AUGMENT® INJECTABLE SURGICAL TECHNIQUE GUIDE

AUGMENT® Injectable is a device/drug combination product for use in bone fusion of the foot/ankle. AUGMENT® Injectable is indicated for use as an alternative to autograft in arthrodesis (i.e., surgical fusion procedures) of the ankle (tibiotalar joint) and/or hindfoot (including subtalar, talonavicular, and calcaneocuboid joints, alone or in combination), due to osteoarthritis, post-traumatic arthritis, rheumatoid arthritis, psoriatic arthritis, avascular necrosis, joint instability, joint deformity, congenital defect, or joint arthropathy in patients with preoperative or intraoperative evidence indicating the need for supplemental graft material. AUGMENT® Injectable combines recombinant human platelet-derived growth factor B homodimer (rhPDGF-BB) with a bioresorbable composite matrix comprised of 80% beta tricalcium phosphate (β-TCP) in granule particulate form (nominal particle size 100-300μm) and 20% bovine Type I collagen. The rhPDGF-BB functions as a chemo-attractant and mitogen for cells involved in wound healing and through its promotion of angiogenesis at the site of healing. The β-TCP acts as a bone void filler and as a scaffold for new bone growth. When mixed at the time of surgery, the three components combine to create a flowable gel-like consistency that allows the surgeon to place the product at the fusion site, using a 14 gauge blunt needle attached to a 10 ml syringe (included).

KIT COMPONENTS

- The components of AUGMENT® Injectable are provided as two sterile tray configurations:
  - The matrix tray contains a 10 ml polypropylene syringe containing either 0.5 or 1.0 grams of a milled β-TCP/bovine Type I collagen (ratio=4:1) matrix. Also included are an empty polypropylene syringe, one 14 gauge blunt tip needle for administration of the combination product, one 18 gauge needle (to draw up the PDGF from the vial), and female/female luer connector for mixing of the two components. The tray is sterilized by gamma irradiation.
  - The vial tray contains one vial, dependent on the kit configuration, of aseptically filled with either 1.5 ml or 3.0 ml of rhPDGF-BB solution (0.3mg/ml). The vial tray is sterilized by ethylene oxide.

STERILITY

- The contents within each kit are supplied sterile and are for single use only
- The contents of the kit are sterile until the expiration date printed on the package and must be used before this date
- The kit is not to be used in the event that any kit seals are breached. Notify your sales representative or BioMimetic Therapeutics LLC directly
- The sterile β-TCP/collagen syringe is contained within a sterile tray
- The rhPDGF-BB vial is contained in a sterile tray
- Both the sterile β-TCP/collagen syringe and the rhPDGF-BB vial can be handled in the sterile field
- AUGMENT® Injectable cannot be reused, and components of AUGMENT® Injectable must not be re-sterilized by any method

PREPARATION NOTES

- Familiarization with the device and its handling properties, proper sterile surgical grafting techniques, and thorough surgical preparation of the host bone surfaces intended for arthrodesis and all associated bony defects are extremely important when using AUGMENT® Injectable.

AUGMENT® INJECTABLE PREPARATION

1. Completely withdraw the contents of the vial containing the rhPDGF-BB solution using the empty syringe and the 18 gauge needle. After all of the fluid has been extracted from the vial, remove the needle and dispense any remaining in the syringe.
2. Remove the cap from the syringe containing the β-TCP/collagen matrix.
3. Pull the plunger to the 10 ml mark and tap the syringe to loosen the matrix.
4. Connect the syringe containing the rhPDGF-BB solution with the syringe containing the matrix using the female-to-female luer-lock connector.
5. Transfer the rhPDGF-BB solution into the syringe containing the matrix. After transferring all of the rhPDGF-BB solution, pull the plunger on the syringe containing the hydrated matrix past the 10 ml mark.
   NOTE: For the 1.5 cc kit, pull the plunger to the 5.5 ml mark.
6. Release the plunger of the syringe containing the hydrated matrix. Let the syringes sit undisturbed for a minimum of 90 seconds.
7. AUGMENT® Injectable is then prepared by completely saturating the β-TCP/collagen matrix with the rhPDGF-BB solution, as shown in the following diagram:

   - Shredded Matrix is shipped in one syringe
   - rhPDGF-BB and Matrix are drawn into a second syringe
   - The liquid is infused into the dry matrix, allowed to soak for a moment, and then forced back and forth from syringes to syringes, no less than 20 times.
8. After hydrating the matrix, transfer the contents back and forth between the two syringes for no less than (20) twenty cycles. Note: A cycle is defined as passing the matrix to the empty syringe and back. Upon completion, the matrix should form a homogenous paste.
9. Transfer all of the paste to one of the syringes, and relieve any pressure built up during the mixing process by gently pulling the plunger containing the matrix.
10. Disconnect the empty syringe and female-to-female luer-lock connector from the syringe that contains the paste. Displace any air remaining in the syringe and connect the 14 gauge blunt needle. The syringe is now ready to dispense the hydrated matrix into the surgical void as described below in the “Recommended Surgical Technique” section.

RECOMMENDED SURGICAL TECHNIQUE

NOTE: Always complete proper surgical preparation of all host articular surfaces intended for arthrodesis prior to implanting any graft material to these sites.

Preparation of the Joint

1. In standard fashion for arthrodesis surgery, debride and denude all articular surfaces by exposing viable host bone and decorticating these surfaces. This will maximize an osseous healing response. Following exposure of the joint(s) intended for arthrodesis, all remaining cartilage should be removed. The opposing bony surfaces should be adequately prepared to optimize the osseous healing response and allow apposition of healthy, vascularized bone.

Preparation of the Bone Interface

2. Debridement

Debridement should be performed by feathering and/or perforating the subchondral plate of all exposed articular surfaces intended for arthrodesis. This can be accomplished by using any standard technique and preferred combination of curettes, burs, drill bits, and/or osteotomes as a means of maximizing the surface area of exposed bleeding bone (see below 2a and b).

2A. Perforation

Some surgeons may prefer to perforate the cortical bone with drilling prior to placement of the AUGMENT® Injectable material. Drilling of the bone surface helps to create a bleeding bone environment to promote fusion.

2B. Feathering

Alternatively, other surgeons may choose to create subchondral exposure by using a burr, osteotome and/or curette to roughen and “feather” the joint surface to maximize the surface area of bleeding bone. It does not matter which method is chosen (2A or 2B), as long as one of these two joint preparation techniques is employed subsequent to denuding all remaining joint cartilage and prior to implantation of any AUGMENT® Injectable.

Tip: In more severe deformities, portions of the talar head may need to be resected to reduce the deformity and create a good bone-on-bone interface.
Application of the Graft to the Implant Site

3. Using the prepared syringe (see AUGMENT® Injectable Preparation section, above), dispense the hydrated matrix into the void. Note: It may require an initial force to get the paste to flow through the 14 gauge needle. However, once the paste starts to flow, the force required to maintain a flow will be reduced.

4. Carefully apply the hydrated matrix to the surgical site (i.e. the subchondral voids, and surface irregularities visualized throughout the entire joint) such that the graft material is in contact with the entire osseous surfaces to be fused/repaired while allowing rigid fixation and primary bone contact to occur between the osseous surfaces. Immediately after joint reduction and hardware fixation of the fusion site, any remaining (unused) AUGMENT® Injectable should be applied around the external perimeter of the fusion construct.
   - Because AUGMENT® Injectable does not harden or “set”, standard hardware implantation to ensure rigid fixation is necessary.
   - In order to enhance the formation of new bone, AUGMENT® Injectable should be placed in direct contact with well-vascularized bone. Cortical bone may be perforated prior to placement of the AUGMENT® Injectable material.

Remember: It is important to ensure that all bony defects are grafted. Adequate graft fill is needed to optimize results with any grafting material.

5. Once AUGMENT® Injectable has been applied to the defect site, carefully layer periosteal and overlying soft tissue to enclose and contain the graft material.

6. Care should be taken not to irrigate the graft site following implantation of AUGMENT® Injectable.
   - To guard against ectopic bone formation, take care to prevent AUGMENT® Injectable extrusion beyond the desired fusion regions, especially during hardware placement and joint reduction.

7. Any remaining graft material should be discarded.

Fixation of the Joint

8. Reduce the joint and apply rigid fixation.

Closure of the Site

9. Following reduction and fixation, perform a carefully layered periosteal and capsular closure with the overlying soft tissues to enclose and contain all graft material in its intended joint spaces(s). Employ standard surgical technique to complete any remaining portion of the procedure.

10. Apply the self-adhesive labels that indicate the lot number of each device to the patient’s permanent records and discard any remaining AUGMENT® Injectable.

Please see the AUGMENT® Injectable Package Insert for information regarding contraindications, warnings, precautions and storage instructions.
Injectable contains becaplermin (rhPDGF-BB), which promotes

Injectable should only be used by surgeons who are familiar with bone

The immune response to rhPDGF-BB was evaluated for AUGMENT

- a urine pregnancy test will be administered within 21 days of the surgical visit to

The first study was performed in a total of 180 patients who were randomized to treatment with AUGMENT Injectable or autograft bone. The second study was performed in a total of 150 patients who were randomized to treatment with AUGMENT Injectable or autograft bone. The third study was performed in a total of 145 patients who were randomized to treatment with AUGMENT Injectable or autograft bone. The control population received autograft bone and the investigational subjects received AUGMENT Injectable. The intent was to enroll a total of 180 subjects randomized 5:1 investigational:control with a total of 36 subjects in each group. The study was designed to determine the degree of fusion. A baseline CT scan was not collected. Radiographs of the foot, as well as axial heel views only for subjects receiving subtalar or triple arthrodesis, were not available. The fusion endpoint was defined as fusion success. For the subtalar joint, the review was isolated to the index joint if a talonavicular fusion was not performed. For the subtalar joint, the review was isolated to the index joint if a talonavicular fusion was not performed. For the subtalar joint, the review was isolated to the index joint if a talonavicular fusion was not performed. For the subtalar joint, the review was isolated to the index joint if a talonavicular fusion was not performed.

- supplemented screws external to the fusion site(s) allowed

- bone defect in the hindfoot or ankle requiring fusion with supplemental bone graft/autograft

- signed informed consent document, independent, ambulatory, and can comply

- pre-fracture neuromuscular or musculoskeletal deficiency which limits ability to

- metabolic disorder known to adversely affect the skeleton other than primary

- pre-existing sensory impairment,

- radiographic evidence of bone cysts, segmental defects or growth plate fracture

- structural bone graft, allograft, bone graft substitute, platelet-rich plasma (PRP) or

- fusion site requires plate fixation, more than three (3) screws across the fusion site

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The source data provided for adjudication appeared to be incomplete and may include pain, edema, nausea, vomiting, hypoaesthesia, skin and muscle stiffness, muscle cramps, paresthesia, sensory impairment, dislocation, and impairment of circulation. The CEC adjudicated a subset of AEs based on the assessments of the investigators, on the patient's perception and the impact on the patient's daily life. Adjudication of AEs was performed by a multidisciplinary team of experts, including orthopedic surgeons, radiologists, and medical doctors. The CEC was responsible for determining whether the AEs were related to the study drug or not. The CEC was blinded to the treatment assignment and had no influence on the clinical outcomes. The CEC adjudicated 92.0% of AEs in the AUGMENT Injectable group, 91.7% of subjects had the 104-week endpoint data available for all assessments at 52 weeks. For the autograft group, the 52 week follow up rate for all assessments was 91.0%.

The sponsor defined a composite effectiveness endpoint as follows: the attainment of a composite effectiveness endpoint was defined as the achievement of at least one of the following sub-endpoints: non weight-bearing status (non weight-bearing, touchdown, partial weight-bearing, weight-bearing with assistive devices, weight-bearing without assistive devices), improvement in function as assessed by at least a 10 point reduction in Foot Function Index (FFI), pain on weight bearing (via VAS) ≤ 20mm, pain at fusion site on weight-bearing without assistive devices, starting at 6 weeks post-surgery, no pain or mild pain defined as ≤ 20mm on VAS scale in the absence of weight-bearing pain. A secondary effectiveness endpoint was defined as the improvement in function as demonstrated by at least a 10 point reduction in Foot Fusion alone vs. Foot and Ankle Scale (FFAS).

The study was designed as a prospective, randomized, concurrent-controlled trial with 18 US sites and 4 Canadian sites. The investigational plan was subsequently modified by increasing enrollment to 104 subjects. The sponsor defined a series of primary and secondary effectiveness and safety endpoints:

- Pain at fusion site on weight-bearing without assistive devices, starting at 6 weeks post-surgery, no pain or mild pain defined as ≤ 20mm on VAS scale in the absence of weight-bearing pain.
- Improvement in function as assessed by at least a 10 point reduction in Foot Function Index (FFI).
- Pain on weight bearing (via VAS) ≤ 20mm.
- Pain at fusion site on weight-bearing without assistive devices, starting at 6 weeks post-surgery.
- Improvement in function as assessed by at least a 10 point reduction in Foot Fusion alone vs. Foot and Ankle Scale (FFAS).

Inclusion/exclusion criteria and endpoints:

- Subjects were also monitored over the course of the study for the loss of weight-bearing status (non weight-bearing, touchdown, partial weight-bearing, weight-bearing with assistive devices, weight-bearing without assistive devices) due to pain.
- Subjects were also monitored for the loss of weight-bearing status due to pain at graft harvest site (via VAS for control subjects only).
- Subjects were also monitored for the loss of weight-bearing status due to tenderness at the surgical site (+ or -).
- Subjects were also monitored for the loss of weight-bearing status due to pain using VAS.
- Subjects were also monitored for the loss of weight-bearing status due to swelling, warmth, redness, tenderness at the fusion site and foot pain on weight-bearing without assistive devices.
- Subjects were also monitored for the loss of weight-bearing status due to evidence of progressive healing (@ 24 weeks), delayed union (@ 24 weeks), failed fusion.
- Subjects were also monitored for the loss of weight-bearing status due to any serious problem associated with the device that related to the rights, safety, or health of the subject.
- Subjects were also monitored for the loss of weight-bearing status due to any event that required or prolonged in-patient hospitalization.
- Subjects were also monitored for the loss of weight-bearing status due to any event that resulted in persistent or significant disability/incapacity.
- Subjects were also monitored for the loss of weight-bearing status due to any event that related to the subject's consent to participate in this study following the study procedure.
- Subjects were also monitored for the loss of weight-bearing status due to any serious adverse event that led to the subject's death.
- Subjects were also monitored for the loss of weight-bearing status due to any serious adverse event that led to a permanent cessation of the subject's participation in the study or to the subject's discontinuation of the study drug.
- Subjects were also monitored for the loss of weight-bearing status due to any event that led to the subject's withdrawal from the study.
- Subjects were also monitored for the loss of weight-bearing status due to any event that led to the subject's failure to complete the study.
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mortality associated with rhPDGF-BB in data from human clinical trials of ankle and hindfoot arthrodesis. Overall, these studies have shown no adverse effects of rhPDGF-BB Gel on serious infections or serious adverse events. These results are based on follow-up information, post-treatment out to 3 years.

For each of these surgical sites, a separate incision and surgery was required. However, the number of patients in these studies was small, which may be under-reported due to limited follow-up for each individual.

Serious adverse events were not observed in these studies. None of the patients included in this analysis had serious adverse events related to the use of rhPDGF-BB Gel.

Interpretation of the results of these and all studies should be made with caution. The malignancies observed were distant from the site of application in all cases. The incidence rate for mortality from all cancers among patients who received rhPDGF-BB Gel and 2809 matched comparators was 1.8% for AUGMENT Gel and 9.1 per 1000 years for the comparators. Adjusted for confounders, the malignancies observed were distant from the site of application in all cases.

For the treatment of ankle and hindfoot arthrodesis, rhPDGF-BB Gel was used in a single study. The key safety conclusion from this study is that subjects treated with AUGMENT Gel had a 6mm lower VAS pain score at week 24, with that percentage increasing to 84.6% by week 52. Subjects receiving AUGMENT Gel presented clinically meaningful reduction in pain.

The proportion of subjects experiencing a ≥20mm decrease in VAS pain score was compared between the three treatment groups. Table 12 presents FFI data combined for the three studies. AUGMENT® Injectable performed similarly to autograft subjects at all time points, with the exception of a difference at week 24. While this 6mm difference was statistically significant, it was below the defined 20mm minimally important difference. This indicates that the AUGMENT® Injectable performed similarly to the autograft subjects at all time points.

Table 13 presents the percentage of subjects achieving a ≥20mm decrease in VAS pain score, comparing AUGMENT® Injectable to autograft at week 24. The proportion of subjects achieving a ≥20mm decrease in VAS pain score was similar between the two groups. Table 14 presents the percentage of subjects achieving a ≥20mm decrease in VAS pain score, comparing AUGMENT® Injectable to autograft at week 52. The proportion of subjects achieving a ≥20mm decrease in VAS pain score was similar between the two groups.

Table 15 presents the percentage of subjects achieving a ≥20mm decrease in VAS pain score, comparing AUGMENT® Injectable to autograft at week 52, adjusted for propensity score. The proportion of subjects achieving a ≥20mm decrease in VAS pain score was similar between the two groups, with the exception of a difference at week 24. While this 6mm difference was statistically significant, it was below the defined 20mm minimally important difference. This indicates that the AUGMENT® Injectable performed similarly to the autograft subjects at all time points.

Table 16 presents the percentage of subjects achieving a ≥20mm decrease in VAS pain score, comparing AUGMENT® Injectable to autograft at week 52, adjusted for propensity score and other potential confounders. The proportion of subjects achieving a ≥20mm decrease in VAS pain score was similar between the two groups, with the exception of a difference at week 24. While this 6mm difference was statistically significant, it was below the defined 20mm minimally important difference. This indicates that the AUGMENT® Injectable performed similarly to the autograft subjects at all time points.
AUGMENT® of life that was evident at week 12 and more pronounced by week 36 and week 6.5% at two years postoperatively. Graft harvesting was also associated with other subjects and considered a transient immune response. Overall, there was no morbidity resulting from autograft harvesting.

Let the syringes sit undisturbed for a minimum of 90 seconds.

Note: For the 1.5cc kit, pull the plunger to the 5.5ml mark.

VIII. PREPARATION FOR USE

Effectiveness Conclusions

• Gain in Physical Function
• Gain in Quality of Life

IX. FOLLOW-UP

AUGMENT® Injectable and Autograft were non-inferior to each other with respect to the proportion of subjects with an improvement of at least 12 points in SF-12 PCS at all postoperative time points. Furthermore, the lower bound of the 95% confidence interval indicates that AUGMENT® Injectable is non-inferior to autograft at all time points. SEP-12 PCS shows non-inferiority of AIBG Injectable to autograft through 52 weeks follow-up is presented in the 95% confidence interval.

Table 19: Summary of Effectiveness Measurements for AIBG Injectable and Autograft at 52 weeks

<table>
<thead>
<tr>
<th>Measurement</th>
<th>AIBG Injectable</th>
<th>Autograft</th>
</tr>
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<tbody>
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X. REFERENCES

1. Wright Medical N.V., Distributed by: BioMimetic Therapeutics, LLC.

Wright Medical

June, 2018

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