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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

Form 8-K

CURRENT REPORT
PURSUANT TO SECTION 13 OR 15(d)OF THE
SECURITIES EXCHANGE ACT OF 1934

Date of report (date of earliest event reported): December 21, 2005

Aastrom Biosciences, Inc.

(Exact name of registrant as specified in its charter)

Michigan	**0-22025**	**94-3096597**
(State or other jurisdiction of incorporation)	(Commission File No.)	(I.R.S. Employer Identification No.)

24 Frank Lloyd Wright Drive
P.O. Box 376
Ann Arbor, Michigan 48106
(Address of principal executive offices)

Registrant's telephone number, including area code:
(734) 930-5555

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

o Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

o Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

o Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

o Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

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Item 8.01 Other Events.

On December 21, 2005, we issued a press release announcing the interim results of the feasibility clinical trial conducted in Barcelona, Spain to evaluate the use of Aastrom's Tissue Repair Cells for maxillary (upper jaw) bone reconstruction in five patients. A copy of the press release is attached hereto as Exhibit 99.1, and a copy of the internal report of the clinical study is attached hereto as Exhibit 99.2.

Item 9.01 Financial Statements and Exhibits.

(c) Exhibits.

Exhibit No.	Description
99.1	Press Release dated December 21, 2005
99.2	Internal report of the clinical study

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Date: December 21, 2005

AASTROM BIOSCIENCES, INC.

By: /s/ Gerald D. Brennan, Jr.
Gerald D. Brennan, Jr.
Vice President, Administrative and
Financial Operations, CFO

Exhibit 99.1

Aastrom BIOSCIENCES INC
P.O. Box 376 • Ann Arbor, Michigan 48106 • Ph: 734-930-5555 • Fax: 734-665-0485
Located at: Domino's Farms, Lobby L

FOR IMMEDIATE RELEASE

CONTACTS:

Kris M. Maly or
Becky Anderson
Investor Relations Department
Aastrom Biosciences, Inc.
Phone: (734) 930-5777

Cameron Associates
Kevin McGrath — Institutions
Phone: (212) 245-4577
Alyson Nikulicz — Media
Phone: (212) 554-5464

AASTROM BIOSCIENCES REPORTS POSITIVE HUMAN JAW BONE RECONSTRUCTION RESULTS FROM FEASIBILITY CLINICAL TRIAL

— Results Indicate Company's Tissue Repair Cell Product Safely Builds New Bone for Dental Implants —

Ann Arbor, Michigan, December 21, 2005 — Aastrom Biosciences, Inc. (Nasdaq: ASTM) announced today the interim results from its feasibility clinical trial conducted with the Teknon Hospital Maxillofacial Clinic in Barcelona, Spain, to evaluate the use of Aastrom's Tissue Repair Cells (TRCs) for maxillary (upper jaw) bone reconstruction in 5 patients, completed to support placement of dental implants. The study results showed clinical safety, and that the TRC treatment sites all exhibited bone growth that was statistically significant and had the desired initial integration with preexisting bone. An internal report of the clinical study, which provides more detailed information, is being filed today on Form 8-K with the SEC. This report may also be accessed on Aastrom's website using the link: http://www.aastrom.com/pdf/Jaw_Barcelona-051220.pdf.

The goal of this proof of concept, internally controlled clinical trial was to evaluate the safety and ability of TRCs — a proprietary autologous bone marrow-derived stem cell product — to increase bone height in the posterior maxilla (upper jaw) of 5 patients, who had severe bone loss in the region and minimal residual bone remaining. The patients were judged to have a poor prognosis with previously lost teeth due to periodontal disease and tooth decay, and additional risk factors that are known to compromise bone regeneration and preservation. These risk factors included many years of smoking, osteoporosis and advanced age. The intent of the TRC therapy was to help rebuild healthy bone so that there was enough bone to accommodate the length of the dental implants. A standard bone graft technique was used as an internal concurrent control on the other side of the maxilla.

All of the primary outcomes described by the trial protocol were successfully achieved. Results showed that all 5 patients treated locally with Aastrom's TRCs, exhibited a statistically significant increase in bone height at the 3-month evaluation point, and the cell graft had started to integrate with the surrounding preexisting bone of the upper jaw by 4 months, with no cell-related adverse events. The results were obtained from radiographs, and from biopsies taken at the interface of the original bone and the new tissue. All patients went on to receive 3-4 dental implants on each side of their maxilla.

The study employed an internal concurrent control, in which the patients were treated on one side of the maxilla with the TRC test treatment added to a standard of care procedure, and on the other side with the control standard of care procedure, a mixture of platelet-poor plasma and commercial bone mineral matrix. There was a statistically significant difference in bone formation and quality between test and control sides. Bone height in the grafted area and integration of graft into surrounding bone were increased in the TRC test maxilla, when compared with control sites receiving standard of care treatment. Post-operative bruising and swelling observed at some (3/5) of the control sites, were not observed in the TRC treated maxillae (0/5). This is the second clinical bone graft trial to report that surgical sites treated with TRCs appear to exhibit less inflammation or swelling than sites treated without TRCs.

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“Edentulous patients who have lost this much jaw bone can be very difficult to treat,” commented Dr. Federico Hernandez-Alfaro, Principal Investigator for the trial. “TRCs may offer an improved treatment over existing therapies because they appear to naturally accelerate integration of new bone with the existing bone in the patient, and increase bone mass for implant placement.”

“Results such as these provide increasing evidence that TRCs can be safely used to regenerate bone in humans whose ability to maintain and repair their skeleton is impaired by disease or trauma,” stated Janet M. Hock, B.D.S., Ph.D., Vice President Global Research and Chief Scientific Officer of Aastrom. “These early clinical studies explore tissue healing and regeneration in patients with compromised conditions, and teach us what to expect from stem cell therapy, and how to optimize the use of TRCs in clinical situations.”

Aastrom is implementing a “proof of concept” clinical plan to evaluate the ability of TRCs to generate three different types of bone: long bone, jaw bone and spine. Trials involving multiple centers in both the U.S. and Europe are actively evaluating TRCs in the repair of severe non-union fractures, where preliminary results have demonstrated both safety and bone growth success. A trial for the regeneration of spine bone (vertebral fusion) has been initiated in the U.S. under a newly approved IND. In addition, the Company is now engaged in a human clinical trial in Germany evaluating the use of its TRCs to treat limb ischemia in diabetic patients through the regeneration of vascular tissue in extremities.

About Tissue Repair Cells

Tissue Repair Cells (TRCs) are Aastrom’s proprietary mixture of bone marrow-derived adult stem and progenitor cells produced using patented single-pass perfusion technology in the AastromReplicell® System. The clinical procedure begins with the collection of a small sample of bone marrow from the patient’s hip in an outpatient setting. TRCs are then produced in the automated AastromReplicell System over a 12-day period. It has been demonstrated in the laboratory that TRCs are able to develop into different types of tissue lineages in response to inductive signals, including blood, bone, cartilage, adipose and vascular tubules. In previous clinical trials, TRCs have been shown to be safe and reliable in regenerating certain normal healthy bone marrow tissues.

About Aastrom Biosciences, Inc.

Aastrom Biosciences, Inc. is developing patient-specific products for the repair or regeneration of human tissues, utilizing the Company’s proprietary adult stem cell technology. Aastrom’s proprietary Tissue Repair Cells (TRCs), a mix of bone marrow-derived adult stem and progenitor cells for tissue regeneration, are manufactured in the AastromReplicell® System, an industry-unique automated cell production system. Aastrom’s TRC cell products are in clinical trials for the following therapeutic indications: severe bone fractures (US: Phase I/II — multi-center; EU: Phase I/II — multi-center), ischemic vascular disease (EU: Phase I/II), jaw reconstruction (EU: proof of concept trial), and spine fusion (US: Phase I/II — single-center).

For more information, visit Aastrom’s website at www.aastrom.com.

This document contains forward-looking statements, including without limitation, statements concerning product development objectives, planned clinical trials, potential advantages of TRCs and the AastromReplicell® System, and potential product applications, which involve certain risks and uncertainties. The forward-looking statements are also identified through use of the words “may,” “expect,” “can,” “plan,” “appear,” and other words of similar meaning. Actual results may differ significantly from the expectations contained in the forward-looking statements. Among the factors that may result in differences are, potential product development difficulties, clinical trial results, potential patient accrual difficulties, the effects of competitive therapies, regulatory approval requirements, the availability of financial and other resources and the allocation of resources among different potential uses. These and other significant factors are discussed in greater detail in Aastrom’s Annual Report on Form 10-K and other filings with the Securities and Exchange Commission.

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Clinical Feasibility Study: The Use of Autologous Bone Marrow-Derived Tissue Repair Cells (TRC) for Maxillary Sinus Floor Augmentation in Edentulous Humans.

F.Hernandez Alfero[1], C Marti[1], L Orozco[1], ML Marinoso[2], L. Rodriguez[3], C Torrico [3], P. Vidal[4], G. O'Brien[4], M Hornberger[4], RD Armstrong[4], JM Hock[4]

1: Maxillofacial Clinic, Institut de Terapia Regenerativa Tisular (Clinica Teknon), Barcelona, Spain
2: Hospital del Mar, Servicio de Patología, Barcelona, Spain
3: Unitat de Terapia Cellular (Centre de Transfusio I Banc de Teixits) Barcelona, Spain
4: Aastrom Biosciences, Ann Arbor, MI 48106, USA

Keywords: (dental implants); (stem cells); (bone marrow stromal cells); (osteoinduction)

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Abstract

A new bone marrow substitute — Tissue Repair Cells (“TRC”, Aastrom Biosciences, Inc.) was evaluated for safety and its ability to induce new bone in the upper jaw (maxilla) of edentulous patients requiring dental implants to replace lost teeth. Patients, who have too little bone remaining to support insertion of dental implants to replace the lost teeth, require grafts to augment the remaining bone. Standard of care is autogenous bone graft, or an acellular bone matrix substitute mixed with plasma, blood or bone marrow. The aim of this proof of concept, prospective, clinical study was to evaluate the safety and ability of TRCs, an ex vivo-cultured, autologous bone marrow-derived cell product, to induce bone to augment the height of the maxillary sinus floor and enable dental implant placement.

In the controlled 8-month study, in which subjects served as their own control, 5 maxillary edentulous females, aged 37-75 years old, received through a standard sinus-lift technique, BioOss graft on one side of the posterior maxilla, and TRC+BioOss graft on the contralateral side, to augment maxillary sinus floor bone. CT images and panoramic radiographs were taken 3 and 4 months, respectively, after grafting. Bone forming surfaces were labeled using the fluorochrome, tetracycline, prior to removal, at 4 months post-graft, of bone cores for histomorphometry, and insertion of 3-4 dental implants in each posterior maxilla, for a total of 38 implants. This report describes results at 2.4 to 6.7 months after cell therapy and 4 months after implants were inserted. Observations will continue for up to 2 years.

There were no TRC cell-therapy related adverse events. Notably, post-operative swelling and bruising were observed in 3 of 5 maxilla receiving BioOss alone, but not in maxilla receiving TRC+BioOss. All TRC treated maxilla formed new bone. CT measures showed TRC enhanced the height ($p<0.01$) and width ($p<0.087$) of the maxillary sinus floor by 3 months. Histomorphometry showed that TRC+BioOss regulated trabecular bone architecture, increased connective tissue volume (Fib V/BV); and reduced the ratio of BioOss surface area to bone surface area (BioOss S/BS). Of the total of 19 implants in each group, 14 implants in TRC+BioOss and 15 implants in BioOss were retained at 2.4 - 6.7 months post-implant placement (the latest data for this interim report). Co-morbidities associated with bone loss and poor implant prognosis, such as a prior history of periodontitis, many years of smoking, osteoporosis, and menopausal status, did not affect healing responses in this small patient sample. All safety and efficacy endpoints were successfully achieved. Our feasibility trial showed that TRC may be safely used to augment the height of maxillary sinus floor bone, and

enable placement of dental implants in patients where such procedures might otherwise be contra-indicated.

Introduction

Bone marrow contains cells that have the potential to induce bone tissue when they are provided the biological direction to do so. Accordingly, bone marrow has been used in different ways to augment new bone growth in a variety of medical procedures such as repair of severe fractures (1-6), and void filling of large bone defects (3;7-9). Inducing new bone tissue in jawbones with minimal residual ridge or basal bone by bone grafting has become an accepted procedure to increase bone thickness enough to allow placement of dental implants to replace lost teeth (10). However, current procedures use autogenous bone from elsewhere in the jaw, or form iliac crest, and are associated with high morbidities, such as pain and loss of innervation that may persist for years.

A new bone marrow alternative, called Tissue Repair Cells (“TRCs”, Aastrom Biosciences, Inc.), was developed as a substitute for a liter or more volume of bone marrow for tissue regeneration. TRCs contain adult stem cells, early and late progenitors and mature cells of the mesenchymal, endothelial and myeloid lineages, while retaining the full spectrum of cell subsets typically found in bone marrow (11-14). Molecular analyses show TRCs express transcripts for many of the known osteogenic and endothelial growth factors, including the osteogenic bone morphogenetic growth factors, BMP2 and BMP4, and vascular endothelial growth factor-receptor. TRC are autologous cells, that is, they are produced from a small amount of native bone marrow of the same patient who will ultimately be treated with the TRC product.

TRCs are produced using a proprietary “single-pass perfusion” technology (15-21). This technology mimics the natural bone marrow cell-growth environment by controlling the microenvironment of oxygen and endogenous growth factor concentrations, while delivering needed nutrients to allow the stem, progenitor, and stromal cell populations to replicate and retain high biological functionality (15;18-21). In preclinical studies using appropriate conditions to induce cell differentiation, TRC may develop into cells of bone, cartilage, hematopoietic, immune system, vascular or adipose tissues. This technology is the subject of multiple issued patents which provide claims for the *ex vivo* replication of stem and progenitor cells found in human bone marrow, and their therapeutic use.

TRCs have been previously successfully and safely used as bone marrow transplants in clinical trials of cancer patients on chemotherapy to restore hematopoiesis. The clinical bone forming capability of TRCs was suggested by the treatment of a patient with hypophosphatasia (22), who received a single intravenous infusion of TRCs, derived from a matched sibling donor bone marrow. The treatment resulted in a significant, prolonged, clinical and radiographic improvement of skeletal bone achieved within a very short time (22). The authors concluded that long-term engraftment of the bone-forming cells in Aastrom TRCs resulted in the amelioration of the child's skeletal disease (22). More recently, Aastrom has completed a feasibility trial to evaluate the ability of TRCs to restore healing competency to severe non-union type fractures that had failed to respond to conventional standard of care treatment. Of the 6 treated cases, all were clinically healthy while 5 of 6 showed radiographic healing at 6 months post-surgery, and 6 of 6 by 12 months.

Dental implants are a highly successful solution to replace missing teeth and restore masticatory function and aesthetics (10;23;24). Success rates vary from 62-96% (25;26). The challenge to successful insertion of implants enters when patients have lost so much alveolar and basal bone that the residual ridge is poor quality bone and insufficient to allow placement of an implant. In this case, grafts are used to increase the height or width of the remaining bone (27). An accepted standard of care is autogenous bone and associated bone marrow taken from the iliac crest, mandibular symphysis (chin) (28), mandibular ramus (28), or from the surrounding area (29;30). All autogenous bone sources carry some risk of morbidity, which may persist for many years (28). To avoid this, alternative bone graft matrix materials such as bovine anorganic bone, from which the organic fraction has been removed (BioOss), ceramics or bioglass, have been used (31-37). These materials are used alone, or mixed with different autologous cells or blood products. Implant retention over time appears to be equivalent to autogenous bone in small controlled and uncontrolled clinical studies (31-35). However, significant time must elapse before materials such as ceramics, bovine hydroxyapatite or bioglass, which have been placed without addition of cells, can be resorbed and replaced in part by bone for osseous integration.

The goal of this proof of concept clinical trial was to evaluate the safety and ability of TRCs to augment bone in the maxillary sinus floor in 5 edentulous patients with minimal residual ridge. We hypothesized that TRC, which have the potential to form bone and blood vessels, when mixed with BioOss, will augment maxillary bone height more than BioOss alone, and modify the

induced bone architecture. Each patient served as their own control. Data were based on radiographic imaging, histomorphometry and clinical observations.

Materials and Methods

Approval for a small Phase I/II study to evaluate the use TRCs in grafts to augment maxillary sinus floor to enable dental implant placement was obtained from the Ethics Committee of CM Teknon, Barcelona, Spain. In a controlled, randomized design in which subjects served as their own control, 5 maxillary edentulous patients received BioOss graft on one side of the posterior maxilla and TRC+BioOss graft on the other maxilla. Autologous bone marrow cells were processed *ex vivo* in the automated AastromReplicell System, and mixed with a bovine anorganic bone matrix (BioOss, Geistlich Biomaterials, Wolhusen, Switzerland). Because of severe bone loss, the unfavorable form and quality of residual maxillary basal bone, and co-morbidities that included a smoking history of more than 20 years in 4/5 patients, a history of chronic periodontitis in 5/5, osteoporosis in 1/5 subjects, advanced age in 1/5 subject, and post-menopausal status in 2/5 subjects (Table 1), all patients were considered to have poor prognosis for implant placement.

Inclusion criteria were partial or total edentulism of the maxilla. Subjects with acute sinusitis, sinus cysts or tumors, oral-antral fistulas or who had been previously irradiated in the maxilla were excluded, as were patients with cancer or psychiatric diseases, uncontrolled systemic diseases, congenital or metabolic bone diseases, chronic renal pathology or with known allergic responses to reagents or drugs proposed for the study. Pregnant women and women not using contraceptives were excluded to avoid potential side-effects of tetracycline on bones and teeth of a developing fetus.

TRC preparation

Twelve to thirteen days prior to the reconstructive surgery, bone marrow was aspirated from the posterior iliac crest, with the patient under conscious sedation and local anesthesia**.** Aspirates were transported to the Centre de Transfusions y Banc de Teixits de Barcelona for cell processing. Nucleated bone marrow cells from 38-64ml aliquot of the marrow aspirate, were isolated by density gradient centrifugation and approximately 275 million cells were inoculated into the AastromReplicell System (ARS) for culture in Iscove's Modified Dulbecco's Media, supplemented with 10% fetal bovine serum, 10% horse serum, hydrocortisone ($5x10^{-6}$M), gentamicin sulfate (5 µg/ml), L-glutamine (4 mM), and vancomycin (20 µg/ml). Bone marrow-derived cells were cultured for 12 days at 37°C, using single pass perfusion conditions

previously established to allow production of a cultured bone marrow cell product that contained multi-lineage stem and progenitor cells. To confirm there were non-detectable levels of bacterial and fungal contaminants and endotoxins, culture medium was sampled at 48 hours prior to harvest. The cells were harvested on Day 12, using trypsin and EDTA, and thoroughly and repeatedly washed to reduce media components by 4-log fold. Tests on this technology done at Aastrom Biosciences, Ann Arbor, MI showed that reagents added during culture, were below detectable limits, using a sensitive ELISA assays (R&D Systems, Minneapolis, MN and Immunex Research Corporation, Seattle, WA). Flow cytometry, cell viability, and clonogenic assays were performed to confirm composition and viability of the cell mixture. The final cell product was suspended in Normosol and 0.5 % human serum albumin, and transported in a sterile bag to the surgical suite.

Surgical Grafting Procedure

On the 12th or 13th day after cells had been inoculated into ARS, subjects were admitted to the hospital for surgery under local anesthesia plus sedation, as appropriate. A standard Caldwell-Luc surgical approach under general anesthesia was employed to access the maxillary sinus floor. The Schneiderian membrane was gently elevated to allow placement of graft directly over the sinus bone floor on each side of the posterior maxilla. A randomized sequence for graft placement meant that BioOss was placed on the left in 3 cases and on the right in 2 cases. At the time of surgery, TRCs were mixed with BioOss matrix, and excess fluid volume was removed using filtration and low-grade vacuum. Next, approximately10% by volume of autologous platelet-poor, fibrin enriched plasma was added to give a final approximate volume of 10ml graft. At the time of grafting, calcium chloride was added to gel the plasma, thus entrapping cells and matrix for ease of handling. For the control side, BioOss alone was mixed with autologous platelet-poor fibrin in an equivalent process to that used for TRC, for a final approximate volume of 8ml graft. Because there were significant differences in the baseline height (Table 2), height and width data were analyzed as change from baseline. The surgical site was closed with resorbable sutures.

Post-operative Care and Sequelae

Both sides of the face were exposed to cold at regular intervals and patients were advised to lean lightly against the head of the bed to reduce post-operative swelling. Within 6 hours of surgery, patients were allowed to eat, and were discharged within 60 to 90 minutes after the surgery. Oral hygiene instructions included Chlorhexidine mouth rinse after brushing 3 times a day for 2 weeks, to reduce risk of intra-oral infection. Upon discharge, subjects were prescribed

oral antibiotics, Amoxicillin 500mg with Clavulanic Acid 125mg, every 8h for 6 days, an oral anti-inflammatory drug, Diclofenac, 50mg every 8h for 5 days, pain reliever drug, magnesium metamizol, 3mg every 8h as needed, and an oral cytoprotective agent, Ranitidine, at 300mg every 24h for 6 days.

Radiographic imaging of posterior maxillae by Panorex and CT were done prior to surgery at the time of patient recruitment, and at 3 and 4 months, respectively, after surgery to evaluate the extent of reconstruction at grafted sites.

Implant placement occurred at 4 months after surgery. From 1 week prior to placement until the end of the study, all subjects were prescribed once daily 12% Chlorhexidine mouth rinses to reduce the risk of intra-oral infections. To prepare for endosseous implants under local anesthetic, a bone core sample was removed using a drill, 2mm thick and 12mm long. Bone cores were coded for identification to ensure double-blinding by the reader and the company, and processed for conventional histomorphometry (38). The drilled core was enlarged with increasing diameter drills at 1500 rpm, under saline irrigation. The implants was placed (implants in BioOss mean length: 15 ± SD 2mm, width 4 ± SD 1mm vs implants in TRC+BioOss mean length 15 ± SD 3mm, and width 4 ± SD 1mm). Testing with Ostell Frequency Resonance Analysis (FRA) immediately after implant placement showed equivalent stability (Ostell FRA for control BioOss: 75 ± SD5 vs TRC+BioOss: 74 ± SD6). The stabilizing screw was placed, and the site closed with resorbable sutures.

Bone Histomorphometry

At 10 weeks after graft surgery, and 6 weeks prior to implant placement, subjects were given 1 tablet of tetracycline hydrochloride, 200mg, 3 times a day for 2 consecutive days, and then 2 weeks later, a second series of 1 tablet of tetracycline, 3 times a day for 2 consecutive days, to label actively mineralizing bone surfaces. Bone cores were fixed, processed for calcified tissue sectioning, and static and dynamic histomorphometry, using conventional techniques and nomenclature established by the American Bone and Mineral Society in 1984 (38). Because the sections showed relatively low percent volume of BioOss, the measurements represent the bone response adjacent to the grafted sites. Attempts to obtain cores directly from the grafted site were technically difficult because of resistance in that region to drilling.

Planned Outcomes To Be Evaluated

Primary outcomes, in at least 4 of 5 cases treated with TRC+BioOss compared to BioOss alone, were the expectation of an increase in height between baseline to 4 months after surgery; equivalent or increased final height; sufficient bone to place an implant and good bone quality, as judged by histomorphometry. Secondary anticipated outcomes were equivalent or reduced post-operative swelling and infection within the first post-operative week, equivalent or increased bone volume and implants in function in 4 of 5 TRC+BioOss maxilla compared to controls. The final outcome to test the long term differences in mobility of implants at 4 months after placement is still to be evaluated.

Statistical Analyses

No adjustments were made for missing data, multiplicity or for covariates. Data from all randomized subjects were included in the full analyses set to determine treatment results. Because only 5 subjects were evaluated, data are shown as listings of measurements by treatment. BioOss was compared to TRC+BioOss by a paired 2-tailed t-test. Data from CT and histomorphometry were averaged within each patient, and then within-patient differences were analyzed. Because there were significant differences in baseline height between the maxilla pairs, data for height and width of graft area was normalized as change from baseline, and then compared. In the histomorphometry data set, data were analyzed including and excluding cores that showed no BioOss. Because the proximity of these BioOss-negative tissue sections to the graft site is unknown, we excluded them in the data analyses reported here.

Given the small sample size for this Phase 1 trial, a significance level of $p<0.1$ was used to indicate potential statistical significant differences. It should be noted that some measures achieved conventional statistical significance at $p<0.05$. Adverse events, concomitant medications and other safety measures are described in the text. The retention of implants for BioOss vs TRC+BioOss was plotted as a Kaplan-Meier survival chart using each implant of the 38 implants placed, as the unit of measurement. The circles on the plot represent implants from each of 5 patients, and their 2.4-6.7 months follow up data (Fig 7).

Results

All primary and secondary anticipated outcomes were met in 5 of 5 cases, exceeding the target 4 of 5 cases. In addition, data from histomorphometry suggested healing may differ when cells are mixed with BioOss, in a way that improves bone quality. The reader is cautioned that

although the benefits of cell therapy are anticipated to occur in the immediate post-operative period of up to 4 months, the longer-term success of overall therapy in retaining functional implants remains to be evaluated. This report represents an interim report of events that encompass up to 6.7 months after grafting, and 4 months after implants were placed.

All cases were Caucasian females, with a mean age of 51.3 years (Table 1). At the time of this interim report, subjects had been enrolled from 6.8-11.1 months; time since implant surgery ranged from 2.4 to 6.7 months (Table 1). Although 4 of 5 subjects had smoking histories of more than 20 years, all claimed to stop smoking prior to entering the study. Subjects 1, 2 and 3 were edentulous; subject 4 was edentulous in the posterior maxilla and subject 5 was edentulous in the maxilla and dentate in the mandible. Subjects 1 and 3 had lower mandibular implants placed 1 and 5 years earlier, respectively. Tooth loss was attributed to chronic periodontitis and caries. Dentate patients exhibited periodontal disease around remaining teeth. All cases exhibited extensive loss of basal bone, unfavorable convex or flat residual ridges (Cawood and Howell Classification III-VI)(39), and poor bone quality manifest as loss or replacement of cortical bone with low density trabecular bone (Lekholm and Zarb Classification 2-4) (40) (for example, see Figure 1). Subject 2 reported with a subcondylar fracture of one temporomandibular joint. Subject 3 had arthritis of the spine, a history of ulcer and hypercholesterolemia, while subject 5 has a history of polyps on her vocal cords and a hiatus hernia. None of these conditions appeared to affect clinical outcomes.

Despite additional co-morbid histories of smoking (subjects 2, 3, 4 and 5), osteoporosis (subject 1), post-menopausal status (subjects 1 and 3), small volume bone aspirates of 38 — 64ml were successfully obtained from the posterior ilium, yielding 236 x 10^6 to 301 x 10^6 mononucleated cells to be inoculated into the AastromReplicell System for enrichment culturing (Table 1).

There were no cell therapy—related adverse events. Subjects 3, 4 and 5 exhibited post-surgical swelling and bruising of the skin and oral mucosa on the control side but not on the TRC+BioOss side (Table 3). In adverse events, not related to cell therapy, subject 3 suffered infection and pain on each side after implants were placed, and was successfully treated with antibiotics. However, the infection resulted in the loss of one implant on the BioOss side and 2 implants on the TRC+BioOss side (Table 3, Figure 7). Such sequelae are anticipated adverse events that can occur after maxillary sinus floor augmentation surgery. Since dental implant placement, patients have maintained good peri-implant health (no bleeding on probing) and oral hygiene.

The bone dimensions measured by CT were increased at 3 months after surgery in TRC+BioOss compared to BioOss alone (Table 2, Figures 2, 3). The gain in height, expressed as change in height between 0 and 3 months post-surgery of maxillary sinus floor bone was greater in TRC+BioOss (mean change in height 11.8 ± SD 4.9mm vs BioOss alone (control) 10.6 ± SD 6.7mm, $p<0.012$ (Table 2). Because there was no significant difference between baseline values for width, we compared post-surgical bone width in pairwise comparisons for each subject. Mean post-surgical width for TRC+BioOss was 7.0 ± SD 3.3mm vs BioOss alone (control) 6.0 ± SD 1.0mm, $p<0.087$ (Table 2).

Histomorphometry showed incorporation of tetracycline label in bone graft regions on both sides, consistent with normal mineralization of bone, and good quality lamellar bone. There was evidence of active bone formation, as eroded surfaces covered with mononucleated cells or osteoblasts could be seen in stained sections, and for active bone resorption as osteoclasts were occasionally observed on eroded surfaces (Figure 4). There was no difference between groups in the fractional volume of BioOss (BioOss V/BV), which was small (Table 4), suggesting that cores were taken in close proximity to, but not through graft regions. Fractional surface area of BioOss, as a ratio to total bone surface area (BioOss S/BS), was decreased in TRC+BioOss, (Table 4, Figure 5). Static measures showed increased fraction of connective tissue volume/total volume (Fib V/BV) $p<0.06$, increased trabecular number (Tr.N) $p<0.07$, and decreased trabecular thickness (Tr.Th) $p<0.08$, in TRC+BioOss, compared to BioOss alone (Table 4, Figures 5, 6). These changes in trabecular architecture suggest TRC may regulate bone homeostasis in the vicinity of the graft. Interestingly, histomorphometry revealed good responders and no-responders to cell therapy (Table 4, Figures 5, 6). Differences in dynamic measures of bone formation and resorption were not significant, but when individual contrasts were plotted, individual differences in 1-3 TRC-treated cases could be observed (Table 4).

In all, 19 test (TRC+BioOss) and 19 control implants were placed at 4 months after grafting and cell therapy. On the side with TRC and BioOss, 14 implants were retained at 2.4 — 6.7 months (Figure 7), the time for this interim report. On the side with BioOss alone, 15 implants were retained at 2.4 — 6.7 months (Figure 7). There was no significant difference between groups on the timing at which implants were lost, or with the mobility that preceded that loss.

Discussion

This reports the first use of ex vivo, expanded bone marrow-derived cells (Tissue Repair Cells or “TRC”; Aastrom Biosciences Inc.) that have been enriched for stem and progenitor cells by single pass perfusion in the automated, process-controlled AastromReplicell System for 12 days, in bone augmentation of the edentulous posterior maxilla. TRC were characterized by flow cytometry for surface protein markers, and for their competency in CFU-f generation, to confirm the presence of stromal, stem and progenitor cells in the cell mix. We have reported that these cells synthesize cytokines required for tissue remodeling (18;21;41). Previously, these cells have been used systemically in cancer patients requiring bone marrow reconstitution (42;43) and in a select number of patients with nonunion fractures to promote bone healing (http://www.aastrom.com/recentpublications.asp). In the present small feasibility Phase 1 controlled trial, all of the desired outcomes to match or exceed effects of BioOss alone, by adding TRC to BioOss were met in 5/5 subjects, thus exceeding the original goal of achieving these outcomes in 4/5 subjects. The addition of TRC to BioOss matrix increased the dimensions of posterior maxillary bone, and regulated trabecular architecture of bone more than BioOss alone.

Cell therapy outcomes are likely to be most effective in the days and weeks immediately following therapy. In the present study, radiographic imaging was done at 3 months after cell therapy, and histomorphometry at 4 months after cell therapy. These are likely times when the direct benefit of adding cells to matrix can be assessed. BioOss is highly resistant to osteoclastic resorption and may persist at surgical sites for a decade or more. Although the fractional volume of BioOss was equivalent between groups, there was desired less BioOss surface area when TRC were combined with the matrix, and more connective tissue. In addition, in bone that had been judged to be poor quality prior to grafting, TRC appeared to induced changes in trabecular architecture associated with bone remodeling as trabecular thickness and number were modified (44). The data showing that there are good responders and non-responders to cell therapy will be critical to developing the appropriate indications for effective cell therapy.

There have been no cell-therapy adverse events associated with either previous studies or with the current study. One patient suffered infection after each side had received the dental implants; this resolved with antibiotics, and was judged to be an anticipated side effect of implant placement, especially in a post-menopausal women with a history of tooth loss due to

periodontitis and a long history of smoking, each one of which represents a risk of failure. In general, this set of cases represented women at high risk for peri-implant bone loss and implant failure, given their co-morbidities (24;29;45-50). In addition to demonstrating safety of TRC therapy in a small number of patients, we have also shown implants may be safely inserted earlier than the standard of care 6 months after grafts are placed, without causing undue mobility or significant premature implant loss.

In summary, the Aastrom Tissue Repair Cells, an autologous derived bone marrow stem cell product, were safely used to provide cellular content to BioOss matrix in procedures to successfully augment the dimensions of maxillary sinus floor bone in a controlled study of 5 edentulous women with severe maxillary bone loss. TRC also improved bone quality by regulating the trabecular architecture, increasing the connective tissue content of bone and reducing the surface area of BioOss. The study will continue for its final data check at 8 months after cell therapy (4 months after dental implants were placed), and patients will be followed for up to 2 years for safety observations only. A larger controlled study is needed to confirm and extend these interesting early findings.

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Table 1. Baseline patient demographics

	Case 1	Case 2	Case 3	Case 4	Case 5
Gender	Female	Female	Female	Female	Female
Age	74.5	37.0	58.0	45.8	41.1
Estrogen status	Post-menopausal	Active birth control	Post-menopausal	Active birth control	Active birth control
Race	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian
Smoking status	Non-smoker	Smoker 20 years	Smoker 25 years; quit 1987	Smoker 30 years	Smoker 20 years
Dentate and Bone status					
Anterior maxilla[1]	C VI	C V	C III	C I	C III
Anterior maxilla: bone quality[2]	4	2	2	3	4
Posterior maxilla[1]	D VI	D V	DIII	D III (R) D V (L)	D VI
Posterior maxilla: bone quality[2]	4	2	2	4	4
Iliac marrow aspirate					
Volume (ml)	37.7	61	61	49	64
No. Cells inoculated into ARS	251 x 10^6	236 x 10^6	299 x 10^6	250 x 10^6	301 x 10^6
No. Tissue Repair Cells/patient	197 x 10^6	70 x 10^6	114 x 10^6	117 x 10^6	120 x 10^6
Viability	90%	96%	95%	97%	90%
Patient disposition					
Duration since initial evaluation (months)	11.1	7.4	6.8	7.9	8.3
Duration since implant placed (months)	6.7	2.6	2.4	3.7	4.2

1 Cawood and Howell classification[39]

2 Lekholm and Zarb classification[40]

Table 2. To show maxillary bone height and width at baseline and 4 months after augmentation grafts (TRC+BioOss = TRC; BioOss alone = control) were placed in each case.

	Case 1		Case 2		Case 3		Case 4		Case 5	
	TRC	Control	TRC	Control	TRC	Control	TRC	Control	TRC	Control
Baseline bone height	6.8	7.4	8.4	10.2	8.4	13.2	3.7	5.7	6.6	8.2
Bone height at 4 months	23.8	22.2	20.2	20.8	19.6	20.2	21.0	21.3	16.8	16.4
Change in bone height	17.0	14.8	11.8	10.6	11.2	7.0	17.3	15.7	10.2	8.2
Baseline bone width	2.2	3.0	6.6	5.2	7.4	8.2	6.7	9.0	8.2	7.6
Bone width at 4 months	4.8	5.2	7.0	6.0	6.4	5.6	10.0	7.3	8.2	6.6
Change in bone width	2.6	2.2	0.4	0.8	-1.0	-2.6	3.3	-1.7	0.0	-1.0

Table 3. Summary Of Adverse Events: Post-operative Sequelae After Graft Placed On Maxillary Sinus Floor, And After Dental Implants Placed.

	Case 1	Case 2	Case 3	Case 4	Case 5
After graft placed					
Post-op swelling and bruising			BioOss	BioOss	BioOss
After implant placed					
Post-op swelling and bruising			BioOss TRC		
Infection (anticipated adverse event unrelated to cell therapy)			BioOss TRC		
No. implants lost	BioOss 1/4 TRC 1/4	BioOss 0/4 TRC 0/4	BioOss: 1/4 TRC: 2/4	BioOss 1/3 TRC 1/3	BioOss 1/4 TRC 1/4

Note: each case served as her own control, with BioOss alone (control) placed on one posterior maxillary sinus floor, and TRC + BioOss placed on the contralateral maxillary sinus floor.

Table 4. Histomorphometry Of Bone Formation And Resorption At Graft Sites, 4 Months After Cell Therapy.

			Formation Measures					Resorption Measures			
		BV/TV	OS/BS	ObS/BS	MAR	MS/BS	BFR/BS	ES/BS	OcS/BS	N.Oc/B.Pm	BioOss V/TV
		%	%	%	µm/d	%	mm/y	%	%	No/mm^2	%
1	C	20.2	18.2	7.23	1.08	7.0	0.04	17.4	1.74	0.36	1.6
2	C	37.9	6.3	1.15	0.51	3.6	0.01	1.14	0.20	0.40	1.6
3	C	25.1	6.3	1.29	0.53	6.0	0.01	4.93	0.47	0.06	1.8
4	C	33.4	10.1	1.58	0.69	2.4	0.01	4.66	0.60	0.12	6.5
5	C	36.1	4.4	0.54	0.72	1.8	0.01	3.67	0.37	0.07	10.5
Mean	**C**	**30.5**	**9.1**	**2.36**	**0.71**	**4.14**	**0.01**	**6.35**	**0.68**	**0.13**	**4.4**
SD		7.6	5.5	2.75	0.23	2.25	0.01	6.34	0.61	0.13	4.0
1	E	29.5	13.5	6.27	1.22	4.2	0.02	5.70	0.85	0.23	10.2
2	E	27.6	3.3	1.78	0.47	25.3	0.05	3.11	0.58	0.08	2.3
3	E	19.8	14.0	3.62	0.52	4.8	0.01	3.86	0.24	0.03	1.3
4	E	57.8	7.4	1.09	2.10	4.9	0.02	4.49	0.34	0.05	7.6
5	E	23.4	9.7	0.48	1.32	4.6	0.02	2.10	0.20	0.05	5.8
Mean	**E**	**31.6**	**9.6**	**2.65**	**1.13**	**8.8**	**0.02**	**3.85**	**0.44**	**0.09**	**5.5**
SD		15.1	4.4	2.34	0.67	9.2	0.02	1.36	0.27	0.08	3.7
p*		ns	ns	ns	ns	ns	ns	ns	ns	ns	ns

C: control, BioOss only; E: experimental, TRC + BioOss + platelet-poor plasma

* Statistical difference, p, was evaluated by parametric Student's t-test and non-parametric signed rank test as analyses of differences between control and experimental side for each patient. Measures with significant differences are shown in Figures

Nomenclature: BV/TV: percent bone volume of total volume; OS/BS: osteoid surface/bone surface; ObS/BS: percent bone surface covered by osteoblasts; MAR: mineralization apposition rate; MS/BS: percent mineralizing surface of total bone surface; BFR/BS: bone formation rate as fraction of total bone surface; ES/BS: percent eroded bone surface; OcS/BS: percent of bone surface covered by osteoclasts; N.Oc/B.Pm: number of osteoclasts per unit bone perimeter; BioOssV/TV: percent volume of BioOss in total volume sampled

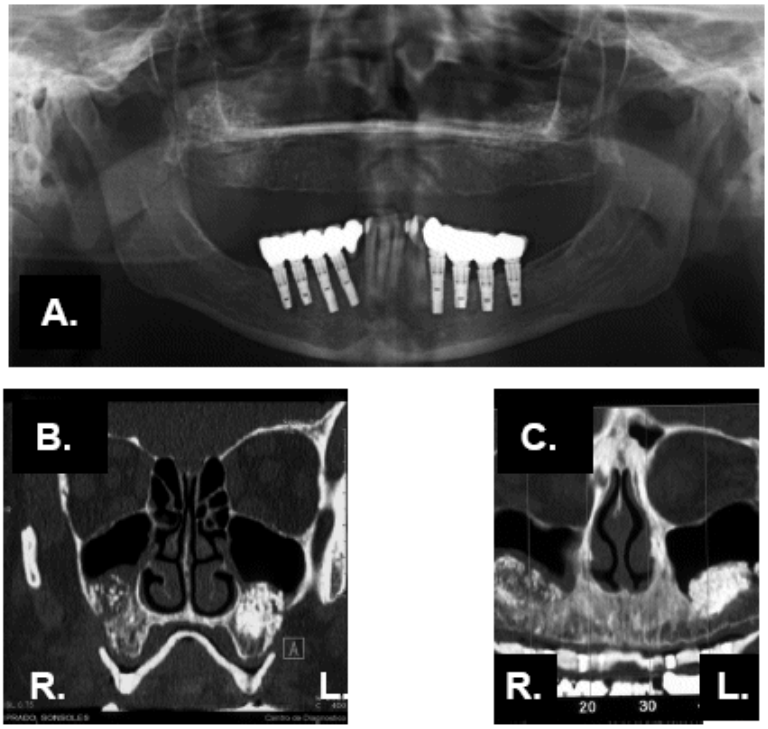

Figure 1. Example of cases to show severe bone loss and graft placement in posterior maxilla. Subject 1. A: Panorex radiograph to show minimal remaining basal maxillary bone, and dental implants in anterior mandible. B: and C: Different planes of “section” through CT radiographic image to show TRC+BioOss on right and BioOss (control) on left maxilla sinus floor.

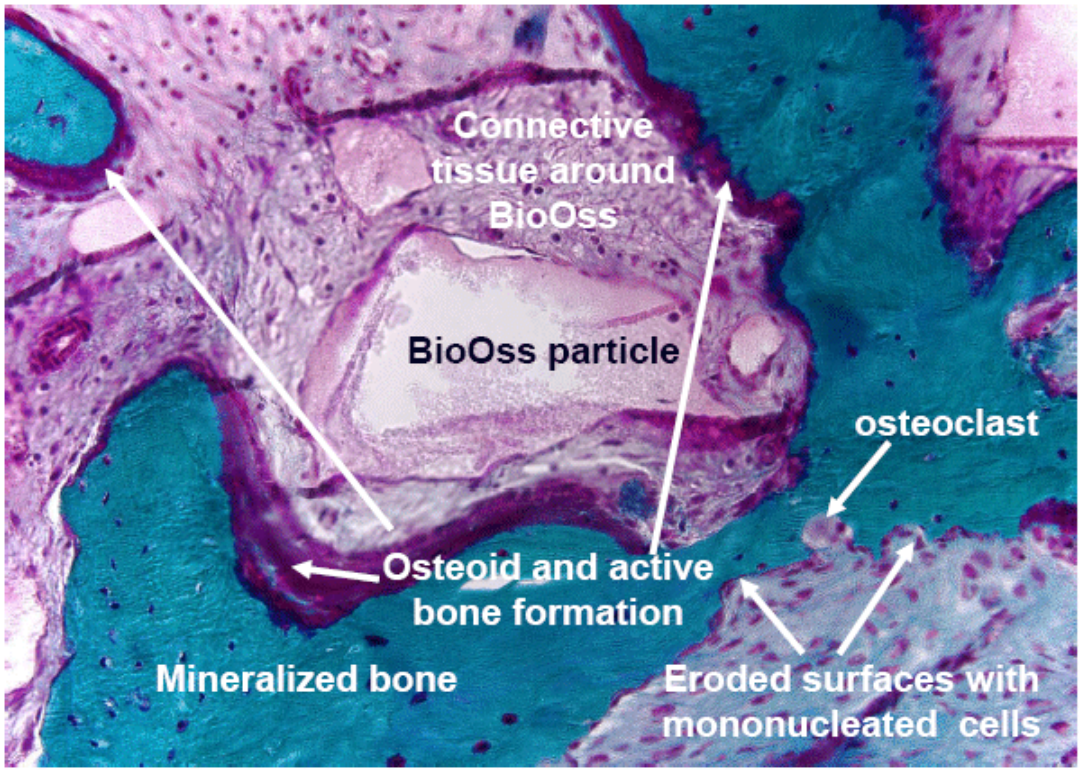

Figure 2. Stained histological section of bone graft to show BioOss and extensive new bone formation and bone turnover in vicinity of graft. Goldner Trichrome stain. Original magnification: 200x

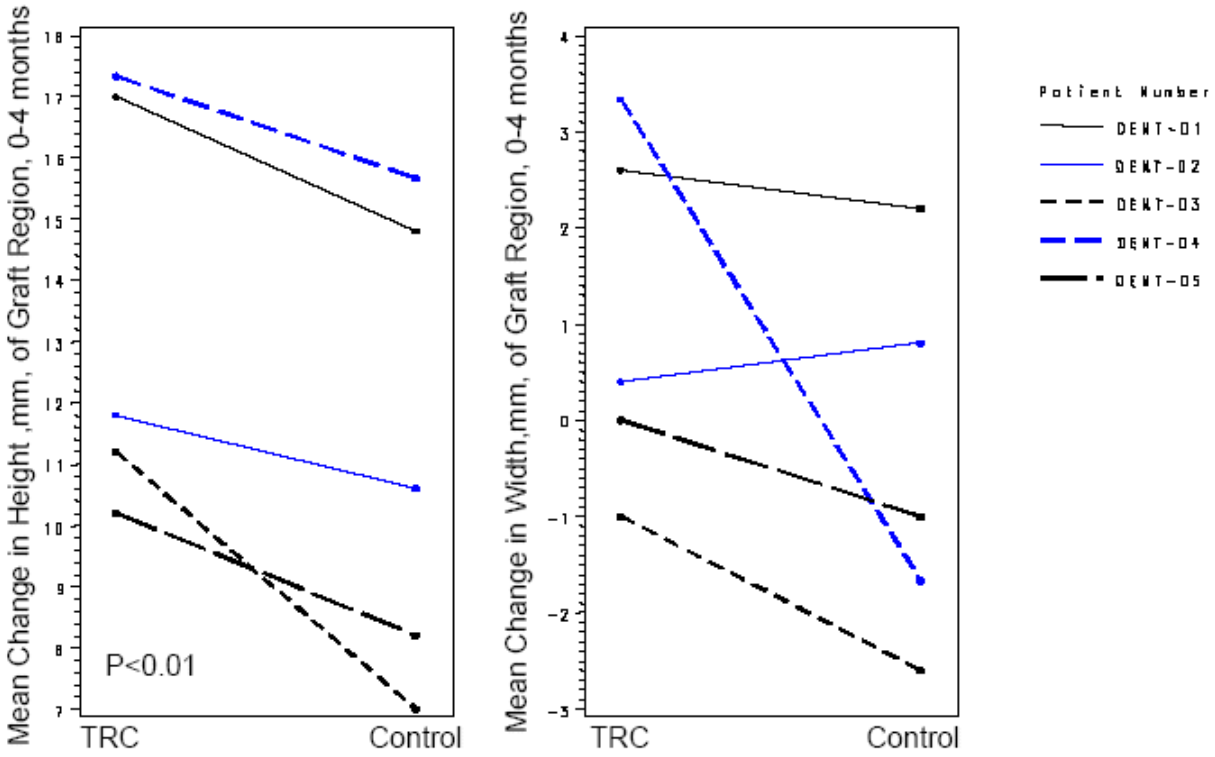

Figure 3. Data shown as difference in height and width of CT images of maxillary graft between 0 and 4 months measures for TRC+BioOss (TRC) and BioOss alone (control) for each case. Note that in all 5 cases, the change in height is increased on TRC+BioOss side, while in 3 of 5 cases, there is also increased change in width for TRC+BioOss.

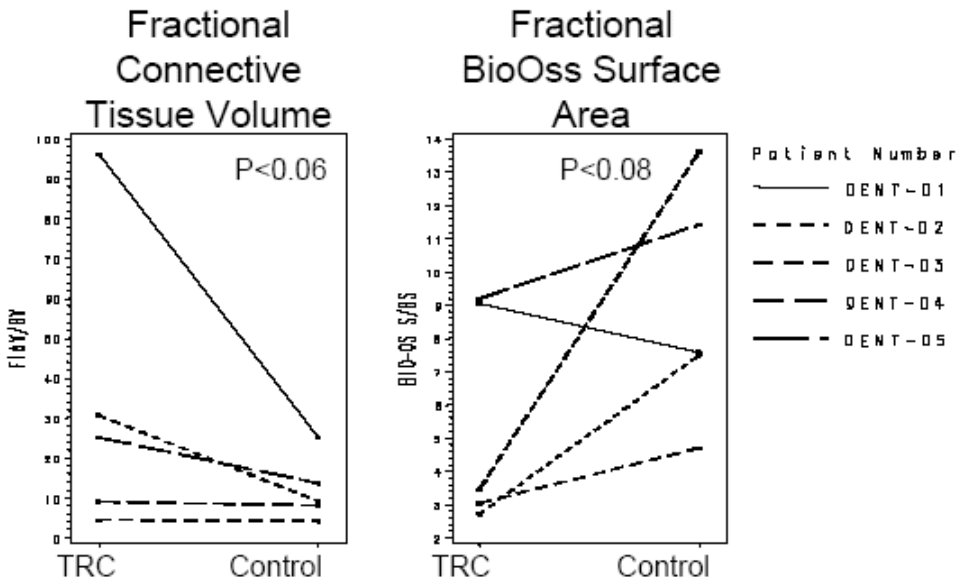

Figure 4. Static histomorphometry data to show fractional volume of connective tissue (Fib V/BV) and ratio of BioOss surface area to total bone surface area (BioOss S/BS) for each of the 5 cases. TRC+BioOss (TRC) is compared to BioOss (control) in each case. Note that 3/5 TRC grafts showed increased connective tissue volume, while 2/5 were equivalent to BioOss control. BioOss surface area decreased in 4/5 TRC grafts, and increased in 1/5 compared to BioOss control. We speculate the increase in connective tissue in TRC graft may be due matrix formed by TRC.

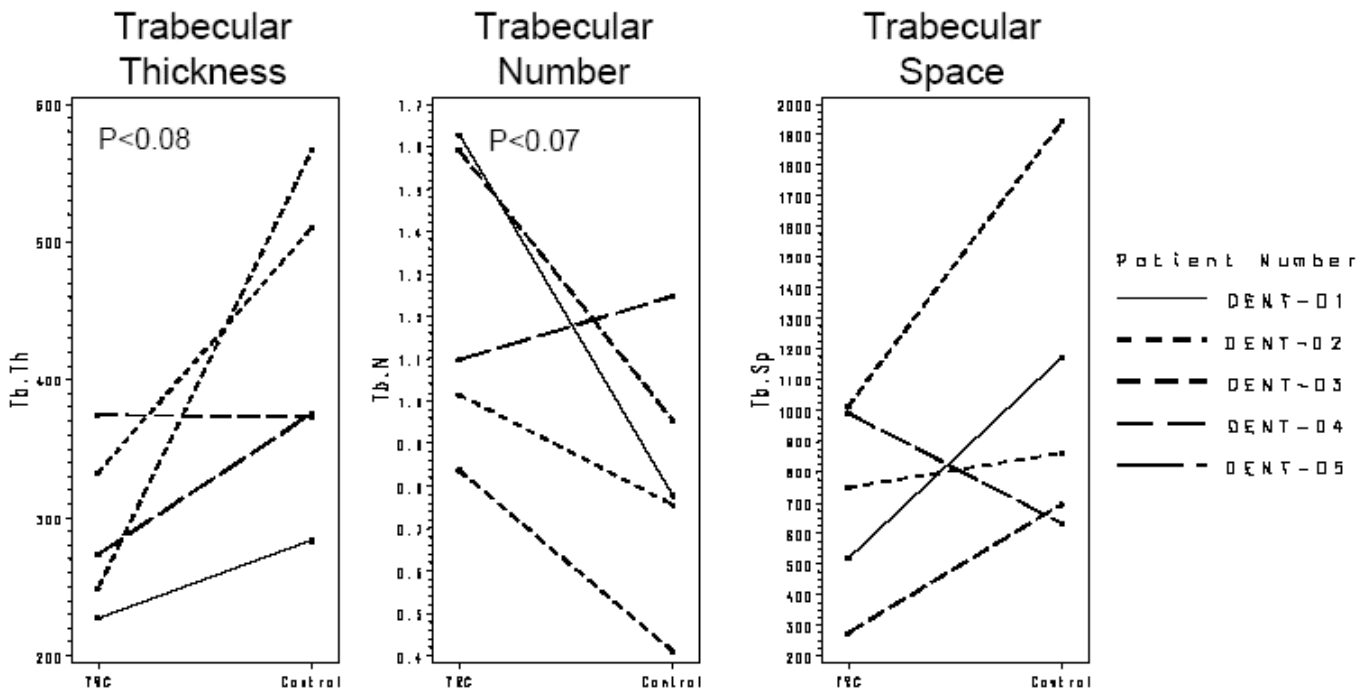

Figure 5. Comparison of static histomorphometry of trabecular architecture in each case, showing each side as TRC+BioOss (TRC) or BioOss alone (control). Note that trabecular thickness decreases in 4/5 cases, and trabecular number increases in 4/5 cases in TRC graft. The 5th case showed no change in trabecular thickness, and a small decrease in trabecular number, suggesting a low responder. Trabecular space decreased in 3/5 cases, increased in 1/5 case and remained equivalent to control in 1/5 case. This measure has high variability of measurement. These type of changes suggest more remodeling of trabecular architecture adjacent to TRC grafts

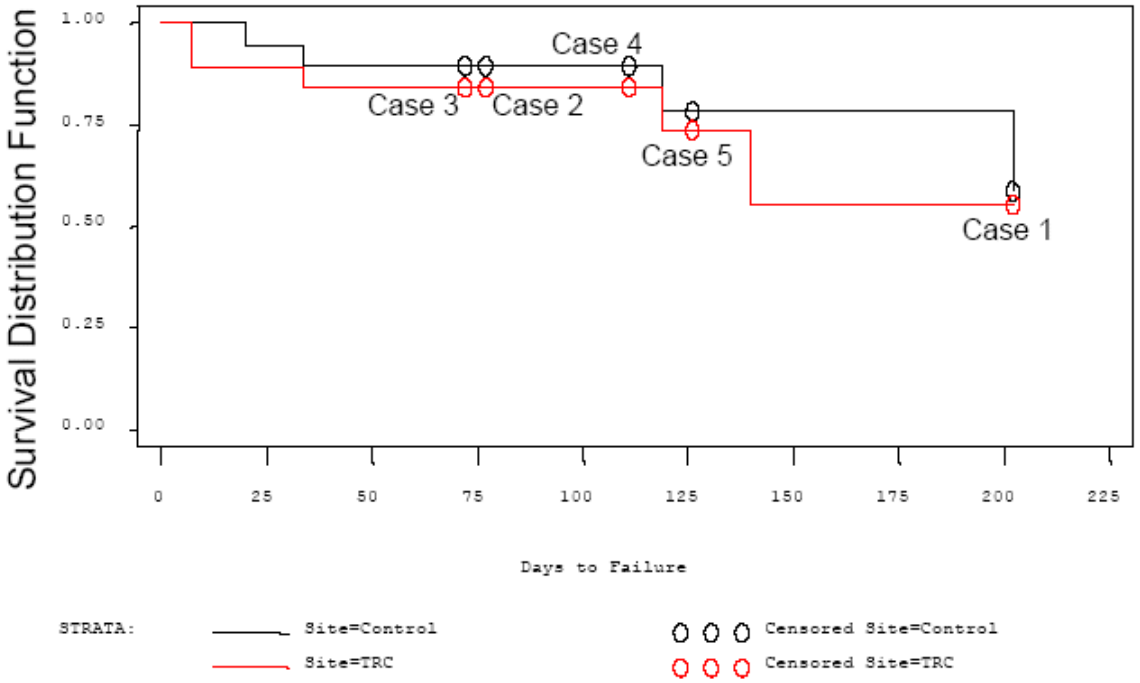

Figure 6. Kaplan-Meier plot of dental implant retention at 2.4 to 6.7 months after dental implants placed, showing no statistically significant difference in failure rate between groups. Day 0 is day of implant surgery; each circle represents superimposed retained ("censored") implants for each of 5 patients. The period of observation ranges from 2.4-6.7 months. A total of 19 implants were placed into the left and right maxilla of 5 cases. In TRC+BioOss (black), 5 of 19 failed and 14 (74%) remain censored (no failure to date). In BioOss alone (control), 4 of 19 implants failed and 15 (79%) remain censored. Subject 2 retained all 4 implants on each side.