FORTIGEN™-P BONE GRAFT

Surface-Modified Veterinary Bone Graft

✓ Engineered to Compete with BMP-2

Powerful, localized bone healing

✓ Augmented Osteoinductive Healing

Surface modifications to enhance intrinsic bone growth factor action

✓ Osteoconductive

Nature's perfect scaffold

✓ The Future of Bone Grafting

Suitable for use wherever bone graft is needed

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PROGENICA THERAPEUTICS

MF#SB2018-1021(0)-N

CLINICAL PERFORMANCE OF SURFACE MODIFIED ALLOGRAFT MATRIX WITH rhBMP-LIKE OSTEOINDUCTIVITY

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BACKGROUND

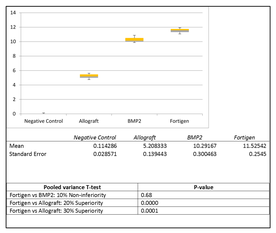
Utilizing grafts engineered with enhanced osteoinductive (OI) features is an integral part of orthopedic surgery. Infuse® and, the veterinary version, Truscient®, are a commercially available example of such a product. The product contains recombinant human Bone Morphogenic Protein-2 (rhBMP-2) that is applied to a bovine collagen and placed at the surgical site leading to a dramatic increase in bone formation. However, the rhBMP-2 is not bound to the collagen scaffold and can migrate away from the implantation site resulting in extra-skeletal bone growth and dangerous side effects including inflammation, swelling, and radiculopathy.

Natural bone allograft contains many growth factors, including rhBMP-2, that will not migrate but the growth factors exist at a relatively lower concentration. This means healing is less robust when compared to Infuse/Truscient however, allograft does not come with the cost or significant complications of extra-skeletal bone formation or the serious side effects attendant with rhBMP-2.

This study evaluates a novel approach to solving the problem of delivering a graft with enhanced OI by using a bone allograft that has been surface treated with osteoinductive growth factors. These factors are bound to the graft surface and remain in the site, thereby generating an enhanced localized healing response and avoiding the adverse effects caused by migration of growth factors away from the site. We refer to the most promising versions of our new product as FORTIGEN-P™.

IN VITRO METHODS

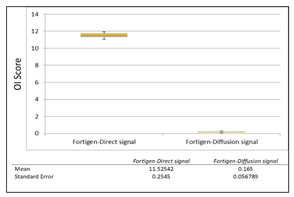
Osteoinductivity Testing: Osteoinductivity was measured using an Alkaline Phosphatase Assay (ALP) (Han et al., 2003). This *in vitro* ALP method is a validated model for assessment of OI. It is based on the ability of inductive agents to transform mesenchymal stem cells into osteoblasts. Controls included positive and negative conditions: a known positive reference lot of rhBMP-2 was used for positive controls; negative controls were cells only or inactivated human DBM without surface modifications (Figure 1). Cell viability studies were also conducted to determine if the modifications had any adverse impact on cell survival (data not shown). ALP activity was normalized to cell survival data. Important additional studies were done to show cellular response was localized to the particles and not due to signal diffusing from the modified particles (Figure 2). This is critical to show that the signal stays with the graft.



	Negative Control	Allograft	BMP2	Fortigen
Mean	0.114286	5.208333	10.29167	11.52542
Standard Error	0.028571	0.139443	0.300463	0.2545

Pooled variance T-test	P-value
Fortigen vs BMP2: 10% Non-inferiority	0.68
Fortigen vs Allograft: 20% Superiority	0.0000
Fortigen vs Allograft: 30% Superiority	0.0001

Figure 1



	Fortigen-Direct signal	Fortigen-Diffusion signal
Mean	11.52542	0.165
Standard Error	0.2545	0.056789

Figure 2

CLINICAL METHODS

Clinical Investigations: We further tested the clinical performance in a compassionate-use case series. The novel nature of the new graft material was explained to the owners and Informed Consents were signed. The cases included dental as well as orthopedic cases. The dental cases (13) included 10 sinus augmentations, 2 mandibular re-constructions, and 1 premaxilla re-construction. The orthopedic cases (25) included various pathological conditions: acute fracture (1); comminuted fracture (3); joint fusion (2); non-union (14); total hip revision (1); TPLO revision (3); and tumor (1). Most of the cases had several pre-operative risk factors (single or multiple factors) including old age, previous treatment failures, long lasting non-union, delayed treatment, infection, excessive wear debris, poor blood supply, and/or poor bone quality.

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IN VITRO RESULTS

Osteoinductivity Testing

Item	Details
Study objectives	To examine FORTIGEN-P's osteoinductivity (OI) in a standardized model
Endpoint	Alkaline phosphatase (ALP) produced by mesenchymal stem cells cultured on FORTIGEN-P's surface in serum free medium at 48 hours
Controls	Negative control: cells only (or inactivated human DBM) Positive control: rhBMP-2 in culture
Success definition	Osteoinductivity Score is not inferior to rhBMP-2 Score
Outcome	Success:
Conclusions	FORTIGEN-P has inductivity that is equivalent to rhBMP2

Osteoinductivity Assay: FORTIGEN-P™ had significantly higher OI when compared to the negative controls (p-values=0.000; n=3). The OI of FORTIGEN-P was similar to the OI of positive control cultures (p-value=0.102 at a non-inferiority margin of 15%; n=3). The data show that these surface modifications can result in substantial increases in standard markers of OI *in vitro* that is comparable to rhBMP-2.

CLINICAL RESULTS

Dental Cases

Item	Details	Notes
Study objectives	To evaluate the clinical performance in dental and cranio-maxillo-facial applications	Indications included sinus augmentation (10); pre-maxillary reconstruction (1); and mandibular reconstruction (4).
Endpoint	Healing time and safety	
Controls	Data were compared to rhBMP-2's historical data	
Success definition	Time to heal (TTH) is not inferior to rhBMP-2	
N	15	
Outcome	Success:	
Conclusions	FORTIGEN-P's TTH is equivalent to rhBMP-2 and no device-related events were reported	Average TTH was 10.3 ± 5.8 weeks

Dental Cases: Radiographic success was seen in all cases and no device-related adverse events were reported (*i.e.,* no hematoma, seroma or ectopic bone formation). The median time to radiographic healing was 8 weeks and the average time was 11.4 weeks ± 5.95 weeks. These outcomes are comparable to the historical data seen with rhBMP-2 in similar cases.

Orthopedic Cases

Item	Details	Notes
Study objectives	To examine clinical performance in various compassionate-use clinical orthopedic applications	The indications included acute fracture (1); comminuted fracture (3); joint fusion (2); non-union (14); total hip reversion (1); TPLO reversion (3); and tumor (1)
Endpoint	Healing time and safety	
Controls	Data were compared to rhBMP-2's historical data	
Success definition	Time-to-heal (TTH) is not inferior to rhBMP-2	
N	25	
Outcomes	Success	
Conclusions	FORTIGEN-P's TTH is equivalent to rhBMP-2 and no device-related events were reported	Average TTH was 11.3 ± 4.7 weeks

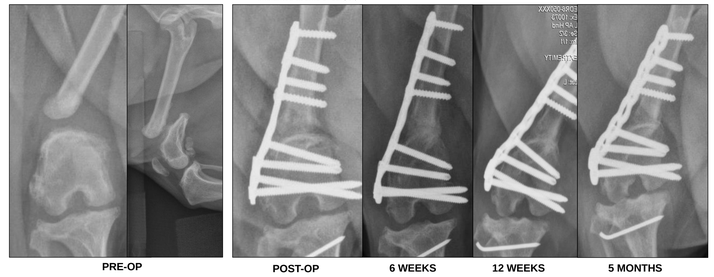
Orthopedic Cases: Success was seen in 20 of 25 cases. These cases were poor prognosis cases with multiple surgical procedures or extremely adverse initial conditions. Five failures (5/25) were seen due to one or more combinations of the following causes: inadequate dose (3); previous repeated failures (4); proven infection (1); lack of mechanical support; and excessive wear debris with granuloma (1). Radiographic data demonstrated new bone formation seen in the remaining 17 cases. The new bone formation was seen as early as 2 weeks post-operatively. The median time to radiographic healing was 12 weeks and the average time to heal was 10.6 weeks ± 4.6 weeks. These outcomes are comparable to the historical data seen with rhBMP-2 in similar cases) (Cory et al., 2012).

CASE STUDIES

NEGLECTED DISTAL FEMORAL FRACTURE REPAIR

"DAISY" 7yo FS Terrier
Dr. Sherry Appels– Veterinary Orthopedic & Surgery Service – Fremont, CA
Femoral fracture repair (neglected non-union)
Surgery: 6August2015

Two 0.5cc doses *FORTIGEN-P* implanted at time of surgery

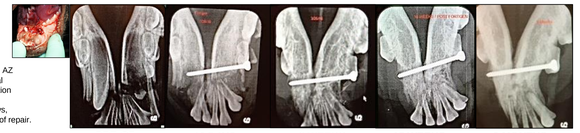


PRE-OP | POST-OP | 6 WEEKS | 12 WEEKS | 5 MONTHS

MANDIBULAR FRACTURE REPAIR

"MADISON" 6mo F-in Puggle
Dr. Rocco Mele / Eastpoint Pet Clinic / Tucson, AZ
Bilateral mandibular fx with separation of rostral segment (fight trauma); Mandibular reconstruction

FORTIGEN-P bone graft in alveoli and at 3 days, because pt returned with traumatic re-opening of repair.
Surgery: 13January2016



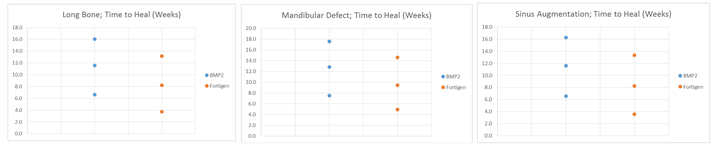
PRE-OP | **13 DAYS** | **9 WEEKS** | **15 WEEKS** | **9 MONTHS**

FORTIGEN consolidating in alveolus at Day 13 and the 10 Day FORTIGEN is filling in the fracture gap in the incisal bone and symphysis is remodeling. About 90% stability of the fragment at Day 13!

"No membrane, cement-like fixation. ROCK SOLID BONE!"

Very pleased with bone formation and outcome

FORTIGEN-P Time-to-Heal (TTH) data compared to rhBMP-2



- rhBMP-2's historical data were based on Cory B. et al.2012.
- We compared TTH data using Bayesian simulation approach
- Data is expressed as confidence of intervals
- The TTH for FORTIGEN-P is short and not inferior to BMP's healing time

FORTIGEN-P has superior safety profile compared to rhBMP-2

Adverse Event	FORTIGEN-P	rhBMP-2	Notes
Swelling	0.0%	35.6%*	
Heterotopic ossification	0.0%	11-21%**	Rates may vary depending on the surgical technique
Radiculitis	0.0%	5-20%***	Rates may vary depending on the surgical technique

* https://www.zoetis.de/products/seiten/truscient/clinical-evidence.aspx; ** http://www.medscape.com/viewarticle/807861_2; *** http://www.medscape.com/viewarticle/807861_2

CONCLUSIONS

- FORTIGEN-P inductivity is not inferior to rhBMP-2 *in vitro*.
- The surface modifications stay with the graft particles of FORTIGEN-P.
- FORTIGEN-P bone graft demonstrates clinically meaningful osteoinductivity.
- Healing times in patients treated with FORTIGEN-P were remarkably short and not inferior to rhBMP-2.
- FORTIGEN-P promoted robust healing in very challenging clinical scenarios including delayed union, non union, comminuted fractures, and large defects alone or in combination with allograft and/or autograft.
- FORTIGEN-P's *safety profile* is clinically attractive and superior to rhBMP-2 because it has no device-related events.

REFERENCES

Cory B. et al., CVJ. 2012 Jul, 53

Han B. et al., J Orthop Res. 2003 Jul;21(4):648-54

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