

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TYMLOS safely and effectively. See full prescribing information for TYMLOS.

TYMLOS® (abaloparatide) injection, for subcutaneous use
Initial U.S. Approval: 2017

INDICATIONS AND USAGE

TYMLOS is a human parathyroid hormone related peptide [PTHrP(1-34)] analog indicated for the:

- Treatment of postmenopausal women with osteoporosis at high risk for fracture or patients who have failed or are intolerant to other available osteoporosis therapy. (1.1)
- Treatment to increase bone density in men with osteoporosis at high risk for fracture or patients who have failed or are intolerant to other available osteoporosis therapy. (1.2)

DOSAGE AND ADMINISTRATION

- Recommended dosage is 80 mcg subcutaneously once daily; patients should receive supplemental calcium and vitamin D if dietary intake is inadequate. (2.1)
- Administer as a subcutaneous injection into periumbilical region of abdomen. (2.2)
- Administer initially where the patient can sit or lie down in case symptoms of orthostatic hypotension occur. (2.2, 5.2)

DOSAGE FORMS AND STRENGTHS

Injection: 3120 mcg/1.56 ml (2000 mcg/ml) of abaloparatide in clear, colorless solution in a single-patient-use prefilled pen. The prefilled pen delivers 30 daily doses of 80 mcg abaloparatide in 40 mL. (3)

CONTRAINDICATIONS

Known hypersensitivity to TYMLOS. (4)

WARNINGS AND PRECAUTIONS

- Osteosarcoma: Avoid use in patients with increased risk of osteosarcoma including patients with open epiphyses, metabolic bone diseases including Paget's disease, bone metastases or history of skeletal malignancies, prior external beam or implant radiation therapy involving the skeleton, and hereditary disorders predisposing to osteosarcoma. (5.1)
- Orthostatic Hypotension: Instruct patients to sit or lie down if symptoms develop after dose administration. (5.2)
- Hypercalcemia: Avoid use in patients with pre-existing hypercalcemia and those known to have an underlying hypercalcemic disorder, such as primary hyperparathyroidism. (5.3)
- Hypercalciuria and Urolithiasis: Monitor urine calcium if pre-existing hypercalciuria or active urolithiasis are suspected. (5.4)

ADVERSE REACTIONS

- Osteoporosis in postmenopausal women: The most common adverse reactions (incidence $\geq 2\%$) are hypercalciuria, dizziness, nausea, headache, palpitations, fatigue, upper abdominal pain, and vertigo. (6.1)
- Osteoporosis in men: The most common adverse reactions (incidence $\geq 2\%$) are injection site erythema, dizziness, arthralgia, injection site swelling, injection site pain, contusion, nausea, diarrhea, abdominal distension, abdominal pain, and bone pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Radius Health, Inc. at 1-855-672-3487 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Treatment of Postmenopausal Women with Osteoporosis at High Risk for Fracture

TYMLOS is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture (defined as a history of osteoporotic fracture or multiple risk factors for fracture), or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, TYMLOS reduces the risk of vertebral fractures and nonvertebral fractures.

1.2 Treatment to Increase Bone Density in Men with Osteoporosis at High Risk for Fracture

TYMLOS is indicated to increase bone density in men with osteoporosis at high risk for fracture (defined as a history of osteoporotic fracture or multiple risk factors for fracture), or patients who have failed or are intolerant to other available osteoporosis therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

- The recommended dosage of TYMLOS is 80 mcg administered subcutaneously once daily.
- Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate.

2.2 Administration Instructions

- Administer TYMLOS as a subcutaneous injection into the periumbilical region of the abdomen. Rotate the site of the injection every day and administer at approximately the same time every day. Do not administer intravenously or intramuscularly.
- Administer the first several doses where the patient can sit or lie down if necessary, in case symptoms of orthostatic hypotension occur [*see Warnings and Precautions (5.2) and Adverse Reactions (6.1)*].
- Visually inspect TYMLOS for particulate matter and discoloration prior to administration. TYMLOS is a clear and colorless solution. Do not use if solid particles appear or if the solution is cloudy or colored.
- Provide appropriate training and instruction to patients and caregivers on the proper use of the TYMLOS pen.

2.3 Treatment Duration

The safety and efficacy of TYMLOS have not been evaluated beyond 2 years of treatment. Use of the drug for more than 2 years during a patient's lifetime is not recommended.

3 DOSAGE FORMS AND STRENGTHS

Injection: 3120 mcg/1.56 mL (2000 mcg/mL) of abaloparatide in clear, colorless solution in a single-patient-use prefilled pen. The prefilled pen delivers 30 doses of TYMLOS, each containing 80 mcg of abaloparatide in 40 mL.

4 CONTRAINDICATIONS

TYMLOS is contraindicated in patients with a history of systemic hypersensitivity to abaloparatide or to any component of the product formulation. Reactions have included anaphylaxis, dyspnea, and urticaria [see *Adverse Reactions* (6.2)].

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Osteosarcoma

Abaloparatide caused a dose-dependent increase in the incidence of osteosarcoma in male and female rats after subcutaneous administration at exposures 4 to 28 times the human exposure at the clinical dose of 80 mcg [see *Nonclinical Toxicology* (13.1)]. It is unknown whether TYMLOS will cause osteosarcoma in humans.

Osteosarcoma has been reported in patients treated with a PTH-analog in the post marketing setting; however, an increased risk of osteosarcoma has not been observed in observational studies in humans. There are limited data assessing the risk of osteosarcoma beyond 2 years of TYMLOS and/or use of a PTH-analog [see *Dosage and Administration* (2.3) and *Nonclinical Toxicology* (13.1)].

Avoid TYMLOS use in patients with (these patients are at increased baseline risk of osteosarcoma):

- Open epiphyses (pediatric and young adult patients) (TYMLOS is not approved in pediatric patients) [see *Use in Specific Populations* (8.4)].
- Metabolic bone diseases other than osteoporosis, including Paget's disease of the bone.
- Bone metastases or a history of skeletal malignancies.
- Prior external beam or implant radiation therapy involving the skeleton.
- Hereditary disorders predisposing to osteosarcoma.

5.2 Orthostatic Hypotension

Orthostatic hypotension may occur with TYMLOS, typically within 4 hours of injection. Associated symptoms may include dizziness, palpitations, tachycardia, or nausea, and may

resolve by having the patient lie down. For the first several doses, TYMLOS should be administered where the patient can sit or lie down if necessary [see *Adverse Reactions (6.1)*].

5.3 Hypercalcemia

TYMLOS may cause hypercalcemia. TYMLOS is not recommended in patients with pre-existing hypercalcemia or in patients who have an underlying hypercalcemic disorder, such as primary hyperparathyroidism, because of the possibility of exacerbating hypercalcemia [see *Adverse Reactions (6.1)*].

5.4 Hypercalciuria and Urolithiasis

TYMLOS may cause hypercalciuria. It is unknown whether TYMLOS may exacerbate urolithiasis in patients with active or a history of urolithiasis. If active urolithiasis or pre-existing hypercalciuria is suspected, measurement of urinary calcium excretion should be considered [see *Adverse Reactions (6.1)*].

6 ADVERSE REACTIONS

The following adverse reactions are described in greater detail in other sections:

- Orthostatic Hypotension [see *Warnings and Precautions (5.2)*]
- Hypercalcemia [see *Warnings and Precautions (5.3)*]
- Hypercalciuria and Urolithiasis [see *Warnings and Precautions (5.4)*]

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Adverse Reactions from Clinical Trial in Postmenopausal Women with Osteoporosis

The safety of TYMLOS was evaluated in a randomized, multicenter, double-blind, placebo-controlled clinical trial in postmenopausal women with osteoporosis aged 49 to 86 years (mean age 69 years) who were randomized to receive 80 mcg of TYMLOS (N = 824) or placebo (N = 821), given subcutaneously once daily for 18 months [see *Clinical Studies (14.1)*].

In this study, the incidence of all-cause mortality was 0.4% in the TYMLOS group and 0.6% in the placebo group. The incidence of serious adverse events was 10% in the TYMLOS group and 11% in the placebo group. The percentage of patients who discontinued study drug due to adverse events was 10% in the TYMLOS group and 6% in the placebo group. The most common adverse reactions leading to study drug discontinuation in the TYMLOS group were nausea (2%), dizziness (1%), headache (1%), and palpitations (1%).

Table 1 shows the most common adverse reactions in the trial. These adverse reactions were generally not present at baseline, occurred more commonly with TYMLOS than with placebo, and occurred in at least 2% of the patients treated with TYMLOS.

Table 1: Common Adverse Reactions Reported in Postmenopausal Women with Osteoporosis*

Preferred term	TYMLOS (N=822) (%)	Placebo (N=820) (%)
Hypercalciuria	11	9
Dizziness	10	6
Nausea	8	3
Headache	8	6
Palpitations	5	0.4
Fatigue	3	2
Abdominal pain upper	3	2
Vertigo	2	2

* Adverse reactions reported in $\geq 2\%$ of TYMLOS-treated patients.

Orthostatic Hypotension

In the clinical trial of women with postmenopausal osteoporosis, the incidence of orthostatic blood pressure decline ≥ 20 mmHg systolic or ≥ 10 mmHg diastolic at 1 hour after the first injection was 4% in the TYMLOS group and 3% in the placebo group. At later time points the incidence was generally similar between the treatment groups. Adverse reactions of orthostatic hypotension were reported in 1% of patients receiving TYMLOS and 0.5% of patients receiving placebo. Dizziness was reported by more TYMLOS-treated patients (10%) compared to placebo (6%) [see *Warnings and Precautions (5.2)*].

Tachycardia

In women with postmenopausal osteoporosis, adverse reactions of tachycardia, including sinus tachycardia, were reported in 2% of patients receiving TYMLOS and 1% of patients in the placebo group. In 5 of the 13 patients receiving TYMLOS who experienced tachycardia, symptoms occurred within 1 hour of administration. TYMLOS has been associated with a dose-dependent increase in heart rate which developed within 15 minutes after injection and resolved in about 6 hours [see *Clinical Pharmacology (12.2)*].

Injection Site Reactions

During the first month of the trial, injection site reactions were assessed daily one-hour after injection. TYMLOS had a higher incidence than placebo of injection site redness (58% vs. 28%), edema (11% vs. 3%), and pain (10% vs. 7%). Severe redness, severe edema, and severe pain were reported among 2.9%, 0.4%, and 0.4% of the TYMLOS-treated patients.

Laboratory Abnormalities

Hypercalcemia

In the clinical trial of women with postmenopausal osteoporosis, TYMLOS caused increases in serum calcium concentrations [see *Warnings and Precautions (5.3)*]. The incidence of

hypercalcemia, defined as albumin-corrected serum calcium ≥ 10.7 mg/dL at 4 hours following injection at any visit, was 3% in TYMLOS-treated patients and 0.1% with placebo. Pre-dose serum calcium was similar to baseline in both groups. There were 2 (0.2%) TYMLOS-treated patients and no placebo-treated patients who discontinued from the study due to hypercalcemia. The incidence of hypercalcemia with TYMLOS was higher in patients with mild or moderate renal impairment (4%) compared to patients with normal renal function (1%).

Increases in Serum Uric Acid

TYMLOS increased serum uric acid concentrations. In the postmenopausal osteoporosis trial, among patients with normal baseline uric acid concentrations, 25% of patients in the TYMLOS group and 6% of patients in the placebo group had at least one post-baseline concentration above the normal range. The hyperuricemia observed in TYMLOS-treated patients was not associated with an increase in adverse reactions of gout or arthralgia over that observed with placebo.

Hypercalciuria and Urolithiasis

In the clinical trial of women with postmenopausal osteoporosis, the overall incidence of urine calcium:creatinine ratio >400 mg/g was higher with TYMLOS than with placebo (20% vs 15%, respectively). Urolithiasis were reported in 2.1% of TYMLOS-treated patients and 1.7% of placebo-treated patients.

Adverse Reactions from the Extension Study in Postmenopausal Women with Osteoporosis

Following 18 months of treatment with TYMLOS or placebo, 1139 women transitioned to treatment with alendronate 70 mg administered orally once weekly. The incidence of adverse events occurring during alendronate treatment was similar in patients with prior placebo or TYMLOS therapy [*see Clinical Studies (14.1)*].

Adverse Reactions from Clinical Trial in Men with Osteoporosis

The safety of TYMLOS was evaluated in a randomized, multicenter, double-blind, placebo-controlled clinical trial in men with osteoporosis aged 42 to 85 years (mean age 68 years) who were randomized to receive 80 mcg of TYMLOS (N = 149) or placebo (N = 79), given subcutaneously once daily for 12 months [*see Clinical Studies (14.2)*].

In this study, no patient from either treatment group had an adverse reaction with a fatal outcome during the trial. Serious adverse reactions were reported by 5.4% of subjects treated with TYMLOS and 5.1% of subjects in the placebo group. Adverse reactions leading to study drug discontinuation were reported for 6.7% of patients treated with TYMLOS and 5.1% of patients receiving placebo. The most common adverse reaction leading to study drug discontinuation in the TYMLOS group was dizziness (2%).

[Table 2](#) shows the most common adverse reactions in the trial. These adverse reactions were generally not present at baseline, occurred more commonly with TYMLOS than with placebo and occurred in at least 2% of the patients treated with TYMLOS.

Table 2: Common Adverse Reactions Reported in Men with Osteoporosis*

Preferred Term	TYMLOS (N=149) (%)	Placebo (N=79) (%)
Injection site erythema	13	5
Dizziness	9	1
Arthralgia	7	1
Injection site swelling	7	0
Injection site pain	6	0
Contusion	3	0
Abdominal distention	3	0
Diarrhea	3	0
Nausea	3	0
Abdominal Pain	2	0
Bone Pain	2	0

* Adverse reactions reported in $\geq 2\%$ of TYMLOS-treated patients.

Orthostatic Hypotension

In the clinical trial of men with osteoporosis, the incidence of orthostatic blood pressure declines of ≥ 20 mmHg systolic or ≥ 10 mmHg diastolic at 1 hour after the first injection was 6% in the TYMLOS group and 3% in the placebo group. Adverse reactions of orthostatic hypotension were reported in 1% of patients receiving TYMLOS and 0 patients receiving placebo. Dizziness was reported by more TYMLOS-treated patients (9%) compared to placebo (1%) [see *Warnings and Precautions (5.2)*].

Laboratory Abnormalities

Hypercalcemia

In the clinical trial of men with osteoporosis, TYMLOS caused increases in serum calcium concentrations [see *Warnings and Precautions (5.3)*]. The incidence of hypercalcemia, defined as albumin-corrected serum calcium ≥ 10.8 mg/dL at 4 hours following injection at any visit, was 3% in TYMLOS-treated patients and 0% with placebo. Pre-dose serum calcium was similar to baseline in both groups. The incidence of hypercalcemia, defined as albumin-corrected serum calcium ≥ 10.8 mg/dL at 4 hours following injection, with TYMLOS was higher in patients with mild or moderate renal impairment (4%) compared to patients with normal renal function (0%).

Increases in Serum Uric Acid

TYMLOS increased serum uric acid concentrations. In the male osteoporosis trial, among patients with normal baseline uric acid concentrations, 7% of patients in the TYMLOS group and 6% of patients in the placebo group had at least one post-baseline concentration above the normal range. The hyperuricemia observed in TYMLOS-treated patients was not associated with an increase in adverse reactions of gout or arthralgia over that observed with placebo.

Hypercalciuria and Urolithiasis

In the clinical trial of men with osteoporosis, the overall incidence of urine calcium: creatinine ratio >400 mg/g was not greater with TYMLOS than with placebo. Urolithiasis were reported in 2% of TYMLOS-treated patients and 1% of placebo-treated patients.

6.2 Postmarketing Experience

The following adverse reactions have been identified during the post-approval use of TYMLOS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Abdominal distension, abdominal pain
- Constipation, diarrhea, vomiting
- Asthenia, lethargy, malaise
- Insomnia
- Hypersensitivity and anaphylactic reactions, dyspnea (in the context of allergic reactions)
- Pruritus, rash
- Generalized pain and pain in bone, joint, back, and extremity
- Muscle spasms of the leg and back
- Injection site reactions including bruising, hemorrhage, pruritus, and rash

7 DRUG INTERACTIONS

No specific drug-drug interaction studies have been performed [*see Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

TYMLOS is not indicated for use in females of reproductive potential. There are no human data with TYMLOS use in pregnant women to inform any drug associated risks. Animal reproduction studies with abaloparatide have not been conducted.

8.2 Lactation

Risk Summary

TYMLOS is not indicated for use in females of reproductive potential. There is no information on the presence of abaloparatide in human milk, the effects on the breastfed infant, or the effects on milk production.

8.4 Pediatric Use

Safety and effectiveness of TYMLOS have not been established in pediatric patients. TYMLOS is not recommended for use in pediatric patients with open epiphyses or hereditary disorders predisposing to osteosarcoma because of an increased baseline risk of osteosarcoma [*see Warnings and Precautions (5.1)*].

8.5 Geriatric Use

Of the total number of patients in the postmenopausal osteoporosis clinical studies of TYMLOS, 82% were age 65 years and over, and 19% were age 75 years and over. In the male osteoporosis study, 74% were age 65 years and over and 23% were age 75 years or over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

No dosage adjustment is required for patients with mild, moderate, or severe renal impairment. A study of a single dose of TYMLOS 80 mcg given subcutaneously was conducted in subjects with normal renal function or mild, moderate, or severe renal impairment. The maximal concentration (C_{max}) and area under the concentration-time curve (AUC) of abaloparatide increased 1.4- and 2.1-fold, respectively, in subjects with severe renal impairment, compared to subjects with normal renal function. Patients with severe renal impairment may have increased abaloparatide exposure that may increase the risk of adverse reactions; therefore, monitor for adverse reactions [*see Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

In a clinical study, accidental overdose was reported in a patient who received 400 mcg in one day (5 times the recommended clinical dose); dosing was temporarily interrupted. The patient experienced asthenia, headache, nausea, and vertigo. Serum calcium was not assessed on the day

of the overdose, but on the following day the patient's serum calcium was within the normal range. The effects of overdose may include hypercalcemia, nausea, vomiting, dizziness, tachycardia, orthostatic hypotension, and headache.

Overdosage Management

There is no specific antidote for TYMLOS. Treatment of suspected overdose should include discontinuation of TYMLOS, monitoring of serum calcium and phosphorus, and implementation of appropriate supportive measures, such as hydration. Based on the molecular weight, plasma protein binding and volume of distribution, abaloparatide is not expected to be dialyzable.

11 DESCRIPTION

TYMLOS injection for subcutaneous administration contains abaloparatide, a synthetic 34 amino acid peptide. Abaloparatide is an analog of human parathyroid hormone related peptide, PTHrP(1-34). It has 41% homology to hPTH(1-34) (human parathyroid hormone 1-34) and 76% homology to hPTHrP(1-34) (human parathyroid hormone-related peptide 1-34).

Abaloparatide has a molecular formula of $C_{174}H_{300}N_{56}O_{49}$ and a molecular weight of 3961 daltons with the amino acid sequence shown below:

Ala-Val-Ser-Glu-His-Gln-Leu-Leu-His-Asp-Lys-Gly-Lys-Ser-Ile-Gln-Asp-Leu-Arg-Arg-Arg-Glu-Leu-Leu-Glu-Lys-Leu-Leu-Aib-Lys-Leu-His-Thr-Ala-NH₂

TYMLOS injection is supplied as a sterile, colorless, clear solution in a glass cartridge which is pre-assembled into a disposable single-patient-use pen. The pen is intended to deliver 30 once daily abaloparatide doses of 80 mcg in 40 mL. Each cartridge contains 1.56 mL of TYMLOS solution which contains 3.12 mg of abaloparatide, and the following inactive ingredients: 9.95 mg acetic acid 99%, 7.8 mg phenol, 7.92 mg sodium acetate trihydrate, and water for injection to a target pH range of 5.1 to 5.2.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Abaloparatide is a PTHrP(1-34) analog which acts as an agonist at the PTH1 receptor (PTH1R). This results in activation of the cAMP signaling pathway in target cells. Once-daily administration of abaloparatide stimulates new bone formation on trabecular and cortical bone surfaces by stimulation of osteoblastic activity. In rats and monkeys, abaloparatide had an anabolic effect on bone, demonstrated by increases in BMD and bone mineral content (BMC) that correlated with increases in bone strength at vertebral and/or nonvertebral sites [*see Nonclinical Toxicology (13.2)*].

12.2 Pharmacodynamics

Effects on Markers of Bone Turnover

A dose-finding study of abaloparatide administered once daily for 24 weeks in postmenopausal women with osteoporosis demonstrated a dose-response relationship for BMD and bone formation markers.

Daily administration of TYMLOS to postmenopausal women with osteoporosis for 18 months increased the bone formation marker serum procollagen type I N-propeptide (sPINP) and the bone resorption marker serum collagen type I cross-linked C-telopeptide (sCTX). The increase in geometric mean sPINP levels peaked at Month 1 at 93% above baseline in postmenopausal women then decreased slowly over time to 45% above baseline at Month 18. The increase in geometric mean sCTX levels in postmenopausal women peaked at Month 3 at 26% above baseline then decreased to baseline levels by Month 18.

Daily administration of TYMLOS to men with osteoporosis for 12 months increased the bone formation marker sPINP and the bone resorption marker sCTX. The increase in geometric mean sPINP levels peaked at Month 1 at 133% above baseline in men then decreased slowly over time to 84% above baseline at Month 12. The increase in geometric mean sCTX levels in men peaked at Month 6 at 46% above baseline and was 35% above baseline by Month 12.

Cardiac Electrophysiology

A 4-way cross-over thorough QT/QTc study was conducted in 55 healthy subjects who received single doses of placebo, subcutaneous doses of abaloparatide at 80 mcg and 240 mcg (three times the recommended dose), and moxifloxacin 400 mg orally. Abaloparatide increased heart rate, with a mean peak increase of 15 beats per minute (bpm) and 20 bpm at the first time point (15 minutes) after dosing with 80 mcg and 240 mcg, respectively. There were no clinically meaningful effects of abaloparatide on QTcI (individually corrected QT intervals) or cardiac electrophysiology.

12.3 Pharmacokinetics

Following seven days of subcutaneous administration of abaloparatide 80 mcg, the mean (SD) abaloparatide exposure was 812 (118) pg/mL for C_{max} and 1622 (641) pg·hr/mL for AUC_{0-24} in postmenopausal women with osteoporosis.

Absorption

The median (range) time to peak concentration of abaloparatide 80 mcg was 0.51 hr (0.25 to 0.52 hr) following subcutaneous administration. The absolute bioavailability of abaloparatide in healthy women after subcutaneous administration of an 80 mcg dose was 36%.

Distribution

The *in vitro* plasma protein binding of abaloparatide was approximately 70%. The volume of distribution was approximately 50 L.

Elimination

Excretion

The mean (SD) half-life of abaloparatide is approximately 1 h. The peptide fragments are primarily eliminated through renal excretion.

Metabolism

No specific metabolism or excretion studies have been performed with TYMLOS. The metabolism of abaloparatide is consistent with non-specific proteolytic degradation into smaller peptide fragments, followed by elimination by renal clearance.

Specific Populations

Male and Female Subjects

Mean serum abaloparatide concentration-time profiles observed in a study conducted in healthy men with a mean (\pm SD) age of 53.1 (\pm 6.9) years were comparable to those observed in the healthy women with a mean (\pm SD) age of 53.7 (\pm 7.1) years using the same dosing regimen.

Geriatric Patients

No age-related differences in abaloparatide pharmacokinetics were observed in men and postmenopausal women ranging from 18 to 85 years of age.

Race

No differences in abaloparatide pharmacokinetics based on race were observed in clinical trials.

Patients with Renal Impairment

A single 80 mcg subcutaneous dose of abaloparatide was administered to male and female patients with renal impairment: 8 patients with mild renal impairment (CLCr 60 to 89 mL/min), 7 patients with moderate renal impairment (CLCr 30 to 59 mL/min), 8 patients with severe renal impairment (CLCr 15 to 29 mL/min), and 8 healthy subjects with normal renal function (CLCr 90 or greater mL/min) matched by sex, age, and body mass index (BMI). Abaloparatide C_{\max} increased 1.0-, 1.3-, and 1.4-fold in patients with mild, moderate, and severe renal impairment, compared to the healthy subjects with normal renal function. Abaloparatide AUC increased 1.2-, 1.7-, and 2.1-fold in patients with mild, moderate, and severe renal impairment, compared to the healthy subjects with normal renal function. Patients undergoing dialysis were not included in the study.

Drug Interactions

In vitro studies showed that abaloparatide, at therapeutic concentrations, does not inhibit or induce Cytochrome P450 enzymes. Abaloparatide is not a substrate of the renal transporters OAT1, OAT3, OCT2, MATE1, or MATE2K.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of abaloparatide or of other abaloparatide products.

Postmenopausal Women with Osteoporosis

Of the patients receiving TYMLOS for 18 months, 41% (318/773) developed anti-abaloparatide antibodies, and 26% (204/773) developed neutralizing antibodies to abaloparatide. Of the patients with anti-abaloparatide antibodies tested for cross-reactivity, 2.4% (7/297) developed cross-reactivity to PTHrP, of which 3 of the 7 patients developed neutralizing antibodies to PTHrP. Only 0.3% (1/297) developed cross-reactive antibodies to PTH, which were not neutralizing to PTH. Antibody formation did not appear to have any clinically significant impact on safety or efficacy endpoints, including bone mineral density (BMD) response, fracture reduction, or adverse events.

Most of the patients with anti-abaloparatide antibodies during treatment with TYMLOS, 86% (275/318), had follow-up antibody measurements every six months after completion of TYMLOS therapy until seroconverting to antibody negative or lost to follow-up. Among these patients, 127 remained antibody positive at 1 year after discontinuing treatment, 55 remained antibody positive at 2 years, and 6 remained antibody positive at 3 years.

Men with Osteoporosis

Of the male patients receiving TYMLOS for 12 months, 25% (36/142) developed anti-abaloparatide antibodies and 1.4% (2/142) developed neutralizing antibodies to abaloparatide. Of the patients with anti-abaloparatide antibodies tested for cross-reactivity, none developed cross-reactivity to PTHrP or PTH. Antibody formation did not appear to have any clinically significant impact on safety or efficacy endpoints, including bone mineral density (BMD) response or adverse events.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In a 2-year carcinogenicity study, abaloparatide was administered once daily to male and female Fischer rats by subcutaneous injection at doses of 10, 25, and 50 mcg/kg. These doses resulted in systemic exposures to abaloparatide that were 4, 16, and 28 times, respectively, the systemic exposure observed in humans following the recommended subcutaneous dose of 80 mcg (based on AUC comparisons). Neoplastic changes related to treatment with abaloparatide consisted of marked dose-dependent increases in osteosarcoma and osteoblastoma incidence in all male and female dose groups. The incidence of osteosarcoma was 0-2% in untreated controls and reached 87% and 62% in male and female high-dose groups, respectively. The bone neoplasms were accompanied by marked increases in bone mass.

The relevance of the rat findings to humans is uncertain. The use of TYMLOS is not recommended in patients at increased risk of osteosarcoma [*see Warnings and Precautions (5.1)*].

Mutagenesis

Abaloparatide was not genotoxic or mutagenic in a standard battery of tests including the Ames test for bacterial mutagenesis, the chromosome aberration test using human peripheral lymphocytes, and the mouse micronucleus test.

Impairment of Fertility

Abaloparatide effects on female fertility have not been assessed nonclinically. No adverse effects of abaloparatide on male fertility were observed in male rats. In a male rat fertility study, abaloparatide was administered via subcutaneous injection 2 weeks prior to mating, through the mating period and for approximately 2 weeks after the mating period (for total of 6 weeks) at doses of 10, 25 and 70 $\mu\text{g}/\text{kg}/\text{day}$. Abaloparatide did not cause adverse effect on mating, fertility indices, conception rate, reproductive organ weights or sperm parameters up to 70 $\mu\text{g}/\text{kg}/\text{day}$ (28-fold the systemic exposure observed in humans following the recommended subcutaneous dose of 80 mcg (based on AUC comparisons).

13.2 Animal Toxicology and Pharmacology

In toxicity studies in rats and monkeys of up to 26-week and 39-week duration, respectively, findings included vasodilation, increases in serum calcium, decreases in serum phosphorus, and soft tissue mineralization at doses ≥ 10 mcg/kg/day. The 10 mcg/kg/day dose resulted in systemic exposures to abaloparatide in rats and monkeys that were 2 and 3 times, respectively, the exposure in humans at daily subcutaneous doses of 80 mcg.

Pharmacologic effects of abaloparatide on the skeleton were assessed in 12- and 16-month studies in ovariectomized (OVX) rats and monkeys, at doses up to 11- and 1-times human exposure at the recommended subcutaneous dose of 80 mcg, respectively (based on AUC comparisons). In these animal models of postmenopausal osteoporosis, treatment with abaloparatide resulted in dose-dependent increases in bone mass at vertebral and/or nonvertebral sites, correlating with increases in bone strength. The anabolic effect of abaloparatide was due to the predominant increase in osteoblastic bone formation and was evidenced by increases in trabecular thickness and/or cortical thickness due to endosteal bone apposition. Abaloparatide maintained or improved bone quality at all skeletal sites evaluated and did not cause any mineralization defects.

In an 8-week study in androgen-deficient orchietomized (ORX) male rats, a male osteoporosis model, the effects of 5 and 25 mcg/kg/day abaloparatide (≥ 47 -fold clinical exposures by AUC) were examined on bone formation, bone mass, and bone strength. Abaloparatide induced bone formation and improved cortical and trabecular BMD, geometry, and architecture without increasing parameters of bone resorption.

14 CLINICAL STUDIES

14.1 Efficacy Study in Women with Postmenopausal Osteoporosis

The efficacy of TYMLOS for the treatment of postmenopausal osteoporosis was evaluated in Study 003 (NCT 01343004), an 18-month, randomized, multicenter, double-blind, placebo-controlled clinical trial in postmenopausal women aged 49 to 86 years (mean age of 69) who were randomized to receive TYMLOS 80 mcg (N = 824) or placebo (N = 821) given

subcutaneously once daily. Approximately 80% of patients were Caucasian, 16% were Asian, and 3% were Black; 24% were Hispanic. At baseline, the mean T-scores were -2.9 at the lumbar spine, -2.1 at the femoral neck, and -1.9 at the total hip. At baseline, 24% of patients had at least one prevalent vertebral fracture and 48% had at least one prior nonvertebral fracture. Patients took daily supplemental calcium (500 to 1000 mg) and vitamin D (400 to 800 IU).

The efficacy study was extended as Study 005 (NCT 01657162), an open-label study where patients were no longer receiving TYMLOS or placebo but were maintained in their original randomized treatment group and received 70 mg alendronate weekly, with calcium and vitamin D supplements for 6 months. Study 005 enrolled 1139 patients, representing 92% of patients who completed Study 003. This included 558 patients who had previously received TYMLOS and 581 patients who had previously received placebo. The cumulative 25-month efficacy dataset included 18 months of exposure to TYMLOS or placebo in Study 003, 1 month of no treatment, followed by 6 months of alendronate therapy in Study 005. Study 005 was then continued to complete 18 months of additional alendronate exposure during which time patients were no longer blinded to their original Study 003 treatment group.

Effect on New Vertebral Fractures

The primary endpoint was the incidence of new vertebral fractures in patients treated with TYMLOS compared to placebo. TYMLOS resulted in a significant reduction in the incidence of new vertebral fractures compared to placebo at 18 months (0.6% TYMLOS compared to 4.2% placebo, $p < 0.0001$). The absolute risk reduction in new vertebral fractures was 3.6% at 18 months and the relative risk reduction was 86% for TYMLOS compared to placebo (Table 3). The incidence of new vertebral fractures at 25 months was 0.6% in patients treated with TYMLOS then alendronate, compared to 4.4% in patients treated with placebo then alendronate ($p < 0.0001$). The relative risk reduction in new vertebral fractures at 25 months was 87% for patients treated with TYMLOS then alendronate, compared to patients treated with placebo then alendronate, and the absolute risk reduction was 3.9% (Table 3). After 24 months of open-label alendronate therapy, the vertebral fracture risk reduction achieved with TYMLOS therapy was maintained.

Table 3: Percentage of Postmenopausal Women with Osteoporosis with New Vertebral Fractures (modified Intent to Treat Population)*†

	Percentage of Postmenopausal Women With Fractures		Absolute Risk Reduction (%) (95% CI‡)	Relative Risk Reduction (%) (95% CI‡)
	TYMLOS (N=690*) (%)	Placebo (N=711*) (%)		
0-18 months	0.6	4.2	3.6 (2.1, 5.4)	86 (61, 95)
	TYMLOS/ Alendronate (N=544†) (%)	Placebo/ Alendronate (N=568†) (%)		
0-25 months	0.6	4.4	3.9 (2.1, 5.9)	87 (59, 96)

* Includes patients who had both pre- and post-treatment spine radiographs in Study 003

† Includes patients who had both pre- and post-treatment spine radiographs in Study 005

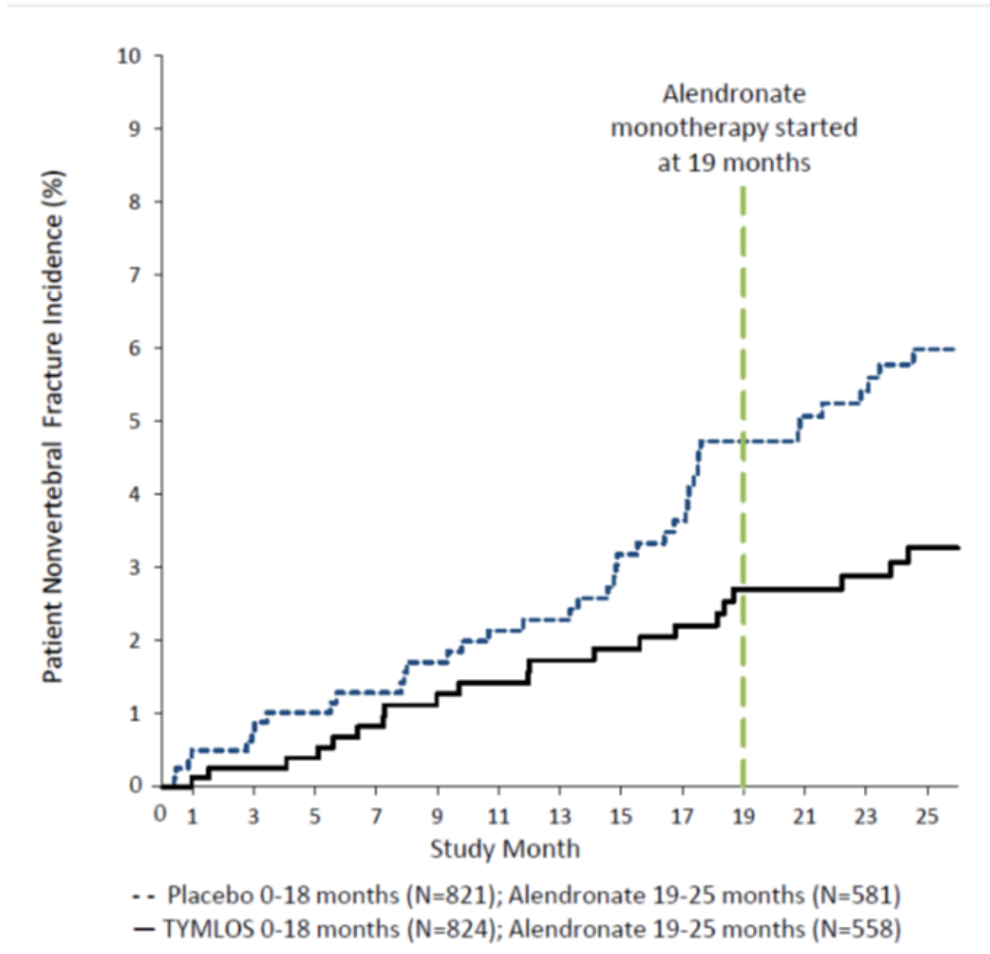
‡ Confidence Interval

Effect on Nonvertebral Fractures

TYMLOS resulted in a significant reduction in the incidence of nonvertebral fractures at the end of the 18 months of treatment plus 1 month follow-up where no drug was administered (2.7% for TYMLOS-treated patients compared to 4.7% for placebo-treated patients). The relative risk reduction in nonvertebral fractures for TYMLOS compared to placebo was 43% (logrank test $p = 0.049$) and the absolute risk reduction was 2.0%.

Following 6 months of alendronate treatment in Study 005, the cumulative incidence of nonvertebral fractures at 25 months was 2.7% for women in the prior TYMLOS group compared to 5.6% for women in the prior placebo group (Figure 1). At 25 months, the relative risk reduction in nonvertebral fractures was 52% (logrank test $p = 0.017$) and the absolute risk reduction was 2.9%.

Figure 1: Cumulative Incidence of Nonvertebral Fractures* over 25 Months (Intent to Treat Population)†



* Excludes fractures of the sternum, patella, toes, fingers, skull and face and those associated with high trauma.

† Includes patients randomized in Study 003

TYMLOS demonstrated consistent reductions in the risk of vertebral and nonvertebral fractures regardless of age, years since menopause, presence or absence of prior fracture (vertebral, nonvertebral), and BMD at baseline.

Effect on Bone Mineral Density (BMD)

Treatment with TYMLOS for 18 months in Study 003 resulted in significant increases in BMD compared to placebo at the lumbar spine, total hip, and femoral neck, each with $p < 0.0001$ (Table 4). Similar findings were seen following 6 months of alendronate treatment in Study 005 (Table 4).

Table 4: Mean Percent Changes in Bone Mineral Density (BMD) From Baseline to Endpoint in Postmenopausal Women with Osteoporosis (Intent to Treat Population)*†‡

	TYMLOS (N=824*) (%)	Placebo (N=821*) (%)	Treatment Difference (%) (95% CI§)
18 Months			
Lumbar Spine	9.2	0.5	8.8 (8.2, 9.3)
Total Hip	3.4	-0.1	3.5 (3.3, 3.8)
Femoral Neck	2.9	-0.4	3.3 (3.0, 3.7)
	TYMLOS/ Alendronate (N=558†) (%)	Placebo/ Alendronate (N=581†) (%)	
25 Months			
Lumbar Spine	12.8	3.5	9.3 (8.6, 10.1)
Total Hip	5.5	1.4	4.1 (3.7, 4.5)
Femoral Neck	4.5	0.5	4.1 (3.6, 4.6)

* Includes patients randomized in Study 003

† Includes patients enrolled in Study 005

‡ Last-observation-carried-forward

§ Confidence Interval

There was no evidence of differences in the effects of TYMLOS on BMD across subgroups defined by age, years since menopause, race, ethnicity, geographic region, presence or absence of prior fracture (vertebral, nonvertebral), and BMD at baseline.

Effect on Bone Histology

Bone biopsy specimens were obtained from 71 patients with osteoporosis after 12 – 18 months of treatment (36 in the TYMLOS group and 35 in the placebo group). Of the biopsies obtained, 55 were adequate for quantitative histomorphometry assessment (27 in the TYMLOS group and 28 in the placebo group). Qualitative and quantitative histology assessment showed normal bone architecture and no evidence of woven bone, marrow fibrosis, or mineralization defects.

14.2 Men with Osteoporosis

The efficacy of TYMLOS for the treatment of men with osteoporosis was evaluated in Study 019 (NCT 03512262), a 12-month, randomized, multicenter, double-blind, placebo-controlled clinical trial in men aged 42 to 85 years (mean age of 68) who were randomized to receive TYMLOS 80 mcg (N = 149) or placebo (N = 79) given subcutaneously once daily.

Approximately 95% of patients were Caucasian, 4% were Asian, and <1% (0.4%) were Black; 16% were Hispanic. At baseline, the mean T-scores were -2.1 at the lumbar spine, -2.1 at the

femoral neck, and -1.7 at the total hip. Patients took daily supplemental calcium (500 to 1000 mg) and vitamin D (400 to 800 IU).

Effect on Bone Mineral Density (BMD)

The primary endpoint was the percent change from baseline in lumbar spine BMD at 12 months in patients treated with TYMLOS compared to placebo. Treatment with TYMLOS for 12 months in Study 019 resulted in significant increases in BMD compared to placebo at the lumbar spine, total hip, and femoral neck, each with $p < 0.0001$ (Table 5).

Table 5: Mean Percent Changes in Bone Mineral Density (BMD) From Baseline to 12 Months in Men with Osteoporosis (Intent to Treat Population)

	TYMLOS (N=149*) (%)	Placebo (N=79*) (%)	Treatment Difference (%) (99% CI[†])
12 Months			
Lumbar Spine	8.5	1.2	7.3 (5.1, 9.6)
Total Hip	2.1	<0.1	2.1 (1.0, 3.2)
Femoral Neck	3.0	0.2	2.8 (1.4, 4.2)

* Includes patients randomized in Study 019

† Confidence Interval

There was no evidence of differences in the effects of TYMLOS on BMD at Month 12 across subgroups defined by age, race, ethnicity, geographic region, presence or absence of prior fracture, and BMD at baseline.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

TYMLOS (abaloparatide) injection is a clear and colorless solution, available as a pre-assembled single-patient-use disposable pen (NDC 70539-001-01) packaged in a cardboard carton (NDC 70539-001-02) with the Instructions for Use and Medication Guide. Each disposable pen embodies a glass cartridge that contains 3120 mcg of abaloparatide in 1.56 mL (2000 mcg/mL). Each pen provides a 30-day supply for once daily injection of 80 mcg abaloparatide in 40 mL.

Sterile needles are not included.

16.2 Storage and Handling

- Before first use, store TYMLOS under refrigeration between 2°C to 8°C (36°F to 46°F).
- After first use, store for up to 30 days at 20°C to 25°C (68°F to 77°F).
- Do not freeze or subject to heat.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Risk of Osteosarcoma

Advise patients that the active ingredient in TYMLOS, abaloparatide, caused a dose-dependent increase in the incidence of osteosarcoma in male and female rats and that it is unknown whether TYMLOS will cause osteosarcoma in humans [*see Warnings and Precautions (5.1)*].

Instruct patients to promptly report signs and symptoms of possible osteosarcoma such as persistent localized pain or occurrence of a new soft tissue mass that is tender to palpation.

Hypercalcemia

Advise patients that TYMLOS may cause hypercalcemia and discuss the symptoms of hypercalcemia (e.g., nausea, vomiting, constipation, lethargy, muscle weakness) [*see Warnings and Precautions (5.3)*].

Instruct patients to promptly report signs and symptoms of hypercalcemia.

Orthostatic Hypotension

Advise patients to sit or lie down if they feel lightheaded or have palpitations after the injection until their symptoms resolve. If these symptoms persist or worsen, advise patients to consult their healthcare provider before continuing treatment [*see Dosage and Administration (2.2)*].

Hypersensitivity Reactions

Advise patients to seek immediate medical attention if they experience signs or symptoms of a hypersensitivity reaction including anaphylaxis, dyspnea, or urticaria [*see Contraindications (4) and Adverse Reactions (6.2)*].

Use of TYMLOS Pen

Instruct patients and caregivers who administer TYMLOS on how to properly use the TYMLOS pen and to follow sharps disposal recommendations [*see Dosage and Administration (2.2)*]. Advise patients not to share their TYMLOS pen or needles with other patients and not to transfer the contents of the pen to a syringe.

Advise patients that each TYMLOS pen can be used for up to 30 days, and after the 30-day use period, to discard the TYMLOS pen, even if it still contains unused solution [*see How Supplied/Storage and Handling (16.2)*].

Manufactured for:

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