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Clinical Trial

AGN1 local osteo-enhancement procedure increases proximal femur volumetric bone mineral density of women with post-menopausal osteoporosis as assessed by quantitative computed tomography analysis

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Abstract

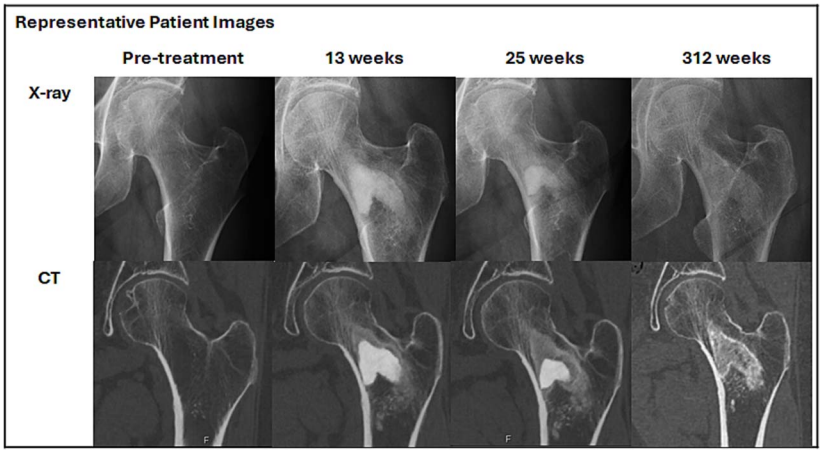
In this study, QCT was used to analyze the AGN1 Local Osteo-Enhancement Procedure (LOEP) as a treatment to form bone in the proximal femurs of patients with osteoporosis. Using this minimally invasive procedure, a resorbable triphasic AGN1 implant material was injected into the left femurs of 12 women with post-menopausal osteoporosis. Computed tomography scans were taken before treatment (baseline) and at 12 wk, 24 wk, and 5-7 yr after treatment. Quantitative computed tomography was used to investigate the resorption of AGN1 within the treated proximal femurs and to analyze the treatment's impact on integral, trabecular, and cortical bone. The untreated right femurs were used as controls. Data illustrated an increase in trabecular volumetric BMD (trab vBMD) of treated hips at all timepoints (baseline: 22 ± 21 mg/cm^3 vs 217 ± 56 mg/cm^3, 161 ± 18 mg/cm^3, and 121 ± 37 mg/cm^3 at 12-wk, 24-wk, and 5- to 7-yr timepoints, respectively), and an increase in integral vBMD of 65% at the 12-wk timepoint and 34% at the 5- to 7-yr timepoint. The increase in trab vBMD was observed in the location where the AGN1 implant material bolus was injected, and at the 5- to 7-yr timepoint, no significant BMD change was observed in the trabecular regions surrounding the original implantation zone (treated: 32 ± 16 mg/cm^3, control: 31 ± 16 mg/cm^3). This QCT study provides a more detailed understanding of the resorption and transformation of the AGN1 implant material into bone and supports, with some limitations, that the AGN1 LOEP treatment can locally increase trabecular bone density in weakened areas of the proximal femur where strength increase is most needed to reduce the risk of hip fragility fracture.

Keywords: bone QCT, osteoporosis, clinical trials, orthopedics, fracture prevention

Lay Summary

Bone loss associated with osteoporosis creates larger holes in bones, including the hips, which weakens them. These expanded holes can be treated by preparing and filling them with a resorbable, calcium-based material (AGN1). This study used special imaging (ie, quantitative computed tomography) to evaluate hips undergoing this treatment. Bone density increased in the treated holes, even at the final time of analysis, 5-7 yr after treatment. This study shows that AGN1 implant material transforms into bone, helping to address reduced bone density and volume in osteoporotic hips, key risk factors for hip fracture.

Graphical Abstract



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Introduction

Osteoporosis impacts over 200 million women worldwide,[1] resulting in significant bone loss and subsequent hip fragility fracture, which leads to increased mortality rates, higher medical costs, and decreased mobility and quality of life. In what many experts consider a "crisis,"[2–4] the number of people who will experience a fragility hip fracture is expected to increase to 3.3 million in the European Union alone by 2030.[5,6] The global burden of disease is projected to nearly double by 2050 when compared to 2018.[7] At best, existing systemic pharmacologic treatments offer a 50% reduction in fragility hip fracture after 12-18 months of consistent therapy, and this effect is further limited by low compliance rates.[8,9] To combat this issue, the AGN1 Local Osteo-Enhancement Procedure (LOEP), a minimally invasive treatment involving the implantation of a triphasic calcium sulfate/calcium phosphate implant material, was designed. AGN1 LOEP treats pathological bone voids in the proximal femur, thereby increasing local BMD. Further histomorphometric analysis of bone from ovariectomized (OVX) rats and dogs shows that AGN1 injection results in new trabecular bone composed of woven and lamellar bone that incorporated residual AGN1 matrix and tricalcium phosphate (TCP) granules and remodeled toward restoration of native microarchitecture over time.[10]

The treatment is currently being studied and adopted in multiple countries.[9] A previous study performed at Copley Hospital in Vermont, USA demonstrated through 2D DXA scans that AGN1 LOEP leads to an areal BMD (aBMD) increase that is both immediate and long-lasting, with the increase detected at the final study timepoint 5-7 yr post-treatment.[11] In the current study of these patients, a new 3D QCT analysis was performed to further analyze the efficacy of AGN1 LOEP in the Copley patient population by providing QCT volumetric BMD (vBMD) and additional quantitative detail about the treatment's effect on bone density.

Materials and methods

Study design and participants

Detailed demographics of this study's patient population and the specific methods used for the AGN1 LOEP treatment were previously published.[11] Briefly, the study patient population consisted of 12 Caucasian post-menopausal women all ≥55 yr of age. All except one patient had a pre-treatment femoral neck aBMD T-score ≤ –2.5 assessed by DXA (Hologic Delphi C). Patients were excluded if they experienced a previous hip fracture or had creatinine > 2.0 mg/100 mL or a glomerular filtration rate (GFR) < 30 mL/min. Presence of osteoarthritis or treatment with bone active agents did not independently affect eligibility.

Each patient had her left femur treated with AGN1 LOEP, while her right femur remained untreated as the contralateral control. The AGN1 LOEP treatment involved injection of the AGN1 implant material, a triphasic, resorbable implant material, consisting of calcium sulfate, brushite, and β-tricalcium phosphate, into a surgically prepared void in the proximal femur. This void, resulting from bone loss associated with osteoporosis, was prepared for enhancement by making a small incision in the lateral thigh and drilling a 5.3 mm diameter portal in the femoral cortex to the base of the femoral head. After accessing the enhancement site, fat, and other non-structural elements were gently removed from the femoral neck and intertrochanteric region through debridement, irrigation with sterile saline, and aspiration. Once the site was prepared, the AGN1 implant material was mixed and injected using fluoroscopic imaging to backfill in all planes the enhancement site from the apex to the cortical access portal.

CT acquisition

For all 12 patients, bilateral CT scans were obtained prior to treatment (baseline), at their 12-wk visit (range: 12-14 wk post-treatment), and at their 24-wk visit (range: 24-27 wk post-treatment) using a Phillips Brilliance 16P CT scanner. For 10 of the 12 patients, a fourth CT scan was obtained at the same imaging facility using a different scanner model (Siemens SOMATOM Definition AS) at a study extension timepoint occurring at an average of 6 yr (313 wk) post-treatment (range: 279-363 wk post-treatment). For most scans, a tube voltage of 140 kV was used, but 120 kV was used for a few scans.

QCT calibration

An in-scan calibration phantom (Mindways, Austin, TX) was used at the extension timepoint, but not for the first three visits (pre-treatment and post-treatment at 12 and 24 wk). Due to the use of a different CT scanner model at the extension timepoint, the CT value-to-vBMD calibration available from the extension timepoint could not be transferred to the earlier visits. Therefore, an approach using DXA total hip aBMD results was taken.

To compare volumetric BMD across all four timepoints, a patient specific multiplicative correction factor a_i was applied to the first three visits. For each patient, this correction factor was obtained from the DXA aBMD results of the pre-treatment and extension visits of the non-treated right femur: $a_i = a\text{BMD}_{\text{extension}} \,/\, a\text{BMD}_{\text{baseline}}$. Based on the assumption that the total hip changes of DXA aBMD were comparable to the total hip changes of QCT vBMD, the factor a_i was used to adjust for the CT scanner difference. The factor a_i, derived for the untreated right femora, was also used for the CT value-to-vBMD calibration of the treated left femora. Correction of cortical vBMD was not possible because the spatial resolution of the two scanners was not identical and cortical thickness was significantly lower with the Siemens compared to the GE scanner, which was used for the first three visits.

QCT analysis

Quantitative computed tomography analysis was performed with a modified version of the Medical Image Analysis Framework (MIAF, version 6.2.0MR), which provides integral, trabecular, and cortical vBMD for the total hip (proximal femur).[12,13] Three-dimensional periosteal and endosteal surfaces of the total hip region excluding the femoral head were segmented using standard MIAF procedures. The distal border of the total hip volume of interest (VOI) was typically set below 2 or 3 cm distally to the lesser trochanter to ensure that in the left femora, all AGN1 implant material was included in the analysis. For a given patient, the distal border was identical in all scans.

For QCT analysis, three different VOIs were defined (Table 1). Since no CT scan was taken immediately after the AGN1 injection, the earliest post-treatment images (taken at the 12-wk visit) were used to virtually define the original baseline volume of the implanted AGN1 bolus, denoted as AGN_i VOI where i stands for "implanted." AGN_i included the

Table 1. VOIs analyzed by QCT.

VOI	Description
AGN$_i$ VOI	Original volume of the implanted AGN1 implant material bolus This volume is identical in size and in the same anatomical location for all timepoints
AGN VOI	A timepoint specific volume of increased density within the treated proximal femur that represents the volume undergoing AGN1 implant material resorption and new bone formation This volume changes at each timepoint. At 12 wk, AGN$_i$ VOI = AGN VOI
coreAGN VOI	Volume of high-density AGN1 implant material (∼1400 HU) present within the AGN VOI This volume changes at each timepoint

Abbreviations: HU, hounsfield units; QCT, quantitative computed tomography; VOI, volume of interest.

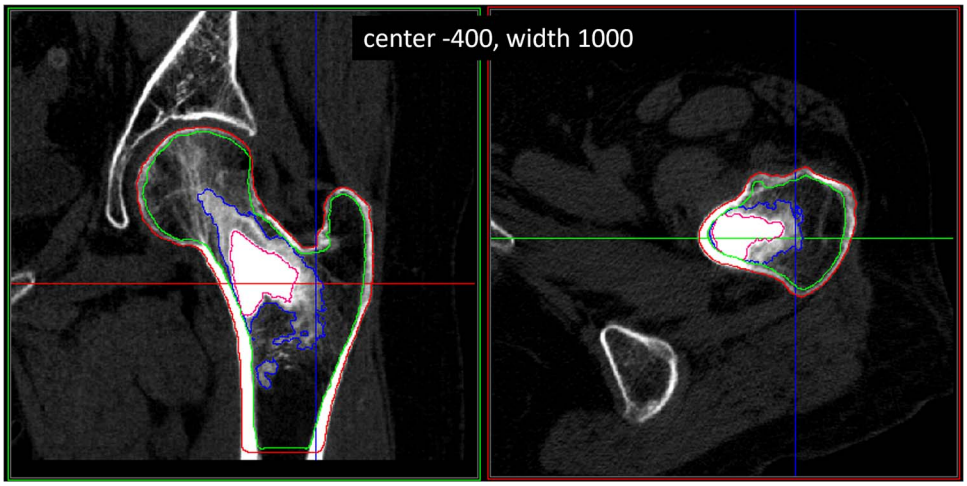

Figure 1. Coronal (left) and axial (right) views of a 12-wk scan showing the dense opaque regions of ∼1400 HU (the bright central area outlined in pink) and the less opaque regions of intermediate density of ∼500 HU (surrounding the bright central area, outlined in blue). Both regions combined define the AGN$_i$ VOI. Periosteal outside region (shown in red) and endosteal interior outer region (shown in green) surfaces of the femur are also shown. Abbreviations: HU, Hounsfield units; VOI, volume of interest.

dense opaque regions of ∼1400 Hounsfield Units (HU), which was presumably unresorbed AGN1, and the less dense area around it, which still differed in density from the surrounding native trabecular bone (Figure 1). It was presumed that immediately after injection (at the virtual baseline visit), the less opaque regions of intermediate density (∼500 HU) also contained AGN1 which was partly resorbed in the period between the time of AGN1 implant material injection and the 12-wk timepoint.

The AGN$_i$ VOI was segmented as shown in Figure 2. First, for a given patient, the difference between the 12-wk and pre-treatment datasets was calculated utilizing 3D registration. In each dataset of differences, a patient-specific threshold T1 was determined from a histogram analysis of the total trabecular VOI, which included the injected AGN1. All voxels with HU values > T1 defined a preliminary VOI. The final AGN$_i$ VOI was then determined after removing isolated voxels and applying connectivity criteria and a final dilation by one voxel. In locations where AGN1 bordered the cortex, separation of the two components was achieved by an interpolation of cortical thickness in the immediate vicinity where cortical bone could still be segmented separately.

For each patient, the AGN$_i$ VOI calculated for the 12-wk visit was 3D registered to the pre-treatment timepoint and all further post-treatment timepoints so that for all timepoints, the AGN$_i$ VOI consistently had the same size and was located in the same anatomical position for analytical purposes. The registration of the AGN$_i$ VOI to the pre-treatment timepoint was included to determine vBMD in the volume that was later filled by implanted AGN1.

Next, the segmentation process described above was also carried out independently for the 24-wk and extension timepoints resulting in a timepoint-specific AGN VOI. Note that for the 12-wk dataset, AGN VOI = AGN$_i$ VOI. Lastly, to calculate the volume of residual AGN1 implant material remaining at each post-treatment visit, defined as the coreAGN VOI, the presumably unresorbed AGN1 was segmented using a second threshold, T2, with T2 > T1. For this purpose, a histogram was again calculated but only using the voxels inside the AGN VOI to identify the highly absorbing material inside the AGN VOI. At the virtual baseline visit it is assumed that the coreAGN VOI = AGN$_i$ VOI.

To allow for comparative control vBMD measurements for each timepoint, all analysis VOIs defined for each treated femur (Table 1) were registered to the patient's untreated control femur (Figure S1). For each registration, the transformation matrix was obtained from a 3D rigid registration of the periosteal surfaces of the treated and untreated femora, which were segmented independently.

Volumetric BMD was measured in the three VOIs defined in Table 1 (AGN$_i$ VOI, AGN VOI, and coreAGN VOI) and in the integral, trabecular, and cortical compartments. The integral compartment, which was used to compare QCT and DXA results, was comprised of the cortical compartment, trabecular compartment, and the AGN$_i$ VOI. To analyze how the bone surrounding the original implantation zone was impacted by the AGN1 LOEP treatment, the trabecular compartment, excluding the AGN1 bolus (AGN$_i$ VOI), was also analyzed. The cortical VOI included the bone between periosteal and endosteal surfaces as segmented by MIAF.

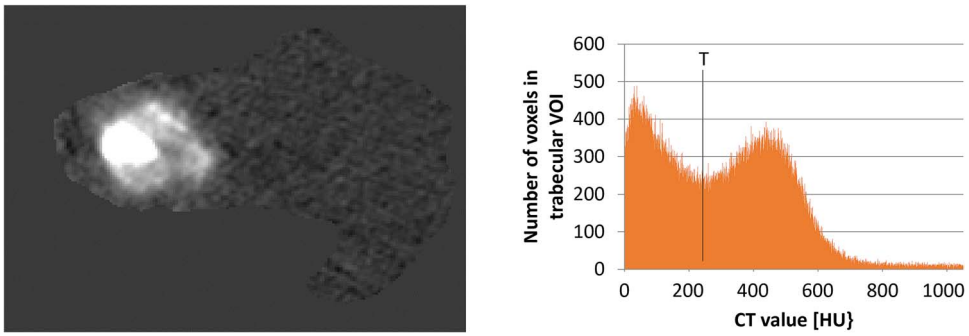

Figure 2. Segmentation of the AGN_i VOI in 12-wk scans. The axial view (left) shows the difference of the trabecular VOI between pre- and post-injection. At locations without AGN1 injection, the difference is small resulting in the noisy pattern. The injected AGN1 gives a much larger contrast because there was no AGN1 in the pre-injected image. This contrast enhancement is used for segmentation of the AGN VOI. The graph on the right shows a CT value histogram of the complete trabecular VOI. A patient-specific threshold T1 (here T1 = 270 HU) was automatically determined using the minimum of the histogram to separate original trabecular BMD from injected AGN1 resulting in the segmentation of the AGN_i VOI shown in Figure 1. Abbreviations: HU, Hounsfield units; VOI, volume of interest; BMD, bone mineral density.

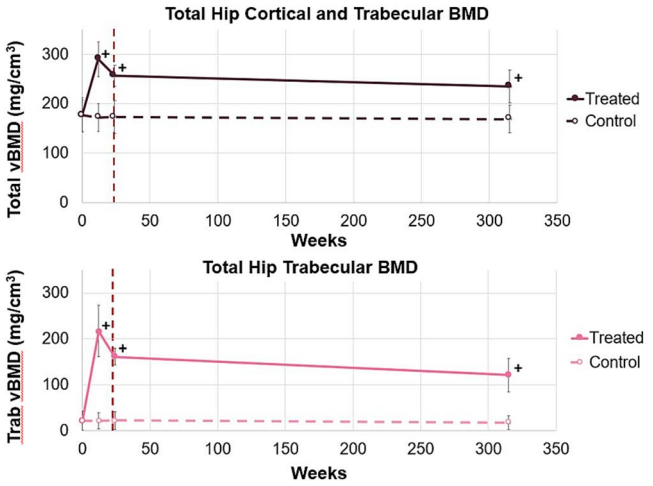

Figure 3. Change of BMD (mean ± SD) in the treated and untreated femurs over time. Top: Integral, combination of trabecular and cortical BMD (total vBMD). Bottom: Trabecular BMD (trab vBMD). + indicates $p < .001$. Vertical dotted line indicates time of 97% coreAGN VOI resorption. Abbreviations: VOI, volume of interest; vBMD, volumetric bone mineral density.

Statistical analysis

Descriptive data are presented as mean ± standard deviation. Ad hoc analysis evaluating change in vBMD of the treated and untreated femurs over time used paired T-tests at each timepoint (Figure 3).

Results

Quantitative computed tomography images across all timepoints demonstrated a clear 3D progression of AGN1 implant material resorption and new bone formation over time (Figure S2). On average, the volume of high-density AGN1 implant material (coreAGN VOI; ~1400 HU) was 81.3 ± 12.8% resorbed after the 12-wk timepoint and 96.8 ± 5.2% resorbed after the 24-wk timepoint (Table S1). By the extension timepoint, those high-density regions (coreAGN VOI) could no longer be detected. In some patients, AGN1 implant material was injected further into the shaft of the proximal femur, but by the extension timepoint, no regions of increased density in the shaft were observed (data not shown). Quantitative computed tomography images also showed that the cortical entry hole created to allow injection of AGN1 was filled with bone in all patients at the 5-to-7-yr extension timepoint (data not shown).

Prior to treatment, there were no integral vBMD differences between the control and treated hips (Table 2, treated: 176 ± 32 mg/cm^3, control: 176 ± 35 mg/cm^3). After the AGN1 LOEP treatment, a 65% increase in integral vBMD was observed in the treated hip, and a 34% increase was sustained out to the extension timepoint of 5- to 7-yr (Table 2, Figure S2, 12 wk: 290 ± 35 mg/cm^3, extension: 235 ± 33 mg/cm^3) (Figure 3). While cortical vBMD values remained consistent between the treated and control hips across the study, there was an increase in trabecular vBMD in the treated hips at every timepoint post-treatment (Table 2). Results from the analysis of the trabecular bone surrounding the original implantation zone (trabecular vBMD excluding AGN_i VOI) showed that while there was a slight increase in the vBMD of the treated hips at intermediate timepoints, there was no significant change in the vBMD in the region around the implantation zone long term (treated: 32 ± 16 mg/cm^3, control: 31 ± 16 mg/cm^3, Table 2).

After the 24-wk timepoint, there was a small decrease in integral vBMD in both hips at the extension timepoint; the treated hip vBMD decreased by ~9%, and the control hip vBMD decreased by 3% over this time period (Table 2). This decrease was expected as the implant material is denser than host bone. As the material is resorbed and replaced by bone, the measured density will decline. However, despite this loss, integral vBMD of the treated hip at extension remained 34% higher than the integral vBMD at baseline for both the control hip and treated hip. Additionally, the volume of increased density within the treated region of the proximal femur (AGN VOI) decreased over time (Table 3), in line with typical bone remodeling processes in this patient population. At the extension timepoint, the volume of the AGN VOI had decreased from 16.1 ± 4.8 to 8.9 ± 3.3 cm^3 (Table 3).

There were no procedure or device-related serious adverse events. Ten adverse events were reported in five patients, none of which were device-related. Three adverse events were at least possibly related to the LOEP surgical procedure (irritation from the injection procedure, small area of wound breakdown, and post-operative nausea), which were mild and resolved without additional medical intervention.

Table 2. vBMD of treated and untreated femurs for all timepoints.

Timepoint	N	Integral BMD (total vBMD) (mg/cm^3)		Trabecular BMD (trab vBMD) (mg/cm^3)		Cortical BMD (cortBMD) (mg/cm^3)		Trabecular BMD, excluding AGN$_i$ VOI (mg/cm^3)	
		Control	Treated	Control	Treated	Control	Treated	Control	Treated
Pre-treatment	10	176 ± 35	176 ± 32	21 ± 20	22 ± 21	570 ± 86	559 ± 75	ND	36 ± 20
12 wk	10	172 ± 28	290 ± 35	21 ± 18	217 ± 56	555 ± 67	561 ± 52	34 ± 18	63 ± 19
24 wk	8	174 ± 33	257 ± 21	22 ± 20	161 ± 18	557 ± 71	566 ± 55	33 ± 19	54 ± 18
Extension	10	169 ± 28	235 ± 33	17 ± 15	121 ± 37	664 ± 71	667 ± 60	31 ± 16	32 ± 16

CT data for two patients were not available at the 24-wk timepoint. Abbreviations: vBMD, volumetric bone mineral density; VOI, volume of interest.

Table 3. vBMD and volume of the AGN VOI.

Timepoint	AGN VOI	
	Vol (cm^3)	vBMD (mg/cm^3)
Pre-treatment	16.1 ± 4.8[a]	26 ± 32
12 wk[b]	16.1 ± 4.8	525 ± 80
24 wk[c]	14.7 ± 4.0	418 ± 50
315 wk[b]	8.9 ± 3.3	536 ± 78

Values reported as mean ± standard deviation. [a]Registered from 12-wk AGN implant volume. [b]$N = 10$. [c]$N = 9$. Abbreviations: vBMD, volumetric bone mineral density; VOI, volume of interest.

Discussion

In the proximal femur, bone loss related to osteoporosis often results in the expansion of a bone void that weakens the proximal femur, thereby increasing the risk of hip fragility fracture.[14,15] In this study, AGN1 LOEP treatment of the proximal femur was used to treat this osteoporotic bone void to increase femoral vBMD in osteoporotic femurs.

Similar to previous findings,[11] this study shows that AGN1 LOEP treatment results in a large increase in aBMD at the earliest QCT analysis timepoint (12 wk post-treatment). In all patients, increased vBMD lasts well after the high-density coreAGN VOI is resorbed (97% resorption after 24 wk post-treatment) and is sustained to at least the extension timepoint at 5-7 yr post-treatment when a 34% increase in vBMD was observed. This vBMD increase following AGN1 LOEP treatment would be expected to substantially increase femoral bone strength since aBMD accounts for 60%-80% of bone strength variance.[8] Typically, pharmaceutical treatment using bisphosphonates results in a 2%-6% increase in aBMD as measured by DXA, which has been shown to correlate with a 16%-40% reduction in fragility hip fractures.[16] Benchmarking against the success of currently available pharmaceuticals to reduce hip fracture risk, it is reasonable to expect that the magnitude of the vBMD increase in the treated hips observed in this study (65% and 34% increase at the 12-wk and extension timepoints, respectively) would correspond to a relatively greater reduction in fragility hip fractures. This aligns with a previously reported summary of Finite Element Analysis (FEA) results of this patient population which support AGN1 LOEP's potential to provide a long-term strength increase (36% increase in FEA-estimated strength after 5-7 yr post-treatment).[11] The strength of this study is the detailed quantitative analysis of the effects of the AGN1 implant material on the various bone compartments, on the implanted material itself, and on the comparison with effects in the untreated contralateral femur. The QCT analysis illustrates that increased vBMD was observed only in regions in which AGN1 was implanted and neither in the surrounding trabecular nor in the cortical compartments. AGN1 LOEP of the treated femurs did not impact the untreated femurs. The small decrease of integral and trabecular vBMD in the untreated femurs at the extension visit can most likely be explained by the ongoing progression of bone loss in this patient population.

The short- and long-term increases in integral and trabecular vBMD of the treated femurs are due to the local vBMD increase of the AGN$_i$ VOI. Since trabecular bone has been shown to play a key role in dissipating forces that can cause fragility hip fracture,[16] AGN1 LOEP's ability to target bone formation and subsequent vBMD increase in trabecular regions suggests patients with osteoporosis may receive a therapeutic benefit.

Encouragingly, the findings from the current QCT study, which provide a new 3D quantitative analysis of the implanted AGN1 material volume and its transition into bone, help to clarify the findings of previous 2D X-ray and DXA results of the same patient population.[11] Quantitative CT provides further evidence that the implant material and newly formed bone in the original implantation zone are behaving and resorbing as expected. Over time, the increased vBMD within the AGN1 implantation region is retained and remodeled in a manner consistent with Wolf's Law, demonstrating that LOEP can improve bone density in specific targeted areas that experience load transfer and stress.

Furthermore, the implant material transformation process observed in both the 2D and 3D analyses of this first in-human study of the AGN1 LOEP treatment is similar to the process seen in multiple animal models (i.e., ovariectomized rats and canines), which demonstrated AGN1's transformation into trabecular bone.[17,18] While in vivo CT resolution is not sufficient to quantify the actual trabecular structure that was seen in a previous study of AGN1's effect in an ovariectomized rat model,[17] the CT images collected in this study clearly illustrate the change in volume of the AGN1 implant material bolus during resorption, the close coupling of AGN1 resorption and trabecular vBMD transformation, and the bone remodeling that occurs across the study timepoints.

This study has several limitations. Only 12 patients were initially included in this study, and only 10 patients were available to continue to the extension timepoint. Further evaluation of the efficacy of AGN1 LOEP in fracture risk reduction is being performed in a larger patient population via a randomized controlled trial.[19] Additionally, as mentioned above, no immediate post-operative CT was taken, so qualitative and quantitative evaluation of the original AGN1 implant material bolus is limited to extrapolation from the 12-wk CT images, where implant material resorption and replacement by bone were already underway. Immediate post-operative fluoroscopic images were taken, which confirmed

that the injection volume boundaries were clear and closely corresponded to the size and configuration of the estimated original implant volume using the 12-wk CT scans. These fluoroscopic images demonstrate that the estimation of the immediate post-operative volumes from the 12-wk images is reasonable, though the exact region of the initial AGN1 injection cannot be fully defined with certainty. Furthermore, no phantom calibration was used during image acquisition for the first three visits (baseline and 12 and 24 wk post-treatment). To overcome this challenge, aBMD results of the untreated femurs obtained by DXA were used to adequately standardize the results. Lastly, while QCT accurately determines the volume and vBMD within the treated regions, the methodology is limited by its inability to assess the quality of the trabecular structure within the VOI.

This QCT analysis expands upon previously published, 2D X-ray analysis to provide a more comprehensive understanding of the volumetric dynamics of AGN1 resorption and bone formation processes post-LOEP treatment. Prior, published research demonstrated that AGN1 LOEP led to an immediate and durable increase in the strength of treated proximal femurs.[11] Similarly, this QCT analysis showed that treatment led to a substantial and durable increase in vBMD at all timepoints, which is expected to correlate with increased strength in the proximal femur. These results suggest that AGN1 LOEP provides a treatment option that can help to locally restore lost trabecular bone to strengthen the femur, and therefore, may reduce the risk of hip fracture risk for patients with bone loss in the proximal femur. Additional study to further validate the AGN1 LOEP treatment's ability to reduce the risk of hip fracture is warranted and ongoing.

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Author contributions

Michelle Chin (Writing—original draft, Writing—review & editing), Ronald Hill (Project administration, Writing—review & editing), Bryan Huber (Conceptualization, Investigation), James Howe (Conceptualization), and Klaus Engelke (Conceptualization, Data analysis, Writing—Original draft, Writing—review & editing)

Supplementary material

Supplementary material is available at *JBMR Plus* online.

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Conflicts of interest

- Michelle A. Chin: Former Employee and Shareholder at AgNovos Bioscience, Rockville, MD.
- Ronald S. Hill: Former Employee and Shareholder at AgNovos Bioscience, Rockville, MD.
- James G. Howe: Co-founder, Member of Board of Directors, Shareholder, and Employee at AgNovos Bioscience, Rockville, MD.
- Bryan M. Huber: Former Employee and Shareholder at AgNovos Bioscience, Rockville, MD.
- Klaus Engelke: Consultant for AgNovos Bioscience, Clario Inc, Hamburg, Germany, Department of Medicine III and Institute of Medical Physics, FAU University Erlangen-Nürnberg and Universitätsklinikum Erlangen, Germany.

Data availability

Data are available upon request.
ClinicalTrials.gov identifier: NCT06799143.

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