A LENDRONATE SODIUM (ALENDRONIC acid, monosodium salt of 4-amino-1-hydroxybutylidene-1,1-bisphosphate) is a member of a class of drugs known as bisphosphonates (1). Bisphosphonates potently inhibit bone resorption (2) by interfering with protein prenylation (3, 4), a process that renders the osteoclast inactive. Oral alendronate (ALN) is approved for use among adults in the treatment and prevention of postmenopausal osteoporosis (5, 6) and glucocorticoid-induced osteoporosis and for the treatment of Paget’s disease of bone (7), whereas iv ALN has been used experimentally in the hypercalcemia of malignancy (8). In recent years, there has been increasing attention to osteoporotic conditions of childhood, including osteogenesis imperfecta (OI, a congenital bone fragility disorder) (9).

There is a need for therapeutic options among children with both congenital and acquired bone fragility. The iv bisphosphonate, pamidronate, has been shown in a number of studies to benefit children with moderate to severe OI, with improved pain, mobility, grip force, bone mass, and reduced fractures impacting positively on quality of life (10–14). Such reports have led to interest in the use of oral bisphosphonates for the treatment of pediatric osteoporosis (15). The goal of the present study was to evaluate the pharmacokinetics of oral ALN and the drug’s short-term tolerability among pediatric patients, 4–16 yr of age, with a mild form of OI.

Patients and Methods

Participants

Twenty-five children living in the Canadian provinces of Que´bec and Ontario were enrolled in the study. The children met the following criteria before study enrollment: 1) age 4–16 yr, with a clinical diagnosis of OI type I according to the Sillence classification (16); 2) ability to follow all dosing instructions (including ability to stand or sit upright for at least 2 h after dosing) and to complete 24-h urine collections; and 3) for females with reproductive potential, a serum β-human chorionic go-
nadroparin level consistent with the nongravid state was required before study enrollment and was repeated before each dosing with ALN. Furthermore, such patients were enrolled only if they agreed to use medically approved contraception for at least 14 d before enrollment and for 14 d after the last dose of study drug. Urine or serum β-human chorionic gonadotropin levels were also determined at 10–14 d after the last dose of ALN in these patients.

The exclusion criteria were: 1) serum ionized calcium level obtained at screening that was below the lower limit of normal; 2) renal impairment defined as an estimated glomerular filtration rate less than 35 ml/min per 1.73 m² body surface area at screening based on the Schwartz formula (17); 3) abnormalities of the esophagus that delayed esophageal emptying (such as stricture or achalasia) and any disease affecting the stomach or proximal small intestine resulting in malabsorption; 4) a recent history (within 1 yr before screening) of major upper gastrointestinal tract disease (above the ileum), a history of upper gastrointestinal tract surgery, and the use of medications that altered gastric acidity; 5) a history of hypothyroidism, unless the patient had been treated with a stable dose of thyroid hormone for at least 3 months immediately before screening and the patient was euthyroid, as defined by a normal serum free thyroxine (T<sub>4</sub>) level (as appropriate); and 6) previous treatment with a bisphosphonate.

Approval for the study was obtained from the McGill University Institutional Review Board. Written informed consent was obtained before enrollment from the parents and from patients who were at least 14.0 yr. Assent was also obtained from participants between the ages of 8.0 and 13.9 yr.

### Adult comparison studies

The ALN oral bioavailability data used for comparison to the results in this report were obtained from four adult studies that were conducted during the development of ALN and that have been reviewed by regulatory agencies (including the United States Food and Drug Administration) as part of the marketing application approval process. The following is a description of these studies, including the gender, age, and ethnicity of participants.

1. **Title**: An open-label, randomized, five-period crossover study in postmenopausal female volunteers to investigate the oral absorption of ALN sodium final production process tablets (with data from ALN 10-mg oral tablet and ALN 125 μg IV treatments). **Demographic data**: Twenty postmenopausal women participated, with a mean age of 58 yr (range, 50–75 yr) (13 Hispanic, six Caucasian, and one American Indian).

2. **Title**: An open-label, randomized, two-period crossover study in male volunteers to investigate the oral bioavailability of ALN sodium (with data from ALN 10-mg oral tablet and ALN 125-μg IV treatments). **Demographic data**: Sixteen adult males participated, with a mean age of 50 yr (range, 25–70 yr) (10 Caucasian and six African American).

3. **Title**: An open-label, randomized, two-period study to investigate the influence of short-term administration of oral corticosteroids on the oral absorption of ALN in healthy volunteers (with data from ALN 20-mg oral tablet without concomitant prednisone and ALN 40-μg IV treatments). **Demographic data**: There were 16 participants (eight males and eight females) with a mean age of 53 yr (range, 25–70 yr) (15 Caucasian and one Black).

4. **Title**: An open, randomized, three-period, crossover study in postmenopausal females to determine the oral bioavailability of the 35- and 70-mg ALN tablets (with data from ALN 35-mg oral tablet and ALN 250 μg IV treatments). **Demographic data**: Thirty-four postmenopausal women participated, with a mean age of 59 yr (range, 50–72 yr) (32 Hispanic, one Caucasian, and one Black).

The use of these studies and the specific data from these studies for the adult control panel was prespecified at the design stage of the current protocol and constitutes the 86 adult subjects shown in Tables 2 and 3 and in Fig. 1.

### Study design

#### Patient procedures

This was an open-label, two-period, crossover study in which patients were administered two single doses (one oral and one IV) of ALN separated by at least a 14-d washout period. Patients weighing less than 40 kg at screening received ALN 35 mg and those weighing 40 kg or more received ALN 70 mg, both as an oral tablet. The IV dose of ALN was 125 μg for all patients. The sequence of oral and IV dosing for each patient was determined by a computer-generated allocation schedule.

Patients were admitted to hospital the evening before ALN was administered. A low-caloric snack was offered, which was followed by an 11-h overnight fast. The study pediatrician (L.M.W.) administered ALN at approximately 0800 h. The oral dose of ALN was given with 180 ml of tap water followed by a 2-h fast in the upright position. The 125-μg IV dose was infused over 2 h. At the start of the ALN infusion, 180 ml of tap water was given to drink, and patients subsequently remained upright during the infusion.

Urine was collected during three defined time intervals that included the 2 h immediately before dosing, and from 0–8 and 8–24 h after ALN dosing. The total volume of urine was recorded for each collection interval. Between 375 and 750 ml of oral fluids were given during each 8-h period after administration of each dose.

**Urine and ALN infusate sample processing for determination of ALN concentration**

Aliquots of urine were stored at −20°C until analysis. ALN concentration was measured by HPLC with fluorescence detection, as previously described (18). The total urinary excretion (TUE) of ALN (TUE-ALN) for the given time periods (−2 to 0, 0–8, and 8–24 h relative to the time of ALN dosing) was determined by multiplying the concentration of ALN in the analyzed aliquot by the total urine volume for the period. Dose-adjusted TUE-ALN was calculated by dividing TUE-ALN by the administered dose of ALN. The exact dose of ALN delivered by IV infusion was assessed by measuring the concentration of ALN in an aliquot of the infusate and multiplying the result by the volume infused, as determined by the difference between the preinfusion and postinfusion weight of the IV ALN solution and infusion apparatus.

The oral bioavailability of ALN was estimated as the dose-adjusted TUE-ALN after the oral dose divided by dose-adjusted TUE-ALN after the IV dose.

**ALN single-dose tolerability**

Patients remained in hospital for 24 h after dosing, and vital signs were assessed regularly. A complete blood count and serum levels of albumin, alanine aminotransferase, aspartate aminotransferase, total bilirubin, blood urea nitrogen, creatinine, glucose, alkaline phosphatase, calcium, potassium, and sodium were evaluated at baseline and 24 h after the second dose. A urinalysis was obtained at the same time periods. Within 10–14 d after the second dose, information regarding potential adverse experiences was obtained by telephone interview.

Adverse experiences were classified by the study pediatrician to be definitely, possibly, probably, probably not, or definitely not related to the study medication, according to the definitions of causality for drug studies (19).

### Statistical methods

Summary statistics to compare the laboratory safety parameters at baseline and after dosing were calculated. For each weight category, the TUE-ALN was analyzed using an ANOVA model appropriate for a two-period, crossover design. The ANOVA model contained the following factors: sequence, subject within sequence, period, and treatment. A log transformation was applied to the TUE data. The oral bioavailability (using TUE) and 95% confidence interval (CI), based upon the t distribution of the dose-adjusted least-squares mean ratio between the oral tablet and 125-μg IV (dose adjusted to a common 1-mg dose) were computed for each pediatric weight category (<40 kg and ≥40 kg). Least-squares means were used to correct for a slight imbalance within the model factor sequence. The model assumptions of normality and homogenous variance were verified by graphical methods.

The bioavailability of ALN was compared with data determined a priori from previously carried out adult studies (n = 86 adult subjects; Denker, A. E., A. Porras, S. Shugarts, W. Kline, C. Mao, A. Maes, P. Larson, and P. Deutsch, unpublished data; see Patients and Methods). Group differences (<40 kg, ≥40 kg, and adult controls) were tested for significance using a one-way ANOVA model. A log transformation was applied to the bioavailability and TUE data. Estimation of both weight categories (<40 kg and ≥40 kg) relative to the adult data on the bioavailability geometric mean ratio (pediatric/adults) was computed along with the corresponding 95% CI using the t distribution. A quantile-quantile plot verified the model assumption of normality, whereas the assumption of
homogeneous variance was verified by Levene’s test. The relative TUE data after the 35-mg oral tablet (\(40\) kg), the 70-mg oral tablet (\(40\) kg), and the 125-\(\mu\)g iv dose for comparison with the adult controls was computed using the adult data, dose adjusted to 1 mg.

### Results

#### Patient characteristics

Twenty-five pediatric patients with a diagnosis of OI type I were invited to participate in the study, all of whom agreed after written, informed consent. Twenty-four patients (ages 4.4–16.0 yr; eight girls) successfully completed the study. One patient (a 6-yr-old Caucasian girl) was unable to swallow the oral 35-mg tablet in the first period and was subsequently withdrawn from the study. Of the remaining patients, 23 were Caucasian and one was of Middle Eastern descent. Patients weighing less than 40 kg had a mean age of 8.1 yr upon study entry (range, 4.4–14.6 yr) and a mean weight of 23.1 kg (range, 13.6–39.8 kg). Patients weighing 40 kg or more had a mean age of 14.4 yr at the time of enrollment (range, 11.6–16.0) and a mean weight of 56.5 kg (range, 40.1–81.0 kg). Nine patients had active secondary medical diagnoses at the time of enrollment that did not impact on eligibility, including mild asthma (\(n = 3\)), migraine (\(n = 3\)), attention deficit hyperactivity disorder (\(n = 2\)), dentinogenesis imperfecta (\(n = 1\)), environmental allergies (\(n = 1\)), benign heart murmur (\(n = 1\)), and myopia with astigmatism (\(n = 1\)).

#### ALN pharmacokinetics

As shown in Table 1, average bioavailability was 0.43 and 0.56% for the smaller and larger weight groups, respectively.

<table>
<thead>
<tr>
<th>Dose</th>
<th>n</th>
<th>LS mean TUE-ALN</th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
<th>sd</th>
<th>Bioavailability (%)</th>
<th>95% CI for bioavailability</th>
<th>RMSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 kg</td>
<td>12</td>
<td>1.9</td>
<td>1.8</td>
<td>0.7</td>
<td>7.0</td>
<td>1.6</td>
<td>0.43 (0.28, 0.64)</td>
<td>0.444</td>
<td></td>
</tr>
<tr>
<td>35 mg</td>
<td>12</td>
<td>1.9</td>
<td>1.8</td>
<td>0.7</td>
<td>7.0</td>
<td>1.6</td>
<td>0.43 (0.28, 0.64)</td>
<td>0.444</td>
<td></td>
</tr>
<tr>
<td>125 (\mu)g iv</td>
<td>12</td>
<td>441.9</td>
<td>459.5</td>
<td>313.4</td>
<td>518.9</td>
<td>61.0</td>
<td>0.43 (0.28, 0.64)</td>
<td>0.444</td>
<td></td>
</tr>
<tr>
<td>≥40 kg</td>
<td>12</td>
<td>2.4</td>
<td>3.0</td>
<td>0.5</td>
<td>4.5</td>
<td>2.1</td>
<td>0.56 (0.36, 0.87)</td>
<td>0.489</td>
<td></td>
</tr>
<tr>
<td>70 mg</td>
<td>12</td>
<td>438.5</td>
<td>438.8</td>
<td>336.6</td>
<td>572.9</td>
<td>90.7</td>
<td>0.56 (0.36, 0.87)</td>
<td>0.489</td>
<td></td>
</tr>
<tr>
<td>125 (\mu)g iv</td>
<td>12</td>
<td>438.5</td>
<td>438.8</td>
<td>336.6</td>
<td>572.9</td>
<td>90.7</td>
<td>0.56 (0.36, 0.87)</td>
<td>0.489</td>
<td></td>
</tr>
</tbody>
</table>

LS, Least-squares (back-transformed from the log scale, dose adjusted to 1 mg); RMSE, root mean square error from the ANOVA model.
Individual bioavailability ranged from 0.18–1.74% in the lower-weight group and from 0.09–1.27% in the higher-weight group. These results were similar to the adult data (Table 2 and Fig. 1).

Bioavailable ALN either localizes to bone or is excreted in the urine. It is therefore possible to estimate the amount of ALN localizing to bone by subtracting the amount of urinary ALN after an iv dose from the total amount of ALN given. As shown in Table 3, from a hypothetical 1-mg iv dose of ALN, an average of 444.0 and 438.5 µg, respectively, was excreted via the kidney in the two weight groups. It therefore follows that in both groups, approximately 56% of the ALN that entered the circulation localized to bone. These results were similar to the adult data (Table 3).

**ALN single-dose tolerability**

**Clinical adverse experiences.** All 24 patients who completed the study were included in the tolerability analysis. No serious adverse experiences were noted. A total of 18 patients reported 44 clinical adverse experiences, of which 38 were assigned probable or possible causality (Table 4). The most common adverse experiences were mild to moderate headache (n = 7), nausea (n = 7), fever (n = 5), and abdominal pain (n = 6). Eighty percent of the adverse experiences (35 of 44) occurred within 48 h of medication administration; 91% (40 of 44) lasted less than 24 h, and 84% (37 of 44) occurred within 48 h of medication administration.

**Laboratory adverse experiences.** Complete blood count and biochemical indices (including serum calcium levels) remained unchanged throughout the study, with the exception of a marginal decrease in absolute lymphocyte count and serum alkaline phosphatase (Table 5). However, lymphocyte counts remained in the reference range for all but two patients. In these two patients, the absolute lymphocyte counts were normal at baseline (1.8 and 1.6 × 10⁹/liter) and subsequently fell to 0.9 × 10⁹/liter in both cases (normal, 1.2–3.4 × 10⁹/liter). In the first patient, lymphocyte counts remained at 0.9 × 10⁹/liter 73 d after the last dose of study drug. The second patient was unavailable for poststudy laboratory monitoring but was reportedly well when telephone contact was made 14 d after the second dosing schedule. The decline in absolute lymphocyte count was not associated with any clinically relevant symptoms in either patient during their observation periods.

Prestudy screening laboratory results (after randomization) in a 15-yr-old boy, who was clinically well at the time, demonstrated abnormal liver function studies, which remained abnormal at the poststudy laboratory safety examination. The patient was subsequently diagnosed with autoimmune hepatitis after a full evaluation by a tertiary care pediatric hepatologist. It was concluded that the elevated liver function studies at the prestudy screening and after the study were a manifestation of this underlying condition.

**Discussion**

In this study, we found that bioavailability of oral ALN in children and adolescents with OI type I averages less than 1%. These observations are consistent with data obtained in adults (20). The low oral bioavailability of ALN results from the formation of insoluble complexes of ALN with multivalent cations in the gastrointestinal tract (1). The bioavailability of ALN is further reduced in the presence of food (1), reinforcing the importance of strict adherence to dosing guidelines.

As shown in this study, the bioavailability of oral ALN can vary by a factor of more than 10 among patients. This wide range in bioavailability might impact on individual therapeutic response. Additional studies of oral ALN are needed to address whether the doses used in this study are efficacious in the treatment of OI and other osteoporotic conditions of childhood.

Similar to results obtained in adults, we noted that about 56% of an iv administered ALN dose localized to bone (21). Thus, the percentage of systemic drug that distributes to bone does not appear to change after 4 yr of age. Because

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**TABLE 2.** Bioavailability (percent) of ALN for pediatric OI patients compared with adult controls

<table>
<thead>
<tr>
<th>Population</th>
<th>n</th>
<th>LS mean for % oral bioavailability</th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
<th>sd</th>
<th>GMR to adult</th>
<th>95% CI for GMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 kg</td>
<td>12</td>
<td>0.43</td>
<td>0.40</td>
<td>0.18</td>
<td>1.74</td>
<td>0.45</td>
<td>0.63</td>
<td>(0.39, 1.04)</td>
</tr>
<tr>
<td>≥40 kg</td>
<td>12</td>
<td>0.56</td>
<td>0.64</td>
<td>0.09</td>
<td>1.27</td>
<td>0.33</td>
<td>0.86</td>
<td>(0.52, 1.41)</td>
</tr>
<tr>
<td>Adult RMSE = 0.810</td>
<td>86</td>
<td>0.65</td>
<td>0.68</td>
<td>0.03</td>
<td>8.17</td>
<td>1.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooled pediatric</td>
<td>24</td>
<td>0.48</td>
<td>0.48</td>
<td>0.09</td>
<td>1.74</td>
<td>0.39</td>
<td>0.74</td>
<td>(0.51, 1.07)</td>
</tr>
<tr>
<td>Adult RMSE = 0.809</td>
<td>86</td>
<td>0.65</td>
<td>0.68</td>
<td>0.03</td>
<td>8.17</td>
<td>1.02</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LS, Least-squares (back-transformed from the log scale); GMR, geometric mean ratio; RMSE, root mean square error from the ANOVA model.

---

**TABLE 3.** Summary statistics for dose-adjusted TUE-ALN (expressed as micrograms of urinary ALN per milligram administered ALN) for adult and pediatric patients after an iv dose

<table>
<thead>
<tr>
<th>Population</th>
<th>n</th>
<th>LS mean</th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
<th>GMR to adult</th>
<th>95% CI for GMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 kg</td>
<td>12</td>
<td>442.0</td>
<td>459.5</td>
<td>313.4</td>
<td>518.9</td>
<td>1.09</td>
<td>(0.92, 1.29)</td>
</tr>
<tr>
<td>≥40 kg</td>
<td>12</td>
<td>438.5</td>
<td>440.5</td>
<td>336.6</td>
<td>572.9</td>
<td>1.08</td>
<td>(0.91, 1.28)</td>
</tr>
<tr>
<td>Adult RMSE = 0.281</td>
<td>86</td>
<td>405.3</td>
<td>420.3</td>
<td>158.6</td>
<td>803.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooled pediatric</td>
<td>24</td>
<td>440.2</td>
<td>459.5</td>
<td>313.4</td>
<td>572.9</td>
<td>1.09</td>
<td>(0.96, 1.23)</td>
</tr>
<tr>
<td>Adult RMSE = 0.280</td>
<td>86</td>
<td>405.3</td>
<td>420.3</td>
<td>158.6</td>
<td>803.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LS, Least-squares; GMR, geometric mean ratio; RMSE, root mean square error from the analysis of variance model.
skeletal mass is lower in younger and therefore smaller OI patients (13), the dose of ALN is likely to be similar for the two weight categories, when adjusted for skeletal mass. This is consistent with the weight-normalized dose regimen currently used for iv pamidronate therapy in OI patients (10). However, it should be recognized that the weight adjustment for orally administered ALN is less precise than for iv pamidronate. For example, the pamidronate protocol described by Glorieux et al. (10) is based upon exact dosing of pamidronate administration to children with OI (25, 26).

In summary, these data suggest that the fraction of bioavailable oral ALN distributing to bone is similar across different age groups. ALN was generally well tolerated in this study of two single doses. Future studies are warranted to assess the longer-term tolerability, safety, and efficacy of ALN in children with osteoporotic conditions through randomized, placebo-controlled studies.

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### References


4. Luckman SP, Coxon FF, Ebetino FH, Russell RG, Rogers MJ 1998 Heterocycle-containing bisphosphonates cause apoptosis and inhibit bone resorption by T cells (23, 24).

A reduction in serum alkaline phosphatase levels was also observed for both weight categories in this study. This observation is consistent with the decline in bone turnover that has been observed histologically and biochemically after pamidronate administration to children with OI (25, 26).

In summary, these data suggest that the fraction of bioavailable oral ALN distributing to bone is similar across different age groups. ALN was generally well tolerated in this study of two single doses. Future studies are warranted to assess the longer-term tolerability, safety, and efficacy of ALN in children with osteoporotic conditions through randomized, placebo-controlled studies.

#### TABLE 4. Summary of the number of patients who developed adverse experiences after a single dose of ALN

<table>
<thead>
<tr>
<th>Adverse experience</th>
<th>No. of adverse experiences</th>
<th>Causality rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>3</td>
<td>Possibly (n = 6); possibly (n = 1)</td>
</tr>
<tr>
<td>Headache</td>
<td>2</td>
<td>Probably (n = 4); possibly (n = 2); probably not (n = 1)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>4</td>
<td>Probably (n = 4); possibly (n = 2)</td>
</tr>
<tr>
<td>Fever</td>
<td>2</td>
<td>Probably (n = 4); possibly (n = 1)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>2</td>
<td>Probably (n = 4)</td>
</tr>
<tr>
<td>Leg/knee pain</td>
<td>2</td>
<td>Possibly (n = 2); possibly (n = 1); possibly not (n = 1)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>Possibly (n = 1); probably (n = 1); possibly not (n = 1)</td>
</tr>
<tr>
<td>Hip pain</td>
<td>0</td>
<td>Possibly not (n = 1)</td>
</tr>
<tr>
<td>Conjunctival injection</td>
<td>0</td>
<td>Possibly (n = 1)</td>
</tr>
<tr>
<td>Cough</td>
<td>1</td>
<td>Possibly not (n = 1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>Possibly (n = 2)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1</td>
<td>Possibly (n = 1)</td>
</tr>
<tr>
<td>Generalized myalgia</td>
<td>1</td>
<td>Possibly (n = 1)</td>
</tr>
<tr>
<td>Heartburn</td>
<td>0</td>
<td>Possibly not (n = 1)</td>
</tr>
<tr>
<td>Shoulder pain</td>
<td>1</td>
<td>Possibly (n = 1)</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>

The causality rating was deemed by the study pediatrician to be possibly, probably, or probably not related to the study medication, according to International Conference on Harmonization Tripartite Guidelines (19).

#### References


4. Luckman SP, Coxon FF, Ebetino FH, Russell RG, Rogers MJ 1998 Heterocycle-containing bisphosphonates cause apoptosis and inhibit bone resorption by T cells (23, 24).


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