Favorable Preliminary Results of MagnetOs as Standalone Alternative to Autograft in a Prospective, Multi-center, Randomized, Intra-patient Controlled Trial

MagnetOs™ Granules Whitepaper

This multicenter trial was initiated to determine non-inferiority of MagnetOs Granules used standalone as compared to autograft in instrumented posterolateral spinal fusion. Initial analysis of 91 patients (128 levels) reported a MagnetOs Granules fusion rate of 79% (101/128 levels) and an autograft fusion rate of 47% (60/128 levels). Furthermore, MagnetOs Granules showed an 80% fusion rate in a smoking population compared to 32% for the autograft group. Publication of the final data is expected in 2024 and will include advanced statistical analyses, interbody data, adverse events, and patient reported outcome measures. The following white paper describes the promising interim data analysis of the first 50 patients comparing MagnetOs Granules to autograft in the intra-patient controlled study.

MAGNETOS™ for predictable fusions

Kuros Biosciences

Introduction

Pseudoarthrosis after spinal fusion is a challenging complication that is estimated to generate 103,215 revision spine surgeries in the United States in 2025.[1-3] Surgeons face several challenges when performing complicated arthrodesis surgeries, one of which is having an adequate supply of autograft available, especially in complex or multi-segment procedures. Iliac Crest Bone Graft (ICBG) is considered the gold standard, but there are known disadvantages to using ICBG including limited availability and an additional procedure for harvesting the graft; as such, many surgeons turn to alternative bone grafts in place of, or to augment, ICBG.[4] Furthermore, evidence suggests significant variability in autograft bone due to age, metabolic disease, or donor co-morbidities.[5]

Because of the disadvantages in obtaining ICBG, multiple substitutes to autograft bone have been developed for bone grafting in spinal arthrodesis surgery. These alternatives include allograft, demineralized bone matrices (DBMs), cell-based allografts (CBAs), and synthetic bone grafts.[6] Each of these categories comes with a unique set of risks and benefits. Synthetic bone grafts have quickly come to the forefront as a reasonable alternative to autograft bone because of their cost-effectiveness and notable safety profile. Formulations include Calcium Sulfate, Hydroxyapatite (HA), β-Tri Calcium Phosphate (β-TCP), Biphasic Calcium Phosphate (BCP), Bioglass, and Silicated Calcium Phosphate (Si-CaP).[6] Because there is significant variability in the quality and quantity of clinical evidence for synthetic bone grafts, it can be challenging for surgeons to identify the best option in terms of efficacy, safety, and cost-effectiveness.

Biphasic Calcium Phosphate (BCP)

In recent years, research on BCP as bone graft substitute has led to increased utilization in spinal arthrodesis surgery. BCP is cost-effective, has been proven to have an appropriate safety profile, and has a low incidence of reaction or material-related complications.[7,8] Interestingly, a novel BCP with submicron needle-shaped surface features, MagnetOs (MagnetOs; Kuros Biosciences BV, The Netherlands), has been shown to promote bone formation even in soft tissue, without the need for added cells or growth factors.[9] MagnetOs is designed to mimic the porous, trabecular structure of cancellous bone, and has a resorption profile equal to anatomic bone due to an optimal ratio of HA to β-TCP. The needle-shaped submicron surface features of MagnetOs triggers bone formation propagating from the core of the graft, while also supporting bony ingrowth through osteoconduction. MagnetOs, therefore, does not solely rely on bone formation via creeping edge repair, as is the case for conventional synthetic bone grafts. Thus far, MagnetOs has led to uniform, solid, and predictable fusions in clinically relevant animal studies and in one retrospective evaluation of cervical and lumbar spinal arthrodesis cases.* However, the current report describes the first clinical results for MagnetOs obtained in an ongoing prospective randomized controlled trial of posterolateral fusion.[10-12]

Objective:
This multicenter trial was initiated to determine non-inferiority of a BCP with submicron-sized needle-shaped surface features, MagnetOs Granules, as compared to autograft in instrumented posterolateral spinal fusion. This is the interim analysis for the safety and fusion rate of the first 50 subjects that were enrolled.

Methods:
This multicenter study was initiated and coordinated by five participating academic centers (Medical Ethics Review Committee number 18-311; Assessment and Registration ABR number NL64652.041.18). Adult subjects qualifying for instrumented posterolateral spinal fusion of one to six levels in the thoracolumbar and lumbosacral region from T10 to S2 were indicated for the analysis. Informed consent was obtained. In all cases, according to study protocol, a standard surgical technique was used for a posterolateral spine approach. After instrumentation and preparation of the bone bed, the randomized side of the graft was disclosed to the surgeon. In all subjects at all levels, one side (right or left) was grafted with 10cc of autograft per level. The autograft was a combination of local vertebral bone supplemented with at least 50% cortico-cancellous bone harvested from the iliac crest. The other randomized side was grafted with 10cc of MagnetOs Granules without added autograft or bone marrow aspirate (standalone bone graft). In obtaining the cortico-cancellous bone from the iliac wing, only one side was harvested, unless that side was inappropriate due to previous harvesting or anatomical reasons. If possible, harvesting was done via the same posterior incision for spinal fusion. In case of an additional interbody fusion procedure, the cage was preferably filled with local autograft bone and positioned before opening of the randomization envelope. If the surgeon decided to use iliac crest bone for the cage, the cage was only inserted after the randomization and related harvesting side had been disclosed. All subjects were evaluated radiologically and clinically at several time points pre- and post-operatively, and all serious adverse events related to the procedure were documented. Prospective follow-up included adverse events, the Oswestry Disability Index (ODI), and a fine-cut (<1mm) Computerized Tomography (CT) at one year. Fusion was systematically scored as "fusion" or "no fusion" per level per side by two spine surgeons blinded for the procedure per the following protocol: both left and right were "no fusion" if none of the levels were fused, both sides were "fusion" if an equal number of levels were fused per side, or "fusion" on one side and "no fusion" on the other side if one side contained more levels with "fusion" than the other side. Disagreements were resolved by panel discussion.

Results:
The inclusion period spanned two years with interim follow up at one-year. One-hundred patients were enrolled, and fifty patients had one year follow-up with CT scan. The first 50 patients with one-year CT scans are included in this report. The average age of this cohort was 57 years old (range 27-79 years); 60% (30 subjects) were female, and 40% (20 subjects) were male. The diagnoses included deformity such as scoliosis or sagittal imbalance in 56% (28/50 subjects), structural instability such as progressive angular deformity or spondylolithesis in 28% (14/50 subjects), and instability from decompression or spinal stenosis in 20% (10/50 subjects).

In total, 71 levels were treated with an average of 1.4 levels per subject. The most common upper level of instrumentation was L5 (42%), followed by L4 (32%); while the most common lower level of instrumentation was S1 (58%), followed by L5 (30%). An interbody device was used 62% of the time. Posterior Lumbar Interbody Fusion (PLIF) was performed in 50% of the cases, and Transforaminal Lumbar Interbody Fusion (TLIF) was performed in 12% of the cases. Appropriately randomized, the paired placement of MagnetOs Granules resulted in 50% left and 50% right.

MagnetOs Granules Fusion Rate

Fusion rate for MagnetOs Granules was calculated both by subject and by level.

The overall fusion rate by subject was 78.0% (39/50 subjects). In single level fusions, MagnetOs Granules achieved a 73.5% fusion rate (25/34 subjects). In two level fusions, MagnetOs Granules achieved a fusion rate of 84.6% (11/13 subjects). In three level and four level fusions, MagnetOs Granules achieved a 100% fusion rate (3/3 subjects). *See Table 1.*

The overall fusion rate by level was 76.1% (54/71 levels). In single level fusions, MagnetOs Granules achieved a 73.5% fusion rate (25/34 levels). In two level fusions, MagnetOs Granules achieved a 73.1% fusion rate (19/26 levels). In three level fusions, MagnetOs Granules achieved a fusion rate of 100% (3/3 levels). In four level fusions, MagnetOs Granules achieved an 87.5% fusion rate (7/8 levels). *See Table 2.*

Autograft Fusion Rate

Fusion rate for autograft was calculated both by subject and by level.

The overall fusion rate by subject was 42.0% (21/50 subjects). For one level fusions, autograft achieved a fusion rate of 47.1% (16/34 subjects). For two level fusions, autograft achieved a fusion rate of 38.5% (5/13 subjects). For three and four level fusions, autograft achieved a 0% fusion rate (0/3 subjects). *See Table 1.*

The overall fusion rate by level was 43.7% (31/71 levels). In one level fusions, autograft achieved a fusion rate of 47.1% (16/34 levels). In two level fusions, autograft achieved a fusion rate of 38.5% (10/26 levels). In three level fusions, autograft achieved a fusion rate of 33.3% (1/3 levels). In four level fusions, autograft achieved a fusion rate of 50% (4/8 levels). *See Table 2.*

Table 1: Fusion Percentages by Subject for MagnetOs Granules and Autograft

	MagnetOs Granules (% subjects)	**Autograft** (% subjects)
Overall	78.0% (39/50)	42.0% (21/50)
1 Level Fusion	73.5% (25/34)	47.1% (16/34)
2 Level Fusion	84.6% (11/13)	38.5% (5/13)
3 Level Fusion	100% (1/1)	0% (0/1)
4 Level Fusion	100% (2/2)	0% (0/2)

Table 2: Fusion Percentages and Number of Levels Fused for MagnetOs Granules and Autograft

	MagnetOs Granules (% levels)	**Autograft** (% levels)
Total Fusion	76.1% (54/71)	43.7% (31/71)
1 Level Fusion	73.5% (25/34)	47.1% (16/34)
2 Level Fusion	73.1% (19/26)	38.5% (10/26)
3 Level Fusion	100% (3/3)	33.3% (1/3)
4 Level Fusion	87.5% (7/8)	50.0% (4/8)

Further analysis confirmed that the fusion on the side randomized to MagnetOs Granules was not contingent upon fusion of the side randomized to autograft. In 42% of cases, the MagnetOs Granules side was fused, while the autograft side was not fused. *See Table 3.*

Table 3: Fusion Distribution

		MagnetOs Granules	
		Fused	*Non-Fused*
Autograft	*Fused*	36.0% (18/50)	6.0% (3/50)
	Non-Fused	42.0% (21/50)	16.0% (8/50)

Adverse Events

Overall, 32% of subjects (16/50 subjects) had an adverse event, with 18% (9/50 subjects) having a serious adverse event. Serious adverse events catalogued that were deemed related to the surgery included death (0/9 subjects), life threatening events (0/9 subjects), hospitalization (7/9 subjects), permanent disability (0/9 subjects), and other (0/9 subjects). Other serious events were deemed unrelated to the surgery (2/9). Most subjects with adverse events showed signs of recovering and were labeled either "fully recovered with sequelae," "fully recovered without sequelae," or "in the process of recovering," while 4 subjects (8% subjects) did not recover from their adverse event. One subject's outcome was unknown. Relevant adverse events included continued pain or loss of sensation with or without motor changes (8 subjects); Dural tear (5 subjects); deep infection requiring irrigation and debridement (3 subjects); rod/screw loosening (2 subjects); screw fracture (1 subject); iliac crest pain (1 subject); and urinary incontinence (1 subject). There were four reoperations, one for removal of a loose screw, and three for irrigation and debridement of deep wound.

Clinical Outcomes

Outcomes were also assessed using the Oswestry Disability Index (ODI) score. Of the 50 subjects, there were 43 (86% subjects) with pre-operative ODI evaluations. The average baseline pre-operative ODI was 46.0 (range 18-80). Overall the ODI score decreased from a mean of 46.0 (±15.0) to a mean of 31.7 (±16.9), and 52.4% of subjects improved with at least a 15-point decrease at one year post-operatively. Repeated post-operative ODI score measurements were tracked at specific time intervals, with the six-week ODI changing from baseline by -5.1, the twelve-week ODI changing from baseline by -15.6, and the 1-year ODI changing from baseline by -15.5.

Statistical Analysis

An overall non-inferiority proportions Z test for paired data (left and right) was performed with a non-inferiority Margin (NIM) of 15%. A McNemar's test was used to determine heterogeneity of a 2x2 table.[13] The observed difference in proportions between MagnetOs Granules and autograft was 36%, with a lower bound of the one-sided 95% confidence interval of 22.2%. With the *p*-value less than 0.01, and lower bound of the confidence interval well above the NIM, there is statistical evidence that MagnetOs Granules is not inferior to autograft ($p<0.001$). *See Table 4.*

Table 4: Primary Efficacy Fusion Performance McNemar's Test Total Population

		MagnetOs Granules
McNemars Test - Non-inferiority[13]		
	Non-inferiority Margin	-15.0%
	Difference (Pm-Pa)	36.0%
	95% Confidence Interval	[22.2%, Inf]
	p-value	<0.001

To control for interbody fusion on the effect of posterolateral fusion, a three-level generalized estimating equations (GEE) models for the dichotomized (binomial) and original (multinomial) data was completed. This included interbody fusion as a separate explanatory factor, with the binomial model using dichotomized interbody fusion performance.

For binomial modeling, the odds ratio was 2.54, showing that on average the odds of fusion occurring in the MagnetOs group was 2.54 higher with 95% confidence. The true odds ratio was between 1.11 and 5.82 for MagnetOs Granules compared to autograft after controlling for interbody fusion. For multinomial modeling, the odds ratio was 2.65, showing that on average the odds of fusion occurring in the MagnetOs group was 2.65 higher with 95% confidence. The true odds ratio was between 1.22 and 5.73 for MagnetOs Granules compared to autograft condition after controlling for interbody fusion. In both binomial and multinomial modeling, the *p*-value was less that 0.05 (p=0.028 and 0.014 respectively), indicating that there is sufficient evidence that the odds of fusion in the MagnetOs Granules condition is greater than in the autograft condition. *See Table 5*.

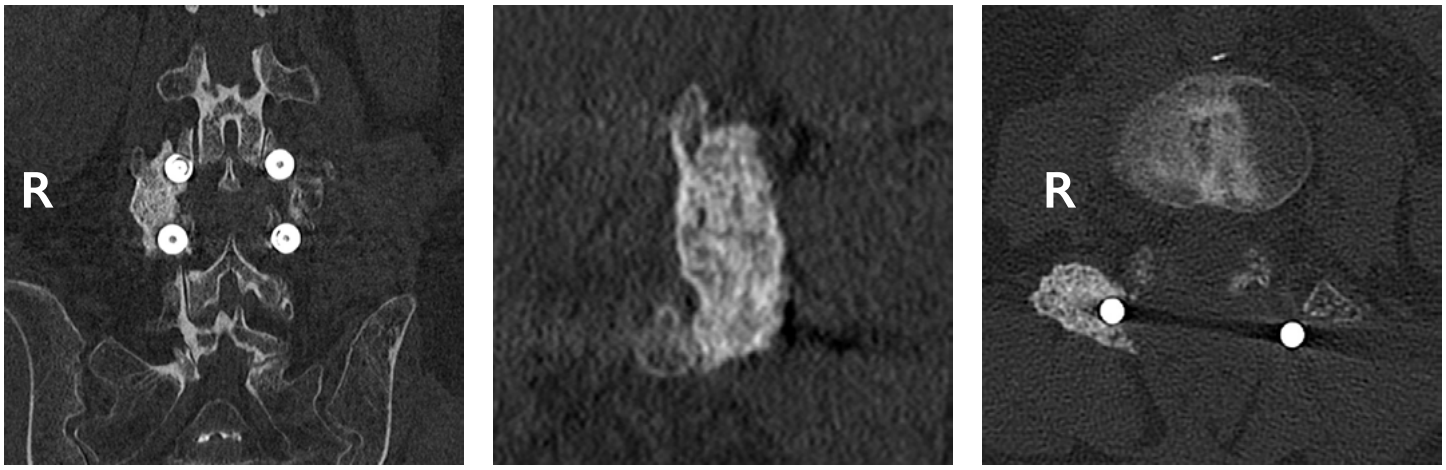
Table 5: Primary Efficacy Fusion Performance GEE Modelling Total Population

	Parameter	Result
GEE Model*		
Binomial	Fusion/No Fusion	
Treatment (M v A)	Odds Ratio	2.54
	95% CI	[1.11, 5.82]
	p-value	0.028
Multinomial	Fusion/Doubtful Fusion/No Fusion	
Treatment (M v A)	Odds Ratio	2.65
	95% CI	[1.22, 5.73]
	p-value	0.014

*A three-level GEE modelling fusion on each side of a vertebra, accounting for clustering within spinal levels and within subjects and including Interbody Fusion as a separate factor, using compound symmetry (or equivalent) correlation structure.

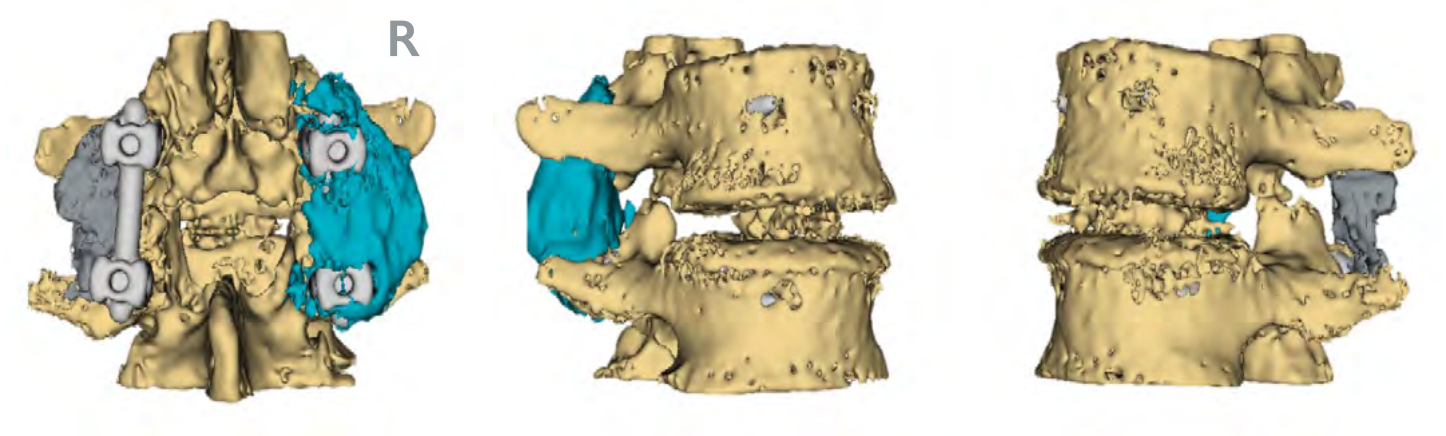
Case Study 1

This case presents a 52-year-old female with a diagnosis of spinal deformity. The subject underwent an L3-L4 Posterolateral Lumbar Fusion (PLF), with MagnetOs Granules on the right and autograft on the left. The PLF was combined with a Posterior Lumbar Interbody Fusion (PLIF). After one year, fine-cut CT scans read by two independent spine surgeons determined that both posterolateral gutters were fused, while the PLIF was not fused. The patient was considered fused. In the MagnetOs fusion bridge, bone remodeling and graft resorption was evidenced by the trabecular structure and loss of granular appearance. A neocortex was appreciated at the border of the MagnetOs fusion mass on the coronal, sagittal and axial images, indicating solid and mature bridging bone tissue.



A B C

(A) Coronal, (B) Sagittal (right); and (C) axial fine-cut CT images of a L3-L4 one-level fusion at one-year follow-up. (MagnetOs Granules right side of subject, autograft left side of subject).



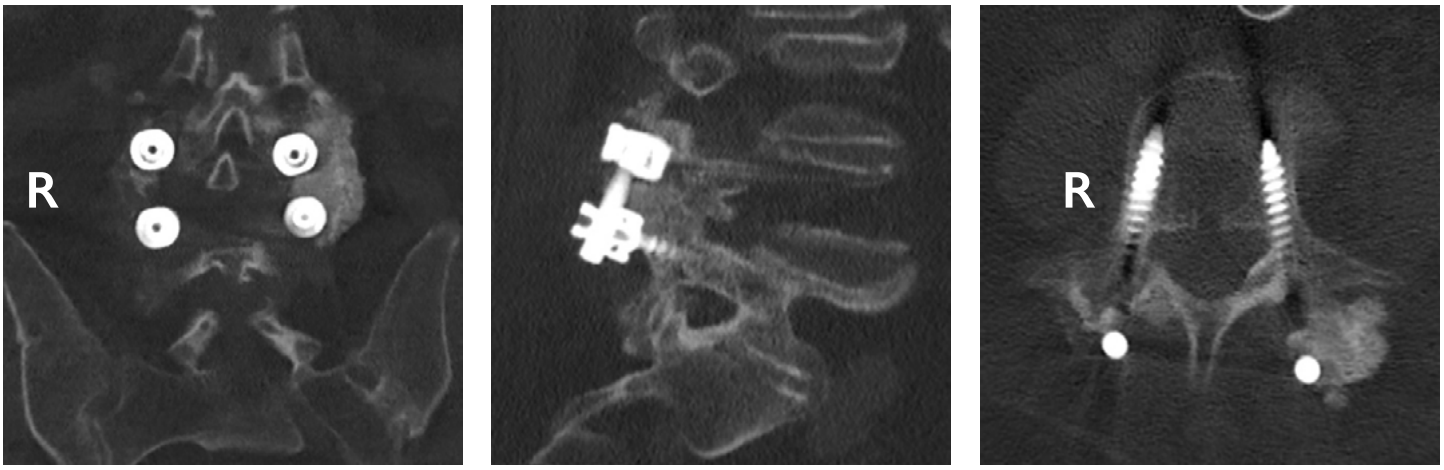
D E F

(D) Coronal, (E) Sagittal (right) and (F) Sagittal (left) 3D reconstructions of a L3-L4 one-level fusion at one-year follow-up. (MagnetOs Granules: Blue; Autograft: Gray; Instrumentation: Light Gray).

Case Study 2

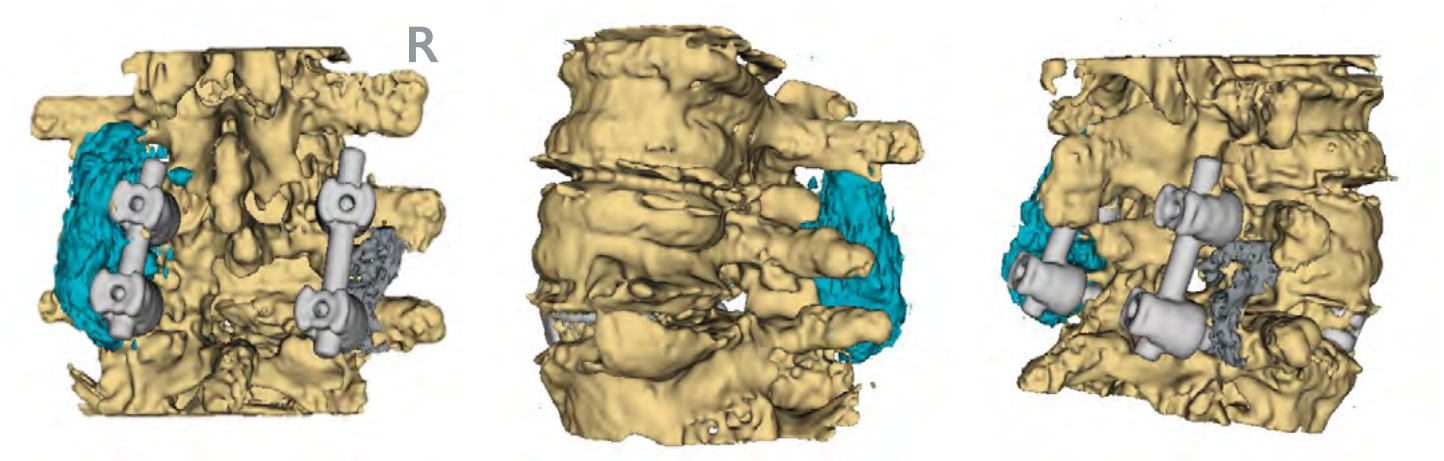
This case presents a 79-year-old female with a diagnosis of instability from decompressive surgery. The patient underwent a PLF at L4-L5 with MagnetOs Granules on the left and autograft on the right. The posterolateral fusion was combined with a Transforaminal Lumbar Interbody Fusion (TLIF). After one year, fine-cut CT scans read by two independent spine surgeons determined that both posterolateral gutters as well as the interbody fusion were fused.

The patient was considered fused. Radiographically, the MagnetOs fusion mass was consolidated with intertransverse bridging. Notably, there was significantly more bone volume on the MagnetOs side when compared to autograft side, which may be indicative of autograft bone resorption. In the MagnetOs fusion bridge, bone remodeling and graft resorption was evidenced by the trabecular structure and loss of granular appearance.



A *B* *C*

(A) Coronal, (B) Sagittal (left); and (C) axial fine-cut CT images of a L4-L5 one-level fusion at one-year follow-up. (MagnetOs Granules left side of subject, autograft right side of subject).

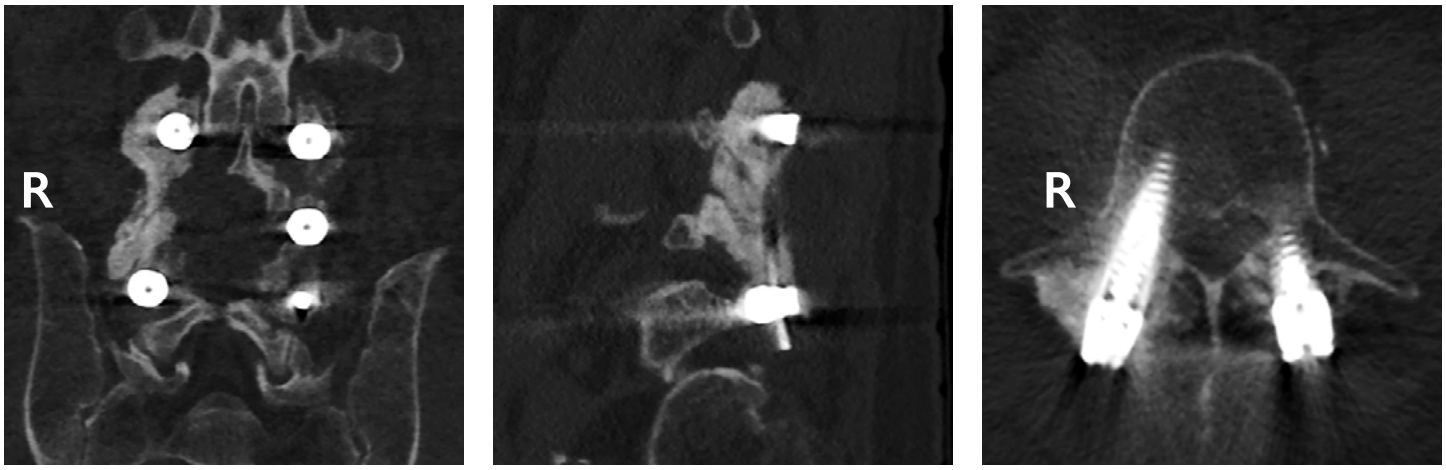


D *E* *F*

(D) Coronal, (E) Sagittal (left) and (F) Oblique 3D reconstructions of a L4-L5 one-level fusion at one-year follow-up. (MagnetOs Granules: Blue; Autograft: Gray; Instrumentation: Light Gray).

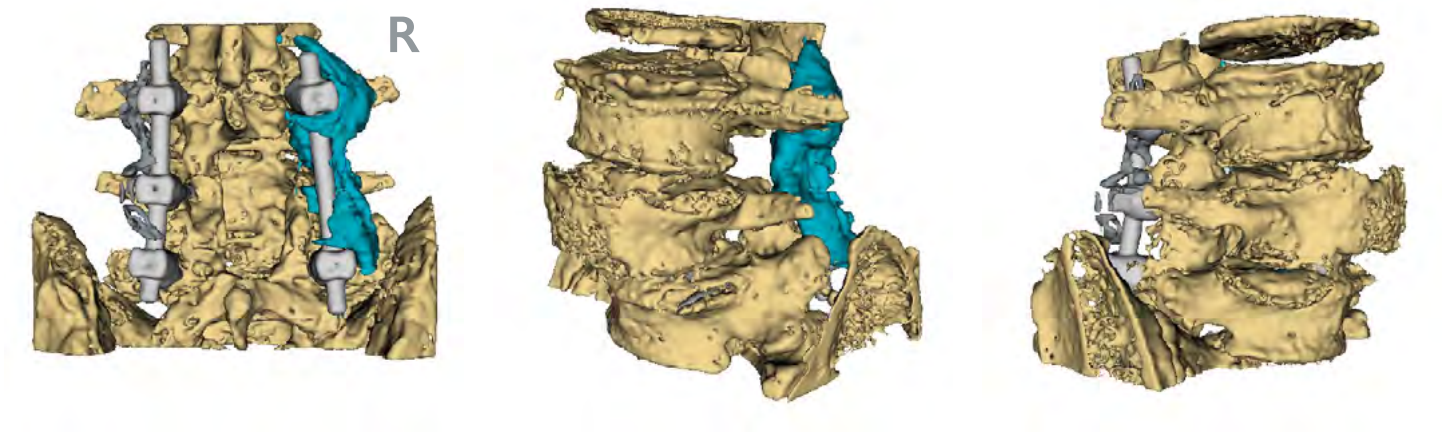
Case Study 3

This case presents a 60-year-old male with a diagnosis of instability from decompressive surgery. The patient underwent an L3-L5 two-level PLF with MagnetOs Granules on the right and autograft on the left. The PLF was combined with a TLIF at L4-L5. After one year, fine-cut CT scans read by two independent spine surgeons determined that on the right the MagnetOs Granules had solidly fused at both levels, whereas on the left the autograft side only fused at one-level (L3-4). In addition, the TLIF was not fused. The patient was considered fused. In the MagnetOs fusion bridge, bone remodeling and graft resorption was evidenced by the trabecular structure and loss of granular appearance. In contrast, the fusion mass on the autograft side was thinner in appearance, suggestive of bone resorption.



A B C

(A) Coronal, (B) Sagittal (right); and (C) axial fine-cut CT images of a L3-L5 two-level fusion at one-year follow-up. (MagnetOs Granules right side of subject, autograft left side of subject).



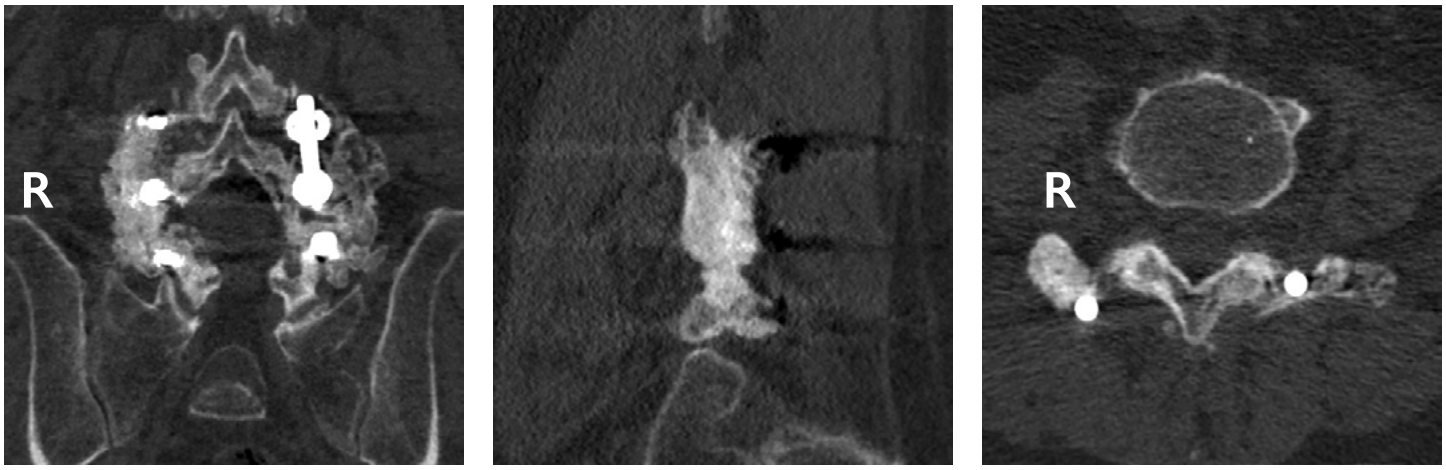
D E F

(D) Coronal, (E) Sagittal (right) and (F) Sagittal (left) 3D reconstructions of a L3-L5 two-level fusion at one-year follow-up. (MagnetOs Granules: Blue; Autograft: Gray; Instrumentation: Light Gray).

Case Study 4

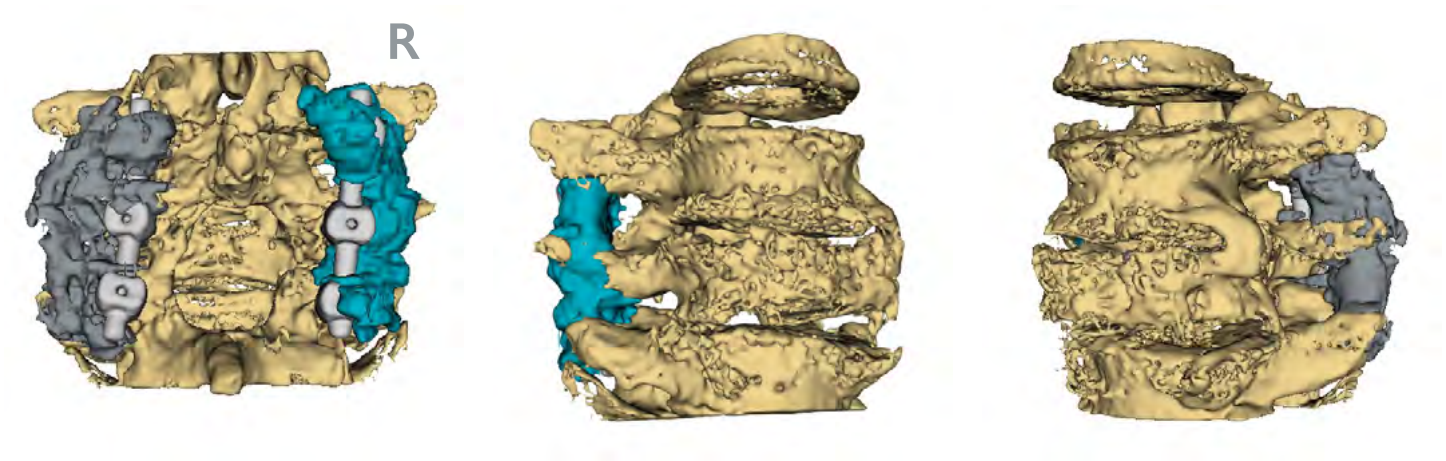
This case presents a 60-year-old male with a diagnosis of spinal deformity. The patient underwent a two-level PLF at L3-L5 with MagnetOs Granules on the right and autograft on the left. After one year, fine-cut CT scans read by two independent spine surgeons determined that both the MagnetOs Granules and autograft sides were solidly fused at both levels. The patient was considered fused.

Both the MagnetOs Granules and autograft fusions presented as large solid masses with intertransverse bridging. The lack of granularity in the MagnetOs fusion mass indicated progressive bone formation and consolidation with gradual resorption and remodeling of the MagnetOs particles.



A B C

(A) Coronal, (B) Sagittal (right); and (C) axial fine-cut CT images of a L3-L5 two-level fusion at one-year follow-up. (MagnetOs Granules right side of subject, autograft left side of subject).

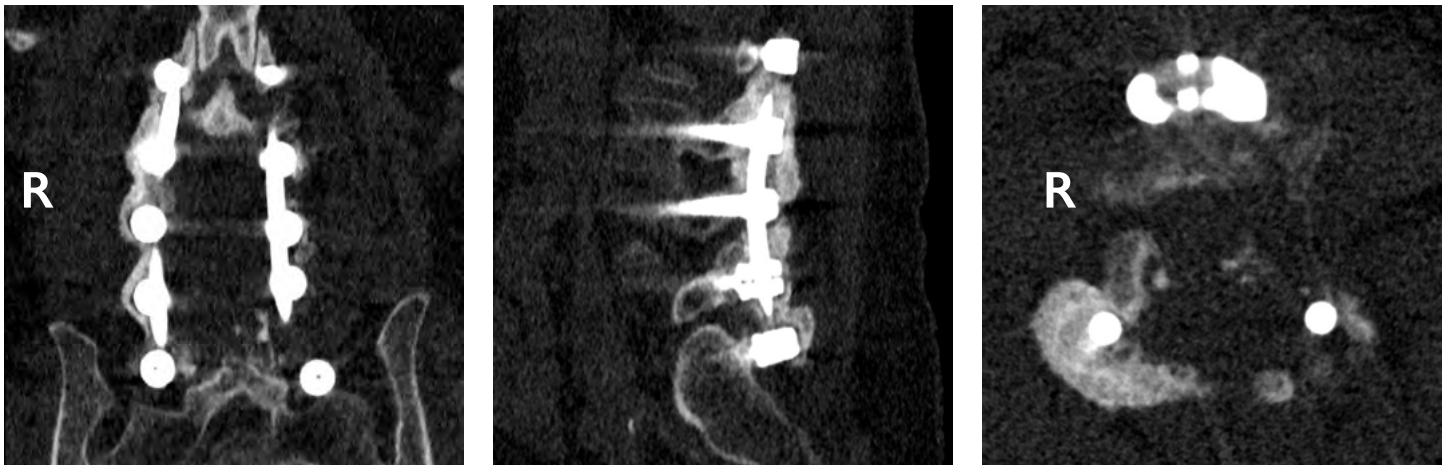


D E F

(D) Coronal, (E) Sagittal (right) and (F) Sagittal (left) 3D reconstructions of a L3-L5 two-level fusion at one-year follow-up. (MagnetOs Granules: Blue; Autograft: Gray; Instrumentation: Light Gray).

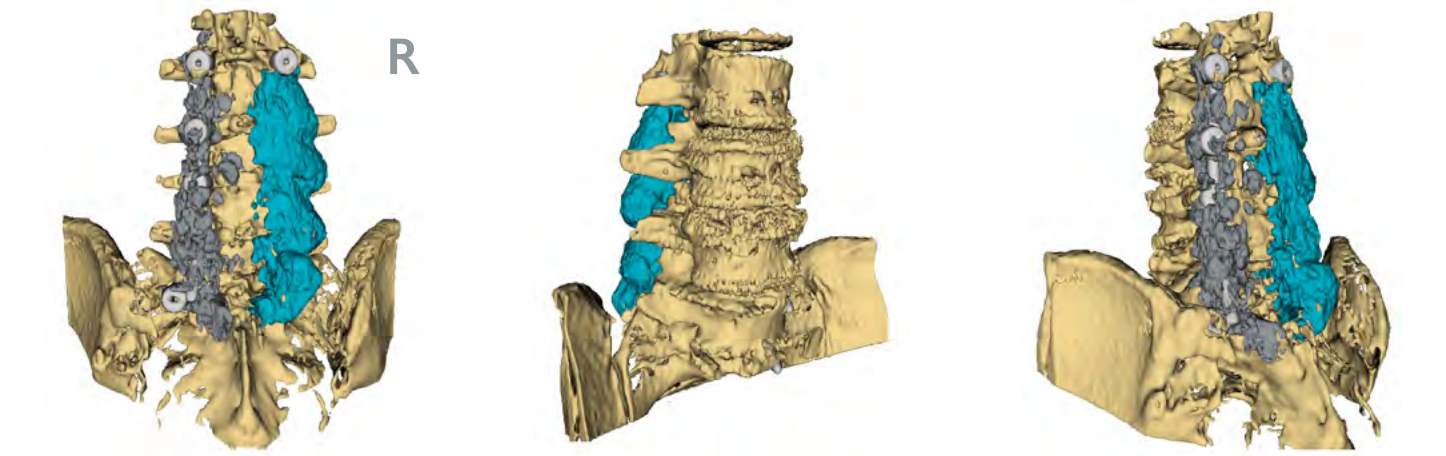
Case Study 5

This case presents in a 67-year-old male with a diagnosis of instability as result of decompressive surgery. He underwent a four-level PLF from L2-S1 with MagnetOs Granules on the right and autograft on the left. The PLF was combined with a TLIF at L3-L4 and L5-S1. After one year, fine-cut CT scans read by two independent spine surgeons determined that the MagnetOs Granules side was fused at three levels and the autograft side was fused at two levels. Both interbody constructs fused. The patient was considered fused. In the MagnetOs fusion bridge, bone remodeling and graft resorption was evidenced by the trabecular structure and loss of granular appearance.



A B C

(A) Coronal, (B) Sagittal (right); and (C) axial fine-cut CT images of a L2-S1 four-level fusion at one-year follow-up. (MagnetOs Granules right side of subject, autograft left side of subject).

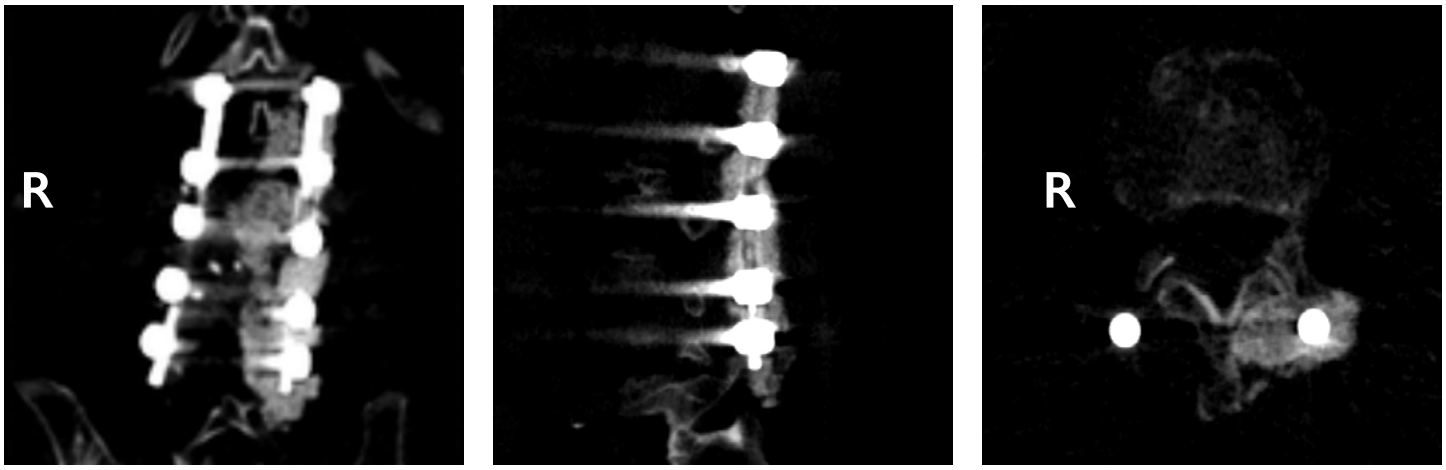


D E F

(D) Coronal, (E) Sagittal (right) and (F) Oblique 3D reconstructions of a L2-S1 four-level fusion at one-year follow-up. (MagnetOs Granules: Blue; Autograft: Gray; Instrumentation: Light Gray).

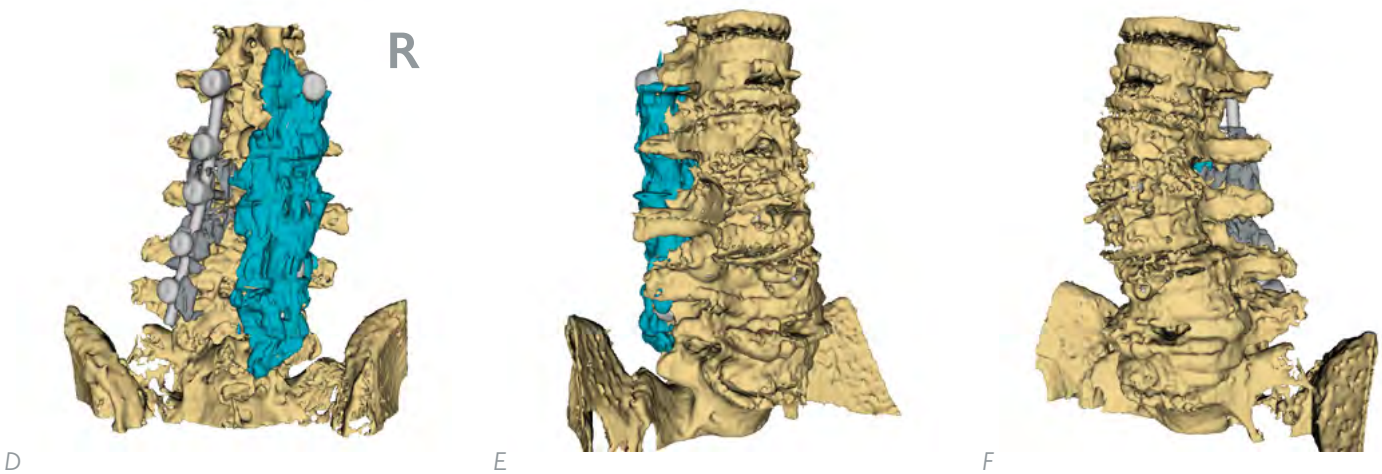
Case Study 6

This case presents a 53-year-old male diagnosed with spinal deformity in the thoracolumbar spine. The patient underwent a three-level PLF from T10 - L1 with MagnetOs Granules on the right and autograft on the left. After one year, fine-cut CT scans read by two independent spine surgeons determined that the MagnetOs Granules side was fused all three levels, whereas the autograft side was fused at one level. The patient was considered fused. In the MagnetOs fusion bridge, bone remodeling and graft resorption was evidenced by the trabecular structure and loss of granular appearance.



A *B* *C*

(A) Coronal, (B) Sagittal (left); and (C) axial fine-cut CT images of a L1-L5 four-level fusion at one-year follow-up. (MagnetOs Granules left side of subject, autograft right side of subject).



D *E* *F*

(D-F) CT reconstructions of a L1-L5 four-level fusion at one-year follow-up. (MagnetOs Granules: Blue; Autograft: Gray; Instrumentation: Light Gray).

Discussion

To decrease the rates of pseudoarthrosis after spinal arthrodesis surgery surgeons carefully consider all facets of the case, including optimizing subject and surgical variables and selecting the most scientifically advanced bone grafts. Although ICBG is the gold standard in bone grafting, there are known limitations such as lack of native supply and the potential need for a second surgical site.[4,5] Recent discoveries in the field of osteoimmunology have indicated that a viable strategy to facilitate and enhance bone healing is to maximize the pro-healing response of the immune system.

In response to tissue trauma or surgery, the immune system reacts by transiently upregulating pro-inflammatory macrophages, also known as the M1 macrophage phenotype. If M1 macrophages remain chronically activated, this leads to a fibrotic healing response, which may ultimately lead to a nonunion. Conversely, if the M2 macrophage phenotype is activated a pro-healing response is initiated, upregulating mesenchymal stem cells, and promoting the formation of bone rather than scar tissue.[14] MagnetOs, a BCP with needle-shaped submicron surface features, polarizes naïve monocytes to the pro-healing M2 phenotype. In preclinical studies, MagnetOs has been shown to promote bone formation even in soft tissue, without the need for added cells or growth factors.[9] MagnetOs bone graft mimics the structure of cancellous bone, with bone formation taking place throughout the bone graft leading to a solid, uniform fusion that has been demonstrated in clinically relevant animal models.*[10,11]

Recent years have generated increased research on second generation synthetic bone grafts, with mixed reported fusion rates. This includes a β-TCP bone graft with microstructured topography, which reached a fusion rate of 55% in subjects undergoing PLF[15]; a Silicated Calcium Phosphate bone graft, which reached a 71.4% fusion rate in subjects undergoing PLF with Posterior Lumbar Interbody Fusion (PLIF)[16]; and a peptide bone graft, which reported a 50% fusion rate in non-instrumented PLF.[17]

The fusion rate of autograft may depend on various factors, such as the volume of autograft used, the harvesting site and bone composition (i.e., cortical vs cancellous bone), the method of fusion assessment (i.e., X-ray vs CT) as well as the timepoint of fusion assessment. Other factors that may influence the fusion rate with autograft are subject characteristics and co-morbidities, which can affect bone quality. The fusion rate for autograft obtained in the current interim analysis is comparable to those reported in other prospective, multi-center, randomized, controlled trials that evaluated synthetic bone grafts compared to autograft.[15-17]

Looking forward, the next generation of synthetic bone grafts is predicated on advanced surface topography modulating an augmented bone healing response. The preliminary results of this prospective, randomized, intra-subject controlled, multi-center study effectively demonstrate the fusion capabilities of MagnetOs with its submicron needle-shaped surface topography. With a 78% fusion rate, the fusion outcomes of MagnetOs surpassed the fusion rates reported for other synthetic bone grafts that were evaluated against autograft in studies of similar design.[17] The fusion rates were further evidenced with statistical analysis to remove co-founding variables such as the presence of an interbody fusion. Aside from independent radiology reports to determine fusion, clinical outcome measures in the form of ODIs were measured, with a significant improvement of 15 points at twelve weeks.

Conclusion

This interim analysis found a 78% fusion rate of MagnetOs Granules by subject, and a 76.1% fusion rate of MagnetOs Granules by level. The results of this ongoing, prospective study aiming to determine the non-inferiority of MagnetOs Granules used standalone as compared to autograft are promising. Ongoing studies with more subjects are forthcoming.

References

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*Results from in vivo and in vitro laboratory testing may not be predictive of clinical experience in humans.
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