DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center - WO66-G609
Silver Spring, MD 20993-0002

Biomimetic Therapeutics, LLC
Russ Pagano, Ph.D.
Vice President, Clinical and Regulatory Affairs
389 Nichol Mill Lane
Franklin, Tennessee 37067

September 1, 2015

Re: P100006
Trade/Device Name: Augment® Bone Graft
Filed: May 7, 2010
Amended: May 7, May 13, November 19, 2010; April 15, August 5, 2011; June 15, July 2, September 13, 2012; September 3, September 5, 2013; February 7, March 31, April 29, June 24, October 31, November 4, November 19, 2014; February 18, and April 9, 2015
Procode: NOX

Dear Dr. Pagano:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for Augment® Bone Graft. This device 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. We are pleased to inform you that the PMA is approved. You may begin commercial distribution of the device in accordance with the conditions of approval described below.

The sale and distribution of this device are restricted to prescription use in accordance with 21 CFR 801.109 and under section 515(d)(1)(B)(ii) of the Federal Food, Drug, and Cosmetic Act (the act). FDA has determined that this restriction on sale and distribution is necessary to provide reasonable assurance of the safety and effectiveness of the device. Your device is therefore a restricted device subject to the requirements in sections 502(q) and (r) of the act, in addition to the many other FDA requirements governing the manufacture, distribution, and marketing of devices.

A 36-month shelf life has been established for each of the two components of Augment® Bone Graft, and the expiration date for the product as a whole has been established as that corresponding to the earlier of the two components. The total product must be stored at refrigerated temperature (2-8°C, 36-46°F). This is to advise you that the protocol you used to

establish this expiration dating is considered an approved protocol for the purpose of extending the expiration dating as provided by 21 CFR 814.39(a)(7).

Continued approval of this PMA is contingent upon the submission of periodic reports, required under 21 CFR 814.84, at intervals of one year (unless otherwise specified) from the date of approval of the original PMA. Two copies of this report, identified as "Annual Report" and bearing the applicable PMA reference number, should be submitted to the address below. The Annual Report should indicate the beginning and ending date of the period covered by the report and should include the information required by 21 CFR 814.84. This is a reminder that as of September 24, 2014, class III devices are subject to certain provisions of the final UDI rule. These provisions include the requirement to provide a UDI on the device label and packages (21 CFR 801.20), format dates on the device label in accordance with 21 CFR 801.18, and submit data to the Global Unique Device Identification Database (GUDID) (21 CFR 830 Subpart E). Additionally, 21 CFR 814.84 (b)(4) requires PMA annual reports submitted after September 24, 2014, to identify each device identifier currently in use for the subject device, and the device identifiers for devices that have been discontinued since the previous periodic report. It is not necessary to identify any device identifier discontinued prior to December 23, 2013. For more information on these requirements, please see the UDI website, http://www.fda.gov/udi.

In addition to the above, and in order to provide continued reasonable assurance of the safety and effectiveness of the device, the Annual Report must include, separately for each model number (if applicable), the number of devices sold and distributed during the reporting period, including those distributed to distributors. The distribution data will serve as a denominator and provide necessary context for FDA to ascertain the frequency and prevalence of adverse events, as FDA evaluates the continued safety and effectiveness of the device.

In addition to the Annual Report requirements, you must provide the following data in post-approval study (PAS) reports for each PAS listed below. Two (2) copies of each report, identified as an "ODE Lead PMA Post-Approval Study Report" or "OSB Lead PMA Post-Approval Study Report" in accordance with how the study is identified below and bearing the applicable PMA reference number, should be submitted to the address below.

1. ODE Lead PMA Post-Approval Study – Extended Follow-up of Premarket Cohort (Long-term PAS Study): The Office of Device Evaluation (ODE) will have the lead for this clinical study, which was initiated prior to device approval. The Extended Follow-up of Premarket Cohort (Long-term PAS Study) is a continued follow-up of the Augment Bone Graft and Autologous graft premarket IDE cohort. It is a prospective, controlled study within the US and Canada comparing Augment Bone Graft to Autograft (in a 2:1 ratio) in hind foot and ankle arthrodesis at 5 or more years post-treatment. The study will address the following objectives: (1) Can it be assessed and confirmed that bridging bone occurs in the long-term after Augment has been resorbed? (2) Are the improvements in clinical outcomes associated with the use of Augment sustained long-term? (3) Does the promotion of existing tumors from a nonmalignant to malignant state at longer time-points in patients treated with Augment exceed the expected rate of promotion in patients not treated with Augment or other growth factors used to promote fusion?

The primary effectiveness endpoints will consist of the following:

- Demonstration of bridging bone via CT
- Patient Function as determined by Pain on Weight Bearing (via VAS), AOFAS Score and Foot Function Index (FFI)

The primary safety endpoints will consist of the following:

- Presence of all adverse events (i.e., description, frequency, incidence, time to onset of first event, severity, duration, treatments administered, etc.)
- Presence of serious unanticipated adverse device effects (UADE)
- rhPDGF-BB antibody status
- At evaluation, subjects will be interviewed regarding significant medical conditions, including incidence of cancer
- Presence of clinically important events as defined below:
    - Musculoskeletal and connective tissue disorders (severe pain, swelling and/or arthralgia in the treated foot/ankle joint(s));
    - Additional surgery of the original treated joint due to non-union.
    - Neoplasms benign, malignant and unspecified (including cysts and polyps) (all lower level terms associated with neoplasms)
    - Complications related to bone graft harvest site

The study will require 150 subjects (100 Augment; 50 Autograft) to be evaluated at a single visit at 5 years or more after original treatment under BMTI-2006-01 study. Hypothesis testing for maintenance of improvements within the Augment group on pain on weight bearing, AOFOS and FFI will be conducted.

2. OSB Lead PMA Post-Approval Study – 2-year New Enrollment Study: The Office of Surveillance and Biometrics (OSB) will have the lead for studies initiated after device approval. The 2-year New Enrollment Study is a prospective, single arm, new enrollment study of patients with ankle and hind foot fusion procedures using Augment Bone Graft. The study will address the following objectives: (1) Can it be assessed and confirmed that bridging bone occurs after Augment has been resorbed? (2) Are the improvements in clinical outcomes associated with the use of Augment in the IDE study confirmed? (3) Does the promotion of existing tumors from a nonmalignant to malignant state in patients treated with Augment exceed the expected rate of promotion in patients not treated with Augment or other growth factors used to promote fusion?

   The primary effectiveness endpoints will consist of the following:

   - Pain on Weight Bearing (via VAS) (Pre-op, Week 12, Week 24, Year 1, Year 2)
   - Confirmation of bridging bone via CT (Year 1, Year 2)
   - Patient Function (Pre-op, Week 12, Week 24, Year 1, Year 2) as determined by AOFAS Score and Foot Function Index (FFI)

   The primary safety endpoints will consist of the following:

- Presence of all adverse events (i.e., description, frequency, incidence, time to onset of first event, severity, duration, treatments administered, etc.)
- Presence of serious unanticipated adverse device effects (UADE)
- rhPDGF-BB antibody status
- At evaluation, subjects will be interviewed regarding significant medical conditions, including incidence of cancer
- Presence of clinically important events as defined below:
    - Musculoskeletal and connective tissue disorders (severe pain, swelling and/or arthralgia in the treated foot/ankle joint(s));
    - Additional surgery of the original treated joint due to non-union.
    - Neoplasms benign, malignant and unspecified (including cysts and polyps) (all lower level terms associated with neoplasms)

The study will require 118 Augment subjects who will be followed through the 2-year time point and provide at least 100 evaluable subjects at the two year follow-up visit. The frequency of follow up will be as follows: Pre-op, Post-op, 12 weeks, 24 weeks, 1 year, and 2 years.

There will be 3 comparators and are outlined as follows:

Comparator 1 Patients serve as own control: Baseline pain and function parameters will be used as comparators in analysis that demonstrates that clinical improvements observed at 2 years post-treatment are clinically meaningful (>20 point difference for Pain on weight bearing (VAS) and AOFAS and 10 point difference for Foot Function Index (FFI), as defined in the SSED.)

Comparator 2 Historical Comparator –Augment IDE Cohort –Will be used to compare success rates for fusion, pain and function endpoints in Augment arm of IDE study to success rates for these endpoints in the 2 year New Enrollment study participants treated with Augment .

Comparator 3 Historical Comparator –Autograft IDE Cohort –Will be used to compare success rates for pain and function in Autograft arm of IDE study to success rates for these endpoints in the 2 year New Enrollment study participants treated with Augment. Primary hypothesis testing for maintenance of improvements as outlined above in "Comparator 1" on pain on weight bearing, AOFOS and FFI will be conducted.

Be advised that the failure to conduct any such study in compliance with the good clinical laboratory practices in 21 CFR part 58 (if a non-clinical study subject to part 58) or the institutional review board regulations in 21 CFR part 56 and the informed consent regulations in 21 CFR part 50 (if a clinical study involving human subjects) may be grounds for FDA withdrawal of approval of the PMA. In addition, the results from any post approval study should be included in the labeling as these data become available. Any updated labeling must be submitted to FDA in the form of a PMA Supplement. For more information on post-approval studies, see the FDA guidance document entitled, "Procedures for Handling Post-Approval

Studies Imposed by PMA Order"
(http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm).

Within 30 days of your receipt of this letter, you must submit a PMA supplement that includes complete protocols of your post-approval studies described above. Your PMA supplements should be clearly labeled as an "ODE Lead PMA Post-Approval Study Protocol" or "OSB Lead PMA Post-Approval Study Protocol" as noted above and submitted in triplicate to the address below. Please reference the PMA number above to facilitate processing. If there are multiple protocols being finalized after PMA approval, please submit each protocol as a separate PMA supplement.

Before making any change affecting the safety or effectiveness of the device, you must submit a PMA supplement or an alternate submission (30-day notice) in accordance with 21 CFR 814.39. All PMA supplements and alternate submissions (30-day notice) must comply with the applicable requirements in 21 CFR 814.39. For more information, please refer to the FDA guidance document entitled, "Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process"
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089274.htm

You are reminded that many FDA requirements govern the manufacture, distribution, and marketing of devices. For example, in accordance with the Medical Device Reporting (MDR) regulation, 21 CFR 803.50 and 21 CFR 803.52, you are required to report adverse events for this device. Manufacturers of medical devices, including in vitro diagnostic devices, are required to report to FDA no later than 30 calendar days after the day they receive or otherwise becomes aware of information, from any source, that reasonably suggests that one of their marketed devices:

1. May have caused or contributed to a death or serious injury; or

2. Has malfunctioned and such device or similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Additional information on MDR, including how, when, and where to report, is available at
http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm

In accordance with the recall requirements specified in 21 CFR 806.10, you are required to submit a written report to FDA of any correction or removal of this device initiated by you to: (1) reduce a risk to health posed by the device; or (2) remedy a violation of the act caused by the device which may present a risk to health, with certain exceptions specified in 21 CFR 806.10(a)(2). Additional information on recalls is available at
http://www.fda.gov/Safety/Recalls/IndustryGuidance/default.htm

CDRH does not evaluate information related to contract liability warranties. We remind you; however, that device labeling must be truthful and not misleading. CDRH will notify the public of its decision to approve your PMA by making available, among other information, a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/default.htm. Written requests for this information can also be made to the Food and Drug Administration, Dockets Management Branch, (HFA-305), 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by submitting a petition for review under section 515(g) of the act and requesting either a hearing or review by an independent advisory committee. FDA may, for good cause, extend this 30-day filing period.

Failure to comply with any post-approval requirement constitutes a ground for withdrawal of approval of a PMA. The introduction or delivery for introduction into interstate commerce of a device that is not in compliance with its conditions of approval is a violation of law.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form. Final printed labeling that is identical to the labeling approved in draft form will not routinely be reviewed by FDA staff when accompanied by a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

All required documents should be submitted in 6 copies, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

U.S. Food and Drug Administration
Center for Devices and Radiological Health
PMA Document Control Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

If you have any questions concerning this approval order, please contact Sarah Brittain at 240-402-3141 or Sarah.Brittain@fda.hhs.gov.

Sincerely yours,

Mark N. Melkerson -S

Mark N. Melkerson
Director
Division of Orthopedic Devices
Office of Device Evaluation
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