1. General Details

Device Name: adbone®BCP

Common Names: Synthetic Bone Graft

2. Objective

This clinical evaluation study is performed in order to:

A. Evaluate the safety and performance of adbone®BCP device with respect to the intended use of the device as a bone graft.

B. Identify and discuss any literature data on synthetic bone graft substitute, based on the same composition and application of adbone®BCP, that support the clinical safety and performance claims of the product.

C. Identify the clinical benefits and foreseeable risks associated with the use of adbone®BCP and if any risks are identified, evaluate if the risks are acceptable when weighed against the benefits to the patient.

D. Evaluate if the clinical evidence demonstrates conformity with relevant Essential Requirements.

3. Scope of the Literature Search

The literature search has focused on identifying relevant evidence about the clinical safety and performance of devices analogous to adbone®BCP through the literature route. The literature route was chosen since hydroxyapatite and beta-tricalcium phosphates have been widely studied, documented and used as bone grafts for over 40 years. Also, adbone®BCP has been manufactured and distributed by Medbone for 6 years and does not bring any novelty to the market. The scope of literature searched included research articles from discipline-specific journals, such as journals specialized in oral, maxillofacial and orthopedic surgeries. Journals dedicated to the science of materials were also included in the search due to their relevance to the topic. The focus of the literature search was on research articles where the benefits and the risks associated to the use of bone substitutes similar to adbone®BCP were assessed in patients in the course of specific surgical procedures.

4. Methods

- **Date of search:** From 29-05-2016 to 31-05-2016

- **Name of person undertaking the literature search:** Filipa Pereira
- **Period cover by search:** No date restriction was applied
- **Literature sources used to identify data:** Potentially relevant literature was identified through searches in the following databases: MEDLINE®/PubMed®, Wiley Online Library and Springer Link.

5. Database Search Details

- For MEDLINE®/PubMed®, the search query was to identify each article with the title/abstract containing "(biphasic calcium phosphate bioceramics)" OR "(hydroxyapatite beta tricalcium phosphate ratio)" OR "(biphasic calcium phosphate bone substitute)" OR "(biphasic bone substitute)" OR "(beta tricalcium phosphate/hydroxyapatite)" OR "(biphasic calcium phosphate bcp") OR ("biphasic calcium phosphate granules)" OR "(hydroxyapatite beta tricalcium phosphate scaffold)" OR "(porous calcium hydroxyapatite ceramic)" with the following filters: Languange (English), Species (Human), Article Types (Clinical Trial OR Clinical Study). The articles retrieved after the filter application, were analyzed (title, abstract and full text in case of need) by the reviewer, and selected or excluded according to the pre-established criteria.
- For Wiley Online Library, the search string was "abstract: (biphasic calcium phosphate bioceramics) OR abstract: (hydroxyapatite beta tricalcium phosphate ratio) OR abstract: (biphasic calcium phosphate bone substitute) OR abstract: (biphasic bone substitute) OR abstract: (beta tricalcium phosphate/hydroxyapatite) OR abstract: (biphasic calcium phosphate bcp) OR abstract: (biphasic calcium phosphate granules) OR abstract: (hydroxyapatite beta tricalcium phosphate scaffold) OR abstract (porous calcium hydroxyapatite ceramic) OR abstract (biphasic macroporous synthetic bone substitutes)" with the filter "Journals". Since the filters used in MEDLINE®/PubMed® are not available on Wiley Online Library, the narrowing of the results was performed using the search string "NOT all fields: (animal) AND all fields: (clinical trial)". The articles retrieved were then selected or excluded by the reviewer.
- For Springer Link, the search query was to identify each article with the title containing "(biphasic calcium phosphate bioceramics)" OR "(hydroxyapatite beta tricalcium phosphate ratio)" OR "(biphasic calcium phosphate bone substitute)" OR "(biphasic bone substitute)" OR "(beta tricalcium phosphate/hydroxyapatite)" OR "(biphasic calcium phosphate bcp") OR ("biphasic calcium phosphate granules)" OR "(hydroxyapatite beta tricalcium phosphate scaffold)" OR "(porous calcium hydroxyapatite ceramic)". All the articles retrieved were analyzed (title, abstract and full text in case of need) by the reviewer, and selected or excluded according to the criteria.
- The data base search strategy was conducted in accordance with the requirements of MEDDEV 2.7.1 rev 3.

6. Selection/Criteria to be applied to published literature

Titles and abstracts were screened and only articles that meet the following criteria were considered eligible:

A. Articles published on recognized, scientific journals specialized in areas relevant to the matter, namely, journals specialized in oral, maxillofacial and orthopedic surgery, science of materials, and related topics.

B. Articles that report the use of synthetic bone substitutes composed of beta tricalcium phosphate in clinical trials, which have identical technical, biological and clinical equivalence of the bone graft substitute reported in the scope of this evaluation. The safety and performance of beta tricalcium phosphate reported in the published clinical trials will be evaluated in order to find a biological, clinical and technical equivalence.

The exclusion criteria were:

A. Articles that did not have any mention to bone graft or related topics.

B. Articles reporting the use of synthetic bone graft substitutes with no technical, biological and clinical equivalence to adbone®TCP.

C. Articles reporting the performance and clinical safety of synthetic bone graft substitutes through animal studies or through *in vitro* studies.

D. Articles focused on the manufacturing methods and/or on the determination of the mechanical properties.

E. Review articles, books, lab protocols, posters, etc. addressing the matter under consideration.

F. Articles reporting the Influence of external factors in the performance of the synthetic bone graft.

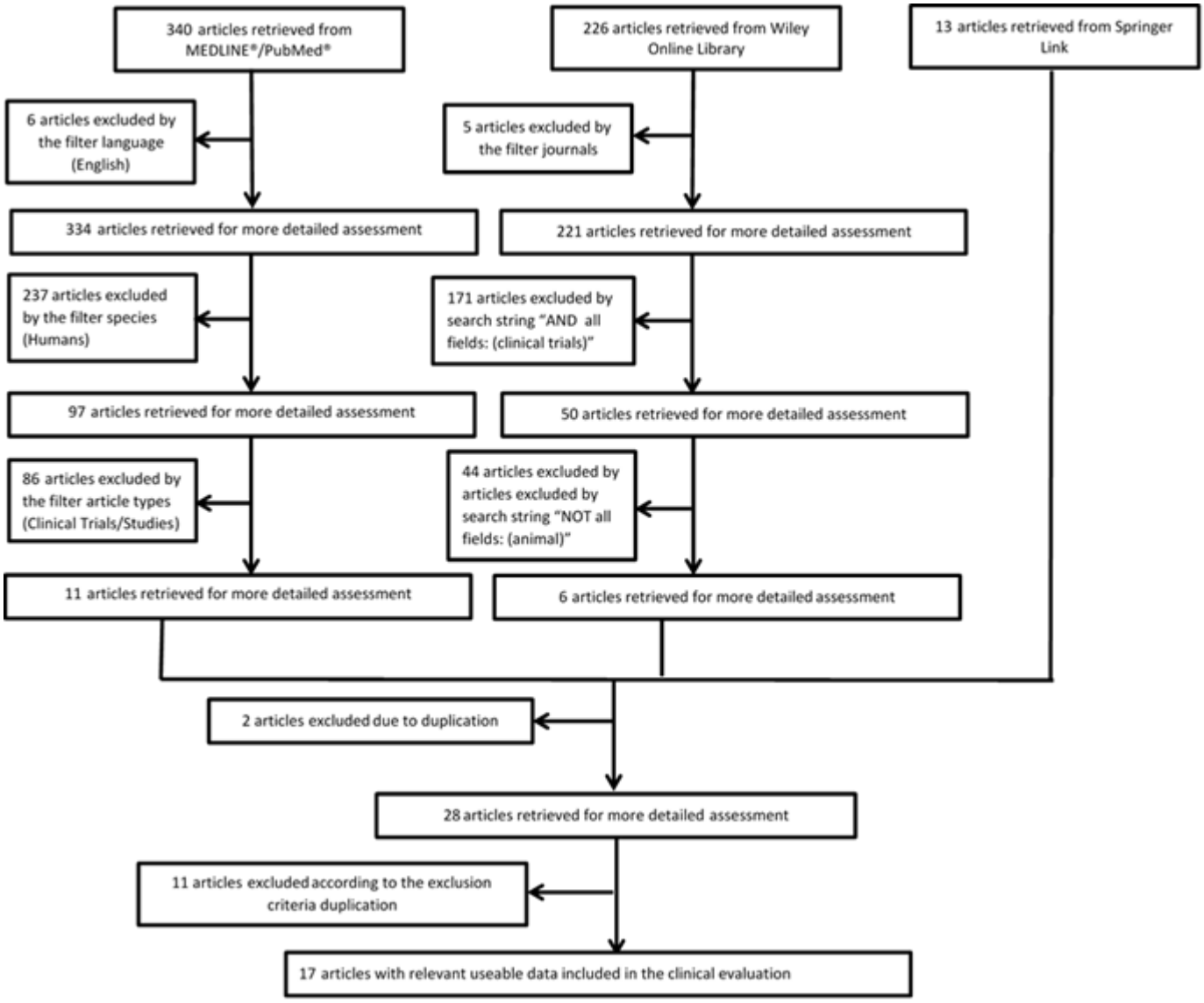
G. Articles published in languages other than English.

The reference management software Mendeley was used to avoid the duplication of data. This citation manager automatically identifies duplicates among imported references, which can subsequently deleted.

7. Outputs

The initial literature search in the databases MEDLINE®/PubMed®, Wiley Online Library and Springer Link resulted in 579 outputs. After the elimination of the duplicated outputs, were obtained 483 outputs.

8. Screening and Selection of the Relevant Literature



9. Context of the Evaluation and Choice of Clinical Data Types

Porous synthetic ceramics, based on calcium phosphates have been used in orthopedic surgery for some years now. adbone®BCP is to be differentiated from existing porous bone implants due to a stable mechanical structure and a flexible production technology allowing the implant to be custom made for a specific need of the patient.

The clinical data used in this evaluation are reports of different geometries of porous biphasic hydroxyapatite and beta tricalcium phosphates used in bone reconstruction surgery. The reports were chosen due to the fact that all reports use a biphasic composition of hydroxyapatite and beta-tricalcium phosphates for bone repair,

which is equivalent to the composition of adbone®BCP. Different geometries were considered in this study that varied from granules, blocks and wedges. These geometries were chosen due to the fact that adbone®BCP is manufacture in the same geometries, having the cylindrical form the only geometry that was not considered in the clinical evaluation.

10. Summary of Clinical Data and Appraisal

During the last decades, there has been a great increase of the use of bone graft substitutes. Bone graft substitutes are a useful alternative to biological materials such as autografts, allografts and xenografts. One of these, calcium phosphate ($CaPO_4$) ceramics, which include hydroxyapatite (HAp) and tricalcium phosphate (TCP), have been the most widely investigated and used in orthopedic surgery. These materials must fulfill certain property compatibility with surrounding tissues, chemical stability in body fluids, compatibility of mechanical and physical properties, ability to be produced in functional shapes and to withstand the sterilization process, reasonable cost of manufacture and reliable quality control.

Many in vitro and in vivo studies have shown that calcium phosphate ceramics are fully biocompatible and the physical and chemical properties of these substances make them bioactive. In addition, calcium phosphate ceramics are osteoconductive and resorbable, i.e. they provide a scaffolding for new bone formation, and their macroporosity allows bone and cells to grow into the ceramic [1].

Hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$] and β-tricalcium phosphate [$Ca_3(PO_4)_2$] ceramics are biocompatible and osteoconductive materials that offer a chemical environment and a conducive surface to new bone formation [3]. These are brittle materials and have low fracture resistance. They can be varied in chemical and structural composition. Different preparative methods lead to either a compact or porous material with interconnective macropores that are spatially and structurally equivalent to cancellous bone. Commercially available hydroxyapatite is resorbed very slowly, under normal physiological conditions, whereas β-tricalcium phosphate is generally resorbed within 6 weeks after implantation.

When used as a mixture, biodegradable hydroxyapatite/β-tricalcium phosphate ceramics have the ability to dissolve, break down, and allow new bone formation and remodeling required to attain optimal mechanical strength without interference [2, 3].

Biphasic calcium phosphate ceramics (BCP -a combination of HA and □-TCP) are currently used for bone filling in spinal, tumoral, orthopaedic, and periodontal applications. Although HA and □-TCP have similar chemical compositions, they have different biological resorption capacities. While □-TCP is a bioactive and bioresorbable material with an affinity for high-speed biologic degradation, HA is relatively less bioactive and nonresorbable. On the other hand, the main attractive feature of the combination of these two materials (BCP granules) is their ability to form a strong direct bond with the host bone resulting in a more powerful interface compared with β-TCP [13].

The goal of the present study was to investigate the long use of the BCP in the surgery in many forms and to show the excellent biocompatibility proved in many clinical situations reported in the literature.

11. Data analysis

These materials have been widely studied in recent years by many researchers as verified by the literature.

Botez et al. [1] showed a clinical, radiological and histological study of the integration of the biphasic synthetic ceramic (Ceraform®). The study reported 5-years follow-up of 43 cases requiring bone substitution: bone tumours; spinal fusions; revision arthroplasty; nonunions; fractures; osteitis.

Ceraform® is a macro porous synthetic phosphocalcic ceramic material. Chemical composition consists of hydroxyapatite 65% and tricalcium phosphate 35%, with 60–85% pore volume and large pore diameter (100–400 µm) which includes the substitute in group of macro porous materials.

This synthetic material was used in 43 patients with different orthopaedic conditions, between October 2001 and October 2007.

Bone substitute was used as a single component of bone replacement in 14 cases (32.55%) whenever there was a need for replacing bone defect in a metaphiseal or ephyphiseal zone resulting from benign bone tumour or dystrophy ablation, in several comminuted fractures and in one case of knee axial correction. The shape of the substitute (grains, rods, blocks) was dictated by the configuration of the defect to be filled and predictable level of mechanical loading after implantation. Limited defects allowing bone continuity were grafted using 5–15 g granular CERAFORM® while in defects not allowing bone continuity the rod or block shape of the material was preferred. In other cases (spinal or joint fusions, 23 cases, 53.48%) the granular bone substitute was mixed with autologous bone marrow harvested from iliac bone or with autologous bone graft considered to be of insufficient quantity to fill the bone loss. Three cases (6.97%) received the bone substitute mixed with allograft, and other three cases (6.97%) Ceraform® mixed with antibiotic (gentamicin 1%).

Patients have been followed up clinically and radiologically at 3, 6 and 18 months postoperatively. Bone biopsies were harvested more than 18 months after implantation (18–26 months) after patient informed consent, during surgical intervention required for osteosynthesis hardware removal. No patient was lost in the follow up. Early and late postoperative evolution showed no local inflammatory phenomena, no superficial or profound sepsis. Radiological results, no material fragmentation or fracture has been observed.

Although different shapes of available Ceraform® were employed: grains; compact block (Figure 1); bars (Figure 2), radiological evolution was similar in all cases with perfect material compatibility, no local side effects and good bone substitute integration.

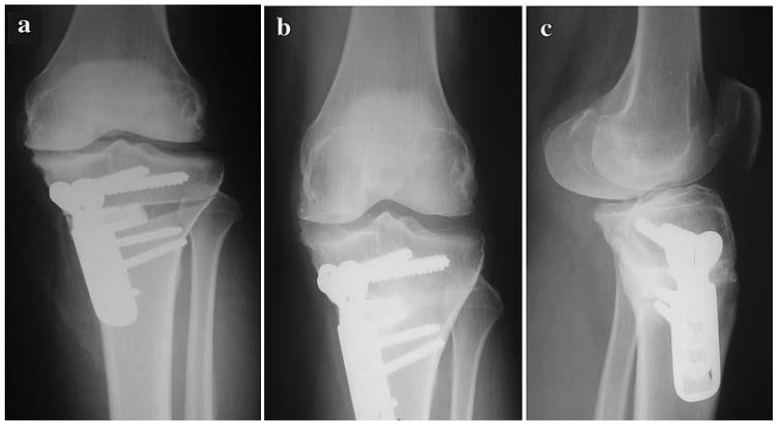


Figure 1 (a) - Knee axial deformity–genu valgum; valgus osteotomy, osteosynthesis and bone substitute Ceraform® compact ray block shaped apposition. a postoperative X-ray; 2 years postimplantation, perfect substitute integration, patient is pain free with mild medial compartment arthrosis, anteroposterior X-ray **(b)** and lateral view **(c)** [1].

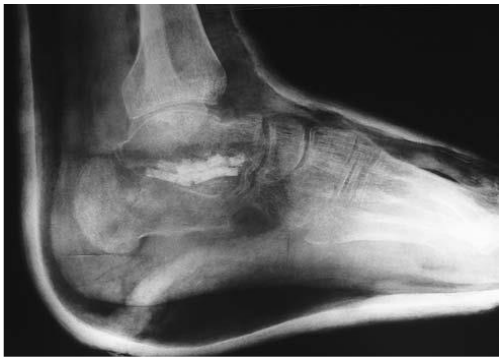


Figure 2 - Subtalar fusion, CERAFORM® (bar shaped) apposition in the fusion site, postoperative X-ray [1].

Histological evaluation of biopsy taken more than 18 months after substitute implantation showed rehabitation of the material by a mineralized tissue with a big similarity to cancellous bone architecture and cellular composition. Presence of mature osteocytes, osteoblasts surrounding bone trabeculae, multinucleated cells osteoclasts-like and vascular buds were proven in the specimen biopsies (Figure 3).

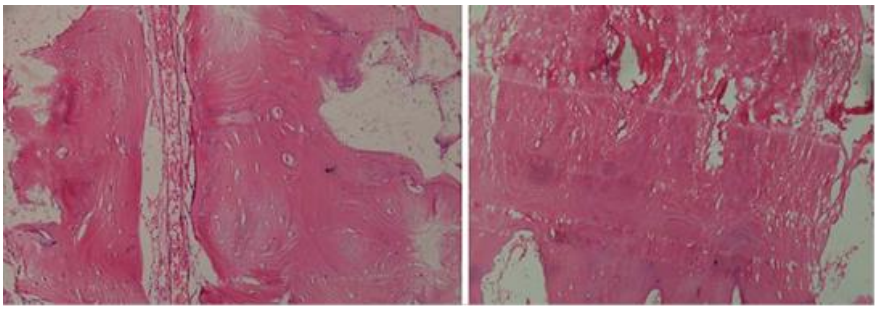


Figure 3 - Histological aspect of bone biopsy 2 years after CERAFORM implantation, Hematoxylin-Eosin staining showing cancellous like trabecular bone with neovasular buds and osteocytes lineing bone trabeculae [1].

In conclusion, clinical, radiological evolution and histological results quantitatively and qualitatively confirmed bone formation/regeneration on the substitution site. No deterioration of the grafted area occurred in the follow up, and biphasic macro porous phosphocalcic ceramic represents a valuable alternative to allografts [1].

Cavagna *et al.* [2] report a clinical study of the use of the macroporous biphasic calcium phosphate (MBCP) as a bone graft substitute for orthopaedic and dental surgery. So, the study investigates the clinical performance of this synthetic porous ceramic in a series of 106 patients, mainly with degenerative spine aetiologies (95/106).

Commercially available MBCP granules (Triosite TM, Zimmer, USA) 2-3 mm in diameter were used as a bone-graft substitute. This material consisted of a macroporous ceramic (70% global porosity, macropores 400 to 600 µm in diameter) containing a 60/40 weight mixture of hydroxyapatite and β-tricalcium phosphate.

The study was performed in 108 patients (57 women, 51 men, and mean age 53 years, range (15-79) from 1992 to 1994. Two of the patients died of extra-surgical causes before the minimum follow up period was reached and were thus excluded from the study, which finally concerned 106 subjects. The series was prospective, non-randomized, and performed by a single operator. Most of the operated patients (93) presented a degenerative disease (spondylolisthesis, scoliosis, kyphosis, lumbar stenosis). Eight had primary spondylolisthesis, and 5 had undergone surgery for various pathologies.

All patients were treated with posterior correction using a semi-rigid spinal system. Spinal fusion was performed using MBCP granules mixed with autogenous bone chips and bone marrow obtained from the local spine.

The patients were follow-up for at least of 2 years (26-50 months), and arthrodesis fusions was assessed by X-ray at 3,6,12, and 18 months, and then once per year. Each evaluation included frontal, lateral, and three-quarter views. In doubtful cases, a CT scan (2D) was performed. All radiographic documents were examined by two observers, the operator and an independent examiner. Only one biopsy was performed during ablation of material after fusion for treatment of a callus defect on L1. No surgical biopsy had been planned, because the material was to be left in place in order not to complicate the treatment of degenerative spine There were no local complications and no inflammatory or infectious effects in this clinical study.

In the radiological results, one hundred arthrodesis were fusioned, and 6 were non-unions. The latter were unmistakable because of either absence of fusion in the X-ray or breakage of a rod before the 6th postoperative month, indicating mobility of the instrumented segment.

This prospective study indicates that MBCP is an efficient substitute for grafting in spinal fusion involving degenerative disorders, biocompatible and provides good perioperative comfort while ensuring a high success rate in the fusion of lumbar arthrodesis [2].

De Coster *et al.* [3] compared bone regeneration in healing extraction sockets substituted with Bone Ceramic® (Straumann, Basel, Switzerland) with unfilled sockets. Biopsies were obtained from the sites during later performed implant bed preparation. Histological sections were examined using transmitted light microscopy after 6–74 weeks (mean 22 weeks). 15 Bone Ceramic® sites were compared with 10 naturally healed sockets. During implant placement, it was observed that bone at the substituted sites was softer than in control sites and large amount of loose biomaterial was found. The histology showed an incomplete healing process in 5

substituted sites. On the basis of these findings, the authors concluded that the use of Bone Ceramic® as a material for bone augmentation for implant placement within 6-38 weeks after extraction, should be revised [3].

Froum and its co-workers [4] were the first to histomorphometrically compare vital bone formation following bilateral sinus grafting with a biphasic calcium phosphate (BCP) (Bone Ceramic®, Straumann, Basel, Switzerland) to an anorganic bovine bone matrix (ABBM) (Bio-Oss®, Geistlich Pharma AG, Wolhusem, Switzerland) 6 to 8 months following graft placement. Straumann bone ceramic (Straumann) is a biphasic calcium phosphate (BCP) that has been widely used as a bone graft substitute in orthopedic and dental surgery. This material is fully synthetic and consists of 60% hydroxyapatite and 40% beta-tricalcium phosphate. The granules are 90% porous with interconnected pores of 100 to 500 pm. BCP has been shown to be safe, non-allogenic, and effective as a scaffold for the for-mation of new bone.

This study involved 12 patients undergoing bilateral sinus augmentations. During the procedure, BCP was placed in one subantral compartment and ABBM was placed in the contralateral subantral compartment, as determined by a computer-generated randomized code. Depending on the sinus anatomy, 3 to 5 mg of material was grafted in each sinus. A trephine core sample (10 mm in length and 3 mm in diameter) was retrieved from within the borders of the original lateral window after 6 to 8 months after the surgical procedure. Cores were obtained from 21 healed sinuses in 12 patients, since nine patients provided bilateral cores, one patient had an intact BCP core but an inadequate ABBM core and two patients had intact ABBM cores but inadequate BCP cores. The retrieved cores were sent for histomorphometric analysis to determine the content of vital bone, connective tissue, and residual graft material.

Histomorphometric analysis of 10 BCP cores and 11 ABBM cores revealed an average vital bone content of 28.35% and 22.27%, respectively. The average percentages of marrow/connective tissue were 43.25% and 51.73% for the BCP and ABBM sinuses, respectively, and the average percentages of residual graft material were 28.4% and 26%, respectively. Histologically, both materials appeared to be osteoconductive. New bone formation was observed adjacent to and surrounding the BCP particles. ABBM particles were surrounded by greater or lesser amounts of new bone and osteoid depending on the patient and sinus observed [4].

In 2014, Kim and his team [5] presented a study to evaluate the use of autologous bone tooth (AutoBT) in comparison to Osteon (Genoss, Suwon, Korea), a synthetic bone graft material that consist of 30% B-TCP and 70% Hydroxyapatite, in bone resorption around implants after a crestally approached sinus lift during the 1-year follow up.

A total of 37 patients were included into study, they were divided into 2 groups. Group I (17 patients) received AutoBT and group II (20 patients) received Osteon when the sinus lift procedure was performed.

From group, I only 11 patients (8 male and 3 female) were included into the statistical analysis because the other six miss the 1-year follow up. From group II only 11 patients (5 males and 6 females) were included as well for the same reasons previously described.

The result obtained in the 1-year follow-up radiograph by Kim *et al.* are showed in Table 1. Kim and his colleagues found no statistical significance between the 2 groups. The authors concluded that AutoBT is a good bone graft substitute achieving comparable result in comparison to the Osteon (Genoss, Suwon, Korea),

synthetic bone graft material compose of 30% B-TCP and 70% Hydroxyapatite. But further studies are requested for the BoneBT [5].

Table 1 - 1-year follow-up radiograph results [5].

	Mean Initial bone height (mm)	Mean increase in bone height (mm)	Mean resorption of bone height (mm)
AutoBT	**9.64**	**4.89**	**0.76**
Osteon	**9.22**	**6.22**	**0.53**
***P*-value**	**0.973**	**0.460**	**0.570**

Lee *et al.* [6] reported a clinical and histological study of bone formation in maxillary sinus augmentation using MBCP as the bone-grafting material.

Between March 2004 and August 2005, 52 patients (24 females, 28 males) were selected, after a medical and dental examination, with insufficient residual bone height (< 6mm). Their ages ranged from 30 to 73 years, with a mean age of 50 years. The patients were divided in three groups of graft materials used in sinus floor augmentation: group I -27 patients received MBCP only, group II - 16 patients received MBCP combined with irradiated cancellous bone and marrow (ICB) at a ratio of 50:50 and group III -the remaining nine patients received MBCP combined with intraoral autogenous bone at a ratio of 80:20.

Macroporous biphasic calcium phosphate (MBCP, Biomatlante Sarl, Nantes, France), with a mixture of 60% HA and 40% β-TCP, has the required porous form for biological exchanges particularly for bone ingrowth and mineralization.

After a healing period (average 6.78 months after surgery), bone cores were harvested for a histological evaluation and the implant fixtures were installed. These bone cores were evaluated via light microscope and implants were followed up for at least six months after loading.

Histologic evaluation could be made of only 18 patients (six from Group I, eight from Group II, and three from Group III), who agreed with harvesting bone core. Histologic evaluation at the time of fixture installation revealed new bone formation in conjunction with resorption of graft particles. Most of the MBCP particles were embedded in or surrounded by newly formed bone and it was possible to observe the close contact between graft particles and newly formed bone trabecules (Figures 4 and 5).

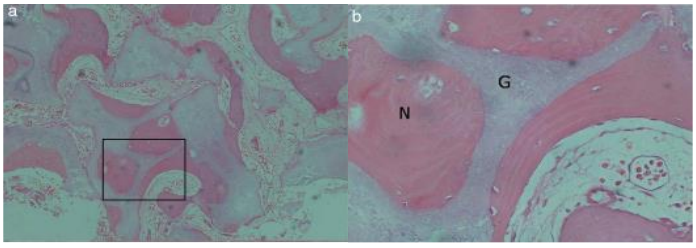


Figure 4 - Histologic finding 10 months after surgery (Group I). **(a)** The macroporous biphasic calcium phosphate particles are fully integrated into new bone and invaginated in woven bone (original magnification x 100). **(b)** Magnified view of: grafted material (G)

and vital bone (N) are in close contact and osteocytes are observed. The reversal line in newly formed bone is obvious (original magnification x 400) [6].

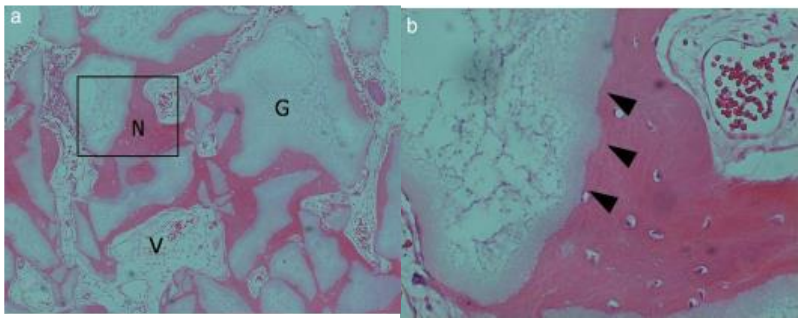


Figure 5 - Histologic findings 6 months after surgery (Group III). **(a)** Macroporous biphasic calcium phosphate (MBCP) particles (G) embedded in newly formed bone (N). Ample marrow space filled with loose connective tissue and abundant blood vessels (V) (original magnification x 100). **(b)** Magnified view of irregular limit between the new bone and residual MBCP particle shows the progress of bone remodeling (arrow head), which ensures the replacement of grafted material (original magnification x 400) [6].

Newly formed bone was characterized by lacunae containing osteoblast, which seemed to be osteocyte, and had abundant medullary space filled with a well-vascularized connective tissue with no histologic markers of inflammation (i.e., neutrophils and macrophage) or foreign body reaction. The new cancellous bone also exhibited incremental basophilic lines (Figures 4 and 5).

The present study evaluated the efficacy of MBCP as a grafting material for maxillary sinus augmentation in both one-stage and two-stage approach. Clinically, only two out of 130 implants were lost, and the 1-year survival rate was 98.46%.

Bone biopsies taken at 4–10 months after sinus graft (average 6.78 months) show initiation of resorption and newly formed bone in contact with residual MBCP particles without any adverse reaction such as the presence of multinuclear giant cells.

To concluded, it can be inferred that MBCP when used as a grafting material for sinus floor augmentation, whether combined with other osteoinductive materials or not, may lead to the predictable results for dental implants on posterior maxillary area with insufficient vertical height for fixture installation [6].

Lindgren *et al.* [7] compared the resorption of a synthetic biphasic calcium phosphate (BCP) (Bone Ceramic®, Straumann, Basel, Switzerland) bone-graft substitute with deproteinized bovine bone (DBB) (Bio-Oss®, Geistlich Pharma AG, Wolhusem, Switzerland) used for human maxillary sinus augmentation. Eleven patients underwent bilateral maxillary sinus floor augmentation with DBB in one side and a BCP (40%beta-tricalcium phosphate (beta-TCP) and 60% hydroxyapatite) in the contralateral side. Simultaneously, with the augmentation on each side a microimplant was placed vertically from the top of the alveolar crest penetrating the residual bone and the grafting material. Eight months after initial surgery the microimplants were retrieved with a surrounding bone core. The composition of residual graft material and surrounding bone was analysed by scanning electron microscopy and energy dispersive X-ray spectroscopy. Electron micrographs of the sections showed woven or mature lamellar bone completely surrounding or adjacent to 10-500 µm particles of DBB and BCP. Bone was seen to have formed within some of the larger and smaller rounded cavities of the BCP particles. Large number of smaller particles down to 1 µm were also present in some areas of non-

mineralized tissue, in case of both graft materials. However, the presence of this particles was more obvious in BCP augmented tissue. Higher magnification of the interfaces (Figure 6) between bone and graft particles revealed that the DBB particle surfaces were relatively smooth and intact, in contrast with the rough appearance of the BCP graft surface. The fragmentation may be aided by the ingress of bony tissue between granules [7].

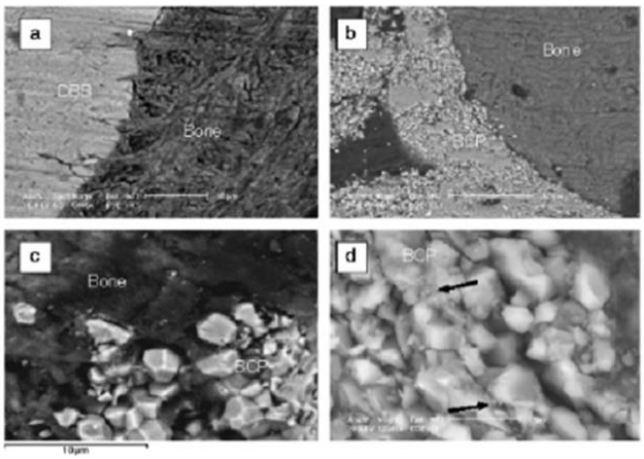


Figure 6 - Typical example of the interfaces DBB and BCP [7].

Median Ca/P ratios (at%), determined from >200 discreet sites within residual graft particles and adjacent bone, were: DBB: 1.61 (confidence interval [CI] 1.59-1.64); BCP: 1.5 (CI 1.45-1.52); DBB-augmented bone: 1.62 (CI 1.59-1.66); BCP-augmented bone: 1.52 (CI 1.47-1.55); P=0.028 for DBB vs. BCP and DBB- vs. BCP-augmented bone. The reduction in Ca/P ratio for BCP over the healing period is consistent with the dissolution of beta-TCP and reprecipitation on the surface of calcium-deficient hydroxyapatite [7].

A prospective 1-year clinical and radiographic study of implants placed after maxillary sinus floor augmentation with synthetic biphasic calcium phosphate or deproteinized bovine bone was conducted by the same author and its team [8].

Nine completely edentulous patients and two partially edentulous patients (mean age, 67 years) who required bilateral sinus augmentation were included in the study. After bilateral elevation of the Schneiderian membrane, all patients were randomized for augmentation with synthetic BCP in one side and DBB in the contralateral side. Implants (62 implants) were placed after 8 months of graft healing. Implant survival, graft resorption, plaque index, bleeding on probing, sulcus bleeding index, probing pocket depth, and implant success rate were evaluated after 1 year of functional loading. After a mean of 118 days, all patients received their fixed prosthetic constructions. One implant was lost in each biomaterial, giving an overall survival rate of 96.8%. Success rates for implants placed in BCP and DBB were 91.7 and 95.7%, respectively. No significant difference in marginal bone loss was found around implants placed in BCP, DBB, or residual bone, respectively. The mean graft resorption was 0.43 mm (BCP) and 0.29 mm (DBB) [8].

The author performed a 3-year clinical follow-up [9]. The mean values for the area of newly formed bone in the retrieved specimens were 29% ± 14.3% and 32% ± 18.0% for BCP and DBB, respectively; the percentage of graft particles in contact with bone was 38% ± 10.9% in the BCP group and 44% ± 12.1% in the DBB group (no statistical significant differences between groups). The mean values for the area of BCP particles and DBB

particles were 20% ± 7.5% and 24% ± 13.5%, respectively (difference not significant). One dental implant was lost from each group, resulting in an overall implant survival rate of 96.8% after 3 years of loading [9].

Lindgren had previously [10] compared bone formation around microimplants with a synthetic biphasic calcium phosphate (BCP) or deproteinized bovine bone graft. Six women and five men with a mean age of 67 years (range, 50 to 79 years) requiring bilateral sinus augmentation were included in the study. After 8 months of graft healing, at the time of ordinary implant placement, all 22 microimplants were retrieved with a surrounding bone core for histologic analyses. The bone-to-implant contact in the BCP group was 64.6% +/- 9.0%, versus 55.0% +/- 16.0% for the DBB group. The difference was not significant. The corresponding values for the area of newly formed bone in the biopsies were 41.1% +/- 9.8% and 41.6% +/- 14.0% for BCP and DBB, respectively. There were significantly more DBB particles in contact with newly formed bone than BCP particles (87.9 +/- 18.2% versus 53.9 +/- 26.1%; Wilcoxon rank sum test; P = .007) [10].

Mordenfeld *et al.* [11] compared survival rates and marginal bone loss of Straumann SLActive implants placed in either BCP (Straumann® BoneCeramic™) or Bio-Oss® (DBB) (control) after sinus floor augmentation. Eleven patients (mean age 67 years) received 100% BCP on one side and 100% DBB on the contralateral side. After 8 months of graft healing, implants were placed. After 5 years of functional loading (6 years after augmentation) of implants, marginal bone levels and grafted sinus height were measured, and implant survival and success rates were calculated. After 5 years, all prosthetic constructions were in function (although two implants were lost in each grafting material). The overall implant survival rate was 93.5% (91.7% for BCP, 91.3% for DBB, and 100% for residual bone). The success rates were 83.3% and 91.3% for BCP and DBB, respectively. There was no statistically significant difference in mean marginal bone level after 5 years between BCP (1.4 ± 1.2 mm) and DBB (1.0 ± 0.7 mm). Graft height reduction (GHR) after 6 years was limited to 6.6% for BCP and 5.8% for DBB [11].

One hundred thirty-seven patients were randomized to one of three treatment groups to evaluate the efficacy of biphasic calcium phosphate (BCP) ceramic in the treatment of periodontal osseous defects. This material was tested against both autogenous bone implant and open flap curettage procedures. Baseline probing attachment level, Navy plaque index, and gingival index were recorded for all patients. These parameters were monitored for 3 years. At the end of this period, 101 patients had completed the study. Although the plaque and gingival indices steadily increased with time, there were no statistically significant differences among the treatment groups. Patients in the ceramic group had a gain in attachment level of 1.0 mm; those in the curettage group, 0.9 mm; and 0.4 mm for those in the bone implant group [12].

Ozalay *et al.* [13] reported a study where evaluated the bone healing and remodeling potential of biphasic calcium phosphate granules.

Between January 2004 and June 2006, fifteen patients (15 knees) with medial unicompartmental knee osteoarthritis and a varus knee axis, underwent biplanar open wedge high tibial osteotomy. Bone gaps were filled with BCP granules. Inclusion criteria were patients aged 50 years or older who had a stable knee with medial joint pain without extension contracture. The mean age was 55.8 years (range 50–60 years).

BCP granules used in the study, were synthetic ceramic bone substitutes which consist of 40% β-TCP and 60% HA with a total porosity of 80 10% and pore sizes ranging from 400 to 600 µm (macro porosity) and 100 to 150 µm (micro porosity).

The mean follow-up was 27.2 months (range 24–42 months). Radiographs were made preoperatively; immediately after surgery; 6 weeks, 3, 6, and 12 months postoperatively; and then annually thereafter. None of the patients had diseases that affected bone healing, and none were regular tobacco smokers at the time of operation.

There were no intraoperative or immediate postoperative complications. At clinical follow-up, there were no wound healing problems, no loss of corrections, and no infections. All patients were able to walk with full weight-bearing as tolerated after 6 weeks postoperatively regardless of their radiologic grades. All osteotomies successfully healed; there were no nonunions and radiographic union was noted to progress from lateral to medial and finally central for all patients.

The author concluded that BCP granules can be successfully used as a bone substitute in pen wedge high tibial osteotomy. The radiographic remodeling and consolidation process of BCP was found to be different from that of b-TCP. The patients in this study with >2 years of follow-up showed that BCP granules did not completely remodel. As a result, this clinical study demonstrated that calcium phosphate granules containing HA had a long period of “creeping substitution” that lasts longer than 2 years [13].

Rouvillain *et al.* [14] reported clinical, radiological and histological findings following high tibial valgisation osteotomy (HTVO) using micro–macroporous biphasic calcium phosphate wedges fixed with a plate and locking screws.

The wedges were parallelogram in shape, measuring 3×3 cm with a thickness of 8–12 mm, corresponding to angles of 8–12°. The wedges were made of micro- and macroporous biphasic calcium phosphate with a 60/40 hydroxyapatite/β-tricalcium phosphate weight ratio. The total micro- and macroporosity were approximately 70%, with 300–600 µm macropores making up 50% of the porosity, 10–300 µm mesopores making up 30%, and micropores of less than 10 µm making up the remaining 20%.

From 1999 to 2002, 42 consecutive patients (13 female, 29 male) were operated on and followed prospectively by two surgeons. There were 43 knees (25 right, 18 left). The patients had a mean age of 46 (range 14–69). The origin of the medial compartment disease was idiopathic in 37 cases, posttraumatic in four cases, and malformative (Blount Disease) in two cases.

All underwent clinical and radiological follow-up at days 1, 90, and 365 to evaluate consolidation and bone substitute interfaces. Additionally, biopsies were taken for histology at least 1 year after implantation from 10 patients who requested plate removal.

No superficial or deep infections occurred. Because of immediate postoperative physiotherapy, all patients recovered their preoperative knee mobility. Radiologically, consolidation was observed in 98% of cases. At 1 year, correction was unchanged in 95% of cases. Histological analysis revealed considerable MBCP resorption and bone ingrowth, both into the pores and replacing the bioceramic material. The new bone was essentially lamellar and its formation progressively increased the mechanical strength of the biomaterial. Polarised light microscopy confirmed normal bony architecture with trabecular and/or dense lamellar bone growth at the expense of the wedge implants. X-ray and micro-CT scan revealed a well organised and mineralised structure in the newly-formed bone.

The good results obtained in this study confirm the reliability of micro- and macroporous biphasic calcium phosphate bioceramics as a bone substitute. The physical and chemical characteristics of these biomaterials make it possible to use them to fill the gap created during HTVO with medial addition [14].

Rouvillan *et al.* [15] showed a human clinical and histological study of the use of micro- macroporous biphasic calcium phosphate wedges in combination with osteosynthesis with adjustable screws for open tibial osteotomy.

Forty-two patients were operated for open tibial osteotomy for valgisation due to incipient medial gonarthrosis. The population was composed of 43 knees (25 right knees and 18 left knees) in 13 women and 29 men, with a mean age of 46 years.

The biphasic calcium phosphate wedges (Biomatlante, France) were parallelepiped in shape (3 x 3 cm), with a thickness of 8 to 12 mm corresponding to correction angles of 8 to 12°. The wedges were made of micro and macroporous biphasic calcium phosphate with a 60/40 hydroxyapatite/β-tricalcium phosphate weight ratio. The total micro and macroporosity was 70 %. The size of the wedges used was 6 mm in 4 cases, 8 mm in 19 cases, 10 mm in 10 cases and 12 mm in 10 cases (Figure 9).

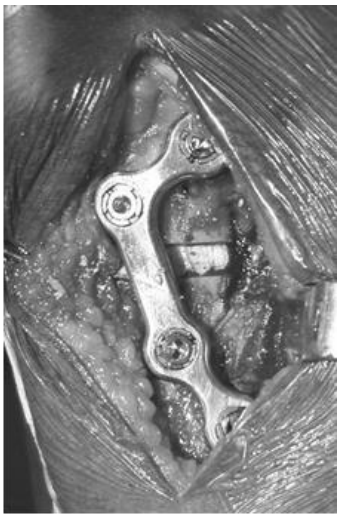


Figure 9 - Example of MBCP wedges of 10mm [15].

Radiological follow-up at D+1, D+90 and D+360 were realized and healing was determined on the basis of the filling of the metaphyseal medial space, appearance of peripheral cortical bridges and osteointegration without radiolucent interface between the host bone and bone substitute.

Consolidation was achieved in 100 % of the cases. The histological analysis confirmed the formation of a new cortical, integrating in places non-resorbed fragments of MBCP. At D+90, all the X-rays showed heterogenous boundary at the level of the bone/substitute interfaces. At D+360, there was no boundary at the level of the substitute/bone interface in 21 cases (87.5 %). At D+360, of the 48 interfaces studied (2 per knee), no boundary was observed in 92 % of cases. However, the wedges remained constantly visible and clearly identifiable at D+360.

The good results obtained in this study confirm the reliability of biphasic ceramics as bone substitutes. The consolidation and fusion rates are high: 100 % fusion in the lumbar arthrodeses using blocks of biphasic ceramic.

The histological observations revealed that even after 18 months there were residual granules measuring a few hundred microns in diameter in the newly-formed bone, resulting in greater mineral density in the implanted area and explaining on the one hand the diffuse interface between the bone edges and the filled area.

The authors concluded in this study that, a clinical, radiological and histological result of biphasic calcium phosphates appears to a good potential to apply these materials in the surgery [15].

The clinical and histological characteristics after sinus floor augmentation with biphasic calcium phosphate (BCP, Straumann BoneCeramic®), anorganic bovine bone (ABB, Geistlich Bio-Oss®), mineralized cancellous bone allograft (MCBA, Zimmer Puros®), and autologous bone (AB) were compared by Schmitt *et al.* [16]. Thirty patients (17 women and 13 men) aged 38–79 years, with a posterior edentulous maxillary situation and a vertical bone height less than or equal to 4 mm were enrolled in this study. 45 sinus met the inclusion criteria and were planned for maxillary sinus augmentation and the insertion of a total number of 94 dental implants. A two-stage procedure was carried out. After augmentation of the maxillary sinus with ABB, BCP, MCBA, or AB followed by a healing period of 5 months, biopsies were taken with simultaneous implant placement. The samples were analyzed using microradiography and histology.

Direct contact occurred between the substitutes and the superimposed newly formed bone in the BCP and ABB groups [Figure 10].

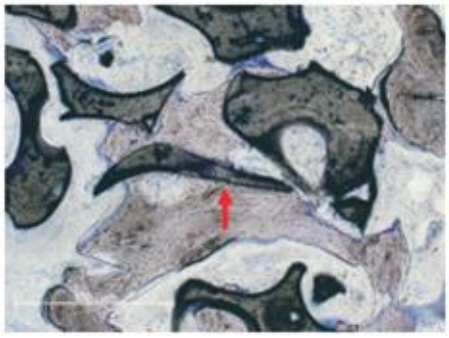


Figure 10 - Histology of the grafted area of a biphasic calcium phosphate (BoneCeramic®) implant. The arrow indicates the close contact of the newly formed bone with the bone substitute [16].

Primary stability of the implants was achieved in all cases independent of the used bone substitute. The amount of newly formed bone in the cranial portion was highest in the AB group (42.74 ± 2.10%), closely followed by the MCBA group (35.41 ± 2.78%). Significant differences were detected when the ABB group (24.90 ± 5.67%) was compared with the MCBA and the AB groups. The BCP group (30.28 ± 2.16%) exhibited a moderate amount of newly formed bone with a significant difference to the AB group. The ABB group had a significant higher amount of remaining bone substitute material in the augmented area (21.36 ± 4.83%) than the BCP group (15.82 ± 2.08%).

In conclusion, the authors referred that BCP, ABB, MCBA, and AB are suitable for the augmentation of the maxillary sinus. Although AB transplant can still be considered the gold standard in maxillary sinus augmentation with regard to newly formed bone in the region of interest, BCP, ABB, MCBA were approximately equally effective, with less patient morbidity than AB [16].

In 2014, Yoon and his colleagues [17] retrospectively evaluate the clinical survival rate of dental implants in the maxillary molar region performed with sinus lift and bone graft. The 44 patients (34 males and 10 females, average age of 52.6) were recruited at the Department of Oral and Maxillofacial Surgery at Chousun University Dental Hospital from September 2009 to February 2012 for this study. A total of 99 implants were placed.

For sinus augmentation material Yoon and his team used allografts, Tutoplast® (Tutogen Medical GmbH, NeunKirchen, Germany) and Allo-oss®(CG-Bio, Seongnam, Korea); Xenograft as Bio-Oss®(Geistlich Pharma AG, Wolhusen, Switzerland); Synthetic bone graft Osteon®(Genoss, Suwon, Korea), and autogenous tooth.

Sinus lift with bone graft was performed via the crestal approach (31 implants, 31.3%) and Lateral approach (68 implants, 68.7%). Yoon and his team achieve a 90.9% survival rate with dental implants. Yoon and his team concluded that the survival rate was not related with the bone graft material but related with patients with low residual alveolar bone height [17].

12. Clinical Evidences

	Adbone®BCP	**Ceraform®** [1]	**BICalPhos®** [13]	**Triosite®** [2]
Technical	Composition: Hydroxyapatite (75 ± 10%) and B-Tricalcium phosphate (25 ± 10% β-TCP)	Composition: Hydroxyapatite (65%) and B-Tricalcium phosphate (35% β-TCP)	Composition: Hydroxyapatite (60%) and B-Tricalcium phosphate (40% β-TCP)	Composition: Hydroxyapatite (60%) and B-Tricalcium phosphate (40% β-TCP)
	Porosity: 40- 90%	Porosity: 60 - 85%	Porosity: 80 ± 10%	Porosity: 60 - 70%
	Resorption time: 6 – 36 months	Resorption time: around 3 - 24 months	Resorption time: around 24 months	Resorption time: around 5-36 months
Biological	Sterilization: Ionizing radiation	Sterilization: Ionizing radiation	Sterilization: Ionizing radiation	Sterilization: Ionizing radiation
	Processing: adbone®BCP bone graft is provided within a vial/pouch or a pouch/blister. The bone graft substitute can be mixed with blood, PRP, Bone Marrow aspirate and serum.	Processing: Ceraform® granules are provided inside a vial that comes within a hard blister. No information was obtained as to how the sticks, block and wedge are processed. The bone substitutes can be mixed with blood and bone marrow aspirate	Processing: BICalPhos® granules are provided inside a vial that comes within a hard blister, the shapes come inside a pouch within a blister. The bone substitute can be mixed with blood or autologous bone graft.	Processing: Triosite®granules are provided inside a vial. No information was obtained as to how the sticks, cones, wedge and disks are processed.
Clinical	Administration: granules, blocks, sticks, wedges, cylinders	Administration: Granules, Sticks, block, wedge.	Administration: Granules, Blocks, cylinders	Administration: Granules, Sticks, Cones, Wedges, Disks

	Adbone®BCP	Ceraform® [1]	BICalPhos® [13]	Triosite® [2]
	Area: Dental and Orthopedic applications	Area: Orthopedic applications	Area: Dental and Orthopedic applications	Area: Orthopedic applications
	Indications: adbone®BCP is a porous synthetic ceramic designed for the filling of voids or defects of the skeletal system, that are not intrinsic to the stability of the bony structure.	Indications: Indicated only for bony voids or defects/gaps that are not intrinsic to the stability of the bony structure	Indications: Indicated only for bony voids or defects/gaps that are not intrinsic to the stability of the bony structure	Indications: Indicated only for bony voids or defects/gaps that are not intrinsic to the stability of the bony structure
	Negative effects: the product has been in use for 5 years. No negative effects has been reported	Negative effects: the company has more than 20 years of field experience	Negative effects: No negative effects has been reported	Negative effects: No negative effects has been reported

	Adbone®BCP	MBCP® [6,15,16]	Straumann®Boneceramic® [3,4,17]	Osteon® [5,20]
Technical	Composition: Hydroxyapatite (75 ± 10%) and B-Tricalcium phosphate (25 ± 10% β-TCP)	Composition: Hydroxyapatite (60%) and B-Tricalcium phosphate (40% β-TCP)	Composition: Hydroxyapatite (60%) and B-Tricalcium phosphate (40% β-TCP)	Composition: Hydroxyapatite (70%) and B-Tricalcium phosphate (30% β-TCP)
	Porosity: 40- 90%	Porosity: 70%	Porosity: 90%	Porosity: 77%
	Resorption time: 6 – 36 months	Resorption time: minimum 18 months	Resorption time: minimum 9 months	Resorption time: minimum 6 months
Biological	Sterilization: Ionizing radiation	Sterilization: Ionizing radiation	Sterilization: Ionizing radiation	Sterilization: Ionizing radiation
	Processing: adbone®BCP bone graft is provided within a vial/pouch or a pouch/blister. The bone graft substitute can be mixed with blood, PRP, Bone Marrow aspirate and serum.	Processing: MBCP ceramic is provided inside a vial or blister. The bone graft substitute can be mixed with blood, autologous bone and serum.	Processing: Straumann®bone ceramic is provided inside a blister The bone graft substitute can be mixed with blood, autologous bone and serum.	Processing: Osteon®bone graft is provided inside a vial. The bone graft substitute can be mixed with blood, autologous bone and serum.
Clinical	Administration: granules, blocks, sticks, wedges, cylinders	Administration: granules, sticks, blocks, wedges	Administration: granules	Administration: granules
	Area: Dental and Orthopedic applications	Area: Dental and Orthopedics	Area: Dental applications	Area: Orthopedic and Dental applications

	Adbone®BCP	MBCP® [6,15,16]	Straumann®Boneceramic® [3,4,17]	Osteon® [5,20]
	Indications: adbone®BCP is a porous synthetic ceramic designed for the filling of voids or defects of the skeletal system, that are not intrinsic to the stability of the bony structure.	Indications: Indicated only for bony voids or defects/gaps that are not intrinsic to the stability of the bony structure	Indications: Indicated only for bony voids or defects/gaps that are not intrinsic to the stability of the bony structure	Indications: Indicated only for bony voids or defects/gaps that are not intrinsic to the stability of the bony structure
	Negative effects: the product has been in use for 5 years. No negative effects has been reported	Negative effects: more than 30 years of clinical background	Negative effects: No negative effects has been reported	Negative effects: No negative effects has been reported

13. Clinical Equivalence Analysis

	Future State	Current Situation	Proposals
Technical Equivalence	Composition: Hydroxyapatite (75 ± 10%) and B-Tricalcium phosphate (25 ± 10% β-TCP)	The technique used to determine phase quantification is XRD. This technique has a margin error of 5% associated with the actual measurement. The phase composition in Ceraform®, BICalPhos®, MBCP®, Triosite®, BCP®Straumann and Osteon® were all determined by XRD, so a 5% margin error is also applied to this measurement. Besides the error margin in the actual analyses equipment, Medbone considered an additional 5% margin in the phase quantification for adbone®BCP, so in fact, the real composition for adbone®BCP has an error margin of ± 10%. No other information regarding error margins were provided for the other products so we will only consider the equipment error margin of 5% for the other products.	The equivalence in composition is confirmed

		Based on this information, the phase composition for the following products is: adbone®BCP:65-85% HAP /15-35% TCP Ceraform: 60-70% HAP / 30-40% TCP BICalPhos®: 55-65% HAP / 35-45% TCP Triosite®:55-65% HAP / 35-45% TCP MBCP®: 55-65% HAP / 35-45% TCP BCP®Straumann: 55-65% HAP / 35-45% TCP Osteon: 65-75% HAP / 25-35% TCP	
	Porosity: 40- 90%	adbone®BCP porosity is equivalent to BICalPhos®, MBCP®, BCP®Straumann, Osteon, Ceraform®, Triosite®.	The equivalence in porosity is confirmed
	Resorption time: 6-36 months	adbone®BCP is equivalent in resorption to Ceraform®, BICalPhos®, MBCP®, Triosite®, BCP®Straumann and Osteon®.	Equivalence confirmed
Biological Equivalence	Sterilization: Ionizing radiation	adbone®BCP is equivalent in sterilization to Ceraform®, BICalPhos®, MBCP®, Triosite®, BCP®Straumann and Osteon®.	Equivalence confirmed
	Processing: adbone®BCP bone graft is provided within a vial/pouch or a pouch/blister. The bone graft substitute can be mixed with blood, PRP, Bone Marrow aspirate and serum.	adbone®BCP is equivalent in processing to Ceraform®, BICalPhos®, MBCP®, BCP®Straumann, Triosite®(vials) and Osteon®. No information is available regarding Triosite®(shapes)	Equivalence confirmed
Clinical Equivalence	Administration: Granules, Crunch, Blocks, Sticks, Wedges and Cylinders	adbone®BCP is equivalent in administration to Ceraform®, BICalPhos®, MBCP®, Triosite®, BCP®Straumann and Osteon®.	Equivalence confirmed
	Area: Dental and Orthopedic applications	adbone®BCP is equivalent to BICalPhos®, MBCP®, BCP®Straumann and Osteon® in the dental area and to Ceraform®, BICalPhos®, MBCP®, Triosite®, and Osteon® in the Orthopeadic area.	Equivalence confirmed

	Indications: adbone®BCP is a porous synthetic ceramic designed for the filling of voids or defects of the skeletal system, that are not intrinsic to the stability of the bony structure.	adbone®BCP is equivalent to Ceraform®, BICalPhos®, MBCP®, Triosite®, BCP®Straumann and Osteon®.	Equivalence confirmed
	Negative effects: the product has been in use for 5 years. No negative effects have been reported	adbone®BCP is equivalent to Ceraform®, BICalPhos®, MBCP®, Triosite®, BCP®Straumann and Osteon®.	Equivalence confirmed

14. Conclusion

Based on the reported studies, we may conclude that synthetic porous bone substitutes are a useful addition or substitution of autogenous grafts in trauma and orthopedic surgery, with very encouraging results for more than 20 years. The synthetic bone substitute appears to be as safe and as effective as autograft when used in trauma situations. Authors of these studies have confirmed that safety and less morbidity makes the bone substitutes effective when compared with other bone grafts.

No negative effects were reported in the clinical investigations nor in the 5-year period that adbone®BCP has been in the market. The life time of the device is not a precise time since it is highly dependent upon the geometry and size of the bone substitute, the age and physical conditions of the patient, but reported articles refer to the total resorption occurring in a period of 6 – 36 months.

The β-tricalcium phosphate is highly bioactive and undergoes total or partial resorption whereas the hydroxyapatite has a slow resorption rate. Since the β-tricalcium phosphate is more soluble than the hydroxyapatite, this biphasic composition enhances the ceramic resorption, allowing an optimal resorption rate compatible with the physiology of the bone cells.

Due to vast range of published articles of clinical investigations, revealing advantages in the use of porous biphasic hydroxyapatite and beta tricalcium bone substitutes, with identical biological, physical and clinical properties of adbone®BCP, clinical investigation using adbone®BCP will not be performed.

The product family adbone®BCP is a safe device and the performance of the device encourages the use of synthetic bone substitutes for bone reconstruction and repair.

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