# A Novel Platform of Demineralized Bone Matrix Products: TruForm and TruForm+

## BACKGROUND

A primary objective when augmenting or reconstructing bone during craniomaxillofacial procedures is to restore the form and function of the skeletal anatomy. Given the compatibility and general availability, autologous bone has historically been considered the "gold standard" for graft materials. However, due to the rate of resorption, challenges with contouring, and donor site morbidity, allograft materials have become a significant surgical tool.[1]

Demineralized Bone Matrix (DBM) represents an alternative option to autologous bone that consists of processed allogeneic bone tissue. The inorganic mineral components are removed and the extracted, organic, collagenous matrix remains. Along with the matrix, inherent proteins and/or growth factors found in native bone are retained in the final product. These proteinaceous growth factors, including but not limited to Bone Morphogenetic Proteins (BMPs), have been shown to be critical components to the production of de novo bone; ie, osteoinduction.[2]

As the demand for DBMs has become increasingly widespread for multiple therapeutic applications in the orthopaedic setting, numerous DBM-based products have become available. These products vary by tissue source, procurement techniques, manufacturing processes and additive carriers/compounds. Because numerous variables determine the eventual composition, the biological properties and subsequent performance of the material will vary.

TruForm and TruForm+ are DBM putty products manufactured by Hans Biomed Co. Ltd. (Seoul, Korea) and distributed by Stryker Craniomaxillofacial (Kalamazoo, MI, USA). Both consist of particles derived from human demineralized cortical bone, while TruForm+ also contains demineralized cancellous bone particles. Approved clinical indications of the TruForm platform include the use as a bone void filler in a wide range of orthopedic and spinal procedures[3]; namely, the reconstruction and augmentation of oral and maxillofacial defects [4].

## PRODUCT OVERVIEW

### *Truform and Truform+*

Hans Biomed Co. Ltd is the only American Association of Tissue Banks (AATB) and US Food and Drug Administration (FDA) accredited tissue bank outside of the United States. Human allograft tissue is considered an HCT/P (human cells, tissues, and cellular and tissue based product), but the TruForm and TruForm+ demineralized bone products are also classified by the FDA as a 510(k) cleared medical device due to the presence of a carboxymethyl cellulose (CMC) carrier. The carrier mixes with the bone powder to form a "putty" and is delivered through a single use syringe of various volumes.

All tissue is obtained from donors found in the United States prior to processing outside of the country. Prior to donation of tissue, the donor's medical and social conditions are screened for conditions and disease that would contraindicate the tissue donation according to standards established by the AATB. Next, samples are collected and screened for aerobic, anaerobic and fungal contaminants. Finally, serological screening is conducted to eliminate samples testing positive for human immunodeficiency virus (HIV type-1 and type-2), Hepatitis B and C and syphilis.

The screened and cleared samples are processed through multiple rounds of physical and chemical steps which consist of soft tissue removal, milling, dehydration, decalcification, and lyophilization. The bone particles are then sorted by size, mixed with the carrier agent, packaged and sterilized via electron beam (E-beam) irradiation. A radiation dose of 15 kGy is used and has been validated according to ISO standards (ISO 11137-2) to meet the Sterility Assurance Level (SAL) of 10-6. TruForm and TruForm+ are packaged in a sterile, single-use injectable syringe. Product storage is at room temperature (1-30°C) for up to 2 years and does not require refrigeration or freezing; allowing already limited inventory space to be saved at the health care facility. [5]

## PRODUCT FEATURES

### *Demineralized Bone and Bone Morphogenetic Protein (BMPs)*

The concept of osteoinduction, or the recruitment and differentiation of cells to form new bone, was introduced in 1971 and largely attributed to bone morphogenetic proteins (BMPs).[2] Osteoconduction is the ability of a surface or material to allow new bone formation. An ideal bone graft should be both osteoinductive and osteoconductive in order to generate the greatest effect toward the production of de novo bone. Because of the

presence of native growth factors such as BMPs and the conductive nature of native bone tissue, DBMs provide a viable graft material.[3]

In an in vitro analysis using enzyme-linked immonsorbant assay (ELISA), triplicate samples from 10 donors of TruForm and TruForm+ were screened for BMP-2 content. A minimum BMP-2 level of 41.18 and 42.48 ng/cc were seen in the products respectively, and the maximum levels of the samples tested were 132.80 ng/cc and 123.50 ng/cc for each (**Table 1**).[6]

| **TruForm** | | | **TruForm+** | | |
|---|---|---|---|---|---|
| **Batch No.** | BMP-2 (ng/cc) | SD | **Batch No.** | BMP-2 (ng/cc) | SD |
| **M09001** | 61.64 | 0.80 | **Q09001** | 47.26 | 1.59 |
| **M09002** | 77.17 | 3.34 | **Q09002** | 51.17 | 0.92 |
| **M09003** | 86.60 | 1.12 | **Q09003** | 74.62 | 1.66 |
| **M09004** | 132.80 | 3.96 | **Q09004** | 123.50 | 4.39 |
| **M09005** | 77.85 | 1.16 | **Q09005** | 53.37 | 1.22 |
| **M09006** | 90.02 | 3.99 | **Q09006** | 94.54 | 2.80 |
| **M09007** | 86.37 | 2.51 | **Q09007** | 62.67 | 2.43 |
| **M09008** | 41.18 | 0.82 | **Q09008** | 44.87 | 1.59 |
| **M09009** | 40.62 | 1.66 | **Q09009** | 42.48 | 2.11 |
| **M09010** | 47.01 | 2.01 | **Q09010** | 42.74 | 2.01 |

**Table 1**: **BMP-2 levels of TruForm and Truform+ as determined by ELISA.**

As shown in **Table 2**, the average particle size of the cortical DBM powder (TruForm) is 291µm (±8.75µm). When combined in an 18:12 ratio with the cancellous bone powder (TruForm+), the average particle size is 300.15µm (±5.38µm). The porosity of the cortical and cancellous powder components are 37.89% and 40.67% respectively; allowing cellular infiltration and boney tissue remodeling.

| **Particle Size (µm)** | | | | |
|---|---|---|---|---|
| | Avg. | sd | Min | Max |
| **TruForm** | 291.00 | 8.75 | 141.84 | 481.45 |
| **TruForm+** | 300.15 | 5.38 | 150.58 | 505.55 |

**Table 2**: **Particle size of TruForm and TruForm+.**

The osteoinductive and osteoconductive effects of the TruForm and TruForm+ products have been demonstrated in a 9 week old, athymic rat model. Heterotopic intramuscular sites were created for DBM implantation over a four to five week period **(Figure 1)**. As demonstrated by **Figure 2**, new bone formation and osteoblast infiltration can be seen surround the matrix material.[6]

**Figure 1: Athymic rat model for osteoinduction.**

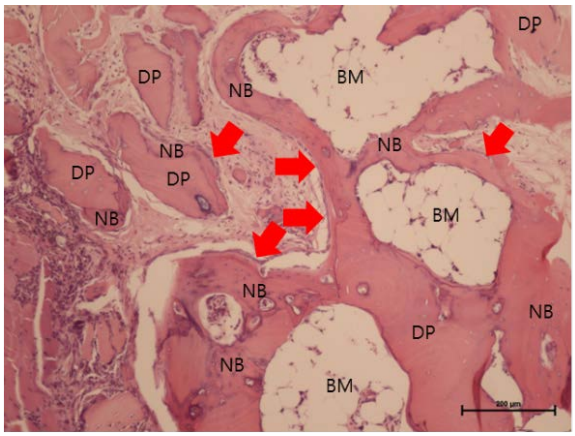


**Figure 2: Five week hematoxylin and eosin (HE) stain demonstrating new bone (NB) and osteoblast infiltration (red arrows) surrounding the DBM powder (DP).**

***Carboxymethyl Cellulose (CMC) Carrier***

TruForm and TruForm+ contain a carboxymethyl cellulose (CMC) carrier which has a number of unique characteristics. CMC is a semi-synthetic, anionic water-soluble polymer derived from cellulose. It dissolves rapidly in water, is physiologically inert, and acts as a water binder, thickener and suspending or rheology agent.[7] CMC is available in standard, food and pharmaceutical grades. It has also been used alone in vivo, or with other polymers in vitro, as a matrix for the delivery of osteoinductive proteins.[3] This biodegradable polymer increases the viscosity and cohesiveness of the delivery vehicle and can modify the release kinetics of certain drugs by acting as a diffusion barrier.[9]

The addition of the binding agent CMC does not adversely affect the healing capability or regenerative effects of implants containing bone morphogenetic proteins (BMPs). CMC putty has been shown to be equivalent to standard collagen carrier treatments radiologically, mechanically and histologically after four months of bone healing.[7] Also, the handling characteristics are thought to be superior to those of a standard collagen carrier. The putty implants are easier to mold, tend to adhere to itself rather than to instruments or surgeon's gloves, and remain in the defect more readily than a collagen carrier.[7] Purified CMC has also been shown to have no systemic toxic

properties with subacute and chronic oral administration in multiple in vivo models, including humans.[7]

## CLINICAL APPLICATION[6]

### *Case 1: Alveolar Ridge Augmentation*

In an example of ridge augmentation, the patient was complaining of pain when wearing their lower dentures **(Figure 3)**. The pre-operative radiographs display bone resorption which caused a loosening of the dentures **(Figure 4)**. The treatment plan consisted of multiple dental implants after reconstruction with TruForm. New bone is well formed around the implants as seen in **Figure 5**.

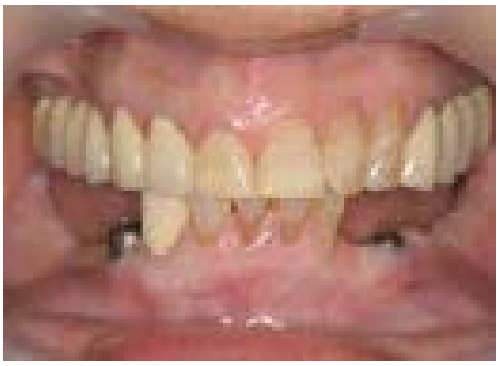

**Figure 3**: **Pre-operative photograph prior to ridge augmentation.**

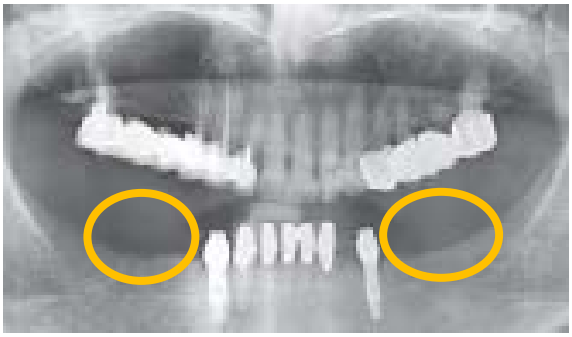

**Figure 4**: **Pre-operative radiograph prior to ridge augmentation.**

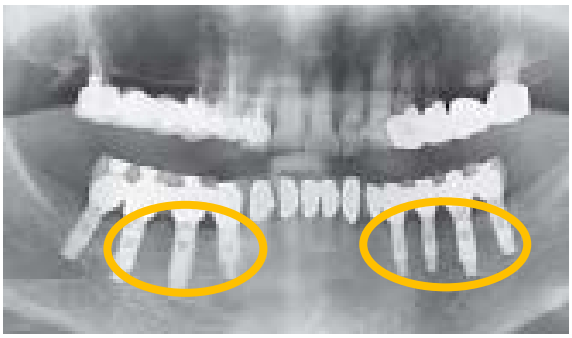

**Figure 5**: **Post-operative radiograph after ridge augmentation with TruForm and placement of multiple dental implants.**

### *Case 2: Sinus Lift*

In an example of sinus elevation, new bone is added in the molar region of the maxilla to allow space between the sinuses and jaw for dental implants. Figure 6 shows the pre-operative state and **Figure 7** demonstrates dental implantation with well-formed bone after treatment with TruForm+.

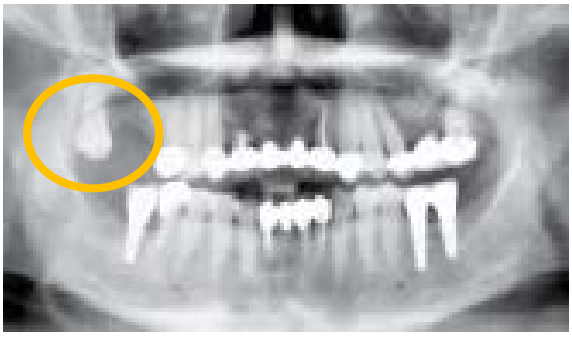

**Figure 6**: **Pre-operative radiograph prior to sinus lift.**

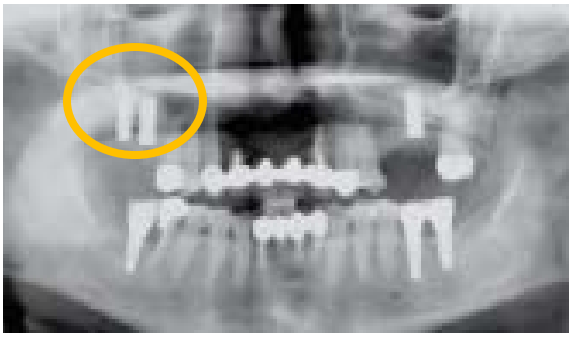

**Figure 7**: **Post-operative readiograph after sinus lift procedure with TruForm+ and placement of multiple dental implants.**

## DISCUSSION

TruForm and TruForm+ are a novel DBM platform for the use in the reconstruction and augmentation of the oral and maxillofacial setting. Their osteoinductive and osteoconductive properties represent critical factors in demonstrating their value as a bone grafting material. Due to the unique carrier blend with CMC, these bone putty products display excellent handling characteristics and minimal washout in situ. Based on the pre-clinical validations and clinical usage shown, TruForm and TruForm+ may offer a safe and effective option for dental and maxillofacial procedures.

## References

TruForm IFU
Case reference- Internal Document on File Hans Biomed


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