no change and 4 showed disease progression.

Sponsor states that among 10 patients with no change in the Skelid group, the "level of confidence for the assessment for 4 subjects was poor." Even after excluding these 4 subjects from the evaluation, the association between Skelid treatment and radiological improvement in pagetic bone lesions was statistically significant ($p=0.004$). A dose-response trend was also reported with respect to radiological improvement of skeletal lesions; of 10 patients assigned to Skelid 400 mg, 6 (60%) showed improvement compared to 3 of 9 patients (33%) in the Skelid 200 mg group. When 4 patients with poor level of confidence were excluded from this evaluation, the difference in proportion of patients with radiological improvement between 200 and 400 mg groups becomes greater (86% vs 38%). Five of nine patients with improvement in the combined Skelid group were reported to show continued improvement at Week 24. Of 10 patients in the combined Skelid group who had no change in skeletal radiographs at Week 12, six continued to show no change at Week 24, but 4 showed disease progression. The sponsor claims that the association between 12 weeks of Skelid therapy and radiological improvement of skeletal lesions at Week 24 was statistically significant (to check with our statistician).

Scintigrams (at screening or at baseline) were performed in about 27 patients. Not all patients had pre and posttreatment scintigraphic scans. Sponsor has submitted only the case reports in an amendment to NDA. Review of these case reports showed some improvement in the bone scintigram after tiludronate therapy in 8 cases. Majority of these patients showed no change to therapy. A few cases showed progression at Week 12 and/or Week 24. The overall scintigraphic data are limited for any conclusion.

Alkaline phosphatase (bone specific)- The results are summarized in Table 15.

Table 15. Mean and median percent changes (from baseline) in bone specific alkaline phosphatase-ITT subjects.

Treatment Gr./Visits	No.of Patients	Results (IF/L) Mean (SD)/Median	p-Values
200 mg Skelid			
Week 12	45	-50.0 (16.8)/3.9	<0.001
Week 24	44	-54.0 (21.3)/-58	<0.001
400 mg Skelid			
Week 12	46	-54.4 (17.2)/-58.1	<0.001
Week 24	45	-63.7 (18.4)/-69.9	<0.001

The overall results are similar to those obtained with total serum alkaline phosphatase. Both overall and pairwise comparisons (with placebo) showed significant decreases after 12 and 24 weeks at two Skelid groups. The difference between 200 and 400 mg treatment groups was also statistically significant ($p < 0.05$).

Changes in urinary pyridinoline cross-links /creatinine (pmol/ μ mol-ITT subjects. The results are summarized in Table 16.

Table 16. Mean and median percent changes from baseline in urinary pyridinoline cross links/creatinine.(pmol/ μ mol) -ITT subjects.

Treatment Gr./Visits	No. of Patients	Mean (SD) Median	p-Values
200 mg Skelid			
Week 12	41	-52 (19.9)/-47.9	<0.001
Week 24	38	-46 (27.9)/-53.3	<0.001
400 mg Skelid			
Week 12	41	-71 (16.7)/-73.3	<0.001
Week 24	41	-66.5 (20.7)/-72.4	<0.001

Both at 200 and 400 mg doses there were significant decreases (from baseline) in urinary excretion of pyridinoline cross links at Week 12. Pairwise comparison also indicated significant differences between the placebo and each of two Skelid treatment groups ($p < 0.05$). The difference between 200 and 400 mg doses was also significant, indicating a greater response at higher dose. At Week 24, decreased levels of pyridinoline cross links remained suppressed significantly from the baseline and in comparison to the placebo group.

8.1.4.4 Efficacy for evaluable patients

Total number of evaluable subjects was 125. A total of 14 subjects (9 in the placebo, 3 in the 200 mg, and 2 in the 400mg groups) were excluded. The reasons for exclusion were: received less than 80% of the study drug (4 in placebo), abnormal baseline serum 25-OHD or calcium values (4 in placebo and 1 in 400 mg groups), study site closed (1 placebo and one each at 200 and 400 mg), subject received chemotherapy (1 in 200 mg group), 12-Week SAP value > 30 days before or after the scheduled visit (1 in 200 mg group).

Demography- There were no significant differences between three treatment groups with respect to demographic characteristics (similar to subjects for ITT analysis of efficacy data). Sixty-six percent of evaluable patient population were male.

The extent of exposure- One hundred percent of patients in three treatment groups received 11-12 weeks of treatment. The majority of subjects (114 of 125, 91%) received between 83 and 84 doses of study drug.

Concomitant medications- Similar to subjects for ITT analysis, for the evaluable patients the use of concomitant medications was comparably distributed among the three treatment groups.

Baseline efficacy data- There were no significant differences between three treatment groups with respect to baseline SAP, U/OHP, pagetic pain score, bone specific alk. phosphatase, and U/Pyr.

Analysis of primary endpoint (for evaluable patients)-

SAP- The results are summarized in Table 17.

Table 17. Mean and median percent changes from baseline in SAP (IU/L) (see also Table 8.3.6.1A, vol. 1,194, p.110)

Treat. Gr./Visits	No. of Patients.	Percent Change Mean (SD)/Median	p-Value
Placebo			
Week 12	38*	0.5 (12.1)/0.1	NA
Week 24	39	5.7 (15.7)/1.9	NA
200 mg Skelid			
Week 12	42	-44.9 (15.1)/-48.8	<0.001
Week 24	42	-45.7 (22.0)/-50.6	<0.001
400 mg Skelid			
Week 12	44	-50.8(15.9)/-53.2	<0.001
Week 24	44	-57.9(17.0)/-61.7	<0.001

The overall results are similar to those for ITT subjects.

8.1.4.5 Secondary endpoints

Treatment success (based on same definition used for ITT subjects)- The results similar to those observed for ITT subjects,

except for a significant difference ($p=0.026$) between 200 and 400 mg groups with respect to the incidence of treatment success.

SAP returned to within the reference range- Three of 39 patients (7.14%) in the 200 and 8 of 36 in the 400 mg groups achieved normalization of SAP at Week 12. Fifteen of 29 patients in the 400 mg group showed normalization of SAP as opposed to 3 of 39 in the 200 mg group at Week 24.

Urinary OHP/Cr excretion- In the evaluable patient population the results were similar to those for the ITT subjects with reference to percent changes from the baseline. However, the difference between the placebo and 200 mg dose group approached significance at $p=0.068$.

Treatment intervention- There was no incidence of treatment intervention during the course of the study.

Pagetic pain score- Changes from baseline in pagetic pain scores were similar to those for the ITT subjects. The number of subjects who experienced "improved" or "worsened" pain scores in three treatment groups are presented in Table 18.

Table 18. Pain scores "improved," worsened, and no change in evaluable subjects.

Treatment Gr./Visits	% Improved	% Worsened	% No Change
Placebo			
Week 12	51	39	10
Week 24	36*	54	10
200 mg Skelid			
Week 12	67	24	10
Week 24	62*	26	12
400 me Skelid			
Week 12	58	33	9
Week 24	54*	40	7

* Baseline vs Week 24 pain scores "improved" or "no change" $p=0.039$.

Proportion of patients with "improved" pain scores in the 200 mg group was significantly greater ($p=0.001$) compared to the placebo group. Among the treatment groups, no other overall comparisons were significant.

Difference in intake of pain medications- Analgesics were the most common medications demanded by the patients and 26%-27% of patients in all three treatment groups asked for analgesics for relief of pagetic pain.

Bone specific alk. phosphatase and Urinary pyridinoline cross links- The overall results with respect to changes due to Skelid treatment are quite similar to those described in ITT subjects.

8.1.4.6 Pharmacokinetic Results

The sponsor had developed the analytical method for determination of plasma concentration of tiludronate. Table 8.4.2A (vol. 1.194, p. 115) presents mean (SD) plasma levels ($\mu\text{g/mL}$) of tiludronate at baseline and at Week 2-24 in the three treatment groups. Because of the large degree of intra and inter subject variabilities in tiludronate plasma levels, the clinical significance with respect to efficacy is not clear. (See Biopharm review for more comments). The results indicate that a steady-state of plasma levels of tiludronate was achieved by four weeks of drug administration. There was no association between plasma levels of tiludronate and demographic characteristics (with the exception of age) of patients. Older subjects (≥ 65 years of age) manifested higher plasma levels of tiludronate compared to subject < 65 years of age at Weeks 4,8, and 12.

8.1.4.7 Safety results

Extent of exposure- There were no significant differences between placebo and Skelid groups with regard to maximum subject years of study drug (0.23 for all groups) and sum of all subject years (minimum plus max. subject years) were 10.49, 10.26, and 10.44 years, respectively for the placebo, 200 and 400 mg groups.

Adverse events (AEs)- The percentage of subjects reporting one or more AEs are summarized in Table 19.

Table 19. Number and severity of AEs.

Severity of AE	Placebo N=48	200 mg Skelid N=45	400 mg Skelid N=46
	Total No. 136	Total No. 137	Total No. 102
Mild	76	84	67
Moderate	50	49	31
Severe	10	4	4

Ninety percent of patients in the placebo and 87% of patients in the combined Skelid group experienced one or more AEs. A total of **19 severe AEs** were reported to be associated with 9 different body systems including CNS, endocrine, G-I, musculo-skeletal, and respiratory systems. Significantly more patients in the placebo group were reported to experience skeletal pain (6 %) and headache (19%) compared to 0% and 7% of patients in the combined Skelid groups.

By body systems (14 listed in Table 8.5.2.1B, vol. 1.194, pp. 122-123), there were no significant differences between placebo and Skelid groups with regard to reports of AEs that occurred in at least 5% of subjects.

Analysis of G-I AEs by demographic characteristics (gender, age, body weight, body surface area, body mass index) showed no association between G-I events and any specific characteristics.

AEs by relationship to study drug - Study drug relationship was classified by the investigators unlikely, unknown, or likely. A total of 70, 82, and 55 drug-related AEs were reported in the placebo, 200 and 400 mg Skelid groups, respectively. In general, there were no clinically significant differences among three treatment groups with regard to percentage of subjects with drug-related AEs. (Table 20).

Table 20. Summary of AEs related to study drug.

Adverse Events	Relationship to Study Drug			
	No	Unlikely	Unkn- own	Likely
<u>Placebo Gr</u> Any Event.	66	52	17	1
Dyspepsia	2	1	2	1
<u>200 mg Skelid</u> Any Event	55	43	30	9
Hyperparathyroidism	-	-	1	1
Dyspepsia	-	1	1	1
Flatulence	-	-	-	1
Nausea	-	-	2	3
Vomiting	-	-	2	2
Anorexia	-	-	-	1
<u>400 mg Skelid</u> Any Event	47	30	21	4
Hyperparathyroidim	-	-	-	2
Nausea	-	-	3	1
Rash	-	1	-	1

There were a total of 13 likely drug-related AEs in the combined 200 and 400 mg Skelid groups compared to 1 in the placebo group. Except for flatulence and anorexia in 200mg Skelid group and hyperparathyroidism in 400 mg group, same AEs occurred as "unlikely" or "unknown."

Reviewer's comments: Because of relatively small number of patients involved in this study, these data on drug-related AEs seem inadequate to draw any definitive conclusion. Postmarketing clinical experience will probably provide adequate information for labeling revision if needed.

Deaths - During the course of 24 weeks of the study, there were no deaths. One patient in the 400 mg Skelid group was reported to die 3 and ½ months after completion of the follow-up period (see Serious AE for details about this patient) .

Serious AEs - Three subjects in the placebo and 2 in 200 mg

Skelid groups, respectively experienced serious AEs. No serious AEs were reported in the 400 mg Skelid group.

**Narrative descriptions of serious AEs-
Placebo group-**

Hematuria (subject # 001-0013)- An eighty-one- year-old male patient with a previous history of a renal cyst and hypertension experienced hematuria. Hematuria started at Day 47 of the study. The subject recovered on Day 118 after a brief stay in the hospital. The event was not considered to be trial drug related.

Congenital bilateral inguinal hernia (subject # 008-0001)- A seventy-seven-year-old male patient with a history of bilateral inguinal hernia required hospitalization for surgical repair of hernia. This event had no relation to study drug.

Cardiac arrhythmias (Subject # 009-0006) - A seventy-four-year-old male patient required hospitalization for cardiac arrhythmias on Day 54 of the study. Patient recovered from cardiac arrhythmias after treatment with coronary vasodilators. Patient dropped out of the study. There seem to be no relation between arrhythmias and placebo.

Skelid 200 mg

Experienced a fall, hypertension and cardiac failure (subject # 008-0026)- A seventy-six-year-old male subject experienced accidental fall and suffered broken ribs on Day 81 of the study. Patient was hospitalized for the fall and during hospital stay, he was diagnosed to have hypertension and cardiac failure. He was treated with antihypertensive and diuretic (furosemide) agents. Patient was discharged from the hospital on day 90 and discontinued from the study. AEs (broken ribs, hypertension, and cardiac failure) were considered not related to study drug.

Death following detection of carcinoma of the lung (subject # 010-0001)- A sixty-two-year-old male patient was diagnosed (confirmed by x-ray, CT scan, and needle biopsy) to have lung (apical) carcinoma on day 94. The subject had a history of tobacco smoking and exposure to asbestos. Subject was treated with antineoplastic drugs followed by surgical resection of the lesion. The patient received the study drug for 11 days prior to the onset of

AEs. The patient died subsequently about 3 and ½ months after completing the follow-up period. The investigator considered the AE as having no relationship to study drug.

Discontinuations from the study- Only two subjects from the placebo group were discontinued from the study. One patient experienced diarrhea and "abnormal micturition frequency" which led to discontinuation. The other patient developed dyspepsia, but completed all study visits and then discontinued. No patient in the Skelid groups was discontinued from the study due to AE.

Discontinuations due to reasons other than AEs- One patient in the placebo group stopped taking study drug after elevation of SAP level (independently tested). One patient each in 200 mg and 400 mg Skelid groups discontinued the study because of closure of study sites. One additional patient in 400 mg Skelid group voluntarily withdrew her consent and declined to participate.

Clinical Laboratory abnormalities-

Serum chemistry -

Calcium (Reference range 8.4-10.3 mg/dL)- In all three groups of the study, serum calcium levels decreased significantly (from baseline) at some visits over 24 weeks. Greater decreases were seen in the placebo group at 16, 20, and 24 Weeks. At Weeks 2 and 8, the 400mg group showed significantly greater decreases compared to 200 mg group. Compared to the placebo group, the 400 mg group showed significant decrease at Week 8. With 200 mg dose of Skelid, decreases in serum calcium levels were relatively small. Though decreases were statistically significant in 400 mg Skelid dose at Weeks 2 and 8, the mean serum calcium level never reached below the lower limit of the reference range.

Serum intact PTH (Reference range 10-65 pg/mL) - Serum intact PTH (iPTH) levels were determined at baseline, and at Weeks 12 and 24. Significant mean increases in iPTH (from baseline) were reported in 200 mg group at Weeks 12 and 24, and at Week 12 in the 400 mg group. Pairwise comparisons also showed significant differences at some Visits, both for the 200 and 400 mg groups when compared to the placebo group. Though significant increases in iPTH were seen in both 200 and 400 mg doses, the upper limit of the mean values never exceeded the upper limit of the reference

range.

Reviewer's comments: Changes in serum calcium in Skelid groups can be attributed to the pharmacological actions of the drug. Increases in iPTH are related to decreases in serum calcium levels. However, in both cases (calcium and iPTH), the mean values were always within the reference ranges. Clinical significance of changes in serum calcium and iPTH is minimal with respect to the safety of tiludronate.

Changes in other serum chemistry parameters - Serum levels of AST, creatinine, bicarbonate, sodium, phosphorus, total protein, and uric acid showed significant mean decrease or increase in all three treatment groups. None of these changes were considered "clinically relevant" by the sponsor. At some visits, serum creatinine level increased in the placebo, 200 mg or 400 mg Skelid groups. Inter group differences were not significant at no time points.

Hematology -The data on hematological parameters (i.e., RBC, WBC, hemoglobin, hematocrit, basophils, lymphocytes, monocytes, platelets, and neutrophils) are presented in a series of Scatterplots of posttreatment versus baseline values (Appendix 6.2.11, vol. 1, 198, pp. 409-429). Review of these Scatterplots reveals no clear indications of any possible or probable adverse effect of Skelid on hemopoiesis. The sponsor claims that none of the changes observed in these parameters due to study drugs were "clinically relevant." Nevertheless, statistically significant mean decreases in neutrophils and WBC were reported in 400 mg Skelid group at several visits. In the placebo group, statistically significant decreases in neutrophils were reported at one visit.

Reviewer's Comments: The overall data accrued from this study with respect to hematological side effects of Skelid are inadequate for drawing any definitive conclusion regarding causality. Reports of leukopenia and neutropenia in placebo and Skelid groups need to be included under Adverse Reactions section of the labeling as mentioned in the package inserts of Didronel and Aredia for the treatment of Paget's disease of bone.

Urinalysis (Cr. clearance, pH, RBC, WBC, and volume) - No clinically significant changes from baseline occurred as a result of treatment with study drugs.

Urine chemistry -Of various parameters studied, Skelid therapy (both 200 and 400mg/day) resulted in significant changes in both calcium/creatinine and phosphorus/ creatinine ratios. Significant decreases (from baseline) were noted in 200 mg group at Weeks 2 and 12. Significant mean decreases (from baseline) were also observed in 400 mg group at Weeks 2 through 20. Pairwise comparison of response between the placebo and 400 mg groups showed significant differences at Weeks 2 through 16. At Week 4, the difference between 200 mg and 400 mg groups was statistically significant. At the end of the observation period (Week 24) mean calcium/creatinine values returned toward baseline in both Skelid groups.

With regard to urinary excretion of phosphorus/creatinine, the overall results appear to be variable. In both placebo and 400 mg groups, significant increases were noticed at some Visits, compared to decreases in 200 mg Skelid group at Weeks 2 through 12.

Reviewer's Comments: Decrease in urinary excretion of calcium/creatinine ratio following treatment with Skelid is expected as the drug inhibits bone resorption. Bisphosphonates are also known to cause variable effects on urinary excretion of phosphate.

Clinically relevant changes in laboratory parameters - Clinically relevant values were defined as values outside the reference range and differed from the baseline values by more than 40% to 80% of the span of the reference range. The overall results showed no consistent pattern of change in clinically relevant laboratory parameters. Number of patients with relevant changes were very small and in most instances there was no marked difference between the placebo and Skelid groups with respect to the number of patients with such changes. No patient was discontinued from the study due to clinically relevant changes in laboratory parameters.

Changes in vital signs- The sponsor claims that there were no significant changes (from baseline) in any of the vital signs monitored.

Bone biopsy- Iliac crest bone biopsy after double tetracycline labeling was performed in following patients:

- Patients with pagetic lesion of the iliac crest (at least one side).
- Patient with no documented history of significant malabsorption.
- Patient with no bone biopsy within one year prior to study entry.
- Patient with normal serum 25-OHD level at baseline and at Week 12.
- Patient who volunteered for bone biopsy.

Bone biopsy was performed in 22 subjects (10 placebo and 12 Skelid groups). Of the 22 subjects, biopsy materials from three subjects were excluded from evaluation because of inadequate sampling or due to artifacts. Biopsy specimens from 5 of 19 subjects were found to have been collected from pagetic bone. Specimens from these five subjects were excluded from the safety evaluation, as the objective was to collect sample from nonpagetic sites.

Fourteen biopsy samples (7 from placebo, 4 from 200 mg and 3 from 400 mg Skelid groups) were evaluated for safety purposes. The following histomorphometric parameters were evaluated:

- Bone volume (BV/total volume,TV; %)-percentage of tissue volume that is bone.
- Osteoid volume (OV/TV and OV/bone volume,BV; %)- OB/BV, percentage of bone volume that is unmineralized osteoid.
- Osteoid surface/bone surface (OS/BS; %)- percentage of total bone surface that is unmineralized osteoid.
- Osteoid thickness (OTh; μm)- mean thickness of osteoid seams.
- Wall thickness (W.Th; μm)- measurement of cortical thickness.
- Trabecular thickness (Tb.Th.; μm)- thickness of trabecular bone (a component of wall thickness).
- Mineral apposition rate (MAR; $\mu\text{m}/\text{day}$ -the average rate of progression of active mineralization front.
- Mineralization surface (MS/BS;%)- percentage of total bone surface that takes up tetracycline label.
- Mineralization lag time (MLT;days)-period between matrix formation and the initiation of mineralization
- Mineralizing surface/osteoid surface (MS/OS; %)-surface estimates of mineralization
- Bone formation rate (BFR; $\text{mm}^3/\text{mm}^2/\text{year}$)-the amount of new bone formed per unit time (expressed as mm^3 of new bone per mm^2 of bone surface per year).
- Formation period (FP; years).

Histomorphometric data are presented in Appendices 6.4.1-4 (see vol. 1.201, pp.291-301). Review of the results presented in these Appendices showed only significantly greater trabecular thickness in the Skelid group compared to placebo group. Box plots of bone volume, wall thickness, osteoid volume, osteoid surface, osteoid thickness, mineralizing surface, MAR, mineralization lag time, MS/OS, osteoclast surface, formation rate, and formation period showed no statistically significant differences between two treatment groups. Sponsor claims some trends in changes of these variables. Skelid treated patients tended to show more osteoid accumulation, as 5 of the 6 highest values for OV/TV and four highest values for OV/BV were in the same group. However, this trend was balanced by no significant change in mineralization parameters. Regarding bone mineralization, 5 of the 6 highest values for mineralization lag time were in the Skelid group. The mean value for the mineral apposition rate for the Skelid group was slightly lower than that for the placebo group.

The sponsor concludes that Skelid has no significant effect on bone remodeling or mineralization.

Reviewer's comments: Increases in OTh and OV with active treatment, mean that higher proportion of total bone was unmineralized in Skelid treated patients compared to placebo treated controls. The primary objective of bone biopsy was to demonstrate that short term Skelid therapy has no deleterious effect on bone mineralization. The variable such as OTh, OV, and MAR, which are generally regarded as the safety endpoints, changed (though not significantly) to reflect mineralization defects. The sample size, however, is not adequate to draw any conclusion.

Occult fecal blood: The results showed no significant differences between three treatment groups with respect to proportion of subjects with positive occult fecal blood during the study.

Optional safety tests (Hearing test, cardiac output, and temperature over long bones): A total of seven subjects in the placebo had these optional tests, and 6 subjects in the Skelid groups had only long bone temperature test performed. Three patients in the placebo group reported decreased hearing during the study. One patient had improved hearing. Of 6 subjects (5 in 200 mg and 1 in 400 mg) who had long bone temperature tested in the Skelid groups, three showed improvement and three had

"fluctuating" results. The data on optional tests for efficacy purpose are too small for any definitive conclusion., Progression of hearing loss in the placebo treated subjects during the study is expected.

For safety purpose three patients in the placebo group had endoscopic examination during the study. Only one patient showed mild prepyloric gastritis. This patient was dropped from the study.

Sponsor's Discussion:

Efficacy - The placebo group showed no effect on the SAP during the course of the study. In contrast, the mean SAP levels decreased significantly in the Skelid groups in a dose-dependent way; greater decreases in the 400 mg level than 200 mg at Weeks 4, 8, 16, 20, and 24 ($p < 0.05$).

At the end of treatment (Week 12), 42% and 61% of patients in the 200 mg and 400 mg Skelid groups, respectively achieved ≥ 50 decrease from baseline SAP levels. None of the subjects in the placebo group had $\geq 50\%$ decrease (from baseline) in SAP levels at Week 12. At Week 24 (end of follow-up period), 52% and 72% of patients in 200 mg and 400 mg Skelid groups, respectively maintained such reduction in mean SAP levels.

At Week 12, 7 % and 20% of patients in 200 mg and 400 mg Skelid groups, respectively achieved normalization of SAP level. At Week 24, 35% of patients in 400 mg Skelid group maintained normalization of SAP.

Skelid therapy resulted in significant decreases in bone specific alk. phosphatase in both 200 mg and 400 mg doses at Week 12 and Week 24 Visits. Compared to the placebo group, the differences were statistically significant for both Skelid groups. The difference between two Skelid groups was not statistically significant at Week 12, but significant at Week 24..

With respect to changes in urinary excretion of OHP/Cr (hydroxyproline/creatinine), Skelid at both doses caused significant reductions compared to placebo. Decrease in U/OHP/Cr started at Week 2 after treatment.

Based on the results of SAP and U/OHP/Cr changes due to Skelid

therapy, 400 mg/day inhibited bone resorption to a greater extent than bone formation.

Skelid at both doses caused significant decreases (from baseline) in urinary excretion of pyridinoline crosslinks/creatinine compared to the placebo. Also, the pairwise comparisons of differences between placebo and each of two Skelid groups were statistically significant.

Although there were no statistically significant differences between three treatment groups with respect to changes in pagetic pain scores, More subjects in the Skelid groups "improved" than "worsened" compared to placebo control. At Week 24, comparison of proportion of patients with pain scores "improved" or "no Change" relative to baseline was significantly different among three treatment groups. Compared to placebo, the proportion of patients with "improved" pain scores in 200 mg Skelid group was significantly greater. Compared to placebo group, the proportion of patients with "improved" pain scores in 400 mg dose was also close to statistical significance for ITT subjects

None of the subjects in placebo group showed radiographic improvement of pagetic bone lesions at Week 12 or 24.

In contrast, association between radiographic improvement of bone lesions and Skelid therapy (for 12 weeks and followed-up for additional 12 weeks) was statistically significant. Moreover, a dose response trend was observed for such improvement in skeletal lesions. The study provided some evidence of radiographic evidence of healing of bone lesions as a result of Skelid therapy.

The temporal relationship between plasma concentrations of tiludronate and reductions in SAP was inconclusive, because of large intra- and inter-subject variabilities in tiludronate plasma concentrations. These observations were consistent with the skeletal effects of tiludronate and bisphosphonates in general. Steady-state plasma concentration of tiludronate in subjects > 65 years of age was greater than subjects < 65 years of age. However, there was no treatment-by-age interactions regarding the SAP response to Skelid.

Safety- There were no significant differences between three treatment groups regarding the percentage of patients with one or more AEs. About 90% of patients in the placebo group and 87%

of patients in the Skelid group experienced one or more AEs.

About equal percentages of patients in three treatment groups experienced "any adverse event" within each body system. More placebo treated patients experienced "body as a whole-general disorders" and headache than Skelid treated patients. With regard to the incidence of serious adverse events, higher incidence of G-I AEs, such as nausea and vomiting was in the Skelid groups.

With regard to changes in some clinically relevant laboratory parameters to Skelid therapy, serum calcium levels decreased in 400mg Skelid group during the treatment phase (first 12 weeks). At no time during the study, did 200 mg dose of Skelid show any significant reduction in serum calcium. The effect of Skelid on serum calcium level was consistent with its mechanism of action on bone turnover, and similar to that of other bisphosphonates. Both active drug groups showed increases in serum intact PTH levels both at Weeks 12 and 24. Change in serum iPTH levels could be attributed to observed decreases in serum calcium levels. Throughout the treatment phase with Skelid, there was a significant decrease in the urinary excretion of calcium/creatinine and it returned toward normal during the follow-up phase of the study.

There were no deaths in any treatment groups during the course of the study.

Iliac crest bone biopsy data from about 14 patients showed no evidence of defects in mineralization due to Skelid therapy. Histomorphometric data do not suggest significant inhibition of bone turnover.

Sponsor's Conclusion:

Skelid at daily doses of 200 mg and 400 mg is significantly more effective than placebo in the treatment of Paget's disease of bone as evaluated by changes in biochemical indices (i.e., SAP and U/OHP/Cr) over a period of 24 weeks (12 weeks of active treatment and 12 weeks of follow-up). The results indicated greater efficacy of daily 400 mg of Skelid than 200mg dose.

Biochemical remission of Paget's disease of bone was associated with radiographic improvement of skeletal lesions over a period of

about 12 weeks after stopping active treatment.

There was no difference between the three treatment groups with respect to mean changes in pagetic pain scores to study drugs. However, more patients in the Skelid groups manifested "improved than worsened" pain scores compared to the placebo group at Week 12. Significantly greater proportion of patients in Skelid 200 mg group showed statistically significant improvement in pain scores at Week 24 compared to placebo. The 400 mg group also approached statistical significance compared to placebo.

There was no correlation between plasma concentrations of tiludronate and skeletal effect. Maximum inhibition of SAP occurred generally after the last dose of Skelid, when the plasma levels of tiludronate were at near or below assay limits.

There were no significant differences between the three treatment groups in the safety profile. Eighty-seven to ninety percent of patients in three treatment groups experienced one or more AEs in the study and within each body system there were no significant differences between these groups.

Bone biopsy data showed no significant effect on bone remodeling or mineralization.

Skelid at a daily dose of 400 mg demonstrated better benefit/risk ratio than 200 mg daily dose for the treatment of Paget's disease of bone.

Reviewer's Comments/Conclusions of Study Results:

This is one of three pivotal controlled trials carried out to demonstrate the safety and efficacy of tiludronate (Skelid) in the treatment of Paget's disease of bone.

The pagetic study population with markedly increased SAP (at least twice the upper limit of normal) was appropriate. Ninety-four to 98 percent of enrolled subjects completed 24 weeks of treatment and observation phases of the study.

The results of a previous open-label study with Skelid (daily 400 mg for 3 or 6 months) showed decrease in SAP from baseline by 49% and 59% after 3 months and 6 months of treatment,

respectively. This finding prompted the sponsor to select a three-month treatment regimen with Skelid in this trial.

Both the efficacy and safety data were analyzed appropriately for the intent-to-treat population.

Almost all of drugs previously approved for this indication demonstrated their efficacy based on significant decrease in elevated levels of SAP along with positive effects on a series of secondary efficacy endpoints (i.e., decrease in elevated levels of U/OHP/Cr, improvement in pagetic bone, neurological deficits, and radiographic improvement in pagetic bone lesions).

Treatment success was defined as $\geq 50\%$ decrease in SAP from baseline. Similar treatment success criterion was used for other bisphosphonates approved for the treatment of Paget's disease of bone. Further evidence in support of the efficacy of Skelid was provided by the above-mentioned secondary efficacy variables.

From safety point of view, beside routine clinical and laboratory evaluations, iliac crest bone biopsy was performed in a small group of patients to study the effect of short-term tiludronate on bone mineralization.

The results demonstrated significant ($p < 0.001$) decreases from baseline in SAP by 46% and 51% in patients treated with Skelid 200 mg and 400 mg daily, respectively at Week 12. The placebo group showed slight increase (about 1%) from baseline at Week 12. Pairwise comparisons between the placebo and two Skelid groups showed significant differences ($p < 0.05$) between placebo and each of the two Skelid groups. There was no statistically significant difference between the two Skelid groups. Review of the data on treatment-by-demographic interactions revealed no clinically significant effect. At the end of follow-up period (Week 4), the two Skelid groups maintained significantly decreased mean SAP levels at -47% and -58%, respectively. The placebo group showed slight increase from baseline mean value. Statistical conclusions regarding pairwise comparisons showed significant differences between the placebo and Skelid groups at Weeks 4, 8, 16, and 20 ($p < 0.05$).

Based on per protocol definition of treatment success, 42% and 61% of patients in Skelid 200 mg and 400 mg groups, respectively

demonstrated treatment success at Week 12. At Week 24, the percent of patients with treatment success were 51% and 72%, respectively. The incidence of treatment success was nil in the placebo group at Weeks 12 and 24.

In the two Skelid groups, 7% and 21% percents of patients **achieved normalization** (returned within reference range) of SAP at Week 12. The overall comparison showed a statistically significant difference of $p=0.003$. In the 400 mg Skelid group, percent of patients with normalization of SAP increased to 35% at Week 24. The difference between the placebo and the latter group was significant ($p=0.001$).

SAP started to fall about 2 weeks after initiation of treatment, and reached the nadir about 4 weeks after completion of Skelid therapy.

Urinary hydroxyproline/creatinine also decreased (from baseline) significantly in both Skelid groups to the extent of -38% and -53%, respectively at Week 12. There was, however, no difference between two Skelid groups with respect to lowering of U/OHP/Cr.

Along with significant biochemical remission of the disease process that resulted from Skelid therapy, more patients in the Skelid groups experienced improvement in pagetic pain scores at Week 12 compared to the placebo group. At Week 24, the overall comparison of proportion of patients with improved pain scores relative to baseline was significantly different among three treatment groups. Compared to the placebo group, significantly greater proportion of patients experienced improved pain scores in the 200 mg Skelid group. Patients in the 400 mg group also showed improved ($p=0.07$) pain scores compared to placebo.

At both Weeks 12 and 24, radiographic evaluation of pagetic bone lesions of skull and long bones showed improvement in both Skelid groups, compared to the placebo group. The 400 mg group appeared to be more effective with regard to healing of osteolytic lesions. There was no evidence of spontaneous healing of bone lesions in the placebo group.

Review of the safety data seem to indicate all three groups are quite similar with respect to proportion of patients with one or more AEs. Slightly greater proportion of patients in the combined

Skelid group experienced **nausea and vomiting**.

Sponsor claims that bone biopsy data showed no evidence of defective mineralization as a result of 12 weeks of Skelid therapy. This reviewer feels that data are too few to draw any definitive conclusion on the effect of Skelid on bone remodeling or mineralization. Data on OTh, OV, and mineralization lag time seem to indicate delayed remodeling.

In conclusion, the results of this controlled study provide clear evidence of suppression of biochemical abnormalities in patients with moderate to severe Paget's disease of bone. More than 50% decrease in elevated levels of SAP in 51% to 72% of patients in Skelid groups was comparable to those of trials carried out by other approved drugs for Paget's disease of bone. The study provides no evidence of any major safety issues for a short-term therapy with Skelid. The study, however, has not provided **any data on recurrence of biochemical abnormality or potential development of resistance to therapy**.

8.2 Trial # 2 (Protocol # 1552/ Study Report 41319B)

8.2.1. Objective/Rationale: To demonstrate that daily 400 mg of Skelid is more effective than the same dose of etidronate disodium in the treatment of Paget's disease of bone.

8.2.2 Design: Randomized, double-blind, active controlled study.

8.2.3 Protocol

A common protocol was used for this European multicenter study.

8.2.3.1 Investigators: This study was carried out in France, Germany, Belgium, Italy, Holland, and Spain. There were 61 centers in France, 8 in Germany, 7 in Belgium, 5 in Italy, 1 in Holland, and 3 in Spain. The principal investigator was Prof. M. Dougados of France. The sponsor assures that all the investigators were qualified.

8.2.3.2 Population, procedure: Patients (of either sex aged over 18 years) with symptomatic Paget's disease of bone confirmed by radiography or bone scan entered into this study. Patients had elevated SAP, at least twice the upper limit of normal range. A total of 234 subjects (78 tiludronate for 3 months, 77 tiludronate

for 6 months, and 79 etidronate for 6 months) were enrolled in this study. The demographic characteristics of the study population are summarized in Table 21.

Table 21. Demographic characteristics.

Demograph. Charact.	Tiludronate 3 Months Treat.	Tiludronate 6 Months Treat.	Etidronate 6 Months Treat.
Gender			
Male	52	49	38
Female	26	28	41
Race			
Caucasian	75 (96%)	76 (99%)	78 (99%)
Negroid	3 (4%)	0	1 (1%)
Other	0	1(1%)	0
Mean Age (range) in Years	68.4(41.3- 85.1)	70.2(42.7- 89.6)	67.8(43.7- 85.2)

A total of 30 subjects (14 on Skelid for 3 mo, 11 on Skelid for 6 mo., and 5 on etidronate for 6 mo) discontinued the study prematurely.

Patients who received treatment with any other bisphosphonates within previous 2 years were excluded from the study. Similarly patients treated with calcitonin within 2 months were also excluded. Other exclusion criteria were routine and similar those of the controlled trials in Paget's disease of bone.

After recruitment (not more than 3 weeks prior to initiation of treatment), subjects were randomly assigned to three groups and clinical and laboratory evaluations were performed on the Day before the start of treatment. Treatment procedure is shown in Table 22.

Table 22. Treatment schedule.

Baseline Period (< 3 wks; until Day 1)	First 3 Mo. of Treatment (Days 0-90)	Second 3 Mo. of Treatment (Days 91-180)
Group 1	Tiludronate 400 mg/day	Tiludronate 400 mg/day
Group 2	Tiludronate 400 mg/day	Placebo
Group 3	Etidronate 400 mg/day	Etidronate 400 mg/day

Tiludronate and etidronate formulations:

Tiludronate 200 mg tablets

Tiludronate placebo tablets

Etidronate 200 mg tablets in size 0 capsules

Etidronate placebo-size 0 capsules

Each subject took two tablets and two capsules daily 2 hours after breakfast.

All laboratory efficacy measurements were performed in a single central laboratory. Some baseline SAP and tolerability measurements were performed in a separate laboratory at each center, or at a central laboratory for the French studies.

Urine calcium, phosphorus, creatinine, and OHP were measured from 2-hour samples collected in the morning.

Schedule of assessments is shown in Table 23.

Table 23. Schedule of assessments

Study Day	Visits	Assessments
DX	0	Preselection Screening
D-1	1	Clin. and Lab. Measurements
D-0	None	Treat. Initiation
D 90	2	Clin. and Lab Measurements
D-180	3	Clin. and Lab. Measurements

Clinical and laboratory measurements were carried out within ± 7 days from the set Visit days. Adverse events were evaluated at

Visits 2 and 3.

8.2.3.3 Endpoints: Primary efficacy endpoint was the same as of Protocol 1845. Secondary efficacy endpoints were amelioration of bone pain (measured by Visual Analog Scale), changes in serum levels of calcium and phosphorus and urinary excretion of phosphate, creatinine, and hydroxyproline. Clinical AEs and laboratory variables were monitored for safety purpose.

Reviewer's Comments on endpoints: The sponsor claims that this study was designed to demonstrate that Skelid (400 mg/day) is more effective than the same dose of etidronate in the treatment of Paget's disease of bone. The proposed efficacy endpoints (biochemical indices of increased bone remodeling) will be supported by improvement (if any) of pagetic bone pain. These efficacy endpoints are generally considered adequate for comparing therapeutic efficacy of Skelid with that of an approved drug, etidronate. The proposed study will not critically compare the effects of two treatment regimens in terms of improvement in bone histology and radiographic evidence of healing of skeletal lesions.

8.2.3.4 Statistical considerations: The proportion of "responders" in the etidronate group was compared to that of the pooled tiludronate groups using Fisher's exact bilateral test. Both ITT and an efficacy analyses were performed.

Analysis of variance (ANOVA) was used for comparison of quantitative baseline parameters. Routine statistical methods were used to compare the proportion of normalized (for SAP) and resistant patients between two treatment regimens. See Statistical review for details.

8.2.4 RESULTS

Efficacy results

8.2.4.1 Patient disposition and comparability

Thirty patients were reported to discontinue the study prematurely (before completing 6 months): 14 patients from 3-mo. tiludronate group, 11 from 6-mo tiludronate, and 5 from etidronate group. Twenty-seven of 30 patients were withdrawn from the study due to AEs, In 3-month tiludronate group, 3 patients were withdrawn from the

study during placebo treatment. The remaining three patients discontinued the study because of protocol violations, non-compliance, or lack of efficacy. All of these patients were included in the ITT analysis.

Of 234 patients entered into this study, data from 219 patients were available for assessment of the effect on bone metabolism and pain at Visit 3.

A total of 66 patients were excluded from the efficacy analysis at Visit 3 (27 tiludronate 3-mo group, 22 6-mo tiludronate group, and 17 etidronate group). The reasons for exclusions were: low SAP at baseline, low SAP at the end of previous tiludronate therapy, visits were outside the timing window, use of drugs not permitted by the protocol, occurrence of other illness, and voluntary termination of the study by the patient.

There was no significant difference between three treatment groups regarding demographic characteristics. The tiludronate groups had more men than women. Men and women were evenly distributed in the etidronate group.

The median duration of Paget's disease was about 5 years in all three groups. The majority of patients had more than one site for pagetic involvement. The common sites were pelvis (77.8%), lumbar spine (43.2%), and the skull (37%).

Regarding previous bisphosphonate therapy of patients enrolled in this study, 44 in tiludronate 3-month, 34 in tiludronate 6-month, and 44 in etidronate groups received previous bisphosphonate treatment for Paget's disease of bone.

Baseline bone pain- Significantly more patients in tiludronate 6-month group had bone pain (particularly dorsal spine) compared to two other treatment groups. But with regard to bone pain at pagetic sites (10 sites identified), the distribution of bone pain was not significantly different among three treatment groups. Three treatment groups were comparable with respect to severity of bone pain at each site and global pain assessed by VAS scores.

Table 25. The number and percent of responders in two treatment groups.

	Tiludronate (N=155)*	Etidronate (N=79)	p-Value
Responders (ITT)	89 (57.4%)	11 (13.9%)	p< 0.0001
Responders (Efficacy/evaluable subset)	73 (67%)	10 (16%)	p< 0.0001

* Combined patients from two tiludronate groups.

The effect of previous bisphosphonate therapy on the response (number and percent of responders) to either tiludronate or etidronate was further analyzed and the results are presented in Table 26.

Table 26. Effect of previous bisphosphonate therapy on SAP response .

	Responders	Nonresponders
Tiludronate		
Prev. bisphosphonate	46 (59.0%)	32 (41.0%)
No prev. bisphosph	43 (55.8%)	34 (44.2%)
Etidronate		
Prev. bisphosphonate	1 (2.3%)	43 (97.7%)
No. prev. bisphosph.	10 (28.6%)*	25 (71.4%)

* p=008, tiludronate vs etidronate (prev. treat. with bisphosphonate).

Comparison of geometric means ratios between baseline and 3 months for two treatment groups were significant for ITT and evaluable subjects. (Comments: clinical significance of this analysis is equivocal).

Proportion of patients with normalized SAP following therapy- Patients who had missing data were considered not normalized. Of a total of 155 patients in the tiludronate groups, 22 (14%) and 4 (5.1%) were reported to achieve

Baseline values for biochemical indices for bone remodeling (primary and secondary efficacy endpoints) are shown in Table 24.

Table 24. Baseline values for SAP and U/OHP, and U/OHP/Cr ratio.

Parameters	Tiludronate 3-mo Gr.	Tiludronate 6-Mo Gr.	Etidronate
SAP-Mean \pm SE Range -IU/L	504 \pm 51.4 174.0-2259.0 N=77	475.4 \pm 36.6 122.0-1901.0 N=75	451.4 \pm 45.1 124.0-2460.0 N=78
U/OHP- Mean \pm SE Range- μ mol/L	376.0 \pm 60.2 11.0-3153.0 N=75	360.0 \pm 45.3 13.0-1864.0 N=76	502.4 \pm 98.3 15.9-6180.0 N=78
U/OHP/Cr- M \pm SE Range-	0.084 \pm 0.02 0.001-1.417 N=75	0.060 \pm 0.006 0.000 - 0.397 N=76	0.081 \pm 0.014 0.001 - 0.814 N=78

There were no statistically significant differences between three treatment groups with respect to these baseline variables ($p=0.50-0.72$).

8.2.4.2 Efficacy Endpoint outcomes

Serum Alkaline Phosphatase, SAP (ITT and efficacy analyses)

The response to tiludronate or etidronate therapy for three months was first compared and the results are shown in Table 25.

normalization, $SAP \leq 105IU/L$ at 3 months, compared to 4 of 79 patients (5.1%) in the etidronate group. A higher proportion of patients in the etidronate group were considered resistant to therapy with respect to decrease ($\leq 25\%$ from baseline) in SAP (58.2% vs 18.1%, $p < 0.0001$). At 3 months, thirteen patients in the etidronate group had their SAP values higher than those at baseline, compared to 7 in the tiludronate group.

Hydroxyproline (OHP) and hydroxyproline/creatinine (OHP/Cr) ratio-

There was significant difference between the two treatment groups with respect changes in urinary excretion of OHP at 3 months. However, the U/ OHP/Cr ratio was significantly ($p=0.03-0.007$ for ITT and efficacy analyses) lower in the tiludronate group than etidronate.

Assessment of pain at 3 months- Significantly less number of patients (compared to baseline) in both treatment groups reported bone pain (at pagetic and nonpagetic sites) at three months. However, there was no significant difference between two treatment groups at 3 months with respect to number of patients with bone pain.

The results are inconclusive regarding the effect of treatment on pagetic bone pain because of difficulty in delineating pain due to osteoarthritis or pagetic bone lesions.

Treatment results at 6 months

SAP-The number and percent of responders to therapy are shown in Table 26a.

Table 26a. The number and percent of responders.

	Tiludronate 3-months		Tiludronate 6-months		Etidronate	
	3-Mo	6-Mo	3-Mo	6-Mo	3-Mo	6-Mo
Responders(ITT)	43 (55.1%)	47(60.3%)	46(59.7%)	54(70.1%)	11(13.9%)	20 (25.3%)
Responders (Efficacy analysis)	33(67.4%)	40(81.6%)	33(66.0%)	42(84.0%)	10(16.7%)	18(30.0%)

There was no significant difference between two treatment groups with respect to the proportion of responders at 6 months. The number of responders was significantly higher in tiludronate 3 and 6 months compared to the number of responders for the etidronate group. In both treatment groups about 26 patients who were nonresponders at 3 months became responders at 6 months. At 6 months, more patients (10 vs 3) in the etidronate manifested higher than baseline SAP values compared to the tiludronate group.

Previous treatment with bisphosphonate resulted in no significant difference in the number of responders at 6 months. In contrast, the percent of responders among patients with no previous bisphosphonate treatment was reported to be higher.

Changes in geometric means ratios of SAP- Comparison of ratios between baseline and 6 months showed significant reductions in tiludronate groups than the etidronate group.

At 6 months, 19 of 78 (24.%) and 21 of 77 (27.3%) patients in tiludronate 3 and 6 months, respectively achieved normalization of SAP. Whereas, in the etidronate group 9 of 79 (11.4%) patients showed normalization of SAP. About 18% -20% of patients were considered resistant to tiludronate as compared to 52% of the etidronate group.

Changes in U/ OHP and U/OHP/Cr ratio- There were no significant differences between two treatment groups with respect to changes in U/OHP and U/OHP/Cr ratios at 6 months. There was a significant difference between

tiludronate 6 months group and etidronate group at 6 months with respect to decreased levels of U/OHP.

Changes in bone pain- In all three groups, significantly lower (compared to baseline numbers) number of patients experienced bone pain at 6 months. The two treatment groups, however, showed no significant difference with respect improvement of bone pain. A higher proportion of patients in the etidronate group compared to tiludronate groups were reported to experience improved pagetic pain of the left lower limb. In the etidronate group, more patients showed "complete disappearance" of pagetic bone pain. But at 6 months, all three groups showed improvement.

Changes in global evaluation by investigators and patients- There were no significant differences between three groups with respect to patients' scores of improvement or aggravation/no change from baseline to 3 and 6 months. The investigators' scores showed significant improvement in tiludronate group at 6 months.

Radiographic changes- Radiographic evaluation was performed in a small sample of patients (7 tiludronate and 5 etidronate). A total of 19 pagetic sites (9 with etidronate and 10 with tiludronate) were compared for changes in characteristic skeletal lesions (osteolysis or sclerosis). The results are inconsistent. One patients in the etidronate group showed fissure fracture. None in the tiludronate group had any significant changes in the type of lesion presented at baseline. Sponsor states that data are too limited for any conclusion.

8.2.4.3 Safety results

Clinical tolerability

A total of 174 AEs were experienced by 102 patients. The AEs were classified according to WHO standard adverse reactions terminology. The results showed 48.1% of patients in the tiludronate 6 months group, 48.7% of patients in the tiludronate 3 months group, and 34.2% of patients in the etidronate group experienced AEs.

The most common AEs were related to gastrointestinal system; 19.3% in the tiludronate 3 months group, 20.8% in the tiludronate 6 months, and 12.7% in the etidronate group. The common G-I adverse events were **abdominal pain**, esophagitis, gastroesophageal reflux, and gastric ulcer in 1 to 2 patients in the tiludronate group only.

Although, three treatment groups were similar with respect to the incidence of AEs as a whole, significantly more patients in the combined tiludronate group experienced G-I AEs than the etidronate group (see Table 27).

Table 27. Incidence of G-I AEs.

Gastrointestinal AEs	Tiludronate N=155	Etidronate N=79
Abdominal Pain	12	1
Colitis	2	0
Constipation	1	0
Diarrhea	1	0
Dyspepsia	3	1
Enteritis	1	0
Flatulence	2	1
Gastric Ulcer	2	0
Gastritis	1	0
Non-specific G-I Disorder	1	0
Gastroenteritis	0	1
Gingivitis	0	1
Nausea	3	1
Esophagitis	1	0
Vomiting	2	0
Total No. of AEs	32	6
Total No. of Patients	27(17.4%)	4(5.1%)*

* p= 0.008

The onset of G-I AEs in the tiludronate group was earlier than the etidronate group (about 42 days for the tiludronate vs 103 days for the etidronate group). About 7% of patients in the tiludronate group dropped out of the study due G-I AEs compared to 1.3% in the etidronate group.

There was no significant difference between 6-month tiludronate and 6-month etidronate groups with respect to total number of patients with musculoskeletal adverse events. However, fewer number of patients in the 3-month tiludronate group experienced musculoskeletal AEs compared to patients in the 6-month etidronate group.

There were 7 withdrawals from the tiludronate group at 3 months due to serious or nonserious AEs which were possibly drug-related. **AEs of 6 of 7 cases were related to esophagus and stomach (esophagitis, gastralgia, nausea, dyspepsis).** In the 6-month tiludronate group, two patients withdrew from the study due to possible drug-related AEs (**gastric burning or allergic reactions**). The patient who suffered allergic reactions developed "intense vaginal pruritus, a feeling of anxiety or breathlessness, eyelid edema and congested conjunctivae" after about 27 days of treatment. In the etidronate group, there were two possible drug-related AEs (pruritus, gingivitis, bitter lacrimation or arthritis of finger) which resulted in withdrawal from the study.

Laboratory safety results

There were 7 laboratory abnormalities reported as AEs and these were: bilirubinemia, increased liver isoenzymes, hypocalcemia, polycythemia, and leukopenia in five patients (each patient with one type of abnormality) in 3-month tiludronate group. Hyperglycemia occurred in one patient each in 3-month tiludronate and etidronate groups, respectively. Only hypocalcemia resulted in withdrawal of the patient. This patient had a history of hypocalcemia at entry which was attributed to malabsorption related to a previous bowel resection. Other laboratory abnormalities were considered not related to study drugs.

Two patients were reported to develop clinically relevant treatment-emergent laboratory abnormalities, one with abnormal baseline values (which were corrected after treatment) and the other with baseline thrombocytopenia (normal values in additional sample).

The overall safety data showed no clinically relevant

difference between the two (skelid vs etidronate) treatment groups. All three treatment groups showed significant decreases in serum calcium at 3 months, followed by an increase; and a significant increase in serum phosphorus at 6 months.

Sponsor's Discussion There were some differences between tiludronate and etidronate groups; tiludronate group had more patients with baseline bone pain and contained more bisphosphonate resistant patients

About 57.4% of patients in the tiludronate group were considered responders compared to 13.9% in the etidronate group at 3 months. ($p < 0.0001$). The percent of responders increased to about 70% after 6 months of treatment in the tiludronate group, compared to 25.3% in the etidronate group. The difference between 3 and 6 months of tiludronate therapy was not significant with respect to percent of achieved responders

The SAP (the primary efficacy endpoint) decreased significantly greater extent from baseline in the tiludronate group than etidronate at both 3 and 6 months.

About fourteen percent of patients in the tiludronate group achieved normalization of SAP, compared to about 5% in the etidronate group at 3 months. After 6 months, 24.4% and 27.3% of patients in tiludronate 3- and 6-month groups, respectively achieved normalization of SAP. In the etidronate group at the corresponding time point 11.4% of patients achieved similar therapeutic effect. The difference between two tiludronate groups was not statistically significant.

A higher proportion of patients in the etidronate group showed reduction of SAP 25% or less (considered resistant to treatment) compared to combined tiludronate group.

There was no significant difference between two treatment regimens with respect to U/OHP/Cr ratio at any time point.

Bone pain assessment showed significant improvement in all treatment groups. Also, global assessment made by the

investigators showed significant improvement in the tiludronate 6-month group than etidronate after 6 months of treatment.

After 3 months of treatment, there were significantly more AEs in patients treated with tiludronate compared to etidronate. More patients in the tiludronate experienced G-I AEs than with etidronate, and G-I AEs appeared earlier in the former group (within 2 months from the onset of treatment). Seven patients with G-I related AEs terminated the study.

There was one serious case of allergic reactions possibly related to tiludronate which resulted in withdrawal from the study.

There were three deaths during the course of the study, but none were considered study drug related.

Abnormalities in laboratory variables occurred at similar frequencies in both treatment regimens.

Tiludronate was found to be clinically superior to etidronate with respect to reduction in elevated levels of SAP. There was no significant difference between 3 and 6 months of treatment with regard to beneficial effect on SAP.

In conclusion, tiludronate 400 mg/day for 3 months is more effective than etidronate (same dose and duration of treatment). The overall success rate (based on SAP changes) after 6 months of treatment (or 3 months of treatment followed by 3 months of placebo) with tiludronate was higher than that with etidronate for 6 months.

There was higher incidence of G-I related AEs with tiludronate than with etidronate and G-I AEs occurred in the former group earlier after initiation of treatment.

8.2.4.4 Reviewer's Comments and Conclusions of Study results:

The objective of the study was to demonstrate that

tiludronate (400 mg/day for 3 months) is "more effective" than etidronate (same dose and duration) in the treatment of Paget's disease of bone.

Etidronate disodium is an approved drug for the treatment of symptomatic Paget's disease of bone. It is recommended for treatment initially for 3-6 months at a daily dose of 5-10 mg /kg/day. For comparison of results after 6 months of treatment with etidronate the sponsor included a parallel group on 6 months of tiludronate. The study was multi-center, randomized, and double-blind. For an active controlled study, the design was appropriate.

The primary entry criterion (with respect to primary efficacy endpoint) for the patient population was in agreement with the requirement that were followed in clinical trials with other approved bisphosphonates (etidronate, pamidronate, alendronate) and calcitonin. The secondary efficacy criteria were also in agreement with those of the clinical trials carried out with above-mentioned approved drugs.

The data obtained from the study were subjected to routine Intent-to-treat and efficacy subset analyses. For 3-month data, two tiludronate groups were pooled, which is acceptable. See Statistical review for any additional comments.

Tiludronate treatment (400 mg/day for 3 months) resulted in at least 50% reduction in elevated SAP in about 55% to 60% of treated patients. Whereas, at corresponding time point in the etidronate group, about 14% of treated patients achieved similar reduction in SAP. Six months of treatment with tiludronate, increased the percentage of patients with similar therapeutic success to about 70%. In the etidronate group, the percentage patients with treatment success also increased to 25%. Both at 3 and 6 months, the difference between tiludronate and etidronate groups with respect to percent of patients with treatment success was highly statistically significant. However, there was no significant difference between 3- and 6-month tiludronate groups with respect to proportion of patients with treatment success.

Tiludronate also appears to be more effective than Calcimar (salmon calcitonin, an approved drug for Paget's disease of bone) in causing biochemical remission. In clinical trials with Calcimar, biochemical abnormalities were substantially improved (more than 30% decrease) in about 75% of patients. In previous clinical trials with etidronate disodium (Didronel), 30% or reduction in elevated SAP was observed in 4 out of 5 patients. However, with alendronate (40 mg/day for 6 months), approximately 85% of patients achieved either normalization of SAP or \geq 60% reduction in SAP from baseline mean values. Pamidronate (Aredia), another approved drug for the treatment of Paget's disease (15-90 mg, a single i.v. infusion for 3 consecutive days) showed \geq 50% decrease in SAP in about 60% of patients.

Both 3 and 6 months of treatment with tiludronate resulted in normalization of SAP in 13% to 27% of patients. In the etidronate group, only about 11% of patients achieved similar results. The difference between the two treatment regimens for this variable was significant at $p < 0.05$ level. Tiludronate appears to be more effective than etidronate with respect to percent of patients with normalized SAP.

About 52% of patients treated with etidronate showed $< 25\%$ decrease in SAP compared to about 18% with tiludronate at 3 months (19.5% at 6 months).

Urinary hydroxyproline/creatinine decreased about 42% to 48% in both groups from baseline mean values, and there was significant difference between the two treatment regimens with respect to changes in U/OHP/Cr ratio at 3 months ($p=0.03$), but not at 6 months.

Significant improvement occurred in bone pain in all three treatment groups.

The overall safety data showed no significant differences between two treatment regimens with respect to the incidence or types of AEs. With the tiludronate group after 3 months of treatment, significantly more AEs occurred

than with etidronate. G-I AEs were more common and occurred early in the tiludronate group. Although, most of the tiludronate treated patients with G-I AEs required "no corrective" treatment, about 7% of patients (11/155) had to drop out due to G-I AEs.

In conclusion, The results of this active controlled study provide evidence of biochemical efficacy (in terms of improvement in SAP and U/OHP/Cr) of tiludronate in the treatment of Paget's disease of bone. Tiludronate at a dose of 400 mg/day for 3 months (followed by 3 months of placebo) appears to be as effective as 6 months of therapy. Compared to the biochemical efficacy of etidronate (active control), tiludronate appears to be more effective in terms of higher percentages of patients with treatment success and normalization of SAP.

With respect to safety, the two treatment regimens appeared to be similar. However, with the tiludronate therapy, G-I AEs were more common than etidronate and more patients dropped out due to G-I AEs.

8.3 Trial # 3 (Protocol # 1619/Study Report 41319)

8.3.1 Objective and rationale: To compare the effects of three doses of tiludronate (200,400, and 600 mg/day for 12 weeks, p.o.) in patients with paget's disease of bone.

8.3.2 Design: Multicenter (16 centers in UK), randomized, placebo-controlled, dose-ranging study.

8.3.3 Protocol

8.3.3.1 Investigators: Principal investigator was Dr. D.A. Heath of Queen Elizabeth Hospital, Birmingham, U.K. The sponsor assures that all investigators were qualified.

8.3.3.2 Population, procedure: One hundred thirteen pagetic patients (aged ≥ 18 years) with radiographically or scintigraphically confirmed bone lesions were randomized. The other entry (biochemical) and exclusion criteria were similar to those of the protocols reviewed earlier. Demographic data are summarized in Table 28.

Table 28. Demographic data

Characteristics	Placebo N=26	Tiludronate 200 mg N= 29	Tiludronate 400 mg N=29	Tiludronate 600 mg N=28
Gender				
Male	12	12	18	18
Female	14	17	11	10
Mean Age	69	70	72	68
Range	47-87	52-82	55-84	51-81

The mean duration of diagnosis of Paget's disease of bone in this patient population varied from 5.5 to 8.5 years at entry. The distribution of bone lesions among four treatment groups was reported to be similar. Pelvis and lumbar spine lesions were most common. Again, with respect to number of pagetic bone lesion sites per patient, there was no difference among the treatment groups.

About 50% of patients in this study received no previous therapy for Paget's disease of bone. Approx. 38% of patients received bisphosphonate therapy previously (but not within 2 years preceding the trial).

Patients were randomly assigned to treatment groups according to a computer generated randomization list.

Tiludronate 200 mg tablets and matching placebo tablets were used. Each patient took 3 tablets/day for 12 weeks. Tablets were taken orally with water each morning at least 2 hours before or after taking food. After completion of treatment, patients were followed-up for additional 12 weeks. All patients were Caucasians except for one "Negroid."

All blood and urine samples were collected at designated intervals (Weeks 0, 2, 4, 8, 12, and 24). Pain was assessed by the investigators (using a questionnaire) and by the patients on Visual Analog Scale (VAS). Clinical and laboratory AEs were monitored during the entire course of the study.

Reviewer's comments: The study population and procedures of this study were quite similar to those of the previous studies and appeared to be appropriate for achieving the study objectives.

8.3.3.3 Endpoints

Efficacy : Primary (changes in SAP) and secondary (changes in U/OHP/Cr, bone pain (by the investigators and patients) were similar to those of studies previously reviewed.

Safety: Routine clinical and laboratory procedures were similar to those of other studies reviewed.

Reviewer's comments : The primary and secondary efficacy and safety endpoints were appropriate to achieve the study objectives.

8.3.3.4 Statistical considerations: Statistical analyses of data were analyzed for ITT and efficacy populations. Efficacy population excluded patients with protocol violations. The proportion of patients with treatment success (a 50% or more reduction in baseline SAP) were compared between treatment groups by Fisher's exact tests. Routine ANOVA method was used to analyze VAS data. See statistical review for more details.

8.3.4 RESULTS

Efficacy results

8.3.4.1 Patient disposition and comparability

Of 113 patients who entered the study, 112 received the study drugs. One patient was withdrawn before initiation of treatment. At Week 12, 100 patients were considered evaluable. There were 13 withdrawals (3 in placebo, 4 in tiludronate 200 mg, 2 in tiludronate 400 mg, and 3 in tiludronate 600 mg, respectively) during the study. The reasons for withdrawal: were dropout, adverse event, protocol deviation, and lost to follow-up. Six patients dropped out of the study during follow-up period. The number of patients with evaluable primary efficacy endpoint are shown in Table 29.

Table 29. ITT population with evaluable primary efficacy endpoint.

No. of Evaluable Pt.	Placebo N=26	Tilud. 200 mg N=29	Tilud. 400 mg. N=30	Tilud. 600 mg N=28
At 12 Wk.	23	25	27	25
At Follow-up	23	26	28	27

In three tiludronate groups, during treatment period 6 patients were withdrawn from the study due to AEs.

Changes in SAP: Table 30 presents geometric mean SAP (IU/L) values

Table 30. Changes in geometric mean SAP values from baseline during the study.

Week	ITT or Efficacy Analysis	Placebo	Tilududronate		
			200 mg	400mg	600mg
Week 0	ITT	387.5(26)*	397.4 (29)	434.5(29)	436(28)
	Efficacy	367.5(22)	425.4(24)	437.7(26)	476.9(24)
Week 2	ITT	378.8(24)	370.8(28)	386.6(27)	416.7(27)
	Efficacy	358.6(22)	403.3(24)	400.7(26)	432.3(24)
Week 4	ITT	403.0(23)	377.3(27)	297 (27)	289(27)
	Efficacy	382.6(21)	328.9 (24)	305(26)	296 (24)
Week 8	ITT	403.2(23)	240 (25)	215.8(27)	186.4(26)
	Efficacy	384.4(21)	247.9(24)	221.9(26)	189.3(24)
Week 12	ITT	409.8(23)	214.8(25)	183.4(27)	155.4(25)
	Efficacy	390.4 (21)	220.6 (24)	187.8 (26)	157.5 (24)
Week 24	ITT	426.1 (23)	184.2 (26)	148.5(28)	121.6(27)
	Efficacy	403.8(21)	194.5(23)	142.9(26)	123.5(23)

* Number of patients within parenthesis.

In all three tiludronate groups mean SAP values progressively decreased from baseline over a 12-Week treatment period and continued to fall at the end of follow-up period. The results also indicated a trend of dose-response with a maximum decrease in SAP at Week 12 with 600

mg/day. (See attached Figure (5.4.1) L. vol 1.186.p. 58). The results of the analysis of efficacy population are similar to those of ITT population in terms of tiludronate-induced decrease in SAP from baseline and compared to changes in the placebo group.

Further analyses of the results showed no significant difference in response between patients with or without previous bisphosphonate therapy. Also, the duration of Paget's disease of bone did not influence the SAP response to tiludronate.

The proportions of patients with $\geq 50\%$ decrease in SAP from baseline (responders) are presented in Table 31.

Table 31. Percentage of responders to study drugs (ITT analysis).

Treatment Group	Time Point	Percentage of Responders	p Value
Placebo	Week 12	0.0	
	Week 24	0.0	
Tiludronate 200 mg/day	Week 12	31.0	< 0.05*
	Week 24	44.8	< 0.05*
Tiludronate 400 mg/day	Week 12	51.7	< 0.05*
	Week 24	69.0	< 0.05*
Tiludronate 600 mg/day	Week 12	82.1	< 0.05**
	Week 24	82.1	< 0.05**

* Compared with placebo; ** Compared with tiludronate 200 mg/day.

Compared to the placebo group, significantly higher proportions of patients in the tiludronate groups achieved treatment success at Weeks 12 and 24. There were significant differences between tiludronate 200 and 600 mg doses with respect to percentage of responders. There was no statistical difference between tiludronate 400 and 600 mg groups with respect to responders. Both in 400 and 600 mg doses, there were significantly higher proportions of responders (34.5% and 71.4%) at Week 8. With tiludronate 400 mg dose, approx. 20% more patients

achieved responder category compared to tiludronate 200 mg at Week 12, but this was not statistically significant.

At Week 12, 12%, 14.8%, and 36% of patients achieved normalization of SAP (≤ 115 IU/L) with tiludronate 200, 400, and 600 mg, respectively. At Week 24, 30.8%, 39.3%, and 44.4% of patients in 200, 400, and 600 mg tiludronate groups, respectively achieved similar response to therapy. None of the placebo treated patients showed normalization of elevated SAP levels during the study.

Approximately, 4% to 8% of patients in the tiludronate groups showed $\leq 25\%$ decrease in baseline SAP levels either at Week 12 or 24. These patients were categorized as resistant to tiludronate treatment.

All tiludronate groups showed progressive, dose-dependent decreases in U/OHP/Cr ratios at Weeks 12 and 24 compared to placebo group. The rapid decrease in U/OHP excretion occurred during the first 4 weeks of treatment. At doses of 400 and 600 mg, tiludronate decreased U/OHP/Cr ratio significantly more than the placebo.

Study of the relationship of changes in SAP and U/OHP/Cr ratio to tiludronate treatment showed early inhibition of bone resorption than bone formation.

Higher proportions of patients in tiludronate 600 mg dose experienced relief of bone pain at Weeks 12 and 24 compared to placebo and two other tiludronate groups. Similarly, median VAS scores were lower in the 600 mg dose group compared to baseline and placebo group. Regarding changes in pagetic bone pain severity, the results were equivocal, no trends were observed in any of the treatment groups.

Plasma levels of tiludronate were determined 1 hour before and after dosing at Week 12 in some patients. Because of small number of samples and due to wide variations in plasma levels, the results were inconclusive.

8.3.4.2 Safety results

The number of patients and the duration of exposure to tiludronate are presented in Table 32.

Table 32. Exposure to tiludronate

	Tilud. 200 mg	Tilud. 400 mg	Tilud. 600mg	Total Tilud.No
No. of Pt. Receiving \geq 1 Dose	29	29	28	86
No. of Pt. Years	6.05	6.40	6.07	18.53

A total of 164 AEs were reported in 79 patients (placebo 14 and 65 tiludronate). In the combined tiludronate groups, 75.6% of patients experienced AEs compared to 53.8% in the placebo group. The percent of patient with AEs increased in a dose-dependent fashion; 65%, 79.3%, and 82.1% in 200, 400, and 600 mg doses, respectively.

Gastro-intestinal AEs (nausea, diarrhea, abdominal pain, dyspepsia) were the most common in the tiludronate groups; 58 events occurred in 40 of 86 patients compared to 4 events in 4 of 26 placebo treated patients.

Non-G-I AEs also occurred more frequently in the tiludronate groups than placebo, but they appeared not to be dose-related.

There were no significant differences in number of G-I AEs with respect to concomitant use or no use of NSAIDs. Also, presence of G-I disorders at entry did not influence the overall incidence of G-I AEs due to tiludronate therapy. However, slightly higher proportion of patients with G-I disorders at entry experienced moderate AEs compared to patients with no G-I disorders at entry. A total of 7 patients in the tiludronate groups required G-I medications for treatment of AEs, compared to 1 patient in the placebo group with esophagitis at entry. Previous bisphosphonate therapy did not influence the incidence of total number AEs.

Two patients in the placebo group and four in the tiludronate groups (3 in 200 and 1 in 400mg groups) experienced serious AEs. Serious AEs included acute renal failure, tibial osteotomy, paraplegia, anemia, myocardial infarction, malignant neoplasm, and pulmonary embolism. None of these serious AEs were considered as drug-related. In the tiludronate group, there were two deaths during the study. One patient died of pulmonary embolism and the other suffered an acute myocardial

infarction 3 weeks after completion of treatment.

There were no significant differences between placebo and tiludronate groups with regard to the incidence of AEs that required discontinuation of therapy or dosage adjustment of study drugs or concomitant treatment. Nine patients (1 of 26 in the placebo and 8 of 86 in the tiludronate) withdrew from the study due to AEs. Three patients in the tiludronate groups and one in the placebo group had possible drug-related AEs that required withdrawal from the study. In the tiludronate groups, the possible drug-related AEs included abdominal pain, nausea, diarrhea, and headache. The patient in the placebo group experienced asthenia and dizziness. One patient in the tiludronate group had temporary discontinuation of treatment for 7 days for non-serious AE.

One patient in the tiludronate 400 mg group experienced traumatic rib fracture (from a fall) after about three weeks of treatment.

During the study period, group wise mean values for serum phosphocalcium variables (total serum calcium, corrected serum calcium, and phosphorus) showed no appreciable change to study drugs. However, corrected serum calcium values showed a tendency toward decrease in about 9 patients from baseline mean in the tiludronate groups. Corrected serum calcium returned to within normal range in seven of nine patients by Week 24.

The overall data showed no trends in hematological variables during the study. Clinically significant low lymphocyte counts were observed in 4 placebo, and 14 tiludronate treated patients during the study of 24 weeks. However, in these patients lymphocyte levels showed no particular trends. The following patients developed abnormal hematological AEs:

Patient # 303: Patient randomized to receive tiludronate developed significantly high level of eosinophilia at Week 8 followed by normalization at Weeks 12 and 24.

Patient # 419: Patient randomized to receive tiludronate 200 mg/day showed persistent (from Week 0 through 24) abnormalities of hematological parameters (red cell count, packed cell volume, monocytes, hemoglobin, and platelet count).

Patient # 422: Patient ("Negroid") randomized to receive tiludronate 400mg had abnormally low neutrophil count from Week 0 through Week 24.

Patient # 903: Patient randomized to receive placebo showed several abnormal hermatological parameters from Week 0 through 24.

Patient #1307: Patient randomized to receive tiludronate 600 mg/day showed clinically significant low white cell count at Week 8.

There were clinically significant changes in routine biochemical parameters (mean values at Weeks 12 and 24). Even in some individual cases with abnormal biochemical parameters, there were no consistent pattern of changes attributable to study drugs.

One patient in tiludronate 600 mg/day dose recorded markedly elevated serum creatinine levels at Week 24.

There were few patients with abnormal hepatic function, retinol binding protein, urinary pH, urinary protein, urinary glucose, urinary blood, or urinary calcium. Because of small number patients, infrequent episodes, and inconsistent pattern of occurrence of one or more of these AEs, it is difficult to assess their causal relationship to study drugs.

Sponsor's discussion and conclusions: A multicenter, randomized, placebo-controlled, dose-ranging 24-Week study was designed and carried out to determine the optimum dose of tiludronate in the treatment of Paget's disease of bone. The doses of tiludronate selected for the study were 200, 400, and 600 mg/day for 12 weeks followed by additional 12 weeks of follow-up. The study population was similar to those selected for other controlled Phase III studies.

The results showed a clear dose-response effect on SAP between 200 and 600 mg/day doses. At Week 12, the percent of patients with successful SAP response was significantly higher with tiludronate 600 mg/day than tiludronate 200 mg/day. Response rate (57.7%) at 400 mg/day was similar to that observed in other controlled study. Improved SAP level was continued to Week 24 (end of follow-up period). Improvement in SAP level was not influenced by the duration of Paget's disease of bone at entry or previous bisphosphonate therapy.

Both doses of tiludronate (400 and 600 mg/day) caused significant decrease in elevated levels of U/OHP/Cr ratio from baseline. Changes in U/OHP/Cr excretion occurred early after initiation of treatment.

There was no statistically significant difference between placebo and tiludronate groups in improvement of pagetic bone pain.

G-I AEs were most common in the tiludronate group. The G-I AEs (e.g., nausea, diarrhea, dyspepsia) occurred in a dose-dependent fashion.

Previous bisphosphonate therapy did not influence the incidence of AEs during the study, and G-I AEs of tiludronate were unrelated to gastric disorders at entry. Eight patients in the tiludronate group withdrew from the study due to AEs, compared to one patient in the placebo group.

There were no trends in changes in mean values of biochemical and hematological parameters during the study. However, few patients in tiludronate as well as in the placebo group showed abnormal values probably unrelated to test drugs. Changes in retinol binding protein, a sensitive indicator of renal tubular damage, were highly variable.

In conclusion, this controlled dose-ranging study demonstrated efficacy in terms of biochemical improvement in the treatment of Paget's disease of bone.

Adverse events to tiludronate were dose-related and frequently observed in 600 mg/day dose. G-I AEs were frequently seen in the latter group. Tiludronate 400 mg/day appeared to be the optimum dose for the treatment of Paget's disease of bone. The 600 mg/day dose of tiludronate provided relatively small gain in biochemical improvement, but such a gain was offset by an increased risk of G-I intolerance.

8.3.5 Reviewer's Comments/Conclusions of Study Results

The study design, selection of pagetic study population, and dosing schedule of tiludronate were appropriate for achieving the stated objectives. The overall protocol was quite similar to those adopted for two other controlled studies. The primary and secondary efficacy endpoints were also similar to those of other studies. Safety considerations were adequate and appropriate for a short-term clinical trial in patients with Paget's disease of bone.

The results of this controlled study seem to have clearly demonstrated biochemical efficacy of tiludronate in patients with Paget's disease of bone. Tiludronate 400 mg/day for 12 weeks appears to be the optimum safe and effective dose of tiludronate for this patient population. Tiludronate 600 mg/day for 12 weeks showed slightly greater efficacy in term of reduction in biochemical markers of increased bone turnover, but this slight benefit was offset by an increased frequency of overall AEs, particularly G-I adverse events. The overall results of this study lend

support to the results of two other controlled studies.

8.4 Uncontrolled Pagetic Studies

The sponsor has listed a total of 12 uncontrolled studies with tiludronate in which 9O1, 3C1, or 1A1 formulations (all tablets except for 1A1 capsules) of the drug were used. Formulations 3C1 (220, 100, and 50 mg) and 9O1 (200 and 50 mg) for tablets, differ in their composition of excipient ingredients, and vehicle (quantitatively and with respect to new ingredients). Formulation 1A1 capsules (200 and 100 mg) differed from tablets in their composition.

These are open-label Phase II and Phase III foreign (one U.S.+Canada) studies carried out in pagetic patients.

These studies are summarized:

Protocol # 1276: A single-dose (400 mg tablet) safety and tolerance study carried out in 6 pagetic patients. The results showed clinical tolerability and laboratory safety. The mean values for C_{max} , T_{max} , and AUC (0-24 hours, mg.h/l) were 1.82 mg/l, 1.1 hr, and 8.4, respectively. Biopharm. review will address pK variables in this and other studies.

Protocol # 1229: an open-label ascending dose short-term efficacy and safety study involving about 23 pagetic patients

Protocol # 1615: Open-label pK study carried out in 8 pagetic and 12 normal subjects with 400 mg tablet once daily for 12 days. There were no adverse events reported in this study. Biopharm. reviewer may have comments on pK data.

Protocol # 2084: An open-label parallel group study to compare the bioequipotency of two tablet (200 mg) formulations (3C1 and 9O1) of tiludronate in patients with Paget's disease of bone.

A total of 90 pagetic patients (confirmed by radiographic and scintigraphic evidence) were enrolled into this study. The inclusion and exclusion criteria were similar to those of the controlled studies.

Forty-five patients in each treatment group were to receive daily 400 mg of tiludronate for about 12 weeks. Actually, 39 and 49 patients started receiving tiludronate tablet formulations 3C1 and 9O1, respectively. Of these total 88 patients, 82 patients (36 on 3C1 and 46 on 9O1) completed

the study. Three patients in each treatment group discontinued the study due to AEs (2 in each group) and for "other reasons" (1 in each group).

The results were analyzed in terms of 90% confidence interval (C.I.) of SAP levels at Days 28, 56, and 84. At each time point, the 90% C.I. of the difference between two formulations was included in the reference interval, thus, showing equipotency of the two formulations. About 28.2% and 30.6% of patients treated with 3C1 and 9O1 formulations (of tablets) achieved normalization of elevated levels of SAP. After about three months of treatment, 69.2% of patients in the 3C1 group and 67.3% in the 9O1 group achieved successful response (based on criterion used in other controlled studies), respectively. At Day 28 and Day 56, the 90% C.I. of the differences between the formulations were within the reference intervals. However, at Day 84 90% C.I. was outside the reference interval, showing difference in two formulations. The two treatment were not comparable for global pain at entry. With formulation 9O1, relief of pagetic pain occurred at higher frequency than with formulation 3C1.

Two formulations appeared to be similar in terms of number of patients with 37 events of AEs. Four patient (2 in each group) discontinued treatment due to AEs.

The study also generated pK data (C_{max} , T_{max}) for two formulations. Biopharm. reviewer will comment on pK data obtained from this study.

The sponsor has concluded that the two formulations (3C1 and 9O1) are equipotent in terms of improvement in biochemical indices of paget's disease of bone.

Protocol # 1419A: An open-label, long-term (up to 3 courses), multi-center safety study with tiludronate. Patients recruited for this study completed the study under Protocol 1419 and achieved the responder status based on changes in elevated SAP levels. According to investigators' opinion, these patients required further treatment with tiludronate. The primary objective of this trial was to determine the long-term safety of tiludronate.

Ninety-three (55 male and 38 female) patients were enrolled into this study for the first course. All of the patients had radiographic evidence of Paget's disease of bone. Exclusion criteria were the same as followed in other controlled studies.

Patients received 400 mg of tiludronate tablets (formulation 3C1) daily for

3 months. Two successive treatment courses were separated by a washout period of 6 months. Tiludronate was administered 2 hours prior to any food intake as specified in other controlled studies.

Long-term safety, related to hematological, renal, and hepatic laboratory parameters was assessed.

A total of 93 patients were recruited for one course, 40 for two courses, and 6 for three courses. Four patients discontinued the study during Course 1 and one during Course 3 due to AEs. A total of 4 patients discontinued the study during Courses 1 and 2 due to other reasons. All 93 patients were evaluated for safety during Course 1.

During the Course 1 treatment period, gastrointestinal side effects were the most common events. About 22.6% of patients experienced abdominal pain, diarrhea, nausea or dyspepsia. G-I AEs represented about 38.5% of a total 78 adverse events reported. Other than G-I AEs, respiratory, musculoskeletal, skin and appendages related AEs occurred in about 4.3% to 7.5% of patients. Frequencies of AEs were similar during Courses 2 and 3. Of a total 5 patients who discontinued the study for AEs, two were due to moderate epigastralgia with or without constipation. Four additional patients experienced serious AEs; patient # 20016-granuloma annular of the inner face of arms, patient # 5005-suffered a stroke, patient # 32000-had preexisting lymphocytic leukemia, patient # 350004-needed total hip replacement for rheumatoid arthritis.

No clinically significant laboratory abnormality (other than hematology of leukemia patient) was noted, nor was any patient discontinued from the study due to laboratory AEs.

With regard to the efficacy of tiludronate therapy, there was significant decrease in SAP (from pretreatment mean value) at the end of treatment period. The nadir of SAP reached at the end of Courses 1 and 2 was similar to that reached at the end of the last course prior to entry into this study.

The interval between the Course 1 (of this study) and the last course preceding entry into this study was, on average 18 months. The interval between Courses 1 and Course 2 was 12 months.

The sponsor concluded that long-term (up to 3 courses) of treatment of patients with recurrence of biochemical indices of Paget's disease of bone with tiludronate for about 12 weeks was generally tolerated well. The

most common side effects of tiludronate observed with repeated courses of tiludronate therapy were related to gastrointestinal system. The frequency and nature of AEs during Courses 2 and 3 were similar to those of Course 1.

Protocol # 2054- An open-label, multi center study in which the efficacy and safety of tiludronate 400 mg/day (formulation 3C1 tablets) for 3 months was determined in the treatment of Paget's disease of bone. These patients were previously included in other tiludronate studies. At entry, SAP values had to be $\geq 130\%$ of that observed at the end of last treatment period. Tiludronate treatment was for 3 months at a dose of 400 mg/day with at least 6 months of follow-up. Follow-up period was extended to nine months if SAP remained under 130% of that achieved at the end of the preceding treatment period.

A total of 93 patients were enrolled into this study, but 74 patients were analyzed. Twenty-one patients were excluded from the analysis, because they received no prior tiludronate treatment. The median duration of Paget's disease in these patients was ten years.

The results were expressed as adjusted values as no centralized laboratory facilities were used. The observed SAP values were adjusted in terms of % increase above the upper limit of the laboratory normal range using the following formula:

Adjusted value (%)= (Observed value-Lab. upper limit value)/Lab.. upper limit value) X100

Compared to baseline value, SAP value significantly improved at the end of treatment and 6 and 9 months after follow-up. None of these patients achieved normalization of SAP. About 32% to 42% of treated patients were considered responders based on 50% or more decrease in baseline values of Courses 1, 2, or 3.

Total duration of exposure was about 233 pt-years in this study. G-I AEs were most frequent among all other events; about one-third of all AEs. One patient required implantation of a pacemaker for arrhythmia. Five patients discontinued the study due to AEs. Bloating (1 patient), diarrhea (2 patient), gastralgia, severe headache, somnolence, confusion, and disorientation (1 patient), and feeling of distension, nausea, blepharitis (1 patient).

There were no clinically significant changes in laboratory parameters.

The sponsor concluded that tiludronate treatment at a dose of 400 mg/day resulted in significant reduction in elevated levels of SAP. Decreased SAP values were sustained at least **9 months after cessation of treatment.**

About 31% of AEs were related to G-I system. The overall rate of AEs did not change with repeat courses of tiludronate.

Protocol # 724.86- An open-label study to evaluate the histological effects of tiludronate on bone in pagetic patients. A total of 10 patients were treated with tiludronate at 400 mg/day (tablet form) or 800mg/day (capsule form) for 6 months. Iliac bone biopsy was performed when possible after double tetracycline labeling. In addition, both biochemical efficacy and safety of treatment were assessed. Two patients received 800 mg/day and 10 patients received 400mg/day for 6 months.

Biopsy results were presented for only two patients who had two pagetic bone biopsies (one before and the other after treatment) performed. For one patient (#2.2), there was decreased osteoid parameters, and decreased number of osteoclasts (on decalcified bone). The other patient (#3.1) showed decreased number of osteoclasts after tiludronate.

With respect to clinical efficacy of treatment, three patients reported improvement of pagetic pain assessed by Huskisson Scale. Thirty-three, 66%, and 89% of patients were considered responders ($\geq 50\%$ decrease from baseline) at Day 60, 90 and 180, respectively.

Some patients showed hematological abnormalities during the study, but these were preexisting.

Sponsor has concluded that biopsy data are limited for any conclusion..

Protocol #856.87: An open-label study to determine clinical, biochemical and renal tolerance of a 6-month treatment course with tiludronate 400 mg/day. Ten patients were enrolled in this study following the usual biochemical criteria for Paget's disease of bone.

One patient developed G-I side effects (corrected by administration of drug once daily). Forty to seventy percent of patients (out of total 10 patients) showed decrease in SAP (considered as responders) and up to 40 percent of patients achieved normalization of SAP at the end of treatment period. Five out of 10 patients maintained their responder status at the end of follow-up period (Day 360). At the end of 6 months of treatment, about

10% of patients were reported as resistant (SAP \leq 25% decrease from baseline).

Protocol #1036: An open-label multicenter tolerability study with tiludronate 400 mg/day for 6-month in patients with Paget's disease of bone. Patients were recruited based on usual biochemical criteria for these patients and a total of 128 patients were treated. The primary study endpoint was to assess the tolerability of the drug.

Forty-seven patients were reported to experience 69 AEs. Of seven patients who discontinued the study due to AEs, 4 of them were due to AE related to gastrointestinal system.

Patient #107.2- After 19 days of treatment, patient developed moderate nausea and vomiting on Day 36. Tiludronate was withdrawn and on rechallenge the patient had recurrence of G-I side effects.

Patient # 207.3- Patient developed mild gastralgia, gastric heaviness, and dysphagia after 5 days of treatment. Tiludronate was withdrawn and treated for G-I symptoms. Patient recovered.

Patient # 202.1- Patient developed severe gastralgia after receiving a single dose of tiludronate 400mg. Tiludronate was discontinued, and the patient recovered.

Patient #501.10- A patient with previous history of gastric ulcer and anxiety developed aggravation of gastric ulcer after receiving tiludronate for about 70 days. Tiludronate was discontinued and the patient was given ranitidine.

When the AEs were analyzed by organ system, G-I AEs constituted about 55% of them. There was one incidence of anemia. Laboratory safety parameters were not analyzed in a central place. The raw data were transformed to provide comparable values in relation to the limits of the normal range. Four patients showed increase in serum creatinine values with tiludronate treatment, but in 3 of 4 cases values were within normal limits. In the remaining subject, creatinine increased to 2.6 mg/dL (with normal BUN value) throughout the study. Additional 6 months of treatment with tiludronate 400 g/day showed no change in the creatinine level. No other clinically significant abnormalities were reported in this study.

There was a significant decrease in SAP from baseline at Day 90 of

treatment with tiludronate 400mg/day. About 16% of patients (N=96) achieved normalization of SAP. At Day 90 and Day 180, 57% and 73% of patients were considered responders. Approximately, 10% of patients were reported as resistant to tiludronate treatment.

The mean urinary OHP/Cr ratio decrease significantly at Days 90 and 180 as a result of tiludronate therapy. Serum calcium showed a tendency to fall with tiludronate treatment.

The report concludes that the digestive system AEs resulted in discontinuation of therapy in about 4% of patients. Tiludronate treatment resulted in significant decrease in serum SAP and U/OHP/Cr ratio from baseline after 6 months. Decrease in bone pain and severity was also observed as a result of tiludronate therapy.

Protocol # 1307: A Phase II clinical and laboratory safety study of tiludronate 400 mg/day for 6 months in 5 patients with Paget's disease of bone. Two patients were reported to experience five AEs (back pain, myalgia, muscle weakness, dyspepsia, and pain). None of these AEs resulted in discontinuation of tiludronate therapy. Mean baseline SAP values decreased markedly after 6 months of therapy. In 3 out of 5 patients, serum SAP was normalized after treatment.

Protocol 1419: A multicenter, open-label study to assess the long-term safety of tiludronate 400 mg/day for 6 months in patients with Paget's disease of bone. Majority of patients had polyostotic Paget's disease of bone of 1-20 years duration. All patients were followed-up for an additional 6 months. The secondary objective of the study was to evaluate the duration of efficacy of tiludronate therapy. The study procedures were similar to those of the controlled study.

The results of the study were subjected to ITT and other routine statistical analyses.

Of a total 286 patients recruited for the study, 283 patients received treatment. Twenty-three patients discontinued the study due to AEs (8 serious and 15 non serious), and another 18 patients were withdrawn for other reasons.

A total of 489 AEs were experienced by 177 patients (62.5%) The sponsor states that due to variations in the forms used for recording AEs, data on their onset, duration, and severity were not obtained. About 31.5% of AEs were related to G-I system. Abdominal pain, nausea, and diarrhea were the

common G-I related AEs. Approx. 50% of AEs occurred during the first three months of treatment. About 10 patients experienced pain or nonpagetic fractures. None of these fractures appear to be related to the study drug. Ten patients experienced AE that resulted in withdrawal. Serious AEs included nausea, epigastric pain, vomiting, gastric burning, and gastric dyspepsia.

The laboratory results indicated a total of 75 patients with clinically significant treatment emergent laboratory abnormalities (TELAs, defined appropriately in this report). According to sponsor's assessment 9 of 75 patients were considered important. Of these 9 cases, hematological abnormalities were in three cases, abnormal liver function tests in 3 cases, abnormal lipid profile in 2 cases, and hypokalemia in 1 case (**Comments: Review of these cases revealed no direct causal relationship to tiludronate therapy and it is difficult to assess their clinical significance objectively**). None of the changes in laboratory variables appeared clinically significant .

From efficacy standpoint, there were significant decreases (from baseline) in transformed (due to wide variation in normal ranges between individual laboratories) SAP data at months 3, 6, 9, and 12. During the follow-up period (month 7-12) decreased SAP values did not change significantly. At Months 3,6,9, and 12, 21.4%, 37.9%, 42.5%, 39.1% of a total 177 patients (who had SAP measurement at every visit) achieved normalization of SAP during the study. Analysis of normalization (at different time points) of SAP data based on previous bisphosphonate therapy revealed significantly more normalized patients with no previous bisphosphonate at Month 9. In general, there was a trend of more patients with no previous bisphosphonate to normalize as a results of tiludronate therapy.

About 59% of patients (N=32) experienced improvement in the severity of bone (skull) pain at Month 6 and improved status remained up to Month 12. Complete disappearance of pagetic bone pain (at sites with bone lesions radiologically confirmed) was observed in 42.9% and 50% of patients (N=112-114) at Months 6 and 12 , respectively. Global assessment based on judgement of both patients and investigators, showed improvement in about 40% of patients at Months 6-12,

The report concludes that there was highest distribution (47.2%) and incidence (31.5%) of AEs during the first three months of treatment. The most frequent AEs were related to G-I system; 31.5% of all AEs. Eleven patients (3.9%) experienced fractures, mostly under treatment. The

laboratory parameters showed no clinically significant changes directly attributable to tiludronate therapy.

Tiludronate therapy resulted in significant decrease in SAP and improvement in bone pain in about half of the treated patients up to 12 months.

Protocol #2242: An open-label, multicenter study of tiludronate for retreatment of pagetic patients who had completed the Study P 1845. The SAP levels of these patients were at twice the upper limit of normal and met all other criteria for inclusion of the initial study (P 1845). This is an interim report of the study. The treatment groups, subgroups, and Tiludronate cycles are presented in Table 33.

Table 33. Classification of subjects.

Treatment Groups	Treat. Subgroups	Cycle of Tiludronate Treat		
		First	Second	Third.
1	<u>Subgroup P/4</u> Received placebo in P 1845 study; received Tilud.400mg in this study (P 2242)	Enroll.1 of this study-P2242		
2	<u>Subgroup 2/4</u> Received 200mg Tilud.in P 1845 study; received 400 mg of Tilud.in enroll.1 of this study.	200mg Tilud.in study P1845	Enroll. 1 of study P 2242	
	<u>Subgroup 4/4</u> Received 400mg of Tilud.in study P 1845; received same in study P2242	400mg Tilud. in study P1845	Enroll. 1 of study P2242	
	<u>SubgroupP/4.4</u> Rceived placebo in study 1845; received Tilud. 400mg in enroll.1 and 2 of study P2242	Enroll.1 of study P2242	Enroll. 2 of study P 2242	
3	<u>Subgroup 2/4.4</u> Received 200mg of Tilud. in study P 1845; 400mg in enroll. 1 of study P2242 and 400mg in enroll.2 of study P2242	200mf of Tilud. in studyP 1845	Enroll. 1 of study P 2242	Enroll. 2 of study P 2242
	<u>Subgroup 4/4.4</u> Received 400mg of Tilud. in study P1845;received 400 mg in enroll. 1 and 2 of study P 2242	400mg Tilud. in study P1845	Enroll. 1 of study P2242	Enroll. 2of study P 2242

All patients in group 2 were in treatment group 1 and subgroup group P/4. Subjects in group 3, subgroup 2/4,4 were in treatment group 2, subgroup 2/4; and all subjects in treatment group 3, subgroup 4/4,4 were in treatment group 2, subgroup 4/4.

The primary efficacy endpoint was percent change in SAP from baseline at Week 12. Secondary efficacy endpoints of the study were: percent of patients with normalization of SAP, percent change in U/OHP/Cr ratio from baseline, and radiographic improvement of skeletal lesions.

The efficacy results are summarized in Table 34.

Table 34. Changes in efficacy variables at Week 12.

Efficacy Variables	<u>Mean Percent Change From Baseline</u>	
	Treatment Group 1/ Tiludronate Cycle 1 (N=40)	Treatment Group 2/ Tiludronate Cycle 2 (N=35)
SAP	-58.1%** (N=38)	-34.4%** (N=33)
SAP (Bone Specific)	-62.5%** (N=38)	-36.4%** (N=32)
U/OHP/Cr	-45.4%** (N=36)	-30.5%** (N=32)

In treatment group 1, four patients achieved normalization of SAP and none in treatment group 2 during the first cycle. However, during their second cycle, 2 patients achieved normalization of SAP.

A small group of 13 patients, showed radiological evidence of healing of osteolytic pagetic lesions.

Most common AEs were related to G-I system (26 of 71 patients, 37%).

The report concludes that repeat cycles of treatment with tiludronate resulted in significant decreases in mean SAP values. Beneficial effects were seen after about 12 weeks of treatment. Biochemical improvement was associated with radiological healing of skeletal lesions.

Retreatment with tiludronate showed no increase in incidence of clinical AEs compared to initial course of the therapy.

Sponsor's discussion of safety data from uncontrolled studies:

Analysis of pooled data from all 12 studies (N=667) showed G-I system related AEs were the most common at both 400 and 600 mg/ day doses. About 26% and 39% of patients at these two doses experienced G-I system disorders such as abdominal pain, nausea, and diarrhea. The incidence of diarrhea was significantly greater at 600mg dose.

Five studies (P 1036, P1419, P 1419A, P2054, and P 2242) were analyzed for efficacy purpose. In all five studies, tiludronate treatment at a dose of 400 mg/day for 3-6 months resulted in significant decrease in SAP from baseline. The mean percent changes from baseline to Month 3 varied from -31% to -58% in these studies.

The sponsor concluded that the results of five uncontrolled efficacy studies demonstrated significant decrease in mean SAP from baseline as a result of treatment with tiludronate at a dose of 400mg/day for 3 and 6 months. Since more G-I AEs occurred with tiludronate \geq 600mg/day, 400mg/day was considered the optimum dose for treatment of Paget's disease of bone.

Reviewer's comments on uncontrolled pagetic studies with tiludronate (3C1 and 9O1 formulations).

These open-label studies were designed to provide additional data in support of the efficacy and safety of tiludronate in the treatment of Paget's disease of bone.

For Paget's disease, each of the five efficacy studies (as considered by the sponsor) were satisfactory in terms of the size of the patient population, inclusion criteria, tiludronate treatment regimen, primary and secondary efficacy parameters, and safety considerations. Instead of a parallel group of patients on placebo, each patient served as his or her own control in these studies.

The overall results of five such studies demonstrated significant decrease in mean SAP values from baseline as a result of tiludronate treatment at a dose of 400mg/day for 3 to 6 months. The primary efficacy of the controlled clinical trials was significant reduction in baseline elevated levels of SAP. In addition, these studies also provided some other information on tiludronate therapy and these are:

- a. The two formulations (3C1 and 9O1 for tablets) were shown to be

equipotent in terms of therapeutic response (decrease in SAP and frequencies of AEs). Protocol #2084

b. Repeat treatment with tiludronate in patients with recurrence of elevated SAP resulted in reduction, as observed with initial treatment in most patients. AEs after repeat courses of tiludronate were similar with respect to frequency and nature of common G-I side effects. Protocols # 1419A and 2242

c. Tiludronate treatment at a dose of 400mg/day resulted in significant decrease in mean baseline SAP value and decreased SAP was **sustained for at least 9 months or more after cessation of treatment**. Protocols # 2054, 1419.

d. With respect to tiludronate treatment response in patients with or without previous treatment with other bisphosphonates, response (normalization of SAP) rate was better in patients without previous bisphosphonate treatment. Protocol # 1419.

The overall efficacy and safety data accrued from these uncontrolled studies are in agreement with those obtained from pivotal controlled studies.

8.5 Other studies

These studies provide no relevant data with respect to proposed Indications and Usage of tiludronate in this NDA submission.

9 Overview of Efficacy

This NDA is for use of Skelid (tiludronate disodium) in the treatment of Paget's disease of bone, characterized by increased bone resorption and formation, resulting in bone pain, deformity, histologically abnormal bone, and increased risk of fractures.

Currently the following drugs are approved for the treatment of Paget's disease of bone:

Calcitonin (salmon and human)
Didronel (etidronate disodium)
Aredia (pamidronate disodium for injection, i.v.)
Fosamax (alendronate sodium)

Three controlled studies (2 placebo- controlled and one positive-controlled) were carried out to demonstrate the safety and efficacy of Skelid in the treatment of Paget's disease of bone. The objective of the active-controlled study with etidronate disodium was to demonstrate that tiludronate (400mg/day for 3 or 6 months) was "more effective" than etidronate (same dose and duration of treatment) in the treatment of Paget's disease of bone.

The controlled clinical trials were carried out with two different tablet formulation of Skelid, 3C1 and 9O1. There were some difference in the bioavailability of these two tablet formulations. Based on AUC and C_{max} , 9O1 tablet formulation was shown to have approximately 15% greater bioavailability than 3C1 tablet. The results of controlled clinical trial have demonstrated no clinically significant differences between these two tablet formulations with respect to changes in primary efficacy endpoint, i.e., changes in SAP. The sponsor intends to market 9O1 tablet formulation.

Three controlled studies were similar with respect to selection of pagetic study population, dosing schedule of tiludronate, primary and secondary efficacy endpoints, plans for statistical evaluation of results, and safety parameters.

Treatment success in all three controlled studies was defined as $\geq 50\%$ decrease in SAP from baseline. Almost all drugs previously approved for this indication demonstrated their efficacy in terms of significant decrease in elevated levels of SAP along with positive effects on a series of secondary efficacy parameters (e.g, decrease in U/OHP/Cr ratio, improvement in pagetic bone pain, neurological deficits, radiographic improvement in pagetic bone lesions).

The results of two placebo-controlled studies have shown significant decreases (ranging from 51%-58%) from baseline mean values. In one study (P 1845), the treatment success was in 61% of patients treated with tiludronate at a dose of 400mg/day for 12 weeks. The success rate was maintained at 72% of patients at the end of follow-up period at Week 24. In the comparative study (P 1552), about 55% to 60% of patients showed treatment success with the same dosage regimen of tiludronate after 3 months. After 6 months of treatment with tiludronate, treatment success was observed in about 70% of patients. The SAP values started to decrease about 4 weeks after initiation of treatment and reached the nadir value between 3 to 6 months.

Tiludronate treatment at a dose of 400mg/day for 3 months also resulted in significant decrease in U/OHP/Cr ratio (marker of bone resorption). Study of relationship between changes in SAP and U/OHP/Cr ratio revealed early inhibition of bone resorption than bone formation.

All three studies demonstrated significant improvement in bone pain as a result of tiludronate therapy after three months of treatment.

The Study carried out under Protocol # 1845 provided some evidence in support of **radiographic healing** of osteolytic pagetic lesions. The same study provided bone biopsy data to show that 12 weeks of tiludronate therapy showed no evidence of mineralization defects after 12 weeks of treatment. **This reviewer feels that biopsy data are too limited to draw any definitive conclusion on the long-term effect of tiludronate on bone formation.**

The results of the active-controlled study have shown that tiludronate at a dose of 400mg/day for 3 months (followed by 3 months of placebo) is more effective than etidronate (400mg/day for 6 months) with respect to percent of patients with normalization of SAP

Four to 19% of patients treated with tiludronate showed resistance to therapy at 3-6 months (Protocols # 1552 and 1619)

The results of uncontrolled studies (about five identified earlier in the review) lend support to overall efficacy (in terms of biochemical and symptomatic improvement) results observed in controlled studies. The following additional information were also obtained from these studies:

- a. Two formulations (3C1 and (O1) for tablets were therapeutically equipotent for the treatment of Paget's disease of bone.
- b. Repeat treatment with tiludronate in patients with recurrence (of biochemical indices) resulted in biochemical improvement, similar to that observed at initial therap in most patients.
- c. Tiludronate (400mg/day)-induced decrease in SAP values was sustained for at least 9 months after cessation of treatment.

In all three controlled studies, the percentages of tiludronate-treated patients who achieved normalization (SAP value within reference range) ranged between 13% to 21% at Week 12 and 27% to 39% at Week 24 (at 6 months).

10 Overview of Safety

There were no significant differences between the three controlled studies with respect to percent of patients with one or more AEs. The percent of patients with AEs increased in a dose-dependent fashion in one study (Protocol # 1619).

Gastro-intestinal AEs (nausea, diarrhea, abdominal pain, dyspepsia) were the most common disorders experienced by the tiludronate treated patients in these studies. Although, G-I AEs required no corrective therapy, in general, about 7% of patients in one study dropped out due to G-I AEs (P1552). **Some of the G-I AEs reported in uncontrolled studies are similar to those reported with alendronate (postmarketing adverse experiences).**

The overall safety laboratory biochemical data showed no clinically significant information on phosphocalcium and hematological variables.

The sponsor has listed all AEs reported in $\geq 1\%$ of pagetic patients in various controlled and uncontrolled studies with a duration of 1 to 6 months in the draft package insert. This list along with presentation of other less frequent AEs that occurred in pagetic patients treated with Skelid (of at least one-month duration) provided adequate information on the safety of the drug.

11 Labeling Review

11.1 **Description** See Chemistry review for comments.

11.2 **Clinical Pharmacology**

Mechanism of Action:

The last two sentences of paragraph are appropriate for incorporation under subheading "Animal Pharmacology" of this section. The statement regarding is not relevant to proposed use for Paget's disease of bone. Regarding its effects on bone mineralization, the information is more appropriate for "animal Pharmacology" subheading under this section.

Pharmacokinetics: Biopharm. reviewer may have comments on ADME (including special populations), and

Drug-Drug Interactions.

Pharmacodynamics: The last paragraph under this subsection may be appropriate for incorporation "Animal Pharmacology" subheading. Sponsor should incorporate a brief description of clinical manifestations of Paget's disease of bone.

Clinical Efficacy:

The last sentence in second paragraph under this subheading should be revised to Read " In two uncontrolled studies the median time to retreatment was 18 months after the first treatment cycle..retreated with Skelid." Information provided under this subheading seems to reflect the results of three controlled studies.

Animal Pharmacology subsection needs to be included under "Clinical Pharmacology" section. Pharmacology review will determine what relevant preclinical information needs to be incorporated under this subsection.

11.3 Indications and Usage

The statement under this section should be revised to read "Skelid is indicated for the treatment of Paget's disease of bone (osteitis deformans).

Treatment is indicated in patients with Paget's disease of bone and level of serum of alkaline phosphatase (SAP) at least twice the upper limit of normal.

11.4 Contraindications

Needs no revision.

11.5 Warnings

This section should incorporate the statement "Skelid, like other bisphosphonates, may cause upper gastrointestinal disorders, such as dysphagia, esophagitis, esophageal ulcer, and gastric ulcer."

11.6 Precautions.

General : Delete from the statement.

Information for Patients : Statements incorporated under this subheading appear to be appropriate.

Drug Interactions :

The following sentence should be added at the end " No specific drug interaction studies were performed with Skelid."

Carcinogenesis, Mutagenesis, Impairment of Fertility :

Pharmacology review may have some comments.

Pregnancy Category C:

Pharmacology review may have comments on this subsection.

Nursing Mothers: Statements incorporated under this subsection are adequate and in conformity with our guidance.

Pediatric Use : incorporated statements are appropriate.

11.7 **Adverse Reactions**

Information on percent of patients with most common AEs, i.e., gastrointestinal system disorders in **controlled and uncontrolled** studies should be summarized in the first paragraph.

11.8 **Overdosage**

Information presented under this section appears to be adequate, considering limited clinical experience with this drug from all controlled and uncontrolled trials.

11.9 **Dosage and Administration**

The second paragraph under this section should be revised to read "Following therapy, allow an interval of 3 months to assess response. Specific data regarding retreatment are inadequate, although results from uncontrolled studies indicate favorable

biochemical improvement similar to initial tiludronate treatment." In a few open studies, up to 3 courses of tiludronate have been tried.

11.10 How Supplied

Chemistry review may have some comments on this section.

Reviewer's Overall Comments on Draft Package Insert

It is suggested that after all the reviews are completed, we should meet and discuss comments and revisions made by all the reviewers, prior to communication to the sponsor.

12. Conclusions and Recommendations:

The results from adequate and well controlled clinical trials of Skelid (tiludronate disodium) have provided substantial evidence of efficacy (in terms of biochemical improvement) and safety of the drug for the treatment of Paget's disease of bone. The controlled studies have also shown improvement in pagetic bone pain and radiological healing of osteolytic bone lesions in some patients. The data from uncontrolled studies seem to support the overall efficacy results of controlled studies.

G-I adverse events, such as nausea, diarrhea, abdominal pain, dyspepsia were common with Skelid therapy.

Compared to other approved drugs for the treatment of Paget's disease of bone, Skelid appears to be more effective than calcitonin and etidronate disodium, and close to Fosamax (alendronate sodium) in terms of proportion of patients with treatment success, normalization of elevated SAP, improvement in pagetic pain, and duration of decreased SAP after cessation of treatment, and radiological evidence of healing of osteolytic bone lesions. Skelid showed no evidence of defective mineralization (based on bone biopsy data) with short-term therapy, but these data are very limited.

Skelid, 400mg/day for 12 weeks appears to be the optimum dose for the proposed indication. The draft package insert requires further revisions based on specific recommendations from the reviewers. Precautions, Warnings, and Adverse Reactions sections particularly need revisions based on our experience with Fosamax.

The NDA 20-707, which provides substantial evidence of efficacy and safety of

Skelid for the treatment of Paget's disease of bone is approvable.



S.N.Dutta, M.D.

CC: Orig. NDA 20-707
HFD-340
HFD-510/SND/11.22..96

Handwritten notes:
S.N. Dutta
1-10-97

Addendum to MOR of NDA 20-707
(Review of 4-month Periodic Safety Update Report)

1. Date of this amendment: June 28, 1996.
2. Materials reviewed: Periodic Safety Update Report (consists of 7 volumes). The safety update report covers the following populations:
 - a. Patients in uncontrolled pagetic studies.
 - b. Patients in controlled and uncontrolled non-pagetic studies.
 - c. Normal healthy volunteers.
3. Summary review:

Uncontrolled pagetic studies-

There are three uncontrolled pagetic studies. Two of these studies (P1611 and P2134) are completed and the remaining one (P2054) is ongoing.

Studies P1611 and P2130- Open-label studies to evaluate "bone tolerability" (histomorphometry) of Skelid (400 mg/day for 3 months) in a total of four patients with Paget's disease of bone. No drug-related clinical or laboratory adverse experiences (AEs) were reported in these patients. Limited data preclude any objective evaluation of the effect of treatment on bone remodeling.

Study P2054 (ongoing) - The cutoff date for interim data analysis for safety was May 15, 1995. A total of 159 pagetic patients received Skelid 400mg/day) for variable periods. The mean duration of Skelid treatment was 15.9 weeks.

Sixty percent of patients (n=159) were reported to experience at least one AE. AEs related to gastrointestinal, musculo-skeletal, and nervous system were reported in 21%, 19%, and 13% of patients. About 12% of patients were reported to experience one or more severe AEs (including those related to musculo-skeletal and G-I systems). About 17% of patients were reported to experience at least one serious AE. Serious musculo-skeletal AEs (i.e., arthralgia, arthritis, bone disorder, fracture pathological) were most frequently reported (in about 3% of patients). Four patients were reported to discontinue the study due to serious or non-serious AEs. Four patients (2 males and 2 females) were reported to experience "fracture pathological" during the course of treatment with Skelid 400/mg/day. In one patient, rib fracture was reported to occur as a result of trauma. Three of four patients with fracture received previous courses of bisphosphonates (tiludronate or other non-specified bisphosphonates). Sponsor states that none of these fractures were due to Skelid treatment.

There were no clinically relevant consistent changes in the laboratory parameters.

The overall results showed that comparable proportion of patients in Study P2054 and Integrated Safety Summary (ISS) population experienced at least one AE (60% vs 57%-63%). Musculo-skeletal AEs were reported to occur at an increased frequency in Study P2054, compared to that of the ISS population (19% vs 7%-10%). (Comments:.. Sponsor states that this study is ongoing and the rate of musculo-skeletal AEs may change with the final analysis of the data).

The Study P2054 and the ISS pagetic population showed no clinically significant differences with respect to changes in relevant laboratory parameters. The number of "fracture pathological" is too small, and these patients are likely to experience fracture as a complication of the disease process. It is difficult to determine the cause of "fracture pathological" from the limited data accrued from these studies.

Non-pagetic studies- There are ten non-pagetic studies listed in this report. Nine of ten studies were presented in the ISS. Safety update report includes four additional blinded osteoporosis studies which are ongoing. Treatment allocation for patients in ongoing studies were not audited. A total of 192 and 444 patients were randomized to receive placebo and Skelid, respectively in ten completed studies. One hundred sixty-six patients in the placebo and 377 patients in the Skelid groups completed the study.(Comments: Sponsor has provided a table on patient accountability (see Table 4.2, vol.1, p.32).

The duration of Skelid treatment varied from >0-<10 weeks to > 14 weeks. The mean duration of treatment at a dose of 400mg/day was 9.2 weeks. The daily dose of Skelid varied from \leq 100mg to \geq 600mg (up to 1200 mg/day in 3 patients).

Proportion of patients with any AE (by Body System) was similar for the placebo (n=188) and Skelid (n=101) 400mg/day (36% vs 37%) groups. Twenty-six percent of patients in the total Skelid group experienced any G-I AE as opposed to 15% of patients in the placebo group (difference was not statistically significant). However, nausea and vomiting occurred in significantly higher number of Skelid treated patients relative to placebo. With respect to musculo-skeletal AEs, there was no significant difference between the placebo and Skelid 400 mg group.

There were no statistically significant differences between treatment groups with respect to proportion of patients with at least one severe AE (including G-I AE). With respect to proportion of patients with at least one serious AE, there was no statistically significant difference between the total Skelid and the placebo groups. In both the placebo and total Skelid groups, 2% of patients were reported to experience "fracture pathological."

The overall safety update data from ten studies showed similar proportion of patients (7% to 9% of patients among all treatment groups), who discontinued from the study and /or study drug due to AEs. There was no significant difference between the placebo and Skelid (at different doses) groups with respect to discontinuation from the study due to G-I

AEs.

For serum chemistry parameters, higher proportions of patients (6% to 18%) with clinically significant increase in GGT were in the Skelid (400 and \geq 600mg/day) groups. In the placebo group, only 1% of patients had clinically relevant increase in GGT.

revealed the following:

In Studies P1900 and P2056, 92% to 96% of patients were reported to experience one or more AEs. There were no significant differences between these two studies with respect to AEs (by Body System) reported by \geq 5% of patients. All four studies were reported to be similar with respect to percent of patients with serious AEs (by Body System). One patient (in Study P2056, # 004-39-008) was reported to experience severe erosive esophagitis with upper G-I bleeding. The patient recovered after hospitalization and parenteral treatment with antiulcer drugs (Prilosec and Carafate). Study drug was discontinued. The blinded code was not broken for this patient.

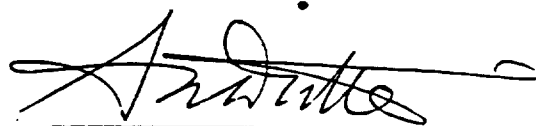
Studies in healthy volunteers- In these two completed studies, a total of 36 subjects were exposed to Skelid 200 mg/day for 2-10 days (n=24) or 400 mg/day for 11-20 days (n=12). Safety data from these studies were similar to those reported by the ISS

population.

Safety data obtained from compassionate use of Skelid in a pagetic patient and from published literature- No new clinically meaningful data provided.

4. Conclusion and recommendation: There were no clinically significant differences between the uncontrolled pagetic population of this report and all ISS populations, with respect to safety profile of Skelid.

The safety update report provides no new clinically significant information for pagetic patients.



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