Orthogem

CE 0086

REGISTERED ISO 13485

TriPore® Summary of Scientific Evidence

Orthogem's scientists designed TriPore from the bottom up by first considering what the optimal microstructure for osteogenic activity should be. Then, with this ideal structure in mind, they set about creating an entirely new manufacturing process to produce this structure.

Orthogem TriPore HA: a New resorbable Hydroxyapatite (HA) Bone Graft Substitute –Proof of Biological Concept in a Long-Term Sheep Femoral Condyle Model

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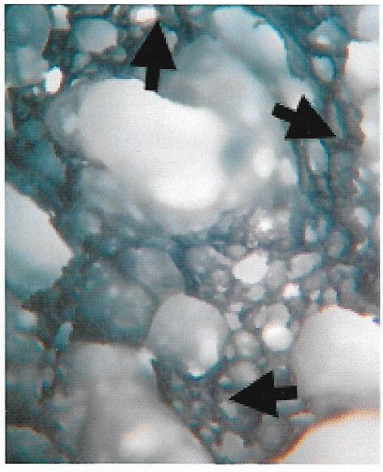
Conclusion

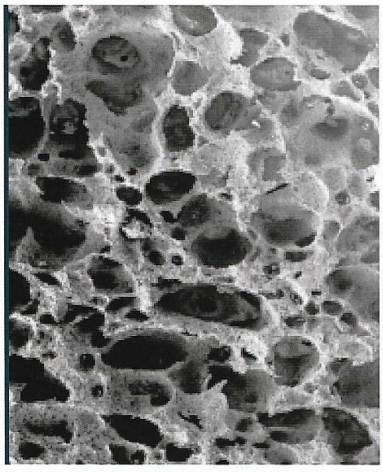
This study shows that the unique porous structure of Orthogem TriPore-HA achieves rapid osteointegration whilst the implant resorption rate matches the rate of bone ingrowth, resulting in a robust and viable implant site. The results also demonstrate the structure efficiently re-establishes a homogenous osteocyte density not only in the macropores but also inside the ceramic implant body to ensure bone remodelling occurs throughout the whole of the implant.

Clinical trials of Orthogem Tripore – HA have now started in patients undergoing lumbar spinal fusion.



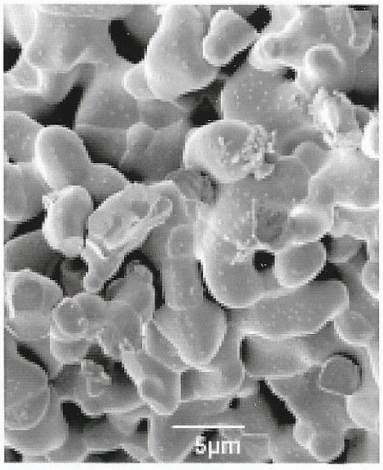
A

Interconected macropores. (SEM)



B

Back Lit optical microscopy showing midipores within the connecting wall.



C

Microspaces among the annealed ceramic particles. (S

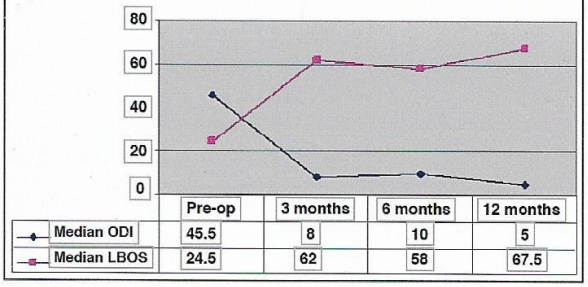
Orthogem TriPore® HA and Bone Marrow Aspirate used in lumbar spinal fusion: 12 month clinical and radiological review

Spinal fusion to treat symptomatic spondylolisthesis or carefully selected cases of degenerative disc disorders of the lumbar spine has become established as a valid treatment over the past twenty years. The biological aim of fusion is to eliminate intervertebral movement by creating a solid arthrodesis. This requires meticulous fusion bed preparation, bone grafting and almost always, supplementary internal fixation. There is no doubt that autologous cancellous bone is the ideal graft material, but its harvest is associated with significant morbidity for many patients.1,2,3,4,5,6,7 As a consequence, there has been extensive research activity during the past three decades, aimed at producing substitutes for iliac crest graft that are effective, cost efficient and avoid graft harvest morbidity.

For a material to be successful as a bone graft it should be osteoconductive and osteoinductive (osteogenic). It may be possible to achieve this in one preparation such as high-concentration demineralised bone matrix, but most effective bone graft substitutes are combinations of conductive materials and inductive agents.8 There is an extensive range of graft substitutes now available ranging from simple ceramics through collagen sponges to allograft preparations and most expensively, recombinant bioactive molecules. However, the ideal graft substitute that combines costefficiency and utility still remains elusive.

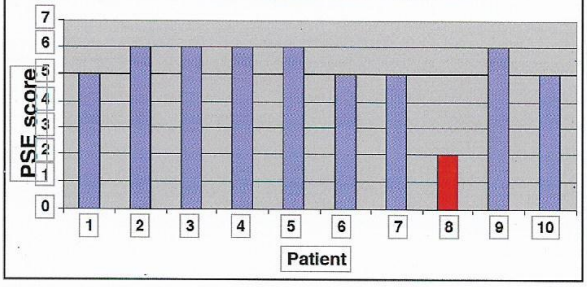
Calcium phosphate ceramic preparations are the closest structural and chemical mimics of the osteoconductive elements of human bone. The commonly used forms are tricalcium phosphate (TCP), hydroxyapatite (HA) and combinations of the two (biphasic preparations). HAis attractive as it is the closest ceramic in chemical and physical form to bone, but in the past it has not been possible to prepare HA that is reliably and progressively resorbed to be replaced by remodelled bone. As a result many researchers and clinicians consider that HAis unresorbable. TriPore HA, developed by Orthogem, has overcome this technical hurdle.

Figure 1 Serial ODI & LBOS measurements



	Pre-op	3 months	6 months	12 months
Median ODI	45.5	8	10	5
Median LBOS	24.5	62	58	67.5

Figure 2 **Patient Satisfaction Evaluation**



Results

All 10 patients in the study were available for regular serial followup evaluation over a 12 month period. On analysis of the data, 9 were deemed successful with 1 failure. The median pre-operative ODI was 45.5 (range 12-70) falling to 5 at the 12 month follow-up (range 0-42). The minimum clinical difference appropriate for a surgical intervention for back pain using the ODI is 14. As a result the results for this group fulfilled the criterion of success according to this disease-specific outcome tool.

The median LBOS score pre-operatively was 24.5 (range 8-66). This rose to a median score of 67.5 (range 23-75) after surgery (Figure 1). The one patient who was subjectively and objectively a failure of treatment had only an 8 point improvement in her ODI and 3 point improvement in her LBOS scores. The subjective, generic Patient Satisfaction Evaluation (PSE) questionnaire revealed that five patients had complete relief of their symptoms; four had good relief and one had no relief of symptoms (Figure 2). On this score, like the ODI and LBOS, **nine out ten patients had a successful outcome**.

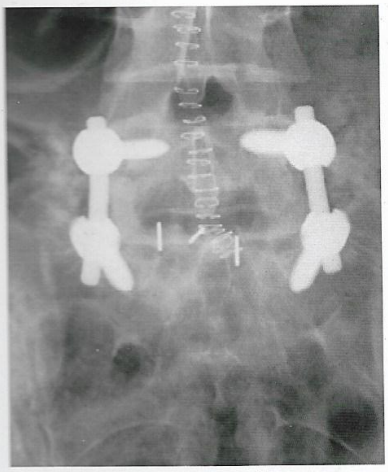


Fig 1

AP x--ray of a patient who had a TLIF at L5/S1 – immediate post--operative view showing granular appearance of TriPore HA graft in the postero--lateral position.

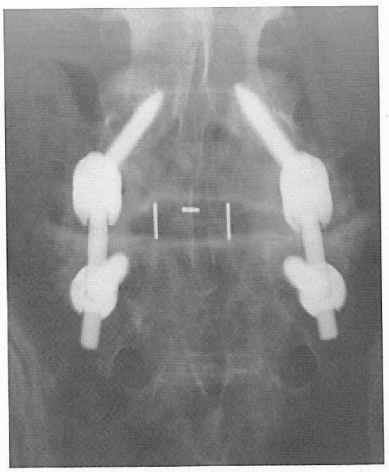


Fig 2

AP x--ray of a patient who had a TLIF at L5/S1 – 6 months post-operative view showing progressive conversion of TriPore granules to bone.

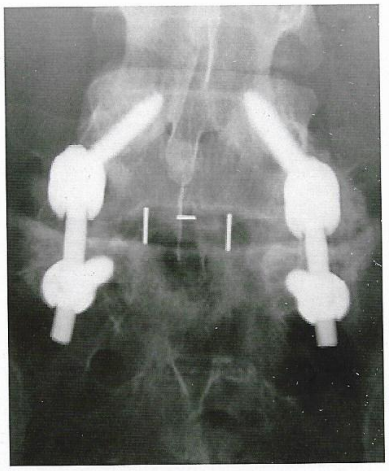


Fig 3

AP x--ray of a patient who had a TLIF at L5/S1 – 12 months post-operative view showing complete conversion of TriPore to mature fusion bone.

Evaluation of TriPore Putty in a Sheep Femoral Defect Model

Internal evaluation of data from In-life study centre and Histopathological processing facility.

Sponsor: Orthogem Ltd, BioCity, Pennyfoot Street, Nottingham, NG1 1GF, UK
In Life Study Centre:, University of Iowa Carver College of Medicine, USA
Sample Processing: Histion, Everett, WA 98204, USA

Objective

The objective of this study is to assess the efficacy of TriPore Putty in metaphyseal bone of a sheep.

Study Goals

The goals of the study are to determine the efficacy of the test articles relative to positive and negative controls on the following outcomes: quantity and quality of new bone formed (measured by histopathology) and host response (measured by histopathology).

Pass/Fail Criteria

Comparing test article to predicate;
Pass - TriPore Putty needs to perform as well as, or better than, TriPore HA granules in terms of percent bone, residual implant, and cellular response.
Fail - TriPore Putty performance is substandard when compared to TriPore HA granules in terms of percent bone, residual implant, and cellular response.

Results Summary

In this femoral defect study completed in sheep, a bone void filler identified as TriPore Putty was compared to a TriPore HA Granules predicate and an empty defect control. H&E and Goldner's trichrome-stained slides from 4-, 8-, 12- and 26-week specimens and Gomori's trichrome-stained slides from Time Zero specimens, were prepared from the lateral, central and medial aspects of filled 10 mm femoral defects. Sections were evaluated microscopically to determine the tissue and cellular response to the implant materials. Images of Goldner's trichrome- and Gomori's trichrome-stained sections were evaluated histomorphometrically to determine percent bone and percent residual implant material present within the defects within the defects at 12 and 26 weeks compared to Empty Defect controls suggest that TriPore Putty was not significantly different than TriPore HA Granules with respect to bone fill and that both implant types performed better than leaving the defect empty:

Based on median values, semiquantitative analysis showed:

- a small amount of fibrosis at 4 weeks in all groups that reduced with time for the TriPore groups. Fibrosis remained high or the Empty Defect group at all time points compared to the TriPore groups.
- Values for neovascularization associated with necrosis trended similarly as expected. No necrosis was seen in any of the groups at any time point.
- Median values for lymphocytes, plasma cells and PMNLs were zero at all time points for all groups, indicating no unwanted inflammatory response
- Both macrophage scores and GC scores were higher at all time points for the TriPore groups than the Empty Defect group.
  – This type of macrophage response is expected, given that the implant materials showed residual implant particles within these cells that were associated with some implant material, which is indicative of active removal.

Conclusion

There was no significant difference in mean percent bone at 4, 8, 12 or 26 weeks between TriPore Putty and TriPore HA Granules, and both groups showed a better result than the Empty Defect control with respect to bone architecture and lower median fibrosis scores at all time points. There was no evidence of a safety issue associated with implantation of TriPore Putty or TriPore HA Granules.

Orthogem Tripore® HA: 11 to 12 Year Post Surgery Clinical Follow-up

- TriPore HA is a unique formulation of hydroxyapatite and is the first bone graft substitute of its kind to show reliable resorption in lumbar spine fusion procedures.
- TriPore has been approved by the EU Regulatory Body since 2006.
- The Putty is readily available, easy to use and there have been no device related complications.
- Clinical Trial results demonstrated successful clinical and radiographical outcomes that showed evidence of bone fusion 12 months post-surgery.

Long Term follow up of 10+ years showed:

- Radiologic evidence of graft consolidation and formation of bone and
- Long term satisfaction with the procedure and functioning.

Background

- TriPore HA is a unique formulation of hydroxyapatite and is the first bone graft substitute of its kind to show reliable resorption in lumbar spine fusion procedures.
- The novel TriPore HA structure consists of macropores, midipores 1, 2 and microspaces. The structure allows early population of the graft by osteocytes, not only inside the connecting macropores but also within the ceramic body. 1, 2
- The first clinical trial to evaluate the use of TriPore in humans was conducted in 10 subjects in 2007-8. Nine (9) of the 10 subjects enrolled demonstrated successful clinical and radiographical outcomes that showed evidence of fusion 12 months post surgery.1
- The current data represents the longitudinal qualitative and radiological assessments for 7 of the 10 original participants, 10+ years after surgery. ng.

Objectives

To assess the following outcomes at 10+ years post surgery:

- Evidence of fusion utilizing plain x-rays.
- Overall health status, pain, lower back function and satisfaction with the treatment utilizing : Euro-QOL 5 Dimension score (EQ5D-5L)
- Oswestry Low Back Disability Questionnaire (ODI), a Back and Leg Pain Visual Analog Scale (VAS) and the NASS Patient Satisfaction Evaluation (PSE)

Participants

- The follow up study group consisted of 7 subjects.
- Out of the original group of 10 participants only Subject 3 was deemed a clinical failure at 12 months post surgery.
- Table 1 outlines the characteristics of the patients that participated in the longitudinal evaluation.

Table 1: Subject Characteristics

Subject	Gender	Age	Follow Up Time	Fusion; Procedure
1	F	76	12 y 2 m	L4-S1; TLIF
2	F	65	11 y 3 m	L4/5; PLF
3	F	60	12 y	L2-L4; PLF (no screws)
4	F	64	11 y 4 m	L4/5; PLF
5	F	52	12 y	L4/5; F&B fusion L5/S1; TDR
6	M	63	12 y 2 m	L3-S1; TLIF
7	F	73	12 y 1 m	Revisions L2-L5; PLF

Methods and Results

Methods: Seven (7) of the 10 subjects that participated in the initial clinical trial that evaluated the efficacy of TriPore consented to long term follow up assessments. Subjects in this cohort had lumbar spine weight-bearing X-rays and completed self assessment questionnaires and scales.
The timeframe of the assessment was relative to the date of surgery and listed in Table 1.

Questionnaire Results:

- EQ5D-5L: 6 of 7 subjects experienced no or slight problems in the domains of Self-Care and none complained of Anxiety/Depression. Three experienced severe problems in the areas of Usual Activities (1) and Pain (2) of which one was the subject failure. The distribution of scores is outlined in Table 2.
- The mean EQ5D Health State score was 69/100 (range: 30-95) where 100 = Best Health and 0= Worst Health. 4 of 7 subjects rated themselves as 75 or higher and 1 subject's self rating was a 30 (initial clinical failure). The mean score represents a positive outlook on overall health.
- ODI: The median ODI score was 20% (range: 0-58%). The majority of subjects scores reflected minimal disability (4) or moderate disability (2). The subject deemed an initial failure was rated as having severe disability.
- VAS Pain: Subjects rated their pain on a scale of 0-10 (0 = No Pain; 10= Worst Pain Imaginable) for their back, and both legs (leg with worse pain and alternate leg). Mean score for both the back and symptomatic leg was 4 whereas the maximum alternate leg score was 1.
- NASS Patient Satisfaction Evaluation (PSE): Revealed 3 subjects had complete relief of symptoms and 3 had good relief indicating successful outcomes.
- NASS: Results listed in Table 3 suggest Satisfaction with procedure using Tripore.

Table 2: EQ5D-5L

	Mobility	Self-Care	Usual Activities	Pain	Anxiety/ Depression
1 - No Problem	3	6	2	3	4
2 - Slight Problem	-	-	2	-	3
3 - Moderate Problem	4	1	2	2	0
4 - Severe Problem	-	-	1	2	-
5 - Extreme Problem	-	-	-	-	-

Table 3: NASS PSE

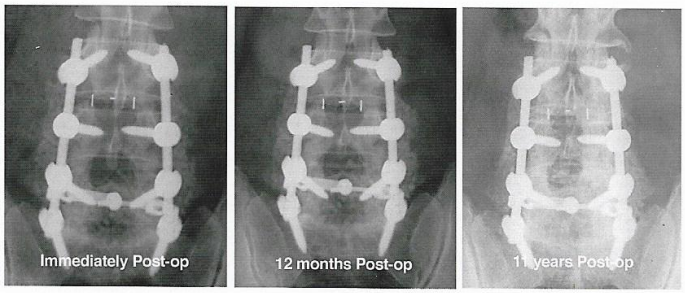
Pain Relief			Yes	No	Unsure
Complete	3	Would have the op again	5	1	1
Good deal	3	Would recommend to friends / family	7	0	0
Little	1	Were there areas for improvement in care	0	7	0
None	0				

Conclusions

- Previous clinical data evaluating TriPore HA at 12 months post surgery supported its use as an alternative to iliac crest autograft in lumbar spine fusions.
- Patient evaluations conducted 10+ years post surgery using TriPore HA demonstrate:
  - Radiologic evidence of graft consolidation and formation of bone, and
  - Long term satisfaction with the procedure and functioning
- Additional studies with larger sample sizes will be needed for a full assessment of efficacy, however this data supports the long term stability of TriPore 10+ years post implant.

X-Ray Results

- Erect lumbar spine X-Rays were performed on all 7 subjects. For the 6 subjects that were not deemed clinical failures in the initial study, long term radiological follow up showed evidence of successful bone formation. There were no cases of instrumentation failure or screw loosening.
- Representative images from Case 5 show a stable fusion following substantial TriPore conversion from its granular form to mature bone with extensive remodeling over 11 years.

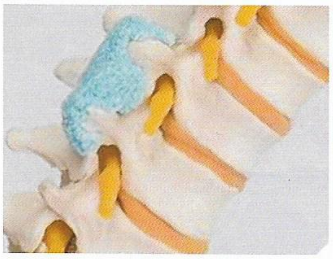


References: 1 D'Souza, W., Birch, N. Orthogem TriPore HA and Bone Marrow Aspirate used in lumbar spinal fusion: 12 month clinical and radiological review. (2008 - data on file: Orthogem Ltd, Biocity, Nottingham) 2 Lo, W., Et al. Orthogem Tripore HA: a new resorbable hydroxyapartite bone graft substitute: Proof of biological concept in a long-term sheep femoral condyle model. Poster at 8th EFORT Congress, Florence, May 2007. **Disclosure**: Nick Birch is a consultant to and shareholder of Orthogem Ltd

Orthogem

TriPore® Putty

TriPore Putty is TriPore HA granules combined with an aqueous gel to create a putty. TriPore Putty has been designed to provide exceptional intraoperative handling. TriPore Putty carries a CE Mark.

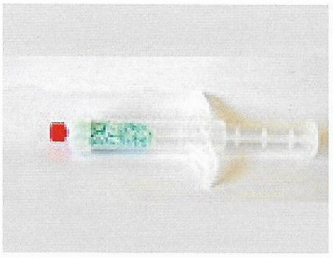


TriPore® Granules

TriPore Granules are designed for use in a number of sites from spinal applications to maxillofacial and dental applications. Available in a wide range of sizes from 250micron to 4mm, and pack volumes, 0.5cc to 30cc, to meet your needs. TriPore Granules carry the CE marking, 510(k) notification for the USA, regulatory clearance in Australia, India and Taiwan.

TriPore® MPA

TriPore MPA is a Multi-Purpose Applicator which is pre packed with TriPore granules for ease of use. It can be used in conjunction with blood/BMA/stem cells as a carrier, or simply for ease of application. TriPore MPA is available in 1-2mm and 1-4mm granules and in a variety of pack volumes. TriPore MPA holds 510(k) notification for the USA, carried the CE marking and is approved for use in Australia.



TriPore® Blocks

TriPore Blocks are made from 100% Pure Hydroxyapatite which is fully resorbable by the body. Blocks are designed to be used in a number of sites, including spinal applications and are available in 2 sizes. The Blocks are easily shaped and cut to size if required. TriPore Granules carry the CE marking, 510(k) notification for the USA, regulatory clearance in Australia, India and Taiwan.

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Product Codes: 2102 – 1205= 5cc putty & 2102 – 1210 =10cc putty