altis biologics (pty) ltd

# altis® OBM · trauma

## osteogenic bone matrix

## INJECTABLE

**Bone Morphogenetic Protein Complex**

altis™ OBM

# what is OBM trauma?

**OBM-trauma is a revolutionary new bone filler used to treat bone voids. OBM-trauma is a naturally derived bone morphogenetic protein complex (OsteaPLEX™) bound to an engineered collagenous bone matrix (AltiCOLL™) that allows instant rehydration into an injectable composite intended for the restoration of bone voids.**

OBM is derived from one year-old heterologous porcine bone matrix, which is naturally endowed with a high abundance on bone morphogenetic protein complex. The unique tissue re-assembly process results in OBM with higher bone morphogenetic protein levels and with bone bridging activity superior to regular DBM, but with equivalent safety profile.

**Unique attributes of Altis™ OBM-trauma**

- Extensive clinical experience in more than 350 patients
- Superior morphogen content endogenously sourced from bone matrix
- Osteoinductivity superior to regular demineralised bone matrix
- Injectable Altis™ OBM-trauma is offered as an injectable system in a prefilled syringe for convenience
- Space maintaining scaffold supporting new bone formation
- Lyophilised-freeze-dried - offers room temperature stability and ease of transportation and storage. The product is reconstituted in theatre with sterile water for injection and can be injected immediately intobone defect sites as needed. BMP is bound to collagen scaffold, reducing risk of ectopic bone formation
- Excellent safety profile- no reports of adverse events to date
- 100% naturally derived collagenous scaffold and morphogen complex
- Histological evidence of osteoinductivity and biocompatibility shown in human
- Extensive preclinical research backing performance and safety of Altis™ OBM
- Cost effective

Preclinical and clinical studies have proven that OBM-trauma is an effective bone void filler material. This conclusion is based on data resulting from rabbit studies, and a prepivotal single-center, prospective, non- randomized, 6 month study involving 24 patients with open long-bone fractures. A post market survey study involving 300 patients has demonstrated a high level of safety and performance of Altis™ OBM in defects including the appendicular and axial skeleton. No reports of adverse events, serious adverse events, excessive inflammation, cancers and ectopic bone formation related to OBM have been reported. A case series involving posterolateral lumbar and thoracic vertebral fusion has demonstrated equivalence of Altis™ OBM versus autogenous bone grafting in achieving full vertebral arthrodesis.

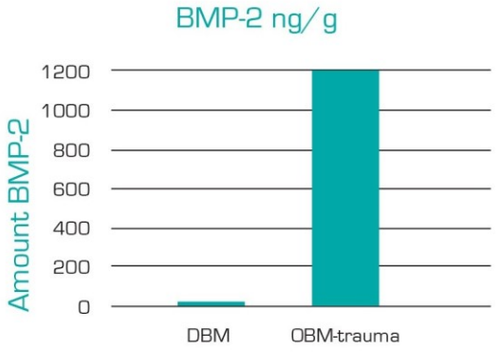
**Formulation** OBM-trauma contains 12 mg of Altis™ BMP complex (OsteaPLEX™) per gram of AltiCOLL™ delivery system.

**Activity** Endogenously sourced BMP-2 and TGF-beta levels 80 times higher than regular DBM.

**Indications** Indicated as a bone void filler of long bones of the appendicular skeleton (ulna, radius, humerus, tibia, and femur), axial skeleton (lumbar and thoracic) and craniomaxillofacial skeletal structures.

**Regulatory** In 2007, the Department of Health of South Africa agreed to allow marketing of Altis™ OBM as a medical device. The company is seeking medical device CE mark approval as a class 3 animal tissue derivative in the European Union.

**Cost and Coverage** Procedures are covered by private medical insurance.




Graph comparing BMP-2 content of OBM-trauma with regular DBM

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**Surgical experience with OBM-trauma and follow up for patients**

- OBM-trauma is packaged with sterile water for reconstitution in the injection device
- Prior to surgery, water is drawn into the injection device to reconstitute the powdered OBM-trauma into a paste
- The OBM-trauma which contains BMP-complex pre-bound to the collagen is allowed to rehydrate for five minutes
- Surgeon opens the fracture site and prepares the bone for the injection of OBM-trauma
- Surgeon injects the OBM-trauma directly into the void, where OBM-trauma promotes and supports the ingrowth of new bone

Orthopaedic surgery with OBM-trauma is essentially the same as traditional autograft procedures, without the need for the additional surgery to harvest bone from the patient's hip. After surgical procedures, patients return to their surgeons for follow-up visits, which may include radiographic evaluations.

**Benefits**

AltisTM OBM-trauma as a bone graft material has the potential to reduce:

- Need for autologous bone graft
- Hospital stay
- Costs – immediately following surgery and over time
- Complications that would require follow-up visits and eliminate pain at harvest site (in autograft procedures)
- Late onset complications from autologous bone harvesting procedure
- Risk of infection
- Blood loss

# Features

OsteaPLEX™ Bone Morphogenetic Protein Complex

**OsteaPLEX™ by Altis™ Biologics is a BMP-complex containing chromatographically enriched bone morphogenetic proteins and other extracellular matrix proteins endogenously sourced from demineralised bone matrix. BMPs are naturally occurring morphogens with potent bone induction capabilities when delivered with appropriate scaffold systems. Since their discovery in 1965 by Marshall Urist[2], hundreds of publications have reported their bone forming potential in animals and humans. BMPs in Altis™ BMP complex synergize with TGF-beta and act in concert with ECM constituents to improve osteoinduction, as demonstrated in experimental baboon models[3,4]. Both recombinant and naturally derived BMPs are capable of bridging critical size calvarial defects in the same animal model[5].**

Hundreds of publications in the literature have consistently demonstrated the osteoinductive ability of recombinant and naturally derived BMPs in preclinical models as well as human clinical studies. Injection of Altis™ OBM-trauma directly into the subcutaneous space of rodents leads to rapid bone formation within 12 days, observed both histologically and biochemically. Altis™ OBM-trauma rapidly bridges surgically created defects in rabbit long bone model[6]. Approximately 20 BMPs with different amino acid structures have been isolated to date, but only six appear capable of initiating bone growth. Of these, BMP-2 has demonstrated the greatest potential to form bone, hence BMP-complex is standardised according to BMP-2 content.

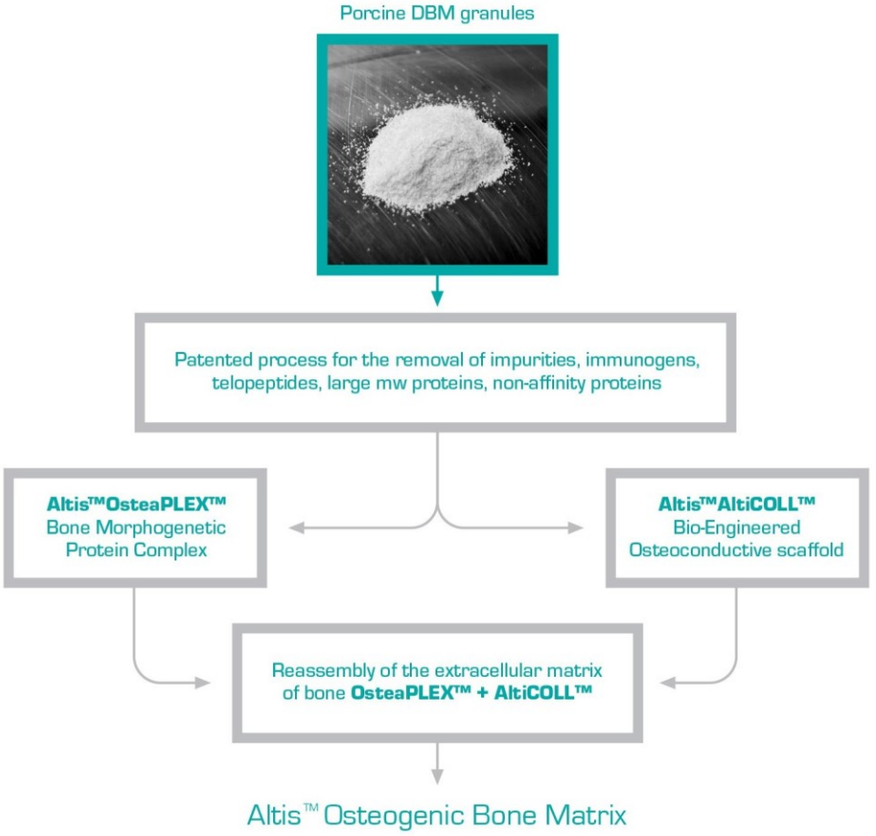
**Biocompatible AltiCOLL™** Telopeptide reduced type I bone collagen. AltiCOLL™, the scaffold system in OBM-trauma has been shown through preclinical studies to resorb at the rate of bone formation. It has been enzymatically treated and chemically swelled to render it biocompatible with reduced inflammatory response. AltiCOLL™ is osteoconductive in animal studies, and has a comparatively low inflammation score. AltiCOLL™ in OBM-trauma is designed to be a space maintaining device of a particle size that creates and maintains interstitial spaces for cellular ingrowth and neovascularisation processes brought about by the patient's system, and aided by OsteaPLEX™. AltiCOLL™ is an activated bone matrix collagen. It is engineered to contain open binding sites for host growth factors and cytokines that promote osteogenesis and wound healing. AltiCOLL™ is considered a 'smart' biomaterial – it is engineered for specific particle size and increased porosity for cellular attachment, differentiation and proliferation. It is formulated with instantised type I collagen for instant rehydration during reconstitution in the theatre.

# overview

of Altis™ OBM-trauma

**Altis™ OBM-trauma is a convenient, injectable bone void filler indicated for clinical specialties including trauma, sports medicine and craniomaxillofacial uses. The product is manufactured using the company's tissue matrix reassembly technology, and is 100% tissue derivative of porcine demineralised bone matrix (DBM).**

**OBM-trauma** contains two DBM derivatives: OsteaPLEX™ and AltiCOLL™. OsteaPLEX™ is a proprietary bone morphogenetic protein complex (BMP complex) that has demonstrated the ability to stimulate, induce and regenerate bone traumas in animal models. These two DBM constituents are processed into OBM- trauma, a biomaterial that encourages new bone formation onto an osteoconductive scaffold. BMPs are highly conserved from an evolutionary perspective, so that they can be used cross-species in humans with good efficacy[1].



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# history

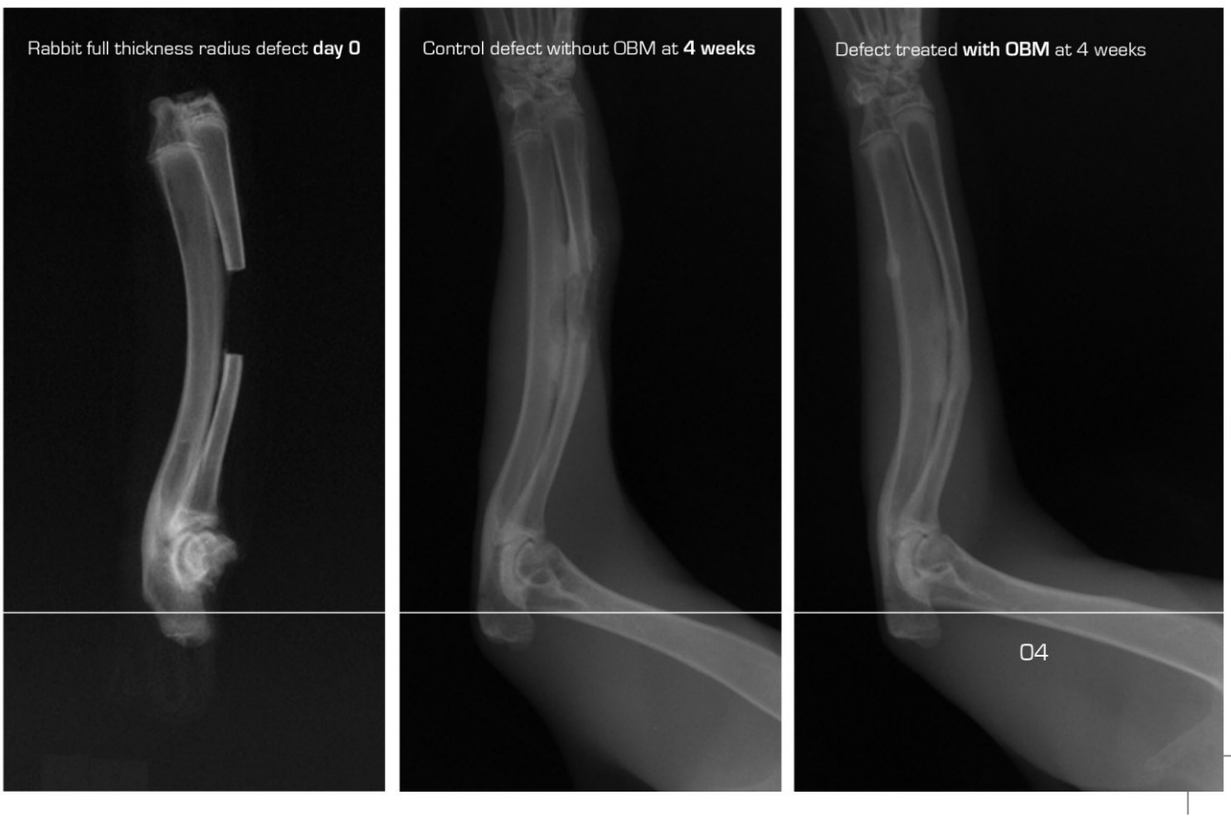
**OBM is the result of the work of South African[3,4] and American[1,2,6] scientists who have pioneered the tissue engineering of bone by deploying the regenerative ingredients of natural bone matrix into clinical practice. American scientist Marshal Urist described the bone inducing properties of demineralised bone matrix in 1965.**

Scientists at Johns Hopkins USA determined that bone matrix contains bone morphogenetic proteins that are responsible for bone induction and regeneration processes following bone trauma[7]. Nature deploys tiny amounts of BMPs to effect bone induction. The discovery that BMP and TGF-ß1 co- operate synergistically during bone induction experiments supported the thinking that nature deploys multiple morphogens in tiny amounts to regenerate bone[3,4]. BMP-complex contains bone morphogens and bone promoting proteins that co-operate synergistically to induce new bone formation, as demonstrated in non-human primate studies[4]. The creation of OBM-trauma begins with the careful isolation of bone collagen and bone morphogens from porcine bone matrix, and culminates in an engineered biomaterial that comprises osteoinductive BMP-complex (OsteaPlex™) bound to a biocompatible and osteoconductive collagen scaffold (AltiCOLL™). OBM-trauma therefore mimics natural bone induction properties of physiological bone matrix.

OBM-trauma is engineered using a multifaceted approach to incorporate aspects of delivery system design, ergonomics incorporating comfortable hand grip, convenient and precise delivery by injection, improved handling characteristics, and use of a biomimetic complex of bone inducing and bone promoting proteins. It has been proven safe and effective as a bone filler in a human clinical study and is cost effective.

**Patented high yield technology** Altis' patented high–yield technology[8] is employed to isolate the cocktail of proteins that are naturally present in demineralised bone matrix[7]. This bioprocessing technology allows porcine BMP complex to be produced and delivered on a purified type I bone collagen carrier that additionally provides an osteoconductive scaffold onto which new bone can grow. A unique binding protocol is employed that binds BMP-complex to the collagenous bone matrix, and later releases the BMP to responding cells.

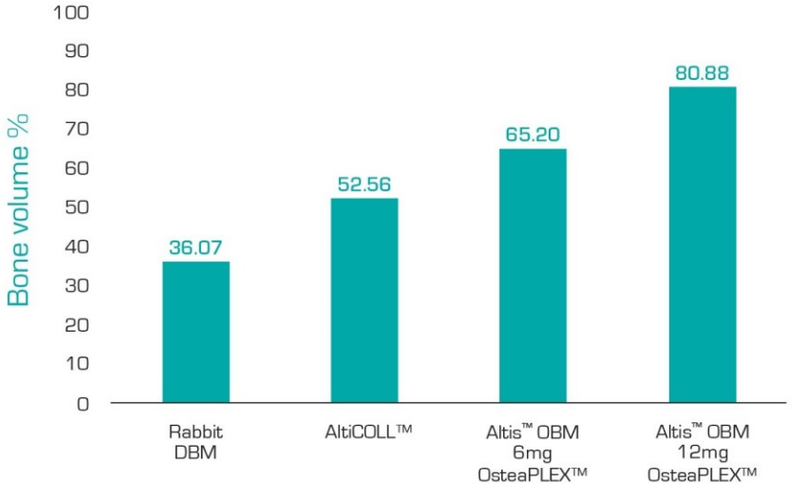
**OBM-trauma bridges critical sized segmental radial defects in rabbit model**



# bone volume percentage

**Bone volume % determined histomorphometrically of regenerated bone tissue in rabbit full-thickness radial defects at 12 weeks.**

OBM-trauma with 6 and 12mg OsteaPLEX™ surpassed allogeneic rabbit DBM in terms of defect bridging and bone volume % in a critical sized radius study in New Zealand White rabbits at 12 weeks. AltiCOLL™, the collagen scaffold developed by the company, also surpassed rabbit allogeneic DBM. The data point to both a high degree of osteoconductivity of the AltiCOLL™, as well as the ability of OsteaPLEX™ BMP complex in promoting bone regeneration in the OBM-trauma 6mg and OBM 12mg groups. OBM-trauma promotes bone morphogenesis where it is needed, and effects rapid bridging of surgically created full thickness rabbit radius defects.



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# clinical experience with OBM-trauma

## Safety and efficacy study in patients with traumatic long bone defects.

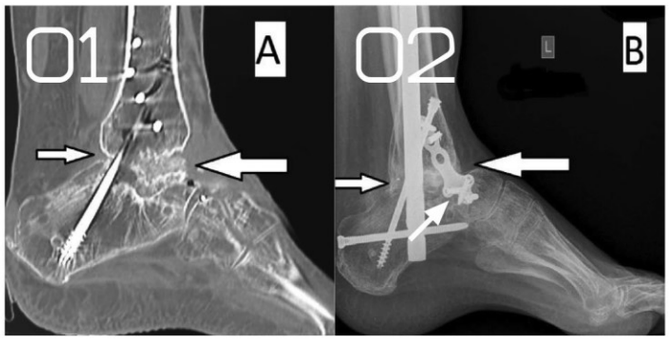
A pre-pivotal open label, non-randomised single centre study was conducted to evaluate the safety of Altis™ Osteogenic Bone Matrix-trauma when implanted into human traumatic long bone defects, to establish incorporation of Altis™ OBM into human bone, to evaluate efficacy in terms of bridging of the defects, and to evaluate the quality of life of the OBM recipients relative to their baseline quality of life.

A total of 24 subjects were enrolled, out of which 7 subjects belonged to observational group; 17 subjects were evaluated for safety and efficacy and 3 subjects were discontinued prematurely. Subjects in the study were all males (100%), all were black and median age was 29 years. Diagnosis and main criteria for inclusion were open long-bone fracture/s graded as per Gustilo and Anderson Grade II, IIIA or IIIB. Overall response to treatment was assessed as the proportion of subjects with bridging/fusion of the fracture and improvement of pain and function at the fracture site. Clinical, biochemical, immunological and radiological follow up was done at intervals of 2, 6, 12 and 24 weeks. Serum IgG anti-body titres to human and porcine type I and type II collagens were studied using ELISA. Bridging was assessed by an independent panel of radiologists. At all-time intervals normal soft tissue healing was evident. Radiographic evidence of cortical bridging varied from complete remodeling to minimal soft callus. 67%(6/9) of patients classified as type II/IIIA fractures, who made follow-up, had achieved full union on 3 of the four cortices at 12 weeks. 6 weeks after the surgery, 77% of 13 fractures treated with OBM had significant cortical bridging versus 25% in the reference group as assessed radiographically by the treating physician. At 12 weeks, the percentage remained the same in the OBM group, but rose to 50% in the reference group. At six months 47.06% had weight bearing and 61.5 % had bridging of the bone defect. No adverse clinical reactions to OBM were reported. Three patients who developed high anti-body titres to porcine type I collagen, were followed up for 1 year- no markers of autoimmune disease or any related clinical consequences were found. The ability of Altis™ OBM-trauma to act as an effective bone filler may reduce the dependency on bone grafts of autogeneic or allogeneic origin.

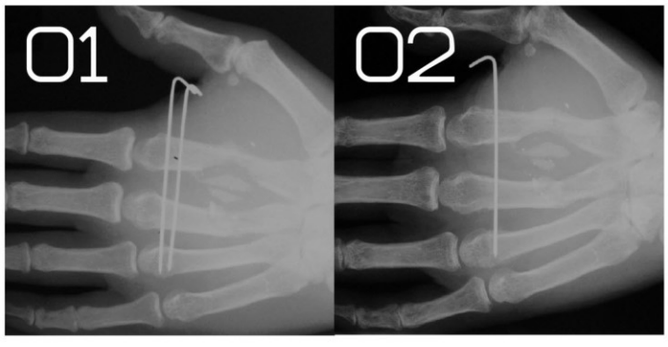
This study showed that treatment with Altis™ Osteogenic Bone Matrix was well tolerated by clinical subjects and there was no evidence of clinically relevant toxicity due to its use. The results of outcome parameters demonstrated an increased level of satisfaction as compared with the baseline. In a case study of a human open bone fracture treated with OBM, full incorporation of the OBM-trauma implant, and new bone formation integrating onto the implanted collagen, replete with osteoblasts, abundant osteoid and neovascularisation was shown.

Pre-pivotal open fracture study results for Gustillo-Anderson (GA) II and IIIA combined

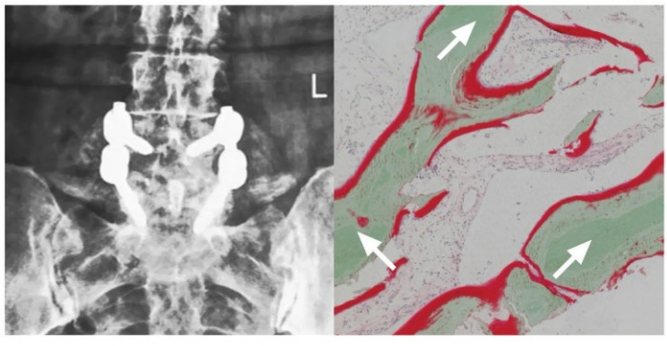
| | Altis™ OBM [n=14] | SOC [n=4] |
|---|---|---|
| Radiographic union | 9/14 | 2/4 |
| Overall success rate | 62% | 50% |




Resection of necrotic talus following unsuccessful tibiocalcaneal fusion using autogenous bone grafting (A) and implantation of OBM trauma together with tissue banked allogeneic spongiosa bone and autogenous bone graft. Results in (B) six months later showing solid tibiocalcaneal fusion.



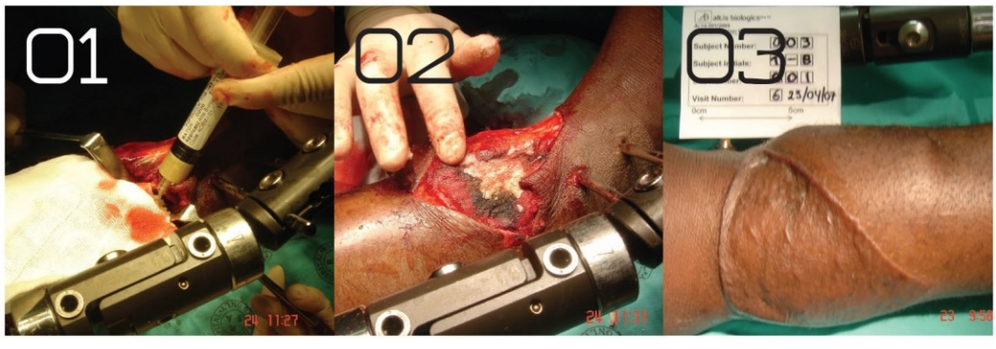

Bone formation and bridging in traumatic defects of metacarpal bone (01) at three months (02) using a single application of Altis™ OBM at the time of surgery.




Biopsy specimen (Villanueva mineralized bone stain) showing implanted OBM as dark green region (white arrows), new appositional bone growth in pale green, colonized by vital osteocytes, and thick osteoid seams in red with osteoblasts lining the new bone.

Instrumented lumbar spine fusion at 6 months, using autogenous bone on the right side, and Altis™ OBM on the left side. Comparable fusion is evidenced.

## Injectable and easy to use - injection of OBM into bone void, and shaping of OBM to defect site




Surgeons implant OBM-trauma instead of tissue-banked bone or autogenous bone. Autogenous bone grafting is associated with added risks and side-effects. The use of OBM-trauma instead of autogenous grafting may therefore eliminate the pain and blood loss associated with iliac crest autogenous bone harvesting, and reduce the amount of time spent in the hospital to treat complications resulting from the second site of surgery.

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11. Rothman B. and Duneas N. (2007) Acid Swelling Overcomes Osteogenesis Inhibition of Xenogeneic Collagenous Matrix Delivery System used for Naturally-Derived Bone Morphogenetic Protein Complex. *29th annual meeting of the American Society for Bone and Mineral Research*


| Catalogue no. | NAPPI code ZA | Description |
|---|---|---|
| OBM-trauma1100 | 112675*001 | Altis Osteogenic Bone Matrix for Trauma-injectable 3.3mL |
| OBM-perio150 | 112677*001 | Altis Osteogenic Bone Matrix for periodontal use -injectable 0.45mL |
| OBM-oral330 | 143285-001 | Altis Osteogenic Bone Matrix for oral use -injectable 1mL |
| OBM-2/12 | 154775-001 | Altis Osteogenic Bone Matrix injectable 12mg/g 2mL |

altis biologics (pty) ltd

**Contact Information:**
**Contact**: +27 (0)12 844 0098
**Email**: nic@altisbiologics.com **or** sales@altisbiologics.com
**Address:** Altis Biologics (Pty) Ltd
1606 Allan Cormack Street
The Innovation Hub,
0087
Pretoria, South Africa

SAHPRA reg. no. 000002464MD

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**Other products in the altis™ OBM Range:**

Altis™ Osteogenic Bone Matrix (OBM)
- Altis™ OBM–trauma
- Altis™ OBM–spine
- Altis™ OBM–oral maxillofacial
- Altis™ OBM–periodontal

AltiCOLL™ ready-to-inject collagen bone void filler
DBMxtra pDBM with naturally high endogenous BMP content
AltiMEM™- GTR collagen membrane for guided tissue regeneration
AltiCERAM™ sintered porcine spongiosa