# An Evaluation of Scientific and Clinical Data Comparing Induce Biologics Natural Matrix Protein® (NMP®) Bioimplant to Medtronic rhBMP-2 INFUSE™ Bone Graft Bioimplant

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## Executive Summary

**The following is an evaluation of scientific and clinical data comparing Induce Biologics' Natural Matrix Protein Bioimplant (NMP) to Medtronic's rhBMP-2 INFUSE Bone Graft Bioimplant (INFUSE).**

### Non-clinical

- In vitro: NMP contains BMP-2, BMP-7, BMP-9, TGF-ß1, PDGF, VEGF, IGF-2 and releases growth factors over several weeks. INFUSE only contains BMP-2, most of which is released within a matter of hours.
- In vivo: Two studies by an independent contract research organization using the athymic rat muscle pouch model demonstrated that NMP was osteoinductive and formed more bone of better quality than INFUSE.
- NMP was shown to form more bone than INFUSE in the athymic rat spine fusion model by an independent investigator.

### Clinical

- NMP has been used in over 15,000 surgeries to date with excellent safety and efficacy outcomes.
- An independent clinical study evaluating NMP in anterior lumbar interbody fusion (ALIF) procedures reported 100% fusion by flexion/extension with improvements in pain and disability and no product-related adverse events. These results were equivalent to the reported outcomes for INFUSE when used in ALIF.

**This data showed that NMP bioimplants demonstrated high fusion rates and a favorable safety profile clinically in ALIF procedures, with outcomes comparable to those reported for INFUSE in ALIF procedures.**


## Introduction

The ability of a bone graft substitute to regenerate bone is dependent upon the presence of bioavailable growth factors to stimulate osteogenesis. Over the past 20 years, the Medtronic rhBMP-2 INFUSE Bone Graft bioimplant has become the gold standard graft for bone regeneration. Concerns about the cost of INFUSE, in addition to serious side effects associated with its use, have led scientists and clinicians alike to search for an affordable alternative with the same regenerative capability, but without the postoperative complications. Induce Biologics' NMP bioimplants, recently introduced to the market, have demonstrated the same regenerative qualities as INFUSE by enhancing the bioavailability of growth factors naturally found in allogenic bone.

## Scientific Rationale

Bone matrix contains a number of growth factors that promote bone regeneration including BMP-2, BMP-7, VEGF, IGF-2 and PDGF-BB[1] and these growth factors work synergistically to promote bone formation.[2] However, even after demineralization, these growth factors remain locked within the bone matrix.[3] The NMP process unlocks these growth factors to produce the NMP bioimplant resulting in their increased release into buffer (Figure 1).[4] In comparison, INFUSE contains only one growth factor, recombinantly produced BMP-2.

## Non-Clinical Evaluation

The NMP manufacturing process has been validated for product sterility. Bioassays have demonstrated that NMP contains BMP-2, BMP-7, BMP-9, TGF-ß1, PDGF, IGF-2 and VEGF and that the NMP process enhances their bioavailability[4] (see Figure 1).

NMP has also been evaluated for osteoinduction in two (2) non-clinical studies.[4,5] Both studies were performed at an independent laboratory (IBEX Preclinical Research, Logan

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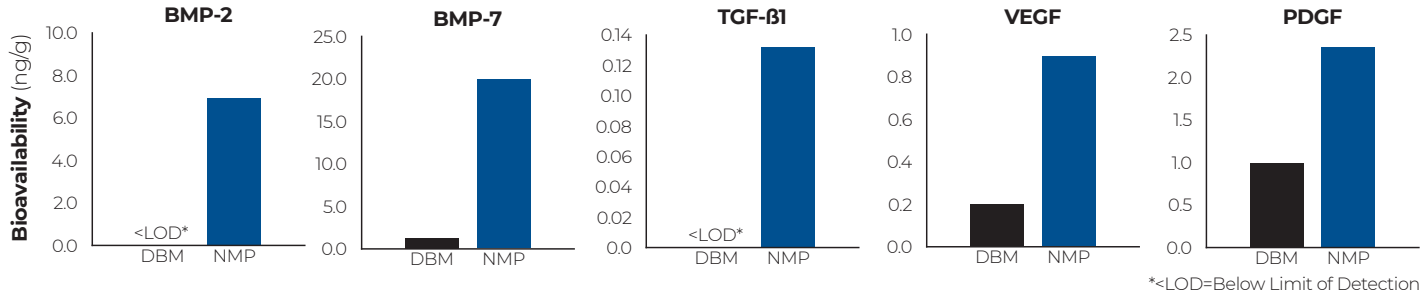
**Figure 1**
*NMP Growth Factor Bioavailability*




*<LOD=Below Limit of Detection

†*Data on File*

[a]Red Rock Regeneration Inc, Toronto, Canada [b]University of Toronto, Toronto, Canada
[c]The Spine Network [d]Spine Institute of Louisiana

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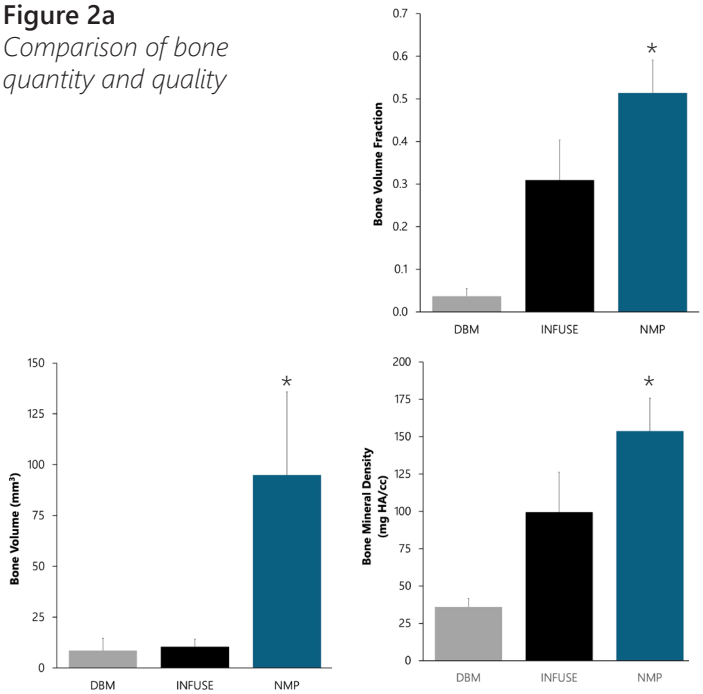
*(continued from pg 1)*

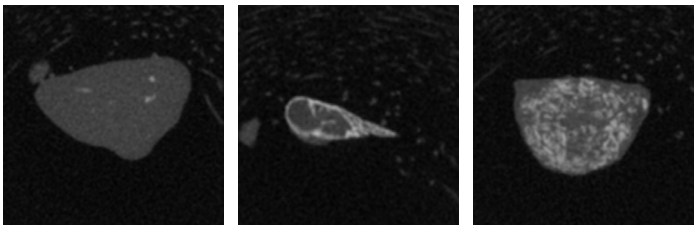
UT) and used the athymic rat muscle pouch model, the results of which are accepted by the FDA as evidence of a product's osteoinductive potential.[6] Bone formation was confirmed by histology and the quantity and quality was measured by microCT. The results of these animal studies demonstrated that NMP was consistently osteoinductive and produced more bone of a better quality than INFUSE, DBM or the other biologic products that were evaluated (Figure 2).[4,5]

**Figure 2a**
*Comparison of bone quantity and quality*




*Statistically significant, p<0.001

**Figure 2b**



DBM INFUSE NMP

Another study evaluated the performance of NMP and INFUSE in spine fusion in the athymic rat, which also demonstrated that NMP produced more bone than INFUSE.[7]

While INFUSE contained more BMP (105µg) than NMP (~10ng) in these animal studies, other studies have shown that cells respond to BMP in the ng/mL range,[8] work synergistically with other growth factors to stimulate bone formation[2] and that INFUSE loses approximately 80% of the BMP within 3 hours and >95% within 3 to 7 days[8,9], while NMP releases BMP over several weeks (Figure 3).[10] This is a potential explanation of why NMP produces more bone than INFUSE in these studies.

## Clinical Safety & Efficacy

NMP has been used clinically in over 15,000 surgeries to date, with no reports of product-related adverse events. Nunley et al. conducted an ambispective study in 50 ALIF patients who had received NMP fibers and reported 100% fusion by flexion/extension x-ray (<3-degree motion) [11]

In contrast, the use of INFUSE is associated with ectopic bone formation, profound inflammation, cyst-like voids in the newly formed bone, radiculopathy, retrograde ejaculation, and cancer.[12,13] Off-label use of INFUSE in the cervical spine was associated with dysphagia, hematoma, seroma, swelling and/or the need for intubation/tracheostomy.[14]

A comparison of the Nunley NMP study with historical 12-month data from the pivotal INFUSE ALIF study[15] is shown in Table 1. The subjects in the Nunley study were on average 18 years older, included a higher percentage of women and subjects who had diabetes, cancer, and were current smokers. All of these factors are known to negatively impact lumbar fusion outcomes.[16] Further, the study included 2-level fusions and fusions above L4-5. While the percentage of subjects with bridging bone by CT scan was higher in the INFUSE study, the NMP-treated subjects had fewer product-related adverse events and re-operations. Subjects in both studies reported clinically significant improvements in pain and disability.

Additional prospective clinical studies on NMP are underway, including a 200-patient evaluation of NMP in cervical and lumbar fusion, a 1,000 patient spine registry study, as well as an ambispective clinical evaluation of 100 lumbar fusion patients.

**Figure 3**
*Release of BMP from INFUSE and NMP*

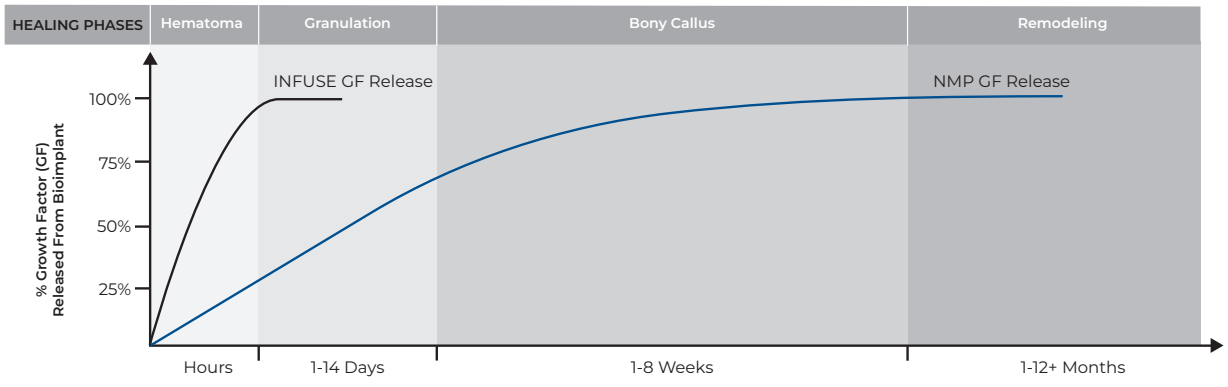


**Table 1: Comparison of Nunley (NMP) and Burkus (INFUSE) ALIF Studies**

| Parameter | INFUSE | NMP |
|---|---|---|
| N | 143 | 50 |
| Age (years) | 43.3 | 61.5 |
| % Male | 55.5 | 38.0 |
| % Female | 44.5 | 62.0 |
| BMI >40 | Excluded | 4% |
| Current Smoker | Excluded | 14% |
| Cancer | Excluded | 6% |
| Autoimmune | Excluded | 6% |
| Diabetic | N/A | 14% |
| OA | N/A | 26% |
| Respiratory Disease | N/A | 28% |
| 1-Level | 100% | 72% |
| 2-Level | 0 | 28% |
| L2-L3 | 0 | 7.8% |
| L3-L4 | 0 | 23.4% |
| L4-L5 | 25.9% | 37.5% |
| L5-S1 | 74.1% | 31.3% |
| Flexion/Extension <3° | N/A | 100% |
| CT Bridging Bone | 96.7% | 89.1% 3A<br>10.9% 2A |
| Length of Stay (days) | 3.1 | 2.3 |
| Second Surgery | 7.0% | None |
| Retrograde Ejaculation | 4.1% | None |

*N/A = Not Available*
*Data was taken from referenced publications and clinicaltrials.gov entries for each study.*

## Regulatory Status in the United States

NMP is regulated as minimally manipulated human tissue-based (HCT/P) products that meet the criteria for regulation solely under section 361 of the FDA Public Health Service (PHS) Act and 21 CFR part 1271.15. NMP is processed according to the FDA Current Good Tissue Practices (cGTPs), at a tissue bank registered with FDA and accredited by the American Association of Tissue Banks.[17]

INFUSE is regulated as a Class III device, the highest risk classification for medical devices.

## Indications for Use

NMP is intended for use as a bone void filler for filling voids and gaps in the skeletal system that are not intrinsic to the stability of the bony structure.[17]

NMP can be used to support bone formation where the stability of the bony structure is not compromised, wherever a bone void exists including any segment of the spine (cervical, thoracic lumbar and sacral) and at multiple levels, in long bones (tibia, femur, humerus, etc.), in the pelvis, and in foot and ankle repair.

In contrast, the use of INFUSE Bone Graft use is limited to:

INFUSE - Spinal Indications

The INFUSE Bone Graft/Medtronic Interbody Fusion Device is indicated for spinal fusion procedures in skeletally mature patients with degenerative disc disease (DDD) at one level from L2-S1, who may also have up to Grade I spondylolisthesis or Grade 1 retrolisthesis at the involved level. For this indication INFUSE must also be used with a Medtronic Interbody fusion device and must be used via an anterior lumbar interbody fusion (ALIF) or an oblique lateral interbody fusion (OLIF) approach.[18]

INFUSE - Tibial Trauma Indications

INFUSE Bone Graft is indicated for treating acute, open tibial shaft fractures that have been stabilized with IM nail fixation after appropriate wound management. INFUSE Bone Graft must be applied within 14 days after the initial fracture. Prospective patients should be skeletally mature.[18]

Use of INFUSE for any other indication in the spine, or without an appropriate additional device or by any other surgical approach would be off label. The FDA issued a public health warning of life-threatening complications associated with off-label use of INFUSE when used in the cervical spine.[19]

## Product Formats, Preparation Time & Handling

NMP Bioimplants are available in the following formats: NMP Fibers, NMP Micro Particulates and InduceXT. They can be rehydrated with whole blood, bone marrow aspirate (BMA), Lactated Ringers, normal saline, or another isotonic solution of choice, are ready for use within 5 minutes, and should be used within 6 hours.[20]

Once hydrated, NMP Fibers and InduceXT behave like a putty, which allows for the complete filling of irregular defects, and once in place, they are resistant to displacement during irrigation.

NMP Micro Particulates, when combined with blood, form a cohesive mass that can be molded to fill defects.

In contrast, INFUSE is comprised of three (3) components including a sterile, absorbable collagen sponge (ACS), sterile water, and sterile rhBMP-2. It takes 30 minutes to prepare and must be used within 2 hours. Irrigation or suction cannot be used near the implant and the sponge must not be excessively squeezed.[21] Once hydrated, the collagen sponge contracts and handles like a wet paper towel and it is recommended that the collagen sponge be rolled up to a fill volume.

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## Disclosures

Performance in vitro & in vivo are not necessarily indicative of human clinical outcome.

NMP bioimplants are intended for use as a bone void filler for filling voids and gaps in the skeletal system that are not intrinsic to the stability of the bony structure.

**Please see the NMP IFU for a complete list of indications, contraindications, warnings, precautions, and other important medical information.**

NMP bioimplants are marketed by Induce Biologics USA (Irvine CA) https://www.inducebiologics.com.



Sean Peel, Ph.D. is the inventor of NMP and is a shareholder in Red Rock Regeneration, Inc. Pierce Nunley, M.D. is on the board of and a shareholder in Red Rock Regeneration, Inc.