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ADISINSIGHT REPORT

Abaloparatide: First Global Approval

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Abstract Abaloparatide (Tymlos™) is a synthetic peptide analogue of human parathyroid hormone-related protein that was developed by Radius Health as an osteoanabolic agent for the treatment of postmenopausal osteoporosis. Abaloparatide acts through selective activation of the parathyroid hormone type 1 receptor signalling pathway. In April 2017, subcutaneous abaloparatide received its first global approval, in the USA, for the treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy. A Marketing Authorization Application for subcutaneous abaloparatide for the treatment of postmenopausal women with osteoporosis was accepted by the European Medicines Agency and is currently under review. Radius is also developing a transdermal formulation of abaloparatide, with administration via a microneedle patch. This article summarizes the milestones in the development of abaloparatide leading to this first approval for the treatment of women with postmenopausal osteoporosis.

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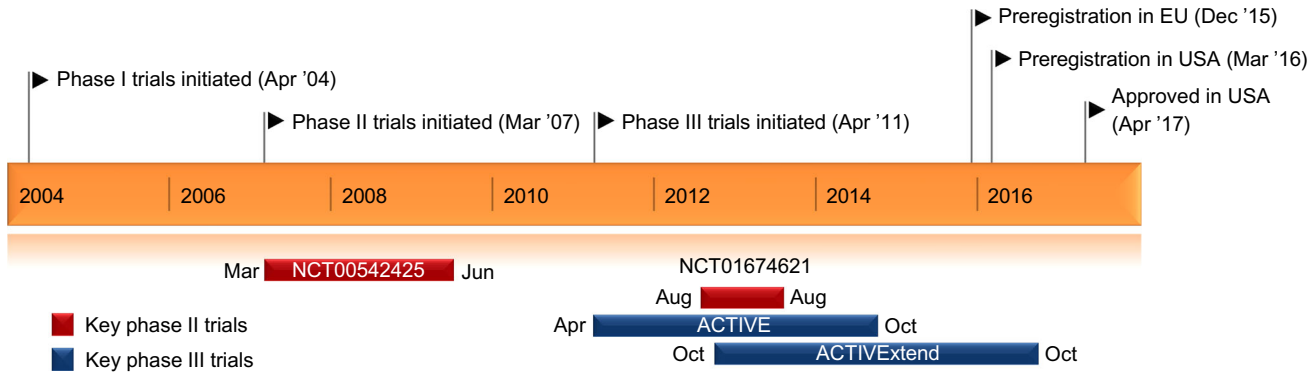
1 Introduction

Abaloparatide (Tymlos™), a synthetic peptide analogue of human parathyroid hormone-related protein (PTHrP), is an osteoanabolic agent that was developed for the treatment of postmenopausal osteoporosis [1]. Similar to teriparatide [PTH(1–34)], abaloparatide is a parathyroid hormone type 1 receptor (PTH1R) agonist [1]. Preclinical studies suggested that abaloparatide may have lower calcium-mobilization potential than teriparatide [2]. Furthermore, it was hypothesized that the greater binding selectivity of abaloparatide relative to teriparatide for the RG conformation of PTH1R may result in greater stimulation of bone formation than bone resorption and thus a greater net anabolic effect [3, 4].

On 28 April 2017, abaloparatide injection for subcutaneous use received its first global approval, in the USA, for the treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy [1, 5]. Its approval in the USA in this indication was based on the findings of the pivotal, placebo- and active-controlled phase III ACTIVE trial (NCT01343004) and the extension study ACTIVExtend (NCT01657162) (see Sect. 2.3). A Marketing Authorization Application for subcutaneous abaloparatide for the treatment of osteoporosis in postmenopausal women was accepted for review by the European Medicines Agency in December 2015 [6].



Clinical development of abaloparatide

Under the US approval, the recommended dosage of abaloparatide is 80 μg once daily, to be administered by subcutaneous injection into the periumbilical region of the abdomen [1]. Abaloparatide is supplied as a single-patient-use prefilled pen intended to deliver 30 doses. The dose should be administered at approximately the same time each day, with rotation of the injection site within the periumbilical region. Postmenopausal women treated with abaloparatide should also receive supplemental calcium and vitamin D if dietary intake is inadequate [1].

The US prescribing information for abaloparatide carries a boxed warning regarding a potential risk of osteosarcoma [1]. A study in rats found that systemic exposures to abaloparatide ranging from 4 to 28 times the exposure in humans receiving the 80 μg dose caused a dose-dependent increase in the incidence of osteosarcoma [1, 7]. The relevance of these findings in rats to humans is not clear. However, the use of abaloparatide is not recommended in patients at increased risk of osteosarcoma [1]. Furthermore, cumulative use of abaloparatide and parathyroid hormone (PTH) analogues (e.g. teriparatide) for >2 years during a patient's lifetime is not recommended [1].

A transdermal formulation of abaloparatide (with administration via a microneedle patch) is currently under development [8].

1.1 Company Agreements and Patent Information

Abaloparatide was originated by Ipsen (formerly Beaufour-Ipsen) and its subsidiary Ipsen Bioscience (formerly Biomeasure). Worldwide rights for the development and commercialization of subcutaneous abaloparatide were acquired by Radius Health in 2005, except for in Japan where Teijin Pharma holds an exclusive license (obtained in 2003).

The abaloparatide transdermal patch formulation is being developed by Radius using 3M's patented Microstructured Transdermal System microneedle technology after Radius entered into an agreement with 3M Drug Delivery Systems in May 2011 (updated in December 2012) [9]. Under the agreement, Radius will have exclusive worldwide rights (including Japan) for commercialization of the transdermal formulation.

Subcutaneous abaloparatide has patent protection in the USA and several other countries until 2027.

2 Scientific Summary

Abaloparatide is a synthetic 34-amino acid peptide analogue of human PTHrP(1–34) [1]. It shares 76% amino acid sequence identity with human PTHrP(1–34) and 41% identity with human PTH(1–34).

2.1 Pharmacodynamics

Abaloparatide is a PTH1R agonist [1]. Compared with teriparatide, it binds PTH1R with greater selectivity for the RG conformation over the R^0 conformation of the receptor [4]. This is proposed to induce more transient signalling responses, favouring net bone formation over bone resorption responses, with less calcium mobilization than teriparatide [3, 4].

Treatment with subcutaneous abaloparatide (80 μg once daily) was associated with significant increases in serum markers of bone formation [procollagen type 1 N-terminal propeptide (P1NP)] and bone resorption [C-terminal cross-linking telopeptide of type 1 collagen (CTX)] compared with placebo [3, 10]. In a subset of participants from ACTIVE (see Sect. 2.3) who were tested for bone turnover markers, those treated with abaloparatide experienced a maximum increase in P1NP levels of 93% above baseline at month 1, after which the increase in P1NP slowly declined over time to levels ~45% above baseline at the end of treatment (18 months) [1, 3]. For serum CTX, a

maximum increase of 43% above baseline was reached after 3 months of treatment, with levels declining to 20% above baseline at the end of treatment. In ACTIVE, the increases in P1NP and CTX levels for abaloparatide recipients were both lower than those for participants treated with teriparatide (20 μg once daily); however, given that the difference was more pronounced for CTX, it was suggested that abaloparatide might have a greater net anabolic effect compared with teriparatide [3].

Clinical studies in women with postmenopausal osteoporosis showed that abaloparatide treatment was associated with significant increases in bone mineral density (BMD) (see Sect. 2.3). Histological and histomorphometric analyses on iliac crest bone biopsy specimens that were obtained from a cohort of patients in ACTIVE after 12–18 months of abaloparatide treatment revealed normal bone microarchitecture with no evidence of mineralization abnormality, excess osteoid or woven bone, or bone marrow abnormalities or fibrosis [11].

Preclinical studies with animal (rat and monkey) models of postmenopausal osteoporosis showed that abaloparatide treatment was associated with dose-dependent increases in bone mass at vertebral and/or nonvertebral sites [1, 12–14]. Increases in bone formation were associated with improvements in trabecular microarchitecture and cortical geometry. Furthermore, the gains in bone mass correlated with increases in bone strength.

In a cross-over QT/QTc study in healthy volunteers, single doses of subcutaneous abaloparatide 80 and 240 μg caused an increased heart rate, with mean peak increases of 15 and 20 beats/min for the respective doses at the first timepoint (15 min post-dose) [1]. Abaloparatide had no clinically meaningful effects on individually corrected QT intervals or cardiac physiology [1].

2.2 Pharmacokinetics

Following subcutaneous administration of an 80 μg dose, abaloparatide reached peak concentration (C_{max}) in a median time of 0.5 h [1]. With once daily administration for 7 days, abaloparatide had a mean C_{max} of 812 pg/mL and a mean area under the concentration–time curve (AUC) from time zero to 24 h of 1622 pg·h/mL. Subcutaneous abaloparatide (80 μg dose) has an absolute bioavailability of 36% in healthy women [1].

Approximately 70% of abaloparatide is bound by plasma proteins in vitro [1]. Abaloparatide has a volume of distribution of ~50 L [1].

Abaloparatide metabolism is consistent with non-specific proteolytic degradation followed by renal elimination of the peptide fragments [1]. The drug has a mean half-life of 1.7 h [1].

Age or race had no apparent effects on abaloparatide pharmacokinetics in clinical trials [1]. Abaloparatide C_{max} and AUC increased 1.4- and 2.1-fold, respectively, in subjects with severe renal impairment relative to subjects with normal renal function [1]. No abaloparatide dosage adjustment is considered necessary in women with mild, moderate or severe renal impairment, although women with severe impairment should be more closely monitored for adverse reactions [1].

Abaloparatide has not been investigated in specific drug-drug interaction studies. No inhibition or induction of cytochrome P450 enzymes by abaloparatide was observed in in vitro studies [1].

Features and properties of abaloparatide

Alternative names	Abaloparatide-TD; abaloparatide-SC; BA 058; BA-058-SC; BA-058-TD; BIM-44058; ITM-058; PTHrP; synthetic human parathyroid hormone 37–70 analogue—Ipsen; TYMLOS
Class	Calcium regulators; osteoporosis therapies; peptide hormones
Mechanism of action	Osteogenesis stimulant; PTH1R agonist
Route of administration	Subcutaneous; transdermal (in development)
Pharmacodynamics	Acts as an agonist at the PTH1R, inducing transient signalling responses; causes increases in serum markers of bone metabolism; has an osteoanabolic effect resulting in increases in bone mineral density; increases in bone mass correlated with increases in bone strength in animal models of postmenopausal osteoporosis
Pharmacokinetics	Maximum concentrations reached 0.5 h post-dose; subcutaneous abaloparatide has an absolute bioavailability of 36%; in vitro plasma protein binding was ~70%; volume of distribution was ~50 L; mean $t_{½}$ = 1.7 h; elimination primarily occurs through renal excretion of peptide fragments following proteolytic degradation
Most common adverse events (with higher incidence than placebo)	Hypercalciuria, dizziness, nausea, upper respiratory tract infection, headache
ATC codes	
WHO ATC code	H05A-A03 (parathyroid hormone)
EphMRA ATC code	H4E (parathyroid hormones and analogues)

PTH1R parathyroid hormone type 1 receptor

2.3 Therapeutic Trials

Subcutaneous abaloparatide has been shown to significantly reduce the incidence and risk of new vertebral and nonvertebral fractures in postmenopausal women with osteoporosis [3, 15]. Treatment with abaloparatide was also associated with significant increases in BMD and with reductions in risk of major osteoporotic fractures and clinical fractures.

In the pivotal, multinational, phase III ACTIVE trial, 2463 postmenopausal women with osteoporosis were randomized (1:1:1) to receive daily subcutaneous injections of abaloparatide 80 μg or placebo in a double-blind fashion, or open-label teriparatide 20 μg, for 18 months [3]. In addition, all participants were provided supplemental calcium (500–1000 mg daily) and vitamin D (400–800 IU daily) [1, 3]. The primary endpoint of the trial was the percentage of participants with one or more new morphometric vertebral fractures, assessed in the modified intent-to-treat population (all randomized participants with both pretreatment and post-baseline spine X-rays) [3].

Compared with placebo, abaloparatide treatment reduced the risk of vertebral fractures by 86% over 18 months [3]. New morphometric vertebral fractures occurred in four participants (0.6%) in the abaloparatide group and in 30 participants (4.2%) in the placebo group [relative risk (RR) 0.14; 95% CI 0.05–0.39; $p < 0.001$]. In the teriparatide group, six participants (0.8%) had new morphometric vertebral fractures (RR vs. placebo, 0.20; 95% CI 0.08–0.47; $p < 0.001$). Abaloparatide also reduced the risk of nonvertebral fractures (secondary endpoint) by 43% compared with placebo (Kaplan–Meier-estimated rates of 2.7 vs. 4.7%; $p = 0.49$), major osteoporotic fractures by 70% (1.5 vs. 6.2%; $p < 0.001$) and clinical fractures by 43% [4.0 vs. 8.3%; $p = 0.02$] (exploratory endpoints) [3]. In ACTIVE, reductions in Kaplan-Meier-estimated event rates for open-label teriparatide recipients versus placebo recipients did not reach statistical significance for nonvertebral fractures [hazard ratio (HR) 0.72; $p = 0.22$], major osteoporotic fractures (HR 0.67; $p = 0.14$) or clinical fractures (HR 0.71; $p = 0.11$) [3].

In other secondary endpoint analyses, abaloparatide treatment was associated with significant improvements in BMD at the total hip (mean % change from baseline, +4.2% in abaloparatide recipients vs. −0.1% in placebo recipients), the femoral neck (+3.6 vs. −0.4%) and the lumbar spine (+11.2 vs. +0.6%) at 18 months ($p < 0.001$ for all comparisons vs. placebo) [3]. Increases in BMD with abaloparatide were also significantly ($p < 0.001$) higher than those with teriparatide at the total hip (2.3 vs. 1.4%) and the femoral neck (1.7 vs. 0.9%) at 6 months (secondary endpoints) [3].

Prespecified subgroup analyses showed that the treatment effects of abaloparatide on vertebral fractures, nonvertebral fractures and BMD were consistent regardless of age, prior fracture history or baseline BMD [16].

Eligible participants in ACTIVE were postmenopausal women aged 49–86 years with radiological evidence of at least two mild or at least one moderate lumbar or thoracic vertebral fractures or a history of low-trauma nonvertebral fracture within the preceding 5 years together with a BMD T-score ≤ -2.5 (or ≤ -2.0 for those older than 65 years) and > -5.0 at the lumbar spine or femoral neck [3]. Women >65 years old who did not meet the fracture criteria but had a T-score ≤ -3.0 and > -5.0 at either site were also eligible. Participants had a mean age of 69 years. At baseline, approximately 24% of participants had at least one prevalent vertebral fracture, 31% had at least one nonvertebral fracture in the preceding 5 years, and 37% had no history of prior fracture. Mean baseline BMD T-scores at the lumbar spine, femoral neck and total hip were −2.9, −2.1 and −1.9, respectively [3].

Participants in the abaloparatide and placebo groups in ACTIVE who completed 18 months of treatment were eligible to enter the ACTIVExtend extension study, in which all participants were treated with open-label oral alendronate 70 mg once weekly for 24 months [15]. There was a 1-month period between studies for re-consenting purposes. During the first 6 months of ACTIVExtend, study personnel and participants remained masked to the ACTIVE treatment group assignment. The primary endpoint of the extension study was the percentage of participants with one or more new morphometric vertebral fractures from the ACTIVE baseline through to month 6 of treatment with alendronate in ACTIVExtend (25 months in total) [15].

Results from a prespecified 6-month interim analysis of ACTIVExtend support the findings from the ACTIVE trial [15]. Over 25 months, new morphometric vertebral fractures occurred in 0.55% of participants who received abaloparatide followed by alendronate compared with 4.4% of participants who received placebo followed by alendronate, representing an 87% relative risk reduction associated with abaloparatide treatment ($p < 0.001$). No participants in the abaloparatide/alendronate group and seven participants in the placebo/alendronate group had new morphometric vertebral fractures during the first 6 months of ACTIVExtend [15]. Abaloparatide/alendronate treatment was also associated with significant reductions in the risk of nonvertebral (52% reduction; $p = 0.02$), major osteoporotic (58% reduction; $p = 0.01$) and clinical (45% reduction; $p = 0.02$) fractures at 25 months compared with placebo/alendronate. In the abaloparatide/alendronate and placebo/alendronate groups, BMD percentage increases from ACTIVE baseline at

Key clinical trials of abaloparatide in women with postmenopausal osteoporosis (Radius Health, Inc.)

Identifier	Phase	Drugs	Location(s)	Status
ACTIVE (NCT01343004)	III	s.c. abaloparatide, teriparatide, placebo	Multinational	Completed
ACTIVExtend (NCT01657162)	III	s.c. abaloparatide, placebo, p.o. alendronate	Multinational	Completed
NCT00542425	II	s.c. abaloparatide, teriparatide, placebo	USA	Completed
NCT01674621	II	t.d. abaloparatide, placebo, s.c. abaloparatide	Denmark, Estonia, Poland, USA	Completed

p.o. per os (oral), *s.c.* subcutaneous, *t.d.* transdermal

25 months were 5.5 vs. 1.4% at the total hip, 4.5 vs. 0.5% at the femoral neck and 12.8 vs. 3.5% at the lumbar spine (all $p < 0.001$) [15].

Early results from the now completed ACTIVExtend study indicate that abaloparatide has a persistent effect on improving bone strength [8]. At the end of the extension study (43 month timepoint), abaloparatide treatment followed by alendronate was associated with significant risk reductions relative to placebo followed by alendronate for vertebral fractures (84% reduction; $p < 0.0001$), nonvertebral fractures (39% reduction; $p = 0.038$), major osteoporotic fractures (50% reduction; $p = 0.011$) and clinical fractures (34% reduction; $p = 0.045$) [8].

2.4 Adverse Events

Currently available clinical data indicate that subcutaneous abaloparatide is generally well tolerated in postmenopausal women with osteoporosis [3, 15]. In ACTIVE, the proportions of participants with treatment-emergent adverse events or serious adverse events were similar across treatment groups [3]. Similarly, the incidence of adverse events was balanced between the groups with prior abaloparatide or placebo therapy in ACTIVExtend where all participants received alendronate, based on the interim analysis [15]. Furthermore, preliminary findings from early-phase clinical data suggest that transdermal abaloparatide has a safety and tolerability profile comparable to that of the subcutaneous formulation [17].

The most common adverse events in abaloparatide recipients in ACTIVE with a numerically higher incidence than in placebo recipients were hypercalciuria (11.3 vs. 9.0%), dizziness (10.0 vs. 6.1%), nausea (8.3 vs. 3.0%), upper respiratory tract infection (8.3 vs. 7.7%) and headache (7.5 vs. 6.0%) [3]. The incidence of adverse events that led to study drug discontinuation was higher among abaloparatide recipients (9.9%) than among placebo (6.1%) or teriparatide (6.8%) recipients. The adverse events most commonly leading to study drug discontinuation among abaloparatide recipients were nausea (1.6%), dizziness (1.2%), headache (1.0%) and palpitations (0.9%) [3].

Abaloparatide was associated with a risk of hypercalcaemia [1]. In ACTIVE, the overall incidence of hypercalcaemia (defined as an albumin-corrected serum calcium level of ≥2.67 mmol/L at any timepoint) was 3.4, 0.4 and 6.4% in the abaloparatide, placebo and teriparatide groups, respectively ($p < 0.001$ for abaloparatide and teriparatide vs. placebo; $p = 0.006$ for abaloparatide vs. teriparatide) [3].

More participants in the abaloparatide group than the placebo group in ACTIVE had occurrences of injection-site redness (58 vs. 28%), oedema (10 vs. 3%) and pain (9 vs. 7%) when assessed 1 h after each injection during the first month [1]. Most injection-site reactions were of mild or moderate severity.

As for all therapeutic proteins, abaloparatide has a potential for immunogenicity [1]. Anti-drug antibodies were developed by 49% of abaloparatide recipients in ACTIVE, 68% of whom had neutralizing antibodies to abaloparatide. Among participants with anti-abaloparatide antibodies, 2.3% developed cross-reactivity to PTHrP [43% (3/7) with neutralizing antibodies to PTHrP]. Development of anti-abaloparatide antibodies had no apparent clinically significant impact on abaloparatide efficacy or safety [1, 10].

2.5 Ongoing Clinical Trials

In April 2017, Teijin Pharma initiated a randomized, double-blind, placebo-controlled phase III trial to investigate the safety and efficacy of subcutaneous abaloparatide 80 μg once daily for 78 weeks in patients (men and women) aged 55–85 years with osteoporosis at a high risk of fracture (JapicCTI-173575).

Radius is currently planning a clinical trial to investigate the bioequivalence of an abaloparatide transdermal patch to subcutaneous abaloparatide [18].

3 Current Status

Abaloparatide received its first global approval on 28 April 2017, in the USA, for the treatment of postmenopausal women with osteoporosis at high risk for fracture defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy [5].

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Additional information about this AdisInsight Report can be found at http://www.medengine.com/Redeem/8798F060199BA726.

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