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ORIGINAL RESEARCH ARTICLE

Phase 1b Evaluation of Abaloparatide Solid Microstructured Transdermal System (Abaloparatide-sMTS) in Postmenopausal Women with Low Bone Mineral Density

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Abstract

Background and Objective Abaloparatide, an anabolic osteoporosis treatment administered by subcutaneous (SC) injection, increases bone mineral density (BMD) and reduces fracture risk in postmenopausal women with osteoporosis. The abaloparatide-solid Microstructured Transdermal System [abaloparatide-sMTS (Kindeva, St Paul, MN, USA)], which delivers abaloparatide intradermally, is in development to provide an alternative method for abaloparatide delivery. The objective of this study was to evaluate the ability of subjects to self-administer abaloparatide-sMTS, based on pharmacokinetic and pharmacodynamic markers.

Methods In this single-arm, open-label, Phase 1b study, 22 healthy postmenopausal women aged 50–85 years with low BMD were trained to self-administer abaloparatide-sMTS 300 µg once daily to the thigh for 5 min for 29 days. The primary endpoint was systemic exposure to abaloparatide. Secondary endpoints included percent change from baseline in serum procollagen type I N-terminal propeptide (s-PINP), patient experience, and safety.

Results All 22 subjects completed the study. At baseline, mean age was 65.2 years, mean total hip T-score was − 1.32, and mean lumbar spine T-score was − 1.98. On Day 1, the median time to reach maximum concentration (T_{max}) for abaloparatide-sMTS was 0.33 h and geometric mean (CV %) maximum concentration (C_{max}) and area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC_{0-t}) were 447 (38.0) pg/mL and 678 (45.3) pg·h/mL, respectively; the pharmacokinetic profile was similar on Days 15 and 29. Median percentage change in s-PINP was 45.4% and 64.4% at Days 15 and 29, respectively. The most common adverse events (AEs) were application site erythema, pain, and swelling, which were mostly of mild or moderate severity. No AEs led to study drug withdrawal and no serious AEs were reported. The success rate for self-administration at first application was 99.7%, and subject acceptability was high (~ 4.5 on a 5-point Likert Scale).

Conclusions Subjects successfully self-administered abaloparatide-sMTS, which provided a consistent pharmacokinetic profile over 29 days and produced s-PINP increases from baseline similar to that observed in the pivotal trial with abaloparatide-SC. Observed patient experience along with the clinical data support continued clinical development of abaloparatide-sMTS.

Trial Registration Number NCT04366726, Date of registration 04/29/2020, retrospectively registered

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Plain Language Summary

Osteoporosis is a serious health condition that causes more than 2 million fractures in the USA annually. Treatment options for osteoporosis include drugs that prevent bone resorption and anabolic agents that build new bone. Bone anabolic agents, such as abaloparatide, have been shown to increase bone mineral density and reduce the risk of fracture in postmenopausal women with osteoporosis. Currently, all bone anabolic agents are delivered by subcutaneous injection. However, some patients do not like injectable treatments, which can negatively impact patients' adherence to prescribed medication. In this study, we describe a novel mode of administration, the abaloparatide-solid Microstructured Transdermal System (abaloparatide-sMTS), which is applied to the thigh for 5 min and delivers abaloparatide intradermally. The study showed that this new method delivered abaloparatide into the blood as effectively as subcutaneous injections and demonstrated signs of activity in the body. Study participants were satisfied with abaloparatide-sMTS and found it easy to use. The most common side effects were skin related, including redness, pain, and swelling, which resolved shortly after dosing.

Key Points

Anabolic drugs that help to build bone are currently all delivered by subcutaneous injection, which may limit their use by both patient and physician.

This study was the first evaluation of a novel delivery method for the anabolic agent abaloparatide using an intradermal delivery system self-administered to the thigh over 29 days in postmenopausal women with low bone mineral density.

The study found that abaloparatide-sMTS administration was effective, easy to use, and not associated with any serious safety concerns.

1 Introduction

Osteoporosis is a serious health condition that causes more than 2 million fractures in the USA annually, with that number expected to substantially increase with the aging population [1, 2]. Current treatment options include antiresorptive drugs, which inhibit osteoclast-mediated bone resorption [3], and anabolic agents [administered by subcutaneous (SC) injection], which stimulate osteoblast production and function to improve bone microstructure and increase bone formation [4]. Despite the availability of multiple therapeutic options, rates of pharmacologic treatment for osteoporosis after a fracture remain low [5, 6]. For patients who do initiate treatment, long-term adherence to osteoporosis therapies is suboptimal and high rates of discontinuation are common, regardless of the mode of intake [7, 8].

A National Osteoporosis Foundation survey found that daily injection was most frequently ranked as the least preferred mode of administration for osteoporosis treatments [9], and, in another recent survey, having to inject medication was considered to be the worst attribute of the anabolic agent abaloparatide-SC in women initiating treatment with this drug [10]. Studies have suggested that intradermal delivery systems have a greater acceptability compared with traditional SC injections [11] and may improve patient adherence, as they do not stimulate nerves that are associated with pain [12]. Thus, availability of a non-injectable anabolic treatment has the potential to improve adherence and provide an additional treatment option for patients with needle aversion.

Abaloparatide, a synthetic analog of the parathyroid hormone-related peptide (PTHrP) and a selective activator of the parathyroid hormone (PTH) type 1 receptor, is approved by the US Food and Drug Administration (FDA) for the treatment of postmenopausal women with osteoporosis at high risk for fracture [13, 14]. In the pivotal phase III ACTIVE study (ClinicalTrials.gov identifier: NCT01343004), abaloparatide-SC significantly increased bone mineral density (BMD) and decreased the risk of fractures in postmenopausal women with osteoporosis [15]. These effects were sustained in patients subsequently treated with alendronate monotherapy for an additional 2 years in the phase III ACTIVExtend trial (ClinicalTrials.gov identifier: NCT01657162) [16, 17]. Radius Health, Inc., in collaboration with Kindeva Drug Delivery, is developing a drug-device combination product for an intradermal method of abaloparatide administration, the abaloparatide-solid Microstructured Transdermal System (abaloparatide-sMTS), which consists of a small polymeric disk of microneedle arrays coated with abaloparatide.

The objective of this study was to evaluate the ability of subjects to self-administer abaloparatide-sMTS (300 µg) each day for 29 days, based on pharmacokinetic and pharmacodynamic markers. The usability of abaloparatide-sMTS as well as safety and tolerability were also assessed.

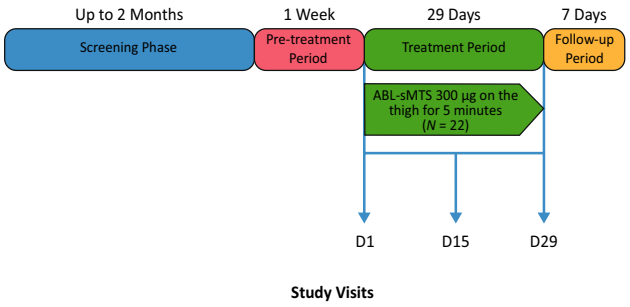

Fig. 1 Study design. *ABL-sMTS* abaloparatide-solid Microstructured Transdermal System, *D* day

2 Methods

This open-label, single-arm, single-center, Phase 1b study evaluated the usability of abaloparatide-sMTS in postmenopausal women with low BMD (Fig. 1). Subjects were trained to self-administer abaloparatide-sMTS 300 µg once daily to their anterior thigh for 5 min (and then remove), alternating on either side, for a period of 29 days. Self-administration occurred under observation at the study site on Days 1, 15, and 29.

The study was conducted according to the recommendations of Good Clinical Practice and the Declaration of Helsinki revised edition (Seoul 2008) and was approved by the ethics committee at the study site. All subjects provided written informed consent.

2.1 Study Subjects

Healthy postmenopausal women, aged 50–85 years inclusive with a body mass index (BMI) up to 33 kg/m^2 and a BMD *T*-score < -1.0 and > -5.0 at the lumbar spine or hip were eligible for the study. Preference was given to subjects with a *T*-score of -2.0 or lower during enrollment.

Subjects were excluded if they had a history of bone disorders other than postmenopausal osteoporosis; cancer within the past 5 years (other than basal cell or squamous cancer of the skin); osteosarcoma at any time; or prior external beam or implant radiation therapy involving the skeleton, other than radioiodine. Subjects previously treated with PTH- or PTHrP-derived drugs or bone anabolic drugs at any time, intravenous (IV) bisphosphonate at any time, oral bisphosphonate within the prior year, or denosumab within the prior 18 months were not eligible for the study. Subjects with application sites on the thigh compromised by scars, inflammation, or skin conditions that affected uniformity of abaloparatide-sMTS application or drug delivery were also excluded.

2.2 Study Drug Administration

Subjects were trained by study personnel to self-administer a single daily dose of 300 µg abaloparatide-sMTS to alternating thighs for 5 min. Subjects were encouraged to drink 8 ounces of water 1–2 h before applying abaloparatide-sMTS and to remove it from refrigeration 1 h before application. Subjects were instructed to clean the application site with an alcohol wipe and to administer abaloparatide-sMTS while in a sitting or lying position. After 5 min, subjects removed abaloparatide-sMTS but remained in the sitting or lying position for approximately 5 min after administration was completed. Self-administration of abaloparatide-sMTS occurred under observation by study staff on Days 1, 15, and 29, and the subject remained under observation for a minimum of 60 min after administration.

2.3 Study Endpoints

Blood samples for pharmacokinetic analysis were drawn from each subject pre-dose and at 10 min, 20 min, 30 min, 1 h, 1.5 h, 2 h, 3 h, and 4 h after abaloparatide-sMTS application on Days 1, 15, and 29. Blood samples were collected into 5.0 mL K3EDTA vacutainer® tubes with aprotinin as a protease inhibitor to stabilize abaloparatide in the samples, and the separated plasma was frozen and stored at – 80 °C until assay.

Serum procollagen type I N-terminal propeptide (s-PINP) was measured within 1 h before abaloparatide-sMTS administration and serum calcium (albumin-corrected) and inorganic phosphorus were measured pre-dose and at 4 h after abaloparatide-sMTS administration on Days 1, 15, and 29. Serum cyclic adenosine monophosphate (cAMP) levels were measured pre-dose and at 30 min after abaloparatide-sMTS administration on Days 1, 15, and 29.

Investigators assessed the application site for the presence of erythema, edema, vesiculation, glazed appearance, erosions, crusting, hyperpigmentation, hypopigmentation, scarring, atrophy, bruising, and bleeding using a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe) before application, 5 min after application (immediately upon removal of abaloparatide-sMTS), and 1 h after application on Days 1, 15, and 29. Subjects were instructed to record symptoms of local skin reaction (pain, itching, burning, tenderness, and swelling) using the 4-point scale described above before application, 5 min after application, and 1 h after application from Day 1 through Day 29 in their subject diary.

Abaloparatide-sMTS adhesion was assessed daily by subjects immediately before removal. Adhesion was scored as follows: 0 = ≥ 90% adhered (essentially no lift off the skin); 1 = ≥ 75% to < 90% adhered (some edges only lifting off the skin); 2 = ≥ 50% to < 75% adhered (less than half lifting off the skin); 3 = > 0% to < 50% adhered, but not detached

(more than half lifting off skin without falling off); 4 = 0% adhered and detached (completely off the skin). Subjects were also instructed to record any user errors in their diary.

Safety assessments included adverse events (AEs), serious adverse events, serious and unanticipated device effects, vital signs, physical examination, electrocardiogram (ECG), and laboratory values.

Subject global satisfaction and satisfaction with convenience of treatment were assessed at Days 15 and 29 using the abbreviated 9-item Treatment Satisfaction Questionnaire for Medication (TSQM-9). Scores for each domain were computed by adding the TSQM-9 items in each domain and then transforming the composite score into a value ranging from 0 to 100, using the algorithm provided in the TSQM User Manual (Version 1.1, October 2018), with higher scores representing higher satisfaction. Subject acceptability of treatment was measured using a 5-point Likert scale (1 being the least acceptable/negative experience to 5 being the most acceptable/positive experience) at Days 1, 15, and 29. Subject preference for treatment attributes at Days 1, 15, and 29 was assessed by posing the following two questions directly to subjects: "Which attributes of the treatment do you find most favorable for you?" and "Which attributes of the treatment do you find least favorable?" No specific response options were provided for the participants to choose from. Instead, verbatim subject comments were categorized by treatment attribute.

2.4 Bioanalytical Assay

Abaloparatide plasma concentrations were determined at Nexelis (formerly Pacific Biomarkers, Seattle, WA, USA) using a validated radioimmunoassay (RIA) method (using ^{125}I-abaloparatide as a radiotracer, Perkin Elmer, Boston, MA, USA). The assay employed a rabbit polyclonal antibody raised against abaloparatide, which shows no significant cross-reactivity to native PTH or PTHrP. The abaloparatide assay calibration standards ranged from 0 to 800 pg/mL, with quality control (QC) sample concentrations of 60, 180, and 600 pg/mL. The assay has a lower limit of quantitation of 20 pg/mL. Approximately 10% of the samples were randomly selected for evaluation of Incurred Sample Reanalysis (ISR), and these assays were performed on the backup sample aliquots, which had not previously been thawed/analyzed.

2.5 Statistical Methods

Pharmacokinetic parameters were calculated with standard noncompartmental methods using Phoenix® WinNonlin® v.7.0. and the linear-up/log-down trapezoidal method for AUC calculations. The apparent terminal phase half-life ($t_{1/2}$) was calculated as $\ln(2)/\lambda_z$, where λ_z is the first-order terminal elimination rate constant calculated from a regression analysis of the plasma concentration versus time data judged to be in the terminal phase of a semi-log plot of the plasma concentration-time curve. Abaloparatide plasma concentration values that were reported as below the limit of quantitation (BLQ) were set to zero for pharmacokinetic parameter calculation and concentration summary statistics.

Pharmacokinetic parameters were summarized using descriptive statistics. In order to estimate the relative exposure [and 90% confidence intervals (CIs)] between Days 1, 15, and 29, the natural log (ln)-transformed area under the plasma concentration-time curve (AUC) from time 0 to the time of the last quantifiable concentration (AUC_{0-t}), AUC from time 0 to infinity (AUC_{0-inf}), and maximum concentration (C_{max}) were compared among visits following the methodology for longitudinal data analysis using a repeated-measures model. This analysis is based upon within-subject pharmacokinetic variability because the pharmacokinetic parameters are derived from the same subjects on multiple occasions.

Actual values, change from baseline, and percentage change from baseline were summarized using descriptive statistics for pharmacodynamic markers—s-PINP, serum calcium (albumin-corrected), phosphorous, and cAMP. Descriptive analyses were used to summarize TSQM-9 satisfaction and convenience domain scores, subject acceptability, subject and investigator assessment of local skin reactions, adhesion, and user error. No formal statistical hypothesis testing was performed for safety endpoints, and the presentations were based on descriptive summaries. All descriptive and statistical analyses were performed using

Table 1 Patient demographics and baseline characteristics (safety population, $N = 22$)

Characteristic	Value
Age, years	
Mean (SD)	65.2 (6.4)
Median (min, max)	68 (51, 72)
Age group, *n* (%)	
< 65 years	7 (31.8)
65 − < 75 years	15 (68.2)
≥ 75 years	0
Race – White, *n* (%)	22 (100)
Ethnicity—not Hispanic or Latino, *n* (%)	21 (95.5)
Weight, mean, kg (SD)	63.3 (10.0)
BMI, mean, kg/m^2 (SD)	24.7 (3.4)
BMD T-score, mean (SD)	
Total hip	− 1.32 (0.76)
Lumbar spine	− 1.98 (0.76)

BMD bone mineral density, *BMI* body mass index, *SD* standard deviation, *sMTS* solid Microstructured Transdermal System

SAS® (SAS institute, Cary, NC, USA) statistical software, version 9.4.

3 Results

3.1 Subject Disposition and Baseline Characteristics

Overall, 22 subjects enrolled in the Phase 1b study. All 22 subjects completed the study and completed all doses of abaloparatide-sMTS. At baseline, mean age was 65.2 years (range 51–72 years) and mean BMD *T*-score was − 1.32 at the total hip and − 1.98 at the lumbar spine (Table 1).

3.2 Pharmacokinetic Parameters

Abaloparatide pre-dose concentrations were all below the level of quantification even after multiple doses on Day 15 and Day 29. After self-administration of abaloparatide-sMTS, median T_{max} (time to reach maximum concentration) for abaloparatide was at 0.33 h on Day 1 and 0.50 h on Days 15 and 29 (Fig. 2, Table 2). Geometric mean (CV%) values for C_{max} and AUC_{0-t} were 447 (38.0) pg/mL and 678 (45.3) pg·h/mL, respectively on Day 1. Exposure to abaloparatide was similar on Day 15 when compared with Day 1, with geometric mean values on Day 15 of 428 (41.5) pg/mL and 703 (54.0) pg·h/mL for C_{max} and AUC_{0-t}, respectively. However, a slight decrease was observed on Day 29 compared with Day 1, with geometric mean values of 400 (41.8) pg/mL and 605 (51.1) pg·h/mL for C_{max} and AUC_{0-t}, respectively. Geometric mean terminal phase $t_{1/2}$ was similar on Days 1, 15, and 29, ranging from 1.3 to 1.4 h.

Although this study was not statistically powered a priori to show bioequivalence in the pharmacokinetic profiles between Days 1, 15, and 29, comparisons of abaloparatide C_{max}, AUC_{0-t}, and AUC_{0-inf} between Day 15 and Day 1 and

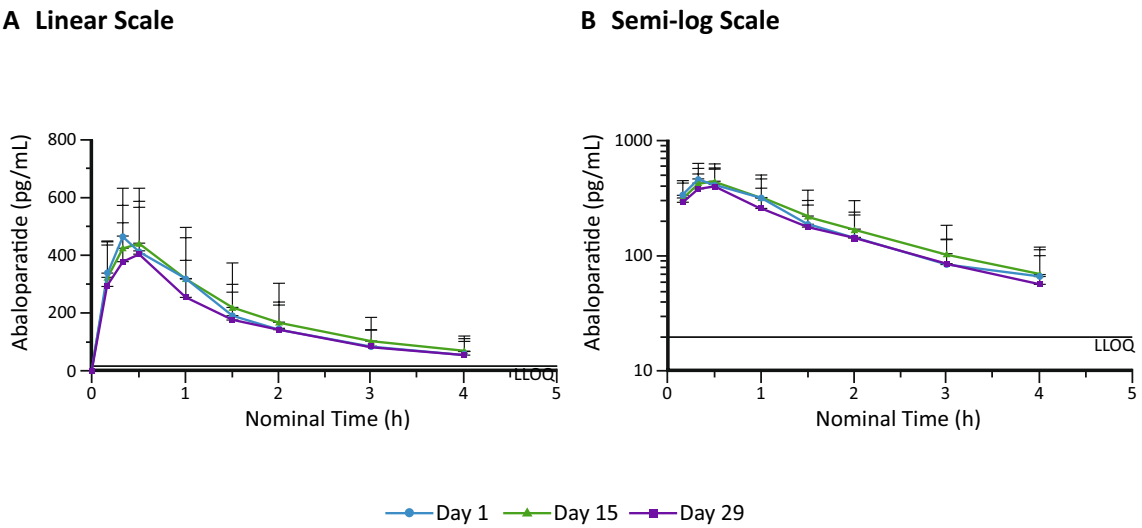

Fig. 2 Mean (±SD) plasma concentrations of 300 µg abaloparatide-sMTS over time ($N = 22$) on a linear scale (**a**) and logarithmic scale (**b**). *h* hour, *LLOQ* lower limit of quantitation, *SD* standard deviation, *sMTS* solid Microstructured Transdermal System

Table 2 Plasma abaloparatide pharmacokinetic parameters[a,b]

Pharmacokinetic parameter	Day 1	Day 15	Day 29
AUC_{0-t} (pg·h/mL)	678 (45.3)	703 (54.0)	605 (51.1)
AUC_{0-inf} (pg·h/mL)	785 (41.1)	830 (49.9)	686 (53.1)
C_{max} (pg/mL)	447 (38.0)	428 (41.5)	400 (41.8)
$t_{1/2}$ (h)	1.4 (21.0)	1.4 (12.9)	1.3 (26.3)
t_{max} (h)	0.33 (0.17–0.50)	0.50 (0.17–0.55)	0.50 (0.17–1.00)

AUC_{0-t} area under the concentration-time curve (AUC) from time 0 to the time of the last quantifiable concentration, *AUC_{0-inf}* AUC from time 0 to infinity, *C_{max}* maximum concentration, *CV* coefficient of variation, *h* hour, *sMTS* solid Microstructured Transdermal System, *$t_{1/2}$* half-life, *T_{max}* time to reach maximum concentration

[a]Values are expressed as geometric mean (CV %), except for t_{max}, which are median (range)

[b]Self-administered abaloparatide-sMTS ($N = 22$)

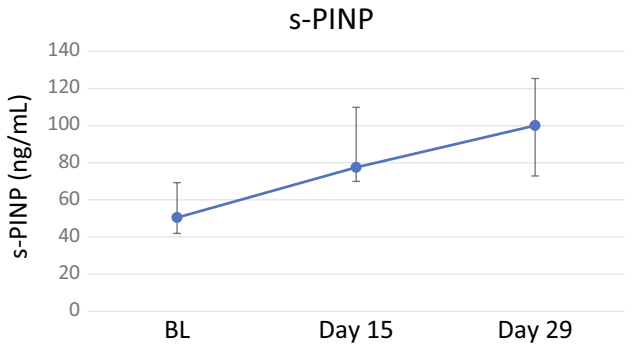

Fig. 3 Median (interquartile range) s-PINP (ng/mL) at Days 15 and 29 ($N = 22$). Baseline is defined as the last non-missing measurement taken prior to first dose. *BL* baseline, *s-PINP* serum procollagen type I N-terminal propeptide

comparisons of $AUC_{0\text{-}t}$ and $AUC_{0\text{–}inf}$ between Day 29 and Day 1 met the strict bioequivalence criteria requiring the 90% CIs to lie entirely between 80% and 125% (data not shown). However, the geometric mean abaloparatide C_{max} was slightly lower on Day 29 and narrowly missed meeting the bioequivalence criteria. The estimate intrasubject CV for these comparisons was approximately 19–20%, with the exception of the C_{max} comparison between Day 29 and Day 1 that exhibited an intrasubject CV of approximately 27% (data not shown).

3.3 Pharmacodynamic Markers

Median (interquartile range) s-PINP was 50.5 (42.0–69.3) ng/mL at baseline and increased to 77.5 (70.0–109.8) ng/mL at Day 15 and 100.1 (72.9–125.4) ng/mL at Day 29 (Fig. 3), a median percentage change from baseline of 45.4% and 64.4% at Days 15 and 29, respectively. No clinically significant changes from baseline for cAMP and no clinically relevant hypercalcemia or hypophosphatemia were seen (data not shown).

3.4 Safety and Adverse Events

All subjects reported at least one AE and at least one skin-related AE (Table 3). The most common AEs were application site erythema, application site pain, application site swelling, and application site edema. Most AEs were mild or moderate in severity.

Two subjects reported severe local skin reactions that were recorded as AEs. One subject reported severe pain and itching at the application site prior to dosing on Day 4 that resolved within 10 min and was not seen after application that day or subsequently. One subject reported severe swelling at application site on Day 7 that resolved by the next day. The investigator did not observe application site swelling at any study visits. No deaths, AEs leading to study drug withdrawal, or serious AEs were reported. No clinically significant changes in any hematology, chemistry, or urinalysis or ECG parameters were seen.

Table 3 Most common (≥ 5%) adverse events (AEs)[a]

System organ class Preferred term	*n* (%)
Subjects with any AEs	22 (100)
General disorders and administration site conditions	22 (100)
Application site erythema	22 (100)
Application site pain	20 (90.9)
Application site swelling	17 (77.3)
Application site edema	14 (63.6)
Application site hemorrhage	6 (27.3)
Application site pruritus	6 (27.3)
Nervous system disorders	2 (9.1)
Burning sensation[b]	2 (9.1)

Each subject was counted once for the same system organ class and the same preferred term

sMTS solid Microstructured Transdermal System

[a]Self-administered abaloparatide-sMTS 300 µg ($N = 22$)

[b]Burning sensation was reported on the thigh for both subjects before administration of abaloparatide-sMTS

3.5 Local Skin Reactions

Investigators assessed local skin reactions prior to abaloparatide-sMTS application and at 5 min and 1 h after application. Mild erythema was seen at 5 min (72.7%, 77.3%, and 50.0% on Days 1, 15, and 29, respectively) and 1 h after abaloparatide-sMTS application (90.9% on Day 1 and Day 15 and 77.3% on Day 29), whereas mild edema was predominantly seen at 1 h after abaloparatide-sMTS removal (45.5% on Day 1 and Day 15 and 18.2% on Day 29). Mild (pinpoint) skin bleeding (4.5%, 13.6%, and 18.2% at 5 min post-dose on Days 1, 15, and 29, respectively) and mild crusting [one subject (4.5%) at 1 h post-dose on Day 1 only] were also seen.

Swelling, pain, and burning were the most common local skin reactions reported by subjects on Days 1, 15, and 29 [Online Supplementary Material (OSM), Table 1]. Local skin reactions reported by subjects were predominantly mild to moderate in severity, with no increase in the severity of the reactions with repeat abaloparatide-sMTS administration. The percentage of subjects reporting swelling increased from Day 1 (50.0%) to Day 15 and Day 29 (59.1% each), whereas the percentages of subjects reporting pain and burning were decreased on Day 15 (13.6% and 22.7%, respectively) and Day 29 (9.1% and 22.7%, respectively) compared with Day 1 (45.4% and 40.9%, respectively). The mean

percentage of applications where a clear mark was identified 24 h after abaloparatide-sMTS application was 73.3%.

3.6 Self-administration and Adhesion

Mean (SD) first application success rate during the study was 99.7% (1.0) [range, 97 (28 of 29 administrations) – 100% (29 of 29 administrations)]. Two women reported difficulty with administration for one of their 29 abaloparatide-sMTS applications but did not specify the reason. For all women, on Days 1, 15, and 29, abaloparatide-sMTS was ≥ 90% adhered (adhesion score of 0). Abaloparatide-sMTS did not detach prior to completion of the 5-min wear time for any subjects. During the treatment period, four subjects (one event each) reported abaloparatide-sMTS as being ≥ 75% to < 90% adhered.

3.7 Patient Experience

The abaloparatide-sMTS had high subject acceptability, with mean (SD) acceptability scores (5 = most acceptable/positive experience) of 4.5 (0.7) on Day 1, 4.6 (0.9) on Day 15, and 4.5 (0.7) on Day 29. Subjects were satisfied with the use and convenience of abaloparatide-sMTS based on responses to the TSQM-9 questionnaire (Table 4). Mean (SD) global satisfaction scores on Day 15 and Day 29 were 64.3 (18.0) and 56.8 (21.7), respectively, ranging from 21.4 to 92.9 on Day 15 and from 14.3 to 100.0 on Day 29. Mean (SD) convenience scores on Day 15 and Day 29 were 74.5 (15.4) and 69.4 (16.9), respectively, ranging from 38.9 to 100.0 on both days. Verbatim comments regarding "treatment attributes" (OSM, Table 2) indicated that most subjects found abaloparatide-sMTS easy to use including the first treatment application on Day 1 of the study. When verbatim comments were categorized by attribute, 64% of subjects (n = 14) commented on "ease of use" (Table 5). Fewer than 10% of the subjects reported issues with the device or the application at any time during the study [device issues: two (9.1%); daily application: one (4.5%)]. Topics related to study site characteristics (i.e., getting up early, frequent blood draws, food) rather than the study drug itself were mentioned by 56% of subjects on Days 1 and 29 and 64% of subjects on Day 15 when asked about treatment attributes they found to be least favorable (OSM, Table 3).

Table 4 Summary of TSQM-9 global satisfaction and convenience domains by visit[a]

Domain	Day 15	Day 29
Convenience		
Mean (SD)	74.5 (15.4)	69.4 (16.9)
Median (min, max)	77.8 (38.9, 100.0)	66.7 (38.9, 100.0)
Global satisfaction		
Mean (SD)	64.3 (18.0)	56.8 (21.7)
Median (min, max)	64.3 (21.4, 92.9)	57.1 (14.3, 100.0)

TSQM scores range from 0 to 100, with higher scores indicating higher satisfaction

SD standard deviation, *sMTS* solid Microstructured Transdermal System, *TSQM-9* 9-item Treatment Satisfaction Questionnaire for Medication

[a]Self-administered abaloparatide-sMTS 300 µg (N = 22)

Table 5 Summary of treatment attributes mentioned by subjects[a,b]

Treatment attributes	n (%)
Ease of use	14 (64)
General like of abaloparatide-sMTS	5 (23)
Convenience	4 (18)
Perceived efficacy	3 (14)
Refrigeration/timing requirement	9 (41)
Adverse reactions	4 (18)
Application site	3 (14)
Device issues	2 (9)
Daily application	1 (5)
General dislike of abaloparatide-sMTS	1 (5)

sMTS solid Microstructured Transdermal System

[a]Data represent verbatim subject comments on Days 1, 15, and 29 categorized by treatment attribute

[b]Self-administered abaloparatide-sMTS 300 µg (N = 22)

4 Discussion

This study was the first evaluation of a self-administered multidose regimen of abaloparatide-sMTS 300 µg over 29 days in postmenopausal women with low BMD. Subjects achieved target pharmacokinetics, indicating that they were appropriately trained and successfully able to self-administer abaloparatide-sMTS with few errors and high subject acceptability for 29 days. Pharmacokinetic exposure was similar on Day 1 (when subjects were first trained to self-administer abaloparatide-sMTS), Day 15, and declined only slightly on Day 29, suggesting subjects were able to consistently self-administer abaloparatide-sMTS.

Importantly, the increase in median s-PINP, a marker of bone formation, over 29 days from 50.5 ng/mL at baseline to 100.1 ng/mL is consistent with the increase in s-PINP observed with abaloparatide-SC in the pivotal ACTIVE study (from 50.6 ng/mL at baseline to 100.5 ng/mL at month 1) [18]. The increase in s-PINP after 1 month of anabolic treatment has been shown to predict the overall increase in BMD at 18 months [18]. The increase in s-PINP after 29

days of self-administered abaloparatide-sMTS 300 µg suggests that self-administration for a longer treatment duration will likely increase BMD, supporting continued clinical development of abaloparatide-sMTS. No clinically significant hypercalcemic or hyperphosphatemic responses were seen.

Subjects were able to successfully self-administer abaloparatide-sMTS daily, as evidenced by a mean first application success rate of 99.7%, along with ≥ 90% adherence at Days 15 and 29. No subjects had abaloparatide-sMTS detached after self-administration, and adhesion scores indicated that abaloparatide-sMTS was firmly attached with essentially no lift off the skin.

Local skin reactions were predominantly mild to moderate in severity, with no increase in severity with repeat abaloparatide-sMTS administration. The only skin condition among the exclusion criteria was a compromised application site, suggesting these findings could be applicable to a broad range of patients. Despite the occurrence of mild to moderate skin reactions, the overall acceptability and satisfaction with use and convenience of self-administered abaloparatide-sMTS were high. Consideration of less favorable attributes, which related to site visits including, but not limited to, frequent blood withdrawals as required by the study, is reflected in a small decrement in overall satisfaction score over the course of the study.

This study is the first of an osteoporosis treatment administered using an intradermal delivery system, which could have the potential to improve compliance. Given the increasing burden of osteoporosis and poor patient adherence to the current medications [5, 6], the development of an alternate, more patient-friendly application procedure would be a significant advance in anabolic osteoporosis therapy. The current findings align with the FDA's Center for Drug Evaluation and Research Patient-Focused Drug Development initiative [19]. Furthermore, as per the 2020–2023 Value Assessment Framework from the Institute for Clinical and Economic Review, documentation of patient perspective of a new delivery mechanism that could improve real-world adherence provides contextual consideration relative to existing therapies [20].

4.1 Limitations

This open-label study was conducted without a concurrent control group or comparator (i.e., abaloparatide-SC), which would have provided a more direct comparison for the interpretation of the observed change in s-PINP. Moreover, the duration of treatment was not sufficiently long to assess the effects of abaloparatide-sMTS on BMD in these subjects. However, the results of this study support further evaluation of abaloparatide-sMTS in the ongoing Phase 3 wearABLe study (NCT04064411) comparing treatment with abaloparatide-sMTS or abaloparatide-SC over 12 months.

4.2 Conclusions

Subjects were able to successfully self-administer abaloparatide-sMTS to provide a consistent pharmacokinetic profile over 29 days and to produce s-PINP increases from baseline at 29 days similar to that observed after 1 month of administration in the pivotal trial with abaloparatide-SC. Subject-rated satisfaction, convenience, and acceptability were high. Taken together, these results support the continued clinical development of abaloparatide-sMTS, and a Phase 3 study is ongoing (NCT04064411).

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Declarations

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Conflicts of interest PDM has received research support from and is a member of an advisory board for Radius Health, Inc. JS is a paid consultant for Radius Health, Inc. and he has also received reimbursement for travel related to this study. ST, RJW, MA, SAW, and BM are employees of and own company stock in Radius Health, Inc.

Availability of data and material Data that underlie the results reported in a published article may be requested for further research 6 months after completion of FDA or EMA regulatory review of a marketing application (if applicable) or 18 months after trial completion (whichever is latest). Radius will review requests individually to determine whether (i) the requests are legitimate and relevant and meet sound scientific research principles, and (ii) are within the scope of the participants' informed consent. Prior to making data available, requestors will be required to agree in writing to certain obligations, including without limitation, compliance with applicable privacy and other laws and regulations. Proposals should be directed to info@radiuspharm.com.

Code availability Not applicable.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional review board and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Approval was granted by the Midlands Independent Review Board (Lenexa, KS, USA).

Informed consent Informed consent was obtained from all individual study participants included in the study.

Authors' contributions All listed authors meet the criteria for authorship set forth by the International Committee for Medical Journal Editors. ST, MA, JS, SAW, and BM contributed to the conception and design of the study; ST and MA acquired the data; the analysis was conducted by ST, MA, and BM; PDM, ST, RJW, MA, JS, SAW, and

BM contributed to the data interpretation. BM wrote the first draft and all authors provided critical review throughout the development and approved the final draft of the manuscript for publication. All authors agree to be responsible for the content of this work.

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