CLINICAL REVIEW

Division of Clinical Evaluation, Office of Cellular Tissue and Gene Therapy, Center for Biologics Evaluation and Research; with consultation from the Office of Device Evaluation, Division of Anesthesiology, General Hospital, Infection Control, and Dental Devices, Dental Devices Branch, Center for Devices and Radiological Health

Application Type	BLA
Application Number(s)	125400
Received Date(s)	13-MAY-2011
PDUFA Goal Date	7-MAR-2012
Division / Office	CBER, with consultation from CDRH
Priority Review	N/A
CBER Reviewer	Agnes Lim, M.D.
CDRH Periodontal Consultant	Robert Betz, D.D.S.
Review Completion Date / Stamped Date	08-MAR-2012 / 08-MAR-2012
Applicant	Organogenesis, Inc.
Established Name	Apligraf
(Proposed) Trade Name	Gintuit
Pharmacologic Class	Cell Therapy
Formulation, including Adjuvants, etc	Allogeneic cultured keratinocytes and fibroblasts in bovine collagen
Dosage Form and Route of Administration	Cellularized sheet – single dose unit; topical application
Indication and Intended Population	For topical (non-submerged) application to a surgically created vascular wound bed in the treatment of mucogingival conditions in adults

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1 TITLE AND GENERAL INFORMATION

1.1 MEDICAL OFFICERS' (M.O.) Review Identifiers and Dates:

BLA #: 125400/0

Related CDRH PMA #: P090027-b(4)-

CBER CLINICAL REVIEWER:	Agnes Lim, M.D. (CBER)
CDRH CONSULTANT:	Robert Betz, D.D.S. (CDRH)
CBER TEAM LEADER:	Bruce Schneider, M.D.
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CBER DIVISION DIRECTOR:	Wilson Bryan, M.D.
CBER OFFICE DIRECTOR:	Celia Witten, Ph.D., M.D.

Submission Received by CBER/FDA: 13-MAY-2011

Review Completed: 08-MAR-2012

1.2 Product

1.2.1 Product Formulation

Gintuit is a bilayered cellularized sheet consisting of an upper layer of allogeneic epidermal keratinocytes and a supporting lower layer of bovine-derived collagen, human extracellular matrix protein, and human neonatal foreskin-derived dermal fibroblast. Each unit of Gintuit consists of approximately ---b(4)--- keratinocyte cells and ---b(4)---- fibroblast cells on a circular disk, approximately 75 mm in diameter and 0.75 mm thick.

This product is the same final product as the commercially available Apligraf product, approved by FDA CDRH in 1998 for the treatment of chronic cutaneous ulcers.

1.2.2 Dosage Form and Route of Administrations

Gintuit is a single dose-unit cellularized sheet that is applied topically (non-submerged) to a surgically created vascular wound bed. The amount of Gintuit used in one application, or one dose, is adjusted according to the size of the wound bed.

Reviewer Comment

1. *In this review memorandum, "Gintuit" refers to the product submitted for oral indications in this Biologic License Application (BLA), whereas "Apligraf" refers to the product that has been approved for chronic cutaneous wounds (VLU and DFU).*

1.2.3 Proper Name or Established Name:

Apligraf

1.2.4 Proposed Trade Name

Gintuit

Reviewer Comment

1 *In the BLA, the investigational product is called CelTx. CBER's Advertising and Promotional Labeling Branch (APLB) has completed the proprietary name review (PNR) for the proposed proprietary name and considers CelTx, short for "cell treatment," misleadingly implies that the product has a unique composition and a unique, cell-dependent mode of action, but this is not supported by data. Among the alternative names that were resubmitted, the trade name Gintuit was found to be acceptable and will be the final trade name.*

1.3 Applicant:

Organogenesis, Inc.

150 Dan Road
Canton, MA 02021

1.3.1 Pharmacological Class or Category:

Cell Therapy

1.3.2 Proposed Indication:

Gintuit is an allogeneic cellularized scaffold product indicated for topical (non-submerged) application in the treatment of mucogingival conditions in adults.

Gintuit is not intended to provide root coverage.

Reviewer Comments

1. *The Applicant's original proposed indication, "CelTx is intended for the treatment of surgically created gingival and alveolar mucosal surface defects. CelTx is applied over a vascular wound bed to regenerate site-appropriate oral mucosal tissue," is unacceptable. The exact clinical indication must be supported by data from the trials. This issue is further discussed below. The indication and patient population for Gintuit were also among the clinical topics that were discussed at the November 2011 AC meeting for this BLA.*
2. *The two clinical studies submitted to support the primary efficacy claim were conducted in subjects with an insufficient zone of keratinized tissue (attached gingiva). The clinical efficacy for alveolar tissue defects was not evaluated in the clinical studies.*

1.3.3 Proposed Population:

Adults (18 years of age and older)

Reviewer Comment

1. *During the early phase of reviewing this BLA, mucogingival conditions, such as gingival recession-type defects, were thought to be uncommon in children. However, at an AC meeting for this BLA in November 2011, some AC members believed that this product could be used in children between the ages of 12 and 18, in orthodontia-related gingival conditions. The regulatory actions that will be implemented to address this pediatric issue will include a PMR for a deferred clinical study in adolescents and a partial pediatric waiver for children less than 12 years of age (See Section 10.4 for further details).*

2 EXECUTIVE SUMMARY

Gintuit is a bilayered cellularized sheet consisting of allogeneic epidermal keratinocytes, dermal fibroblasts, extracellular matrix proteins, and bovine-derived collagen. The product is applied topically (non-submerged) to a surgically-created vascular wound bed. Gintuit for oral use is the same final product as the commercially available Apligraf that has been approved by CDRH since 1998 for the treatment of chronic cutaneous wound ulcers.

The Biologic License Application (BLA) included study reports from two clinical studies (Studies 05-PER-001 and 06-PER-002) for topical (non-submerged) application of Gintuit, and from Study 07-PER-004 for the submerged (under a flap) application of Gintuit. These studies evaluated the efficacy and safety of Gintuit for the treatment of mucogingival recession-type defects associated with insufficient zones of keratinized tissue. The trials were regulated by the US Food and Drug Administration (FDA), Center for Devices and Radiological Health (CDRH).

The data supporting efficacy claims were derived from two prospective, randomized, within-subject controlled (matched for teeth and gingival condition), treatment comparison clinical trials. The overall design of the first study (Study 05-PER-001) was similar to the design of the subsequent study (Study 06-PER-002); therefore, efficacy results from Study 05-PER-001 are relevant to the proposed clinical indication and are included. The duration of the studies was six months. In these studies, each subject received Gintuit and a control consisting of a free gingival graft (FGG) taken from the subject's palate. The study did not provide root coverage or treat the underlying periodontal disease. A total of 107 subjects from the two studies are included in the efficacy analysis.

The first study, Study 05-PER-001 (N=25) was conducted at a single center. The study population consisted of adults with an insufficient zone of attached gingiva that required soft tissue grafting. The first three subjects participated as training subjects and were not included in the efficacy analysis (n=22 for efficacy analysis). The study was designed to rule out a greater than 1-mm decrease in the change in attached gingiva for Gintuit relative to control. In this study, keratinized tissue (KT) width was a secondary endpoint. At six months, Gintuit sites in 14/22 (63.6%) subjects showed an increase in attached gingiva, compared to 21/22 (95%) for control sites. The mean increase in attached gingival was 0.85 mm (95% CI 0.48, 1.21) for Gintuit sites and 2.43 mm (95% CI 2.06, 2.79) for control sites. Thus, Gintuit failed to demonstrate non-inferiority to control for the primary efficacy

endpoint. For the secondary endpoint, keratinized tissue (KT) width, at six months, at least 2 mm of KT width was established in 18/22 (81.8 %) of Gintuit sites; the mean increase in KT width was used to guide the design of the subsequent study, Study 06-PER-002.

The second study, Study 06-PER-002 (N=96) was a multi-center study conducted at four sites in the US. The study population and treatment procedure were similar to Study 05-PER-001. Eleven of the 96 subjects participated as training subjects and were not included in the efficacy analysis (n=85 for efficacy analysis). The primary efficacy was measured as the percentage of Gintuit sites with ≥2 mm KT at six months, using a superiority comparison to a pre-defined standard (50% success) in a single-arm comparison. Eighty-one of the 85 subjects (95.3%) met success criteria of ≥2 mm KT at the Gintuit site. Although success was not compared to control for the primary efficacy endpoint, all 85 subjects met the primary endpoint at the control site. There were six secondary efficacy endpoints, pre-specified and conducted sequentially. Gintuit was found statistically superior to control for color matching, texture matching, and patient preference, but it was not found to be superior to control for the last two secondary endpoints (surgical site sensitivity and absence of pain after three days).

The safety data come from Studies 05-PER-001 and 06-PER-002 and a third pilot study (Study 07-PER-003) that used a different application procedure (submerged under a flap). The integrated safety population consists of 136 trial subjects, all of whom received one application of Gintuit (25 from Study 05-PER-001, 96 from Study 06-PER-002, and 15 from Study 07-PER-003). This BLA seeks approval of Gintuit for a non-submerged use; however, the submerged study provides additional safety information for Gintuit in the oral environment. Additionally, there is extensive safety information derived from postmarket experience with Apligraf for chronic cutaneous wounds. The most common adverse reactions observed in the clinical trials (≥1%) included sinusitis, nasopharyngitis, respiratory tract infection, aphthous stomatitis, and the local effects of oral surgery. Overall, there have been no significant immune-related AEs and there has not been any case of malignancy attributed to Apligraf in clinical trials or commercial use of the product. However, the safety of Gintuit has not been evaluated beyond six months or in children in clinical trials.

This BLA was the subject of an FDA Cellular, Tissue, and Gene Therapy Advisory Committee (CTGT AC) meeting on November 17, 2011. The clinical topics discussed at the AC meeting included safety, effectiveness, indication for the product, the intended population, and concerns about Gintuit being used in children, should Gintuit be approved. Based on the safety and efficacy data presented, the AC Members voted that the product was safe (14/15 votes) and effective (15/15).

Gintuitis is expected to have a favorable risk-benefit ratio when used as described in the label. The review team recommends approval of this BLA. There has been no safety issue identified that warrants a Risk Evaluation and Mitigation Strategy (REMS) in adults. A clinical postmarketing requirement (PMR) under the Pediatric Research Equity Act (PREA) will be issued requiring the Applicant to conduct a postmarketing study to evaluate the safety and effectiveness of Gintuit for topical (non-submerged) application to a surgically created vascular wound bed in the treatment of mucogingival conditions in children between the ages of 12 to18 years. The Applicant has agreed to conduct this

postmarketing study and has agreed to submit the final study protocol by December 31, 2012; to complete the study by September 30, 2016; and to submit the final study report by March 31, 2017.

3 CLINICAL AND REGULATORY BACKGROUND

3.1 Regulatory Background

This product is manufactured using a process similar to the Applicant's commercially available, FDA-approved medical device, Apligraf. Apligraf was approved by FDA for the treatment of Venous Leg Ulcers (VLU; P 950032) on May 22, 1998 and for the treatment of Diabetic Foot Ulcers (DFU; P950032/S016) on June 20, 2000. Gintuit was the subject of three IDE studies for oral indications prior to submission of BLA 125400 on May 13, 2011:

- G050122 – 05-PER-001: "A Pilot trial of Apligraf in establishing a functional zone of attached gingiva"
- G070012 – 06-PER-002: "A clinical trial to evaluate CelTx (Apligraf) as an alternative to tissue from the palate to enhance oral soft tissue regeneration and wound healing"
- G070178 – 07-PER-004-CTX: "A prospective, randomized, controlled pilot study of CelTx (Apligraf) as an alternative to tissue from the palate in the treatment of gingival recession requiring root coverage"

Assignment of the lead center for the review and regulation of a combination product is determined by its primary mode of action (PMOA), in accordance with section 503(g)(1) of the Federal Food, Drug, and Cosmetic Act and 21 CFR section 3.4. In this case, the biological component of the combination product was determined to provide the PMOA for the dental indication.

The Applicant has sponsored and completed two clinical investigations with Gintuit under Investigational Device Exemptions (IDEs), pilot Study 05-PER-001 (IDE G050122) and pivotal Study 06-PER-002-CTX (IDE G070012). In both studies, the investigational agent was applied topically (non-submerged; i.e., not under a surgical flap) to an area of insufficient zone of attached gingiva that required soft tissue grafting in adults. The efficacy and safety data collected from these two clinical studies, coupled with the additional histological evaluation from Study 05-PER-001, independent photo assessment and prospective ancillary biomarker study from Study 06-PER-002, were submitted in support of this marketing application.

In addition, a third oral study was conducted in a submerged clinical application, performed under IDE G070178. Since this BLA seeks approval of Gintuit for a non-submerged use (i.e., it is placed on top of the surgically created mucosal surface defect or surgical wound bed and is not placed under a surgical flap) the efficacy results from the 07-PER-004 submerged study were not evaluated as supportive data for the intended indication;

however, safety results from this study were included to evaluate the safety of Gintuit in the oral environment.

CBER received the Biologics License Application (BLA) on May 13, 2011. The application included study reports on three clinical trials. The clinical regulatory histories of Apligraf and Gintuit are summarized in Table 1 below.

Table 1 Clinical Regulatory Histories of Apligraf (CDRH) and Gintuit (CBER)

	CDRH
JAN 17, 2007	Received IDE (G070012.0), for a clinical study of Apligraf for cutaneous wounds
MAY 22, 1998	Original approval by FDA/CDRH/DGRND for Apligraf in the US for the treatment of venous leg ulcers (VLU) under P950032
JUN 20, 2000	Apligraf, approved by FDA CDRH for the treatment of neuropathic diabetic foot ulcers (DFU) under P950032/S016
DEC 8, 2008	Pivotal Study 006-PER-002-CTX completed (OCT 15, 2007 – December 8, 2008); Final Study Report completed on November 17, 2009
DEC 19, 2009	PMA (P090027) submitted to CDRH
FEB 1, 2010	FDA issues a 45-Day "Refuse to File" letter. (The Agency assigned jurisdiction for review of the new indication to CBER).
Date	**CBER**
MAY 13, 2011	FDA CBER received the Biologics License Application (BLA) for Gintuit.
NOV 17, 2011	This BLA was the subject of an FDA Cellular, Tissue, and Gene Therapy Advisory Committee (CTGT AC) meeting in Silver Spring, MD.
FEB 22, 2012	PeRC Subcommittee Meeting: 1) Partial pediatric waiver, for children younger than age 12; and 2) Deferral for post-marketing study in adolescents (ages 12 - 18) to evaluate the safety and effectiveness of Gintuit for orthodontal-related gingival recession.

3.2 Disease or Health Related Condition(s) Studied

Mucogingival Conditions
Mucogingival conditions are soft tissue defects that disrupt the normal anatomic relationship between the gingival margin and the mucogingival junction. They may be caused by anatomic, traumatic, or chronic inflammatory conditions secondary to trauma or infection. Chronic inflammation may predispose to risk of progressive loss of gingival attachment, resulting in gingival recession and root exposure. Gingival recession with exposure of the root surface has a number of potential implications, including root sensitivity, root caries, complications of home care procedures, and poor aesthetic appearance.

Treatments/Interventions for Proposed Indication
Surgical intervention is warranted when the inflammation and/or gingival attachment loss can no longer be controlled with conservative oral hygiene measures. The main objective of periodontal mucogingival surgical procedures is to arrest or reduce the risk of gingival attachment loss; improvements in aesthetics may also result. Soft tissue autografts, such as the free gingival grafts (FGG), are widely used for the treatment of mucogingival conditions. These procedures act to increase the zone of keratinized gingiva around teeth with soft tissue keratinization. In 2005, 1.5 million soft tissue grafting procedures were performed in the United States. Approximately 600,000 of those procedures were performed to treat gingival recession.

Mucogingival surgical procedures may be used to treat

1. Anatomic soft tissue defects such as:
    a. An insufficient zone of attached gingiva caused by an abnormally positioned tooth (naturally occurring or secondary to orthodontic treatment),
    b. Aberrant or high frenum placement, causing muscle pull against the gingival margin, and
    c. Abnormally shallow vestibular anatomy defects

2. Mucogingival soft tissue defects causing chronic gingival inflammation, due to any of the following:
    a. Improper dentogingival contouring
    b. Improper tooth brushing technique
    c. Damage to oral tissues caused by intraoral piercings
    d. Drug abuse caused by direct intraoral placement of recreational drugs
    e. Periodontitis

Gintuit is proposed to be administered in the treatment of mucogingival problems such as the ones described above. When root coverage is warranted, other surgical techniques and barrier membranes may also be used to obtain root coverage, including, but not limited to pedicle graft procedures, coronally positioned flap grafting procedures, and guided tissue regeneration (GTR). Soft tissue autografts can be used in an initial step to increase the zone of attached gingiva in preparation for pedicle or coronally positioned graft procedures. In some cases, multiple and sometimes sequential procedures may be necessary (Nicolucci 2011; Oh 2009).

4 SIGNIFICANT FINDINGS FROM OTHER DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

Stability of Cell Banks

Karyotypic stability of the culture-expanded fibroblasts and keratinocytes was identified as a potential safety concern. New cell banks are introduced on a periodic basis for Apligraf manufacture. To date, the Applicant has an extensive cell banking history to date, which

allows for comparison of numerous cell strains. The testing results for cytogenetic analysis of all master cell banks (MCBs) generated since 2000 were submitted to the BLA and the data showed a consistently low frequency of chromosomal aberrations.

4.2 Clinical Pharmacology

Mechanism of Action

Gintuit does not function as a tissue graft and the cellular components of Gintuit do not persist long-term in oral mucosal wounds. The mechanism of action by which Gintuit increases keratinized tissue at the treated site has not been identified.

Reviewer Comments

1. *Gintuit has not been claimed to integrate with connective tissues to heal wounds by primary intention. The Applicant has stated that Gintuit acts predominantly as a stimulus to improve the rate of healing wounds by secondary intent.*
2. *The mechanism of action by which Gintuit increases keratinized tissue at the treated site has not been identified. In vitro studies have shown that Gintuit secretes human growth factors and cytokines, and contains extracellular matrix proteins. Growth factors, cytokines, and extracellular matrix proteins are known to be involved in wound repair and regeneration.*

4.3 Pharmacovigilance

The Applicant has submitted a detailed pharmacovigilance plan, following ICH E2E PVP guidance. For the proposed oral indication, the adverse event profile appears to be small. There have been no documented clinical or histological reports of tumor formation at the site of application. The FDA Office of Biostatistics and Epidemiology (OBE) has determined that the Applicant's pharmacovigilance plan for Gintuit is acceptable.

Routine pharmacovigilance activities will be conducted by the Applicant's regulatory Affairs and Medical Affairs Departments under standard operating procedures to determine causality, relationship and severity of an adverse event. Organogenesis will oversee an outside pharmacovigilance contract organization (PVCO) to generate MedWatch forms for each adverse event, maintaining the Gintuit pharmacovigilance database and compiling periodic Safety Update Reports. The PVCO has not been selected yet.

4.4 Statistical

There were no major statistical issues that would impact the interpretation of the results of Study 006-PER-002.

5 CLINICAL DATA SOURCE, REVIEW STRATEGY, AND DATA INTEGRITY

5.1 Material Reviewed

The following studies were used to assess effectiveness.

- G050122 – 05-PER-001: "A Pilot trial of Apligraf in establishing a functional zone of attached gingiva"
- G070012 – 06-PER-002: "A clinical trial to evaluate CelTx (Apligraf) as an alternative to tissue from the palate to enhance oral soft tissue regeneration and wound healing"
- G070178 – 07-PER-004: "A prospective, randomized, controlled pilot study of CelTx (Apligraf) as an alternative to tissue from the palate in the treatment of gingival recession requiring root coverage"

The safety review is based on data from all three studies plus postmarketing data from the commercially available Apligraf for chronic cutaneous wounds.

5.2 Review Strategy

The evidence of effectiveness is primarily based on review of the efficacy data from 06-PER-002. The safety review included analysis of the datasets supplied by the sponsor and is based on the safety dataset from Studies 05-PER-001, 06-PER-002, supplemented by safety information from Gintuit in a submerged study, as well as by the postmarketing experience for Apligraf. The dataset was also reviewed for potential study design and conduct issues, such as eligibility, blinding, response assessment, imbalance between arms, dropout rates and missing data, protocol deviations, and efficacy and safety results across subgroups. Individual Case Report Forms (CRFs) for particular subjects/sites were reviewed, where indicated. The sponsor's analyses were reproduced and additional FDA statistical analyses were performed using these datasets. The data provided on the CRFs were also assessed for recording accuracy and adherence to protocol stipulations by the FDA Bioresearch Monitoring (BIMO) review process and site inspections that were conducted at three selected study sites.

5.3 Data Quality, Integrity and Compliance with Good Clinical Practice

The clinical studies were conducted according to Good Clinical Practice (GCP). All clinical studies have been conducted with IRB approval and appropriate informed consent.

The BIMO Branch of the Division of Inspections and Surveillance, Office of Compliance and Biologics Quality performed investigator and site inspections in support of this BLA. Study protocols, subject enrollment, geographic distribution, and serious adverse events were among the factors used to select the inspection sites.

5.4 Financial Disclosures

Certification of financial disclosure (Form 3454) was provided by the applicant. The applicant certified that, as the sponsor of the submitted studies, no financial arrangement with the clinical investigators listed have been entered into whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a).

One investigator had financial arrangements or held financial interests with the sponsor. He was a clinical investigator in all three oral indication Organogenesis Protocols, as shown in the Table 2. From August 05, 2005 through February 24, 2010 (one year after Study 06-PER-002 was completed), inclusive, this investigator received payments and other compensations from the sponsor totaling ---b(4)b(6)--- for general consulting on oral regeneration. The majority of this consulting –b(4)b(6)-- occurred after the last patient, last visit of the 06-PER-002 study.

Table 2 Clinical Sites at which the Dental Provider was an Investigator

Protocol Number	**Protocol Title**	**Date of Subject's First Visit***	**Date of Subject's Last Visit**	**Number of Subjects at Investigator's Site/Total # Trial Subjects**
05-PER-001	A Pilot Clinical Trial to Assess the Safety and Efficacy of Apligraf in Establishing a Functional Zone of Attached Gingiva	11/1/2005	4/26/2006	25/25
06-PER-002	A Clinical Trial to Evaluate Apligraf as an Alternative to Tissue from the Palate to Enhance Oral Soft Tissue Regeneration and Wound Healing	10/15/2007	12/8/2008	34/96
07-PER-004	A Prospective, Randomized, Controlled Pilot Study of Apligraf as an Alternative to Tissue from the Palate in the Treatment of Gingival Recession Requiring Root Coverage	6/17/2008	9/22/2010	15/15

*Date of surgery (Day 0) took place at Subject's first visit.

This investigator treated 18 of the 34 subjects (53%) at his clinical site and 19% (18/96) of the total subjects treated in the 06-PER-002 Pivotal Study. His clinical site treated approximately one third of the subjects in the multicenter (4 centers) 06-PER-002 Pivotal Study (34/96).

Reviewer Comments

1. *BIMO's inspection included this investigator and sites where he treated study subjects.*
2. *FDA statistician's examination of this investigator's site to see if there were any troubling patterns of differences in results compared to other sites did not reveal any important differences in efficacy results. At this investigator's site, Gintuit did slightly worse on the primary endpoint than at other sites, slightly better vs. control on color and texture matching (but not enough to affect the statistical significance of the comparison to control), and no different on patient preference, for KT ≥ 1mm, sensitivity, or pain.*
3. *This investigator performed the surgical treatment procedure, but he did not perform the outcome measures for the primary or secondary efficacy endpoints. In all three oral indication trials, all efficacy outcome measures were performed by evaluators, called calibrated examiners, who underwent calibration measurement training against a standard examiner prior to study initiation.*

6 ANALYSES OF EFFICACY – DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study 05-PER-001 (Non-submerged)

Title
"A pilot Clinical Trial to Assess the Safety and Efficacy of Apligraf in Establishing A Functional Zone of Attached Gingiva"

6.1.1 Objectives

The objectives were to assess the safety and preliminary efficacy of Gintuit in establishing a functional zone of attached gingiva in patients with an insufficient zone of attached gingiva.

6.1.2 Design Overview

This was a prospective, randomized, single-center, within-subject controlled (matched for teeth and gingival condition), pilot study of 25 subjects.

The first three subjects participated as training subjects to help determine surgical and material handling technique. Subsequent subjects were enrolled when the first three had completed four weeks of follow-up. Anatomical treatment site and order of treatment were randomized. Following randomization, subjects received both a palatal graft and Gintuit.

For safety monitoring, pre-treatment, Day 0 and post-treatment clinical assessments of all subjects, including training subjects, were performed to rule out local or systemic reactions,

and infection. Additional safety assessments consisted of monitoring and recording potential adverse events and serious adverse events (SAEs). The investigator queried the subjects on possible adverse events at each visit.

The primary efficacy evaluation occurred at Month 6, with interim visits at Week 1, Month 1, and Month 3. For efficacy analysis, the training subjects were not included.

Additionally, a laboratory study was simultaneously conducted to examine the histology and tissue architecture of surgical tissues obtained from seven study subjects' Apligraf and control treatment sites. DNA persistence studies were also performed on the biopsy specimens from two of these seven biopsy specimens. (See Section 7.4 for further details).

Reviewer Comment

1. *It is difficult to evaluate relatedness to product for systemic adverse reactions reported in within-subject controlled studies.*

6.1.3 Population (Inclusion/Exclusion Criteria)

Eligibility: Subjects were adult males and females with an insufficient zone of attached gingiva associated with at least two non-adjacent teeth; root coverage was not desired.

Inclusion Criteria
1. Age 18 to 70
2. At least two non-adjacent teeth with an insufficient zone of attached gingiva, which required soft tissue grafting. The two selected teeth needed to be located in contralateral quadrants. (In case of adjacent teeth requiring grafting, only one tooth at each site acted as test or control tooth, but both teeth got the same treatment)
3. Root coverage not desired or indicated at the time of grafting

Exclusion Criteria
1. Teeth that had an insufficient zone of attached gingiva that would be best treated using soft tissue grafts to cover the denuded root surface
2. Any systemic conditions (i.e., diabetes mellitus, cancer, HIV, bone metabolic diseases) that could compromise wound healing and preclude periodontal surgery
3. Currently receiving or had received within one week prior to study entry, systemic corticosteroids (including inhaled), immunosuppressive agents, topical antibiotics, topical cytotoxic agents, radiation therapy, and/or chemotherapy, which could compromise wound healing and preclude periodontal surgery
4. Presence of acute infectious lesions in the areas intended for surgery
5. Patients who smoke
6. Teeth requiring treatment were molars
7. Teeth with axial mobility
8. Known hypersensitivity to bovine collagen

9. Patients enrolled in medical, dental, or any investigational device study for any disease within the past four weeks before study assessment
10. Patients who had received an investigational drug or biological treatment within the three months prior to study enrollment (medical or dental)
11. Patientts previously treated with Apligraf, Dermagraft or any other skin graft at the target site(s)
12. Patients who, in the opinion of the investigator, for any reason other than those listed above, would not be able to complete the study per protocol

6.1.4 Study Treatments Mandated by the Protocol

Preparation of the oral mucosal defects for Gintuit placement in surgically created recipient sites involves current standard soft tissue preparation techniques. The recipient site is anesthetized using standard local anesthetic procedures. This is followed by placement of Gintuit that has been properly folded and adapted to fit the recipient site. Gintuit is then sutured into place. Additional sutures may be placed to tack down the alveolar mucosal flap.

In the pilot (and pivotal) studies with Gintuit for the oral indication, investigators were instructed to remove the mucosa and any underlying connective tissue from the facial aspect of the mucogingival deformity, as well as to remove any muscle fibers with scissors to create a clean periosteal bed prior to placing either Gintuit or the FGG control. Thus, an “oral mucosal defect” (i.e., surgical wound bed) was created prior to the non-submerged placement of Gintuit.

Gintuit was prepared in an “s-fold” to form a 3-layer construct (epidermal side out) and trimmed to the size needed according to the number of teeth treated and the subject's anatomy. Gintuit was applied to the base of the mucosal defect within 15 minutes of removing it from the storage container. The prepared Gintuit was placed in direct contact with the appropriate randomized study mucosal defect bed, centered on the study tooth (any remaining length could have been used to treat adjacent teeth), and sutured in place at the papilla with resorbable sutures. If possible, Gintuit was secured apically at the discretion of the surgeon. If technically feasible, a criss-cross (i.e., suspensory) suture was placed over Gintuit to enhance stability and help maintain direct contact with the base of the mucosal defect.

An additional layer of Gintuit that extended laterally beyond the wound margins was placed over the entire preparation. The additional layer was placed in close apposition to the base of the mucosal defect and sutured at the four corners, when possible. The lip or cheek adjacent to the mucosal defect was placed under tension to make certain that Gintuit was free of movement during muscle traction. Coe-Pak surgical dressing was placed over the treatment site. Coe-Pak was left in place until it fell off on its own or was removed by the investigator by the two-week follow-up visit. The investigators were permitted to re-apply a new piece of Gintuit if the original piece was dislodged within the first 48 hours after surgery.

One to three teeth could be treated. In case of adjacent teeth requiring grafting, only one tooth at each site acted as treatment or control tooth, but all teeth received the same treatment. Root coverage at the identified study teeth was not performed at the time of grafting.

Procedure for Palatal Graft /Control Site

The palatal site (also called harvest site or donor site in the submission) was harvested and grafted according to standard practice. The width of all palate grafts was 5 mm with the length dictated by the size of the mucosal defect. Preparation of the oral mucosal defects for the control site (also called control recipient site in the submission) followed current standard of care.

Concomitant Therapy

Medications listed in the exclusion criteria were not permitted. Only those agents specified in the protocol were to be used in the oral cavity. These were to be recorded in the case report forms at each visit. All patients were instructed to rinse with 0.12% chlorhexidine, a prescribed antiseptic mouth rinse, for one minute twice daily for the first four weeks to maintain plaque control in the surgically treated areas. Topical antibiotics were only allowed if a clinical infection was diagnosed after treatment.

6.1.5 Site and Center

The single investigational site (Site 01) was located in Houston, Texas and included two investigators.

6.1.6 Monitoring Schedule

The study and monitoring schedule for pilot study 05-PER-001 is shown in Table 3.

Table 3 Study and Monitoring Schedule for Pilot Study 05-PER-001

	Baseline Screen	**Treatment**			**Follow-up**	**Final Study Visit**
Study Procedures:		Day 0 Surgery ± 2 days	Week 1 (Day 7) ± 2 days	Month 1 (Day 28) ± 2 days	Month 3 ± 7 days	Month 6 ± 14 days
Dental and Medical History	X					
Pregnancy Test	X					
Review Hygiene Procedures	X		X	X	X	X
Surgery		X†				
Plaque Score	X				X	X
Bleeding	X				X	X
Probing Depth		X†				X
Cementoenamel Junction	X	X†				X
Mucogingival Junction	X	X†				X
Recession Depth	X		X	X	X	X
Clinical Attachment	X					X
Resistance of Muscle Pull	X					X
Inflammation Score	X	X†	X	X	X	X
Keratinized Tissue	X	X†			X	X
Radiograph	X					X
Photographs	X	X†	X	X	X	X
Persistence						X
3 mm Biopsies						X
Subject Discomfort Questionnaire			X			
Subject Aesthetics Questionnaire						X
Medication	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X

† The Baseline and Surgery (Day 0) visit may be combined into a single visit.

6.1.7 Endpoints and Criteria for Study Success

The safety outcome included the number of spontaneous adverse events and serious adverse events (SAEs) reported and clinically assessed to detect local or systemic reactions, and infection. MedDRA was used to classify adverse events.

The primary efficacy endpoint was the change in the amount of attached gingiva at Month 6 compared between treatments. The trial was designed to demonstrate non-inferiority between Apligraf (oral) treatment and free gingival graft (FGG) control in the amount of change in attached gingiva over six months.

Assessment method for primary efficacy endpoint:
- The amount of attached gingiva was evaluated using a calibrated periodontal probe, measured to the nearest 0.5 mm.

Criterion for success for primary efficacy endpoint:
- The absolute change in the amount of attached gingiva over 6 months, using a non-inferiority comparison of Gintuit to control.

The secondary efficacy endpoints were:
1. Inflammation
2. Color and texture match of the graft to the adjacent tissue
3. Resistance to oral muscle pull
4. Probing depth
5. Clinical attachment level
6. Subject preference or satisfaction (including pain experience)
7. Change in recession depth
8. Width of keratinized tissue

Assessment methods for secondary endpoints are summarized below. All evaluations except for the subject satisfaction questionnaire were performed by the efficacy outcome evaluator.

- Color compared to surrounding tissue: More/ Less/ Equally Red; at 1 week, 3 months, and 6 months
- Texture compared to surrounding tissue: More/ Less/ Equally Firm; at 4 weeks, 3 months, 6 months
- Inflammation: Scored by an examiner on a scale of 0 (absence of inflammation) to 4; at Week 1, Months 1, 3, and 6
- Probing Depth and KT width: Measured in mm
- Clinical Attachment Level: Calculated from probing measurements
- Resistance to Muscle Pull: Free gingiva movement when cheek/lip retracted; assessed at 6 months
- Subject Satisfaction: Based on responses to two questionnaires:
    1. Subject Aesthetics Questionnaire – marked response on a line between "Disappointed" and "Fully Satisfied"
    2. Subject Discomfort Questionnaire - queried subjects for perceptions of the severity of pain, bleeding, swelling, and sensitivity for the Gintuit site, control site, and palate site. These were rated as None, Mild, Moderate, or Severe.
- Recession depth: The examiner answered either "No" or "Yes" to whether recession was found on clinical examination, with probing depth recorded in mm.

Criteria for success for secondary efficacy endpoints
- There was no detailed statistical analysis plan for secondary endpoints, and no adjustments were made for multiplicity

6.1.8 Statistical Considerations and Statistical Plan

Efficacy outcome Assessment Methodology:
The first three treated subjects were excluded from statistical analysis. The efficacy analysis population was 22 subjects.

The primary efficacy variable, the absolute change in the amount of attached gingiva at six months, was analyzed using a non-inferiority comparison of the mean within-subject difference in gingival attachment between Gintuit and control. The non-inferiority margin was a 1.0 mm difference in change in gingival attachment. Calculations at 5% significance level determined that 20 evaluable subjects were sufficient to detect non- inferiority with over 95% power when the margin of equivalence is a 1.0 mm change in amount of attached gingiva and the true difference is 0 mm.

Secondary efficacy outcomes, listed above, were evaluated using superiority comparisons. There was no statistical analysis plan for secondary endpoints. In particular, there was no pre-specified order of testing, and no adjustments were made for multiplicity. The assessment methods for these endpoints are briefly described above in Section 6.1.6. The time points for these assessments are summarized in Table 3.

6.1.9 Study Results - Efficacy Analysis

Subject Disposition

Twenty-five subjects were enrolled in the study. All 25 subjects completed all visits.

Demographics

Baseline characteristics of the 25 subjects are provided in Table 4.

Table 4 Study 05-PER-001: Demographics of Study Populations

Demographics	Efficacy Analysis (N=22)* Statistics Mean (n%)	Safety Analysis (N=25)* Statistics Mean (n%)
Age – mean (range)	50.0 years (31-69)	49.1 years (31-69)
Gender		
Male	7 (31.8%)	8 (32.0%)
Female	15 (68.2%)	17 (68.0%)
Race/Ethnicity		
Caucasian, non-Hispanic	19 (86.4%)	22 (88.0%)
Hispanic	1 (4.5%)	1 (4.0%)
Asian/Pacific Islander	1 (4.5%)	1 (4.0%)
Middle Eastern	1 (4.5%)	1 (4.0%)

***** Data from the three training subjects were not used for efficacy analysis; data from all 25 subjects were used for safety analysis. Fifty percent of the subjects were former smokers; no current smokers were enrolled in the study.

Analysis of Efficacy

Primary efficacy endpoint
At six months, Gintuit sites in 14/22 (63.6%) subjects showed an increase in attached gingiva, while 21/22 (95%) of control sites showed an increase in attached gingiva. The average increase in the amount of attached gingiva at Month 6 was 0.85 mm (0.48, 1.21) for Gintuit and 2.43 mm (2.06, 2.79) for control. Thus Gintuit failed to demonstrate non-inferiority to control for the primary efficacy endpoint. The results are summarized in Table 5.

Table 5 Primary Endpoint Results for Study 05-PER-001 (N=22)

	Baseline Mean (95% CI)	**6 Months** Mean (95% CI)	**Change** Mean (95% CI)[1]
Attached Gingiva			
Apligraf	0.30 (0.13, 0.46)	1.14 (0.77, 1.50)	0.85 (0.48, 1.21)
Control	0.27 (0.11, 0.44)	2.71 (2.34, 3.07)	2.43 (2.06, 2.79)

Secondary Endpoints
Width of keratinized tissue was a secondary endpoint. At six months, at least 2 mm of keratinized tissue width was established in 18/22 (81.8%) Gintuit sites and in 22/22 (100%) control sites. At six months, the mean increase in KT width was 1.37 mm (0.97, 1.77) at Gintuit sites and 3.33 mm (2.93, 3.74) at control sites. Thus, there was a larger change from baseline to 6 months in the width of keratinized tissue in the control sites compared to the Gintuit sites.

Regarding assessment of periodontal health around test and control teeth, there were no differences between Gintuit and control in the change from baseline to six months in probing depth, recession, and clinical attachment. There was also no important difference in resistance to muscle pull, inflammation, or bleeding on probing within the two groups. Table 6 shows the results for Gintuit and control sites for the secondary endpoints of probing depth, recession, clinical attachment, and keratinized tissue width. The applicant presents data for changes in the first three parameters as baseline minus 6 months.

Table 6 Change in Secondary Endpoint Clinical Variables from Baseline to 6 Months in Study 05-PER-001 (N=22)

	Baseline Mean (95% CI)	**6 Months** Mean (95% CI)	**Change (Baseline to 6 months)** Mean (95% CI)
Probing Depth			
Gintuit	1.37 (1.18, 1.56)	1.41 (1.24, 1.58)	-0.04 (-0.26, 0.18)
control	1.36 (1.17, 1.55)	1.68 (1.51, 1.85)	-0.32 (-0.54, -0.11)
Recession			
Gintuit	2.42 (2.17, 2.66)	2.16 (1.89, 2.44)	0.25 (0.09, 0.42)
control	2.36 (2.11, 2.60)	2.02 (1.74, 2.30)	0.34 (0.18, 0.50)
Clinical Attachment			
Gintuit	3.79 (3.49, 4.08)	3.58 (3.32, 3.83)	0.21 (-0.05, 0.47)
control	3.71 (3.42, 4.01)	3.70 (3.45, 3.95)	0.01 (-0.25, 0.28)
Keratinized Tissue Width*			
Gintuit	1.13 (0.92, 1.33)	2.50 (2.18, 2.82)	1.37 (0.97, 1.77)
control	1.24 (1.03, 1.44)	4.57 (4.25, 4.89)	3.33 (2.93, 3.74)

* The sponsor expressed changes in KT width by subtracting the baseline from the 6-month values. Changes for the three other parameters are expressed as baseline minus 6 months.

At Month 6, Gintuit was numerically superior to control for the following secondary endpoints: tissue color (more sites equally red compared to surrounding tissue), texture matching (more sites equally firm compared to surrounding tissue), and patient preference. These results are shown in Tables 7 and 8.

Table 7 Gingival Characteristics at Month 6 by Treatment Groups (N=22)

Gingival characteristic	**Gintuit**	**control**
Tissue color:	($p<0.001$)	($p<0.001$)
Less red	0	91%
Equally red	100%	9%
More red	0	0
Tissue texture:		
Less firm	0	0
Equally firm	91%	0
More firm	9%	100%

Table 8 Patient Preference* at Month 6 by Treatment Group (N=22)

	Mean ± SD**	**Median**	**Range**
Patient Preference:			
Gintuit	89.1% ± 18.2	93%	13% to 100%
control	83.7% ± 15.7	90%	50% to 100%

* See Section 6.1.6 for explanation of Patient Preference.
** Secondary endpoint analysis did not account for multiplicity, therefore no p-value is included.

The perception of pain at Week 1 was one of the variables in the patient preference assessment, evaluated by the Subject Discomfort Questionnaire. Using the four-point scale described above, there was no evidence of a decrease in reported pain between the Gintuit and control recipient or donor sites. At Week 1, more subjects reported severe pain at the Gintuit graft site than at either the control graft or donor site.
Results for pain at Week 1 in Study 05-PER-001 are shown in Table 7.

Table 9 Evaluation of Pain at Gintuit/control Graft/Palate Sites at Week 1, Study 05-PER-001 (N=22)

	Pain at Specified Site			
Grading:	**Gintuit**	**control (c)**	**palate (p)**	**c/p***
None	3 (13.6%)	2 (9.1%)	8 (36.4%)	1 (4.5%)
Mild	5 (22.7%)	9 (40.9%)	9 (40.9%)	8 (36.4%)
Moderate	9 (40.9%)	10 (45.5%)	4 (18.2%)	11 (50.0%)
Severe	5 (22.7%)	1 (4.5%)	1 (4.5%)	2 (9.1%)

* C/P stands for Control (Graft Site)/Palate and represents the more severe of the pain scores reported by the subject for the palate and control graft sites.

Due to the lack of adjustment for multiple testing across secondary endpoints, statistical testing of these results is not included here.

Subpopulation Analyses

There was no subgroup analysis for Study 05-PER-001.

Reviewer Comment

1. *FDA's subgroup analysis for Study 06-PER-002, the study that provided the primary efficacy data for effectiveness, is performed (see Section 6.2).*

Protocol Deviations

There were six lack-of-compliance protocol deviations during the study, among four subjects. Four of the deviations were for "Visit outside of the window" for the Week 1 visit. There was one deviation for "Visit outside of the window" for the Week 4 visit. There was one deviation for nasal steroid use during the fifth month, noted during the Month 6 Visit. No subject was discontinued from the study because of a protocol deviation.

Summary of Efficacy Results

In summary, Gintuit failed to demonstrate success in the non-inferiority primary endpoint of establishing a zone of attached gingiva comparable to that of a free autogenous palatal graft. There was some indication of success in three (tissue color matching, texture matching, and patient preference) of the eight secondary endpoints. For tissue color matching, 100% of subjects graded Gintuit sites as equally red (compared to surrounding tissue). In contrast, 9% of subjects graded control sites as equally red, and 91% of subjects graded control sites as less red. For tissue texture matching, 91% of subjects

graded Gintuit sites as equally firm (compared to surrounding tissue), and 9% of subjects graded Gintuit sites as more firm. In contrast, 100% of subjects graded control sites as more firm. Based on the results of Study 05-PER-001, the Applicant chose an increase in KT as the primary efficacy endpoint in the subsequent study, 06-PER-002.

6.2 Study 06-PER-002 (Non-submerged)

Title
"A Clinical Trial to Evaluate CelTx (Apligraf) as an Alternative to Tissue from the Palate to Enhance Oral Soft Tissue Regeneration and Wound Healing"

6.2.1 Objectives

The primary efficacy objective was to assess the ability of Gintuit to achieve a "clinically acceptable threshold for keratinized tissue (KT) at 6 months (≥ 2 mm KT)."

Five of the six secondary objectives (numbers 1, 2, 4-6 below) were to determine if Gintuit was superior to FGG. The other secondary objective (number 3 below) was to measure superiority of Gintuit compared to a pre-specified 80% success standard of achieving KT ≥ 1mm. The secondary objectives, in pre-specified order of statistical testing, were:

1. Color same as adjacent tissues after 6 months
2. Texture same as adjacent tissues after 6 months
3. KT ≥1 mm for Gintuit after 6 months (superiority vs. an 80% success standard)
4. Patient preference after 6 months
5. Surgical site sensitivity mild or absent after 1 week
6. Pain absent after 3 days

6.2.2 Design Overview

This was a prospective, randomized, within-subject controlled (matched for teeth and gingival condition), treatment-comparison, pivotal, multicenter (four sites in US) trial of 96 subjects with insufficient zone (≤ 1 mm) of attached gingiva requiring soft tissue grafting.

After meeting entry criteria, each subject was assigned an identification number that was sequentially assigned to correspond with the order of the enrollment into the study. Study teeth in contralateral quadrants were selected by the investigator at the baseline visit; however, randomization of study teeth to receive either Gintuit or control treatment did not occur until immediately prior to surgery at Day 0. Each side of the mouth received a different treatment (and treatment order) as determined by a randomization assignment on Day 0. For each subject, the study tooth sites were randomly selected to receive either Gintuit or Control (FGG). To prevent bias in assigning treatment, a sealed envelope contained a predetermined computer generated randomization scheme that included randomizations for both treatment assignments for the two teeth and order of implementing

treatment administration. The first two subjects treated per investigator participated as training subjects for surgical and material-handling techniques and were excluded from the efficacy analysis.

A single application of Gintuit was applied to an oral mucosal defect on one study tooth at Day 0. The control treatment consisted of a free gingival graft (FGG) harvested from the subject's palate and applied to an oral mucosal defect on a second, contralateral study tooth on Study Day 0. Due to the nature of the control treatment, neither the investigator nor the subject could be blinded to study tooth treatment assignment or order of surgical procedure. In addition, according to the Applicant, given the distinct appearance of the FGG, it was not possible to ensure blinding of a third-party evaluator.

The primary efficacy evaluation occurred at Month 6, with interim visits at 48 and 72 hours, one and two weeks, Month 1, and Month 3. There were no follow-up visits or contacts for safety or efficacy beyond six months.

In addition, the Applicant conducted an adjunct biomarker laboratory study. The objective of this study was to compare the expression of angiogenic biomarkers involved in the wound healing process of the Gintuit - vs. FGG-treated sites. (See Section 8.7.4 for further details.)

6.2.3 Population (Inclusion/Exclusion Criteria)

Adult males and females with an insufficient zone of attached gingiva associated with at least two non-adjacent teeth in contralateral quadrants of the same jaw; root coverage was not desired. The study enrollment criteria are shown below.

Inclusion Criteria
1. Age 18 - 70 years
2. At least two non-adjacent teeth in contralateral quadrants of the same jaw with an insufficient zone (≤1 mm) of attached gingiva that requires soft tissue grafting. One to three teeth may be treated. In case of adjacent teeth requiring grafting, only one tooth at each site will act as test or control tooth, but all teeth will receive the same treatment.
3. Root coverage not desired at the time of grafting.

Exclusion Criteria
1. Class III recession in the presence of a shallow vestibule, or class IV recession
2. Vestibule depth of less than 7 mm from base of recession
3. Any systemic conditions that could compromise wound healing and preclude periodontal surgery (i.e., diabetes mellitus, cancer, HIV, bone metabolic diseases)
4. Currently receiving, or has received within two months prior to study entry, systemic corticosteroids, immunosuppressive agents, radiation therapy, and/or chemotherapy which could compromise wound healing and preclude periodontal surgery
5. Presence of acute infectious lesions in the areas intended for surgery
6. Patient who has used any tobacco product within 3 months
7. Patient who is taking intramuscular or intravenous bisphosphonates

8. Only molar teeth suitable for soft tissue grafting
9. Teeth that have Miller Grade 2 or higher mobility
10. Known hypersensitivity to bovine collagen and/or iodine (shellfish allergy)
11. Patient who has received an investigational drug or biological/bioactive treatment within 30 days prior to study enrollment
12. Patient who was previously treated with Apligraf, Dermagraft or any other skin graft at the target site(s) or immediately adjacent teeth
13. Patient, who in the opinion of the investigator, for any reason other than those listed above, will not be able to complete the study per protocol

6.2.4 Study Treatment Mandated by the Protocol

The surgical treatment procedure performed in this study was similar to that of Study 05-PER-001. However, in this study, the Gintuit product was "z-folded", rather than "s-folded," for treatment application. The minimum Gintuit size was 5 mm wide by 10 mm long, and the product was sized to fit the defect. (See Section 6.1.1 for further details of treatment procedure).

The palatal graft harvest followed standard procedures. In this study, the width of all grafts was 4mm, whereas graft widths were 5 mm in Study 05-PER-001.

Reviewer Comment

1. *Although Gintuit was "s-folded" in Study 05-PER-001 and it was "z-folded" in Study 06-PER-002, both procedures resulted in a three-layered sheet before it was trimmed and applied to the surgical wound bed.*

Concomitant Medications and Treatments

Medications listed in the exclusion criteria were not permitted. Only those agents specified in the protocol were to be used in the oral cavity. These were to be recorded in the case report forms at each visit. All patients were instructed to rinse with 0.12% chlorhexidine for one minute twice daily the first four weeks to maintain plaque control in the surgically treated areas. Topical antibiotics were only allowed if a clinical infection was diagnosed after treatment.

6.2.5 Sites and Centers

The study was conducted at four centers, including single centers in Houston, Texas (Site 10), San Antonio, Texas (Site 15), Ann Arbor, Michigan (Site 16), and Boston, Massachusetts (Site 17).

6.2.6 Monitoring Schedule

Following screening and randomization, subjects received both Gintuit and a free gingival graft.

The first follow-up visit occurred one week post-surgery. Any adverse events or changes in medications were documented. The subject's surgical procedure preference and determination of sensitivity were recorded and oral hygiene instructions reviewed. Additional follow-up evaluations occurred at 4 weeks, 3 months, and 6 months post-surgery.

Changes in medications and adverse events were documented at each visit.

Photographs of the test sites and clinical measurements were obtained and texture and color of the test areas were evaluated.

At 4 weeks, pain and sensitivity were also assessed. An oral exam was performed at 4 weeks and 6 months. At 3 and 6 months post-surgery, a dental cleaning was performed. At 6 months post-surgery, a Subject Preference Questionnaire was completed and radiographs of the study teeth obtained. The study events schedule is shown in Table 10.

Table 10 Study Schedule for Pivotal Study 06-PER-002

	Screen	**Baseline**	**Treatment**	**Follow-up**						**Final Visit**
Study Procedure:		(16 days post screen)	**Day 0/Surgery** (14 days post baseline)	**48 & 72 hr**	**1 Wk**	**2 Wk**		**4 Wk**	**3 Mo**	**6 Mo**
						Visit	Phone Call			
Medical and History	X									
Oral Hygiene Procedures	X	X	X		X	X		X	X	
Surgery			X*							
Telephone Well-Being Check				X			X			
Plaque Score		X							X	X
Bleeding on Probing		X							X	X
Probing Pocket Depth		X								X
Proximal Probing Depth		X								X
Recession Depth		X			X	X		X	X	X
Clinical Attachment		X								
Muscle Pull Resistance		X								
Inflammation Score		X			X	X		X	X	X
Keratinized Tissue Width		X							X	X
Radiographs		X								X
Photographs			X		X	X		X	X	X
Texture and Color Match								X	X	X
Sensitivity, Bleeding, Swelling					X	X		X		
Dental Cleaning		X							X	X
Subject Surgical Preference					X					
Subject Preference Questionnaire										X
Medication	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X

* Re-treatment with Gintuit may occur if original treatment was lost within 48 hrs. of surgery.

Reviewer Comment

1. *There were no pre-specified plans on how the photographs would be analyzed in the statistical analysis plan/protocol. Therefore, results of the photographs will not be discussed in this review.*

6.2.7 Endpoints and Criteria for Study Success

Methodology for Outcomes Evaluation
Subjects were given a paper diary to be completed daily through Day 14. Subjects were asked if the surgical dressing stayed on at each of the surgical sites and the palatal donation site. Subjects recorded pain associated with each surgical site and the palatal graft donation site by assessing the pain for each as none, mild, moderate, or severe. Additionally, this diary was used to record any medications the subject had taken for mouth-related pain. In addition, study personnel placed telephone calls to subjects at 48 hours post-surgery, 72 hours post-surgery, and at two weeks post-surgery to perform a wellbeing check.

All clinical measurements were performed by investigators, who were specifically trained to make the specific assessments (training protocol 06-PER-003). Measurements included probing depth, recession depth, and identification of the mucogingival junction (as used to obtain keratinized and attached gingiva measures).

Keratinized tissue was measured by the roll technique with Schiller's Iodine Stain. Measurements were taken with a UNC-15 probe and rounded to the nearest 0.5 mm. Within each clinical study site, attempts were made to have the same examiner complete the clinical measurements for all subjects and all visits.

Assessments of color and texture of treated (Gintuit or control) oral mucosal defects compared to adjacent, non-treated mucosa were performed at Months 1, 3, and 6 and were rated, in terms of redness and firmness, as either less, the same, or more, compared to redness and firmness of adjacent mucosa.

At six months, Subject Preference was assessed by asking subjects to respond to the question "Taking into account all aspects of treatment (surgery, recovery, and appearance) which treatment is preferred?" Subject Surgical Preference was assessed at one week.

Sensitivity was assessed by elicitation with a three-second puff of air. The subject was asked to report the amount of sensitivity at each site (none, mild, moderate, or severe).

Criteria for Evaluation
The primary and six secondary efficacy outcome variables are listed in Section 7.2.1. The primary efficacy variable, the per cent of Gintuit sites with $\geq$ 2 mm KT at six months, was analyzed using a superiority comparison to the pre-defined standard (50% success).

Five of the six secondary endpoint evaluations were superiority comparisons between Gintuit and control. The other endpoint was a superiority comparison of Gintuit to pre-specified benchmark. For all six secondary endpoints, the order of testing was pre-specified, and tests were conducted sequentially.

Safety Evaluations
Safety was assessed by monitoring and recording treatment-specific and systemic adverse events. (Safety results are provided separately in Section 8.4).

6.2.8 Statistical considerations and Statistical Plan

The superiority of Gintuit relative to a pre-defined standard (50% success) for a ≥ 2 mm KT threshold after six months was tested with an exact binomial test, using a Type I error rate of 0.05 for analysis of the primary efficacy endpoint.

The secondary hypotheses were tested using a superiority closed testing strategy, in which the order of testing is pre-specified. This strategy allows each test to be conducted sequentially at the 0.05 level until a test is found not to be statistically significant, at which point no subsequent secondary endpoints are tested for statistical significance.

Reviewer Comment

1. *The Applicant did not provide an explanation for the selection of a 50% benchmark.*

Analysis Populations Definitions

The following populations were defined for analyses:

- Intent-to-Treat (ITT) consisted of all subjects randomized into the trial
- Modified Intent-to-Treat (mITT) population consisted of all ITT subjects who received the treatment as randomized to each side of the mouth and were followed for at least one week.
- Per Protocol (PP) population consisted of all mITT subjects followed through Month 6.
- Safety Population consisted of all subjects (including training cases) treated with Gintuit and/or Control (Free Gingival Graft)

The following cohorts of subjects were defined:

- The training cohort was comprised of the first two subjects treated by each surgeon; this cohort was included in the statistical analysis for baseline and effectiveness summaries (but not effectiveness testing; see below) and safety analysis.
- The efficacy analysis cohort contained all subjects not identified as training cases.

Effectiveness was analyzed on all subjects not identified as training cases (n=85). Safety was assessed on all subjects (n=96).

The original data analysis plan called for the primary efficacy analysis to be performed on a modified ITT population, consisting of all randomized subjects who received Gintuit and control, with support from the per-protocol analysis. However, patient disposition was such that the three populations (ITT, mITT, and PP) were identical.

Pre-Specified Methods of Handling Missing Data

Missing data were considered relevant for subjects withdrawn prior to the six-month endpoint, or if a subject was not withdrawn but the data were missing. In the event of missing data, sensitivity analyses were planned using exit analyses for the mITT population for the primary and secondary effectiveness analyses,
where the last post-baseline observation would be carried forward. These analyses were not to be performed if there were no losses to follow-up.

None of the subjects in the study withdrew, and all key assessments were made, so these analyses were not performed.

6.2.9 Study Results – Efficacy Analysis

Subject Disposition

Of the 119 subjects screened, 23 did not meet the inclusion/exclusion criteria. Major reasons for screen failure were lack of teeth in contralateral quadrants with insufficient gingiva, previous treatment with graft at target or adjacent teeth, use of a prohibited medication, use of tobacco within 3 months, and subject unwillingness to follow study procedures and instructions.

Eleven of the 96 subjects enrolled were considered training subjects and were not included in the primary efficacy analyses; their results were analyzed separately and also pooled with pivotal subjects in supportive analyses. The remaining 85 subjects were considered 'pivotal' subjects for the primary efficacy analyses.

Of the 96 subjects enrolled, all completed the study.

Subjects were enrolled at four US study sites with a total of six investigators. However, one site treated only three subjects, all of whom participated as training subjects. Therefore, all of the 85 pivotal subjects were treated at three sites by four surgeons/investigators. Pivotal subject sample sizes were approximately evenly distributed across these three sites (30, 27, and 28).

Dropouts and/or Discontinuation:

All 96 subjects completed the six-month study and all required study visits (Weeks 1 and 4, Months 3 and 6).

Demographics

Demographic characteristics of the efficacy population (n=85) and overall subjects

(n=96) are shown in Table 11.

Table 11 Demographics for Non-Submerged Study 06-PER-002

Parameter	Statistics	Efficacy	Training	All
Gender				
Female	n (%)	46 (54.1%)	6 (54.5%)	52 (54.2%)
Male	n (%)	39 (45.9%)	5 (45.5%)	44 (45.8%)
Age (years)	n	85	11	96
Min – Max		18.0 - 70.8	21.2 - 70.3	18.0 - 70.8
Mean (SD)		46.9 (12.7)	49.4 (16.67)	47.1 (13.13)
Median		48.3	53.3	48.8
Race				
White	n (%)	77 (90.6%)	10 (90.9%)	87 (90.6%)
Black/African American	n (%)	1 (1.2%)	0	1 (1.0%)
Native Hawaiian/Other Pacific Islander	n (%)	0	0	0
Asian	n (%)	4 (4.7%)	1 (9.1%)	5 (5.2%)
American Indian/Alaska Native	n (%)	0	0	0
Other	n (%)	3 (3.5%)	0	3 (3.1%)
Site				
Site 10	n (%)	30 (35.3%)	4 (36.4%)	34 (35.4%)
Site 15	n (%)	0	3 (27.3%)	3 (3.1%)
Site 16	n (%)	27 (31.8%)	2 (18.2%)	29 (30.2%)
Site 17	n (%)	28 (32.9%)	2 (18.2%)	30 (31.3%)
Previous Tobacco Use				
Yes	n (%)	34 (40.0%)	4 (36.4%)	38 (39.6%)
No	n (%)	51 (60.0%)	7 (63.6%)	58 (60.4%)

Analysis of Efficacy

Efficacy Outcomes

Analysis of Primary Endpoint
Eighty-one of the 85 subjects (95.3%) met success criteria of ≥ 2mm KT at the Gintuit site (exact binomial 95% CI 88.4%, 98.7%). Results are shown in Table 12.

All 11 subjects in the training cohort also met the primary endpoint at the Gintuit-treated site, and all 96 subjects met the primary endpoint at the control site. The success rate at the Gintuit site was not compared to the success rate at the control site.

Table 12 Primary Efficacy Endpoint (KT ≥2 mm at the Gintuit site at 6 months), Study 06-PER-002 (N=85)

Month 6	Statistics	Gintuit
	N	85
Subjects with KT width ≥ 2 mm	n (%) 95% CI p-value*	81 (95.3%) (88.4, 98.7) < 0.001*
KT width (mm)	Mean (SD) Median Min., Max.	3.21 (1.14) 3.0 1.0, 6.0

* Comparison to a pre-defined standard of 50% of subjects with KT width ≥2 mm.

Reviewer Comment

1. *By study center, the number (percent) of subjects in study 06-PER-002 who met the primary endpoint of KT ≥ 2 mm for the Gintuit site at six months was 26/30 (87%) at Site 10, 27/27 (100%) at Site 16, and 28/28 (100%) at Site 17.*

Analysis of Secondary Endpoints

There were six secondary efficacy endpoints. The order of testing was pre-specified and conducted sequentially as follows: color matching, texture matching, KT ≥1 mm, patient preference, surgical site sensitivity, and absence of pain at three days. Five of the six secondary endpoint evaluations were superiority comparisons between Gintuit and control (FGG); the other secondary endpoint (KT ≥1 mm) was a superiority comparison of Gintuit to a pre-specified benchmark of 80% success rate. The study showed superiority of Gintuit to control in three of the six secondary endpoints: color matching ($p < 0.0001$), texture matching ($p < 0.0001$), and patient preference ($p < 0.0001$). The proportion of Gintuit sites with KT ≥ 1 mm was also significantly greater than a pre-defined success standard of 80%. There was no significant difference in surgical site sensitivity (p-value = 0.32), the fifth secondary endpoint. Therefore, the absence of pain at three days, the sixth secondary endpoint, was not tested. Although the pain measurement was not tested statistically, results showed no important differences between Gintuit and control sites in this outcome measure. Results for the secondary endpoints are summarized in Table 13.

Table 13 Secondary Endpoint Efficacy Results for Pivotal Study 06-PER-002

Endpoints:	**Results**
Color (compared to surrounding tissue)	(Month 6) p<0.001 **Gintuit**: Equally Red / Not Equally Red **control** Equally Red: 23 / 0 Not Equally Red: 56 / 6 p<0.0001*
Texture (compared to surrounding tissue)	(Month 6) **Gintuit**: Equally Firm / Not Equally Firm **control** Equally Firm: 46 / 0 Not Equally Firm: 35 / 4 p<0.0001*
KT ≥ 1mm (80% success standard)	(Month 6) **Gintuit**: 85 (100%) **control**: 85 (100%) p<0.0001** 95% CI (95.8, 100)
Subject Preference	(Month 6) **Gintuit** / **control** Overall: 61 (71.8%) / 24 (28.2%) Appearance only: 65 (76.5%) / 20 (23.5%) p<0.0001*
Surgical Site Sensitivity	(Week 1); (N=71) **Gintuit**: Not Sensitive / Sensitive **control** Not Sensitive: 67 / 3 Sensitive: 1 / 0 p=0.32
Pain	(Day 3); (N=84) **Gintuit**: No Pain / Pain **control** No Pain: 54 / 7 Pain: 5 / 18

* Superiority comparison; ** Measured against a pre-defined success standard of 80%.

Reviewer Comments

1. *For the surgical site sensitivity secondary endpoint, per protocol, if the post-Gintuit placement Coe-Pak dressing was adherent at Week 1 it was to be left in place and not manually removed until the Week 2 visit. Surgical Site Sensitivity was assessed only if the Coe-Pak was no longer present. There were 14 subjects who had a Coe-Pak present at Week 1; therefore, the Surgical Site Sensitivity endpoint at Week 1 was based on 71 subjects.*

2. *For the secondary endpoint, pain after three days, evaluation was based on data in the subjects' self-reported diary. One subject did not complete the diary at Day 3, and therefore only 84 subjects are reported for the Pain secondary endpoint.*

Exploratory and *Post Hoc* Analyses

Other Effectiveness Endpoints

The FDA requested post-hoc statistical analyses of 12 other effectiveness endpoints: Recession Depth, Recession (%), Probing Pocket Depth (including mesial and distal), Clinical Attachment Level (CAL), Keratinized Tissue Width (including mesial and distal), Attached Gingiva, Bleeding on Angulated Probing, Muscle Pull Resistance, Plaque scores (buccal and lingual), Inflammation Score, Bleeding, and Swelling.

The Applicant assessed changes from baseline to Month 6 in each of the endpoints listed above. The p-values from these post hoc analyses are not readily interpretable, but the major quanlitative results are summarized as follows. For Gintuit-treated sites, there were improvements from baseline to Month 6 in KT, attached gingiva width, and recession depth. For attached gingiva, 76/85 (89%) had some positive increase in attached gingiva from baseline to Month 6; 70/85 (82%) had ≥ 1 mm increase in attached gingiva from baseline to Month 6. No other endpoints yielded clinically important changes from baseline to Month 6. For control site, there were significant improvements from baseline to Month 6 in KT width and attached gingival width. There was no clinically important improvement in recession depth at the control site.

The sponsor also compared the Gintuit and control sites on each of these endpoints at Month 6. The control site had greater KT width and attached gingival width at Month 6 than the Gintuit site. The mean (SD) KT width at Month 6 was 3.21 (1.14) mm for the Gintuit site compared to 4.57 (1.00) mm for the control site. The mean (SD) attached gingival width at Month 6 was 1.77 (1.32) mm for the Gintuit site compared to 3.17 (1.17) mm for the control site. There were no other differences between sites on other effectiveness endpoints at Month 6.

Subpopulation Analyses

Gender, Race, Age and Other Special/Subgroup Populations:

Of the 85 pivotal subjects in study 06-PER-002, 39 (46%) were men and 46 (54%) were women. All 39 men met the primary efficacy endpoint of KT > 2 mm at Month 6, while 42 / 46 (91%) of the women met the primary efficacy endpoint. In terms of race, 77 subjects (91%) were White and 8 (9%) were non-White. The primary efficacy endpoint was met by 74/77 (96%) of White subjects and by 7/8 (88%) of non-White subjects. For age, 79 subjects (93%) were between the ages of 18 and 65 and 6 (7%) were 65 or older. The primary efficacy endpoint was met by 75/79 subjects (95%) between the ages of 18 and 65, and by all 6 subjects aged 65 or older. There were no subjects studied under the age of 18.

Protocol Deviations

Several protocol deviations occurred during the course of the study that were minor, mostly related to procedural and study schedule deviations. There were no deviations that led to dropout.

Summary of Efficacy Results

In summary, 81/85 (95.3%) subjects met the primary endpoint of month 6 KT ≥ 2 mm at the Gintuit site, which yielded an exact binomial 95% CI of (88.4%, 98.7%). The study met its primary efficacy endpoint of demonstrating that the proportion of Gintuit sites with 6 month KT ≥ 2 mm exceeds 50%. Gintuit was superior to control for three of the four secondary endpoints and met criteria for the fourth (KT ≥ 1 mm success rate). There was no significant difference between Gintuit and control in surgical site sensitivity, the fifth secondary endpoint. Therefore, the absence of pain after three days, the sixth secondary endpoint, was not tested statistically. Although the pain measurement outcome was not tested statistically, results showed no important differences between Gintuit and control sites in this outcome.

Review Comment

1. *The rate of healing was not evaluated in any of the oral indication trials. These study protocols did not address the speed of healing of Gintuit sites as compared to control sites.*

6.3 Integrated Efficacy Summary and Conclusions

The claim of effectiveness for Gintuit in the oral indication comes primarily from the results of Study 06-PER-002, a within-subject controlled trial involving 96 subjects with 85 subjects included in the efficacy analyses. The study met its primary efficacy endpoint of achieving KT ≥ 2 mm at 6 months in at least 50% of subjects. Eighty-one of 85 subjects met this success criterion at the Gintuit site. Gintuit also met four of six secondary efficacy endpoints: superiority in color matching and texture matching relative to control, KT ≥ 1 mm success rate in excess of 80% of subjects, and superiority in patient preference to control; but it did not meet the fifth secondary endpoint (sensitivity), and pain was not tested due to prespecified fixed testing sequence.

In the first trial, Study 05-PER-001 did not meet its primary efficacy endpoint of showing that Gintuit was non-inferior (1 mm margin) to control in change in width of attached gingiva from baseline to six months. In fact, when Gintuit was compared to control, control sites showed a greater change from baseline in the amount of attached gingiva compared to Gintuit sites ($p<0.001$). There was also a significantly larger change from baseline to six months in KT width in control sites compared to Gintuit sites ($p<0.001$).

This BLA was the subject of a Cellular, Tissue, and Gene Therapies Advisory Committee meeting held on November 17, 2011. Efficacy-related topics that were discussed at the AC meeting included clinical effectiveness and safety of Gintuit, and statements describing the indication and intended patient population. There were voting questions on effectiveness. All fifteen voting members of the committee voted "Yes" on the question, "Based on the data provided, is Gintuit effective for the treatment of surgically created gingival surface defects in adults?" Members of the Committee agreed that the product was effective, in that it met the primary outcome of increasing the zone of keratinized tissue, and met four of the secondary endpoints that were previously described in the review.

Efficacy Conclusion:

Based on the results of Studies 05-PER-001 and 06-PER-002, and considering the deliberations of the Advisory Committee, the BLA contains substantial evidence of the effectiveness of Gintuit for increasing KT.

Efficacy review issues include the following

- Based on the results of Study 05-PER-001, the amount of KT, rather than the amount of attached gingiva, was selected as the primary efficacy endpoint for Study 06-PER-002. However, the amount of attached gingiva is more clinically meaningful than the amount of KT.
- In Study 06-PER-002, the primary efficacy outcome of 2 mm KT at the Gintuit site was compared to a 50% success rate. The clinical meaningfulness of a 50% success rate is unclear. However, efficacy results showed that 95% of Gintuit-treated sites met the primary efficacy endpoint.
- The duration of treatment outcome of Gintuit beyond six months has not been evaluated in clinical trials. This issue is addressed in the Prescribing Information by informing care providers of these limitations on the available data.
- The efficacy of repeat applications of Gintuit in the oral environment has not been evaluated in clinical trials. This issue is addressed in the Prescribing Information by informing care providers of these limitations on the available data.
- The efficacy of Gintuit has not been evaluated in children. This issue is addressed by a required postmarketing study in adolescents (see Section 10.4 for details).
- The geriatric and race/ethnicity demographic subgroups were under-represented in the oral clinical studies. The numbers of subjects in these subgroups was too small to draw any conclusion regarding efficacy in these subgroups. These issues are addressed in the Prescribing Information by informing care providers of the limitations on the available data in these populations. In addition, see Section 6.b. *Pediatrics* regarding a required postmarketing study in adolescents.
- Smokers and diabetics were excluded from the trials. The safety and efficacy of Gintuit have not been established in these groups.

7 SAFETY ANALYSIS OF GINTUIT

7.1 Safety Analysis of Clinical Studies for Oral Indications

As previously described, the study design, study population, and treatment procedure were similar for Studies 05-PER-001 and 06-PER-001. Subjects in these two studies were exposed to single topical applications of Gintuit and autologous free gingival graft at Day 0 with a six month follow-up. An integrated safety analysis will be presented for these two studies. A third early-phase study that placed Gintuit in a submerged (under a flap) application will be briefly presented in this review because it provides additional safety information for Gintuit in an oral environment. Since all three oral indication studies were within-subject controlled trials, it is difficult to judge relatedness of systemic adverse events to Gintuit. Additional supportive safety data come from more than 12 years of postmarketing experience with Apligraf for the treatment of chronic cutaneous wounds.

Integrated Report of Adverse Events in Studies 05-PER-001 and 06-PER-002

Studies 05-PER-001 and 06-PER-002 were randomized and within-subject controlled (i.e., each subject received both Gintuit and control treatment). The control treatment was a free gingival graft (FGG), using donor graft tissue from the subject's palate. The duration of the studies was six months following Gintuit application. Study 05-PER-001 was a single-center study (n=25) to evaluate the safety and efficacy of Gintuit in establishing a zone of attached gingiva (AG). Study 06-PER-002 was a multicenter study (n=96) to evaluate the safety and efficacy of Gintuit in establishing keratinized tissue (KT) in a similar study population. Adverse events were actively elicited during each study visit (visit schedule provided for each study in above sections). At the subject level, multiple occurrences of an event for the same subject were counted only once for a given system organ class or a preferred term. At the event level, every occurrence was counted.

The study design for Study 05-PER-001 is described in Section 7.1.2; the study design for Study 06-PER-001 is described in Section 7.2.2. Subjects were predominantly white and female in both studies. The demographics for the two studies are summarized in Table 14.

Table 14 Demographics and Baseline Characteristics for Studies 05-PER-001 and 06-PER-002

Demographics	Gintuit	
	05-PER-001	**06-PER-002**
N	25	96
Age (years) Mean (SD)	 50.0 (9.6)	 47.2 (13.1)
Sex Male Female	 31.8% 68.2%	 45.8% 54.2%
Race Caucasian Black Hispanic Asian Middle Eastern Other	 86.4% - 4.5% 4.5% 4.5% -	 90.6% 1.0% - 5.2% - 3.1%

A total of 65 adverse events were reported for 41 subjects in Studies 05-PER-001 and 06-PER-002. For most events, there were only one or two reported occurrences. In terms of system organ class, the two organ classes with the most reported events were Gastrointestinal Disorders (12 subjects with 13 events) and Infections and Infestations (13 subjects with 16 events). Within these two system organ classes, one type of event was reported more than twice (five subjects with six reports of sinusitis). The other specific adverse event reported in more than two subjects was hypersensitivity (four events in four subjects). Table 15 lists all adverse events that were reported for the two studies.

Table 15 Adverse Events: Integrated Safety Summary of 05-PER-001 and 06-PER-002, Safety Population (N=121 Subjects)

System Organ Class **Preferred Term**	**Subject** **N (%)**	**Event** **N**
Overall	41 (33.9%)	65
INFECTIONS AND INFESTATIONS	13 (10.7%)	16
Mastitis	1 (0.8%)	1
Nasopharyngitis	2 (1.7%)	2
Oral Herpes	1 (0.8%)	1
Pneumonia	2 (1.7%)	2
Respiratory Tract Infection	2 (1.7%)	2
Sinusitis	5 (4.1%)	6
Upper Respiratory Tract Infection	2 (1.7%)	2
GASTROINTESTINAL DISORDERS	12 (9.9%)	13
Abdominal Pain	1 (0.8%)	1
Aphthous Stomatitis	2 (1.7%)	2
Dental Caries	2 (1.7%)	2

System Organ Class Preferred Term	Subject N (%)	Event N
Gingival Pain	1 (0.8%)	1
Gingivitis	1 (0.8%)	1
Mouth Ulceration	1 (0.8%)	1
Oral Pain	2 (1.7%)	2
Paraesthesia Oral	1 (0.8%)	1
Stomach Discomfort	1 (0.8%)	1
Toothache	1 (0.8%)	1
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	5 (4.1%)	5
Gingival Injury	1 (0.8%)	1
Joint Injury	1 (0.8%)	1
Mouth Injury	2 (1.7%)	2
Post-Procedural Hemorrhage	1 (0.8%)	1
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	5 (4.1%)	5
Hypoaesthesia Facial	2 (1.7%)	2
Psoriasis	1 (0.8%)	1
Skin Exfoliation	1 (0.8%)	1
Urticaria Papular	1 (0.8%)	1
IMMUNE SYSTEM DISORDERS	4 (3.3%)	4
Hypersensitivity	4 (3.3%)	4
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	4 (3.3%)	4
Back Pain	1 (0.8%)	1
Bursitis	1 (0.8%)	1
Temporomandibular Joint Syndrome	1 (0.8%)	1
Tendonitis	2 (1.7%)	2
VASCULAR DISORDERS	3 (2.5%)	3
Hypertension	1 (0.8%)	1
Thrombosis (wound site)	1 (0.8%)	1
Wound Hemorrhage	1 (0.8%)	1
INVESTIGATIONAL	2 (1.7%)	2
Blood Cholesterol Increased	1 (0.8%)	1
Prostate Exam Abnormal	1 (0.8%)	1
Weight Decreased	1 (0.8%)	1
NEOPLASM BENIGN, MALIGNANT AND UNSPECIFIED (INCLUDING CYSTS AND POLYPS)	2 (1.7%)	2
Follicular Thyroid Cancer	1 (0.8%)	1
Malignant Fibrous Histiocytoma Metastatic	1 (0.8%)	1
RESPIRATORY, THORACIC AND MEDIASTINAL	2 (1.7%)	2
Pharyngolaryngeal Pain	1 (0.8%)	1

System Organ Class Preferred Term	Subject N (%)	Event N
Pleural Effusion	1 (0.8%)	1
SURGICAL AND MEDICAL PROCEDURES	2 (1.7%)	2
Tendon Operation	1 (0.8%)	1
Tooth Extraction	1 (0.8%)	1
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (0.8%)	1
Anemia	1 (0.8%)	1
CARDIAC DISORDERS	1 (0.8%)	1
Bifascicular Block	1 (0.8%)	1
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.8%)	1
Chest Pain	1 (0.8%)	1
NERVOUS SYSTEM DISORDERS	1 (0.8%)	1
Migraine	1 (0.8%)	1
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1 (0.8%)	1
Vaginal Hemorrhage	1 (0.8%)	1

The most common adverse reactions observed in the clinical trials (≥1%) included sinusitis, nasopharyngitis, respiratory tract infection, aphthous stomatitis, and the local effects of oral surgery.

Reviewer Comments

1. *Adverse events in Study 05-PER-001 were re-coded to MedDRA terms after the study was completed. This AEs re-coding procedure was examined during the review of this BLA, and is found to be acceptable.*
2. *Three subjects in the 05-PER-001 study were reported to have one adverse event each of allergies that were re-coded to the preferred term "hypersensitivity." These adverse events were reviewed and are consistent with seasonal allergies. One subject in Study 06-PER-002 had an adverse event of "environmental allergies" and this was also coded to the preferred term "hypersensitivity."*

Safety Results for Study 05-PER-001 can be summarized as follows: Twenty-two Adverse Events were reported among 17 subjects. All were judged unrelated to treatment. None were severe. There were no reports of infection at the wound site. In addition, there were no reports of clinical immune response to Gintuit treatment (sensitization or rejection) at any time point. There were no serious adverse events, deaths, or dropouts due to adverse events.

The **summary of safety results for Study 06-PER-002** is below.

A total of 119 subjects were screened and 96 were enrolled and treated in the study. All 96 subjects were treated with Gintuit and the control free gingival graft (FGG). No subjects

withdrew from the study: all subjects completed the required study visits (Weeks 1 and 4, Month 3, and Month 6). There were three SAEs and no deaths.

Overall, 25% of the subjects experienced an adverse event during the study, with a total of 43 adverse events reported. Fifteen AEs reported by six subjects were assessed by the investigator to be related to study treatment.

Three SAEs were reported during the study and all three adverse events were assessed by the investigator to be either not related (pneumonia and chest pain) or of unlikely relationship (metastatic malignant fibrous histiocytoma). An additional non-oral cavity malignancy, a follicular thyroid neoplasm, which the investigator assessed as not related, was reported during the study.

Seven adverse events occurred at the three treatment locations (the Gintuit-treated site, control-treated site, and the palatal harvest site):

- Three subjects experienced AEs occurring at the Gintuit-treated site. Two subjects, both in the training cohort, had inadvertent placement of the Gintuit polycarbonate base (a film that sits between the container and the Gintuit product) to the treatment site at the time of Gintuit placement, which resulted in AEs of gingival injury and gingival pain. For both of these subjects, the membrane was able to be removed without sequelae and ≥ 2 mm KT were regenerated at the treatment site. The Applicant addressed this safety issue by training the investigators, and these types of adverse events were not seen beyond the training cohort. The third subject experienced an AE of mouth ulceration.
- Two AEs occurred at the control-treated site. One subject had gingivitis and one subject had gingival mucosal exfoliation).
- Two AEs occurred at the palatal harvest site. One subject had postprocedural hemorrhage and one subject had thrombosis).

There were no significant immune-related adverse events.

Reviewer Comment

1. *Palatal harvest morbidity is an expected risk with harvest of a FGG.*

Safety Results of Study 07-PER-004

This was a prospective, single-center, randomized, within-subject controlled treatment comparison six-month pilot study. Subjects were given both Gintuit and a palatal graft on Day 0. The main criteria for enrollment were adults with at least two non-adjacent teeth in contralateral quadrants of the same jaw with Miller Class I or II buccal recession (≥3 mm) that required tissue grafting. Other than requirement for root coverage, the remaining criteria were similar to those of the two previous trials.

Results:
Of the 19 subjects screened, 15 were enrolled and treated. Fourteen completed the assessment schedule through Month 6. One subject dropped out (reasons not provided by Applicant) and was lost to follow-up. There were 11 (73.3%) females, 12 (80%) Caucasians, and the mean age was 42.5 (SD 11.0) years. All 15 subjects in this study received one treatment (one dose) of Gintuit at Day 0, placed under a surgical flap (submerged). The amount of Gintuit used in one application (or one dose) depended on the size of the wound.

The technique of Apligraf application was modified twice in the study. This resulted in three distinct groups of subjects that resulted in analytical populations that were too small to yield informative efficacy data. The Applicant terminated the study after 15 subjects were enrolled and treated.

There were 20 reported adverse events in this study. Two subjects experienced two AEs at the Gintuit-treated site; two subjects experienced two AEs at the control-treated site; and four subjects experienced seven AEs in areas of the mouth other than the Gintuit and control-treated sites. Five subjects experienced nine AEs in locations other than the mouth.

Relatedness: One AE was judged by the investigator to be related to treatment. Subject --b(6)------- had impaired healing of the right target tooth that was considered to be mild and probably related to treatment with Gintuit. The subject underwent treatment with Orabase and an additional gingival suture, and the AE resolved.

Severity: All AEs were judged by the Investigator to be mild in severity, with the exception of esophagitis, which was judged to be of moderate severity. None of the AEs were considered to be severe. Of the 15 treated subjects, 14 completed the study. The reason for discontinuation of one subject was not provided.

7.2 Safety Experience for Gintuit for Chronic Cutaneous Wounds

Postmarketing Adverse Events Reported to FDA

From approval in 1998 to June, 2011, over –b(4)-- units of Apligraf have been shipped for patient treatment of wounds. A total of 11 adverse events resulted in medical device reports (MDRs) submitted to the FDA MAUDE database. All MDRs have been reviewed at FDA. A summary of the 11 MDRs is shown in Table 16.

Table 16 Summary of Post-Marketing Adverse Events Reported to FDA (1998 to June 30, 2011)

Event Date	Event Type and Patient Outcome	Adverse Event	Relationship to Tx (as assessed by the Applicant)
27 Sept 1999	Injury, Requiring Intervention	Erosion Skin Inflammation Eschar	Related
13 Dec 2001	Injury; Other	Bacterial Infection	Related
27 July 2004	Injury, Requiring Intervention	Allergic Reaction	Related
26 May 2006	Injury; Hospitalization	Suspected Wound Infection	Related
22 May 2008	Injury, Requiring Intervention	Growth observed near periwound area. Biopsy; Squamous Cell Carcinoma	Unlikely
16 Sept 2010	Injury	Allergic Reaction; Acute Respiratory Distress Syndrome	Not Related
13 Jan 2011	Injury; Requiring Hospitalization	Pain, Chills, Increased Fibromyalgia	Related
23 Mar 2011	Injury; Requiring Intervention	Dramatic Blistering	Related
23 Mar 2011	Injury; Requiring Intervention	Dramatic Blistering	Related
Source: FDA MAUDE Database			

Review of the case report forms showed that the first case of allergic reaction consisted of local redness at the Apligraf site. The second allergic reaction occurred in an off-label use of Apligraf in an abdominal wound after major abdominal surgery, occurring in a patient with a history of multiple allergic reactions; any relationship to Apligraf is remote.

The two reports of dramatic blistering on March 23, 2011 involved two separate patients, but under the clinical care of the same physician. Both patients had identical reported adverse events on the same day. Both patients had blistering occurring on the plantar and dorsal aspects of the foot at the site of a treated wound where a contact cast had been placed. The relative contributions of Apligraf and the cast could not be determined. A case of squamous cell carcinoma was reported in a patient; however, the carcinoma was located at the site of a lesion that was present prior to application of the product.

Reviewer Comments

1. *There were no reports of off-label use of Apligraf in any medical or dental procedure in the oral cavity.*
2. *Because postmarketing events are reported voluntarily by a population of uncertain size, and because there are no controls, it is not possible to determine their frequency in the exposed population or establish a causal relationship to exposure to Apligraf. In addition, the extent to which postmarketing safety data from Apligraf can be extrapolated to use of Gintuit in the oral environment is unclear. However, because of similarities in the products and their indications, there is a reasonable likelihood that adverse events that have been associated with Apligraf may also occur with oral use of Gintuit. The Gintuit Prescribing Information informs care providers of these Apligraf postmarketing adverse reporting data.*

7.3 Relevant Non-Clinical, Clinical and Laboratory Studies/Data

Animal Studies

In addition to the nonclinical studies submitted to the Apligraf PMA, limited nonclinical studies were also submitted to this BLA. One of the testing conducted in mice was biocompatibility testing. This biocompatibility testing paradigm did not reveal any findings of significant biological concern (See Nonclinical Pharmacology/Toxicology review for details).

Histology Study for Study 05-PER-001

In the pilot study 05-PER-001, biopsy specimens were taken from seven subjects at baseline and at 6 months from the control and Gintuit-treated sites for histologic evaluation to examine the cellular composition and tissue architecture of the surgical tissues. The objective of this histological study was to see if there were differences between Gintuit-treated and control sites in the type, distribution and arrangement of collagen fibers six months after treatment, and whether there were treatment-related changes in the extracellular matrix, protein composition, and vascularity between the palatal graft and Gintuit-treated sites, and between the tissues present at six months compared to baseline. The specific aim was to see whether changes in histology were consistent with the formation of site-appropriate tissue (i.e., keratinized gingival tissue).

Results

- The six months biopsies generally showed the presence of both gingival and alveolar mucosal phenotypes with a transition zone between these two tissue types at the biopsied sites.

- The cellular origins of these tissue phenotypes were not determined in this study.

DNA Persistence of Gintuit

Testing for persistence of DNA from Gintuit was done on biopsy specimens from two of the seven subjects in Study 05-PER-001; tissue samples were provided at baseline and Month 6. Persistence of allograft cells at the Apligraf-treated site was evaluated by polymerase chain reaction (PCR) analyses of DNA.

Results

- At six months, there was no evidence of DNA persistence at the Apligraf site; the control sites were also negative for allograft DNA.

Reviewer Comment

1. *Review of the DNA persistence study found that no positive control was used for the study, i.e., there was no demonstration of Gintuit genotype right after surgery. Therefore, there could not have been persistence at six months.*

Biomarker Adjunct Study 06-PER-002

Gingival crevicular fluid (GCF), a serum transudate found in the gingival sulcus was collected from Gintuit- or FFG-treated sites at baseline (pre-treatment), 1, 2, 3, and 4 weeks post-treatment from 29 - 44 subjects.at baseline. Wound fluid samples were also collected from the palatal donor site from the FGG group at the same time points.

The gingival crevicular fluid and wound fluid samples were analyzed with a human angiogenesis array kit (RayBiotech, Inc.; Norcross, GA) for the following proteins: angiogenin (ANG), angiostatin (ANT), fibroblast growth factor-2 (FGF-2), plateletderived growth factor-BB (PDGF-BB), interleukin-8 (IL-8), interferon-inducible protein-10 (IP-10), granulocyte macrophage colony-stimulating factor (GM-CSF), tissue inhibitor of metalloproteinases-1 and -2 (TIMP-1 and TIMP-2), and vascular endothelial growth factor (VEGF).

Results

- Results from wound fluid samples showed no biomarker correlations to the quality of healing results (i.e., color, texture, pain, and inflammation) in either treatment group.

Immunogenicity

An acute rejection phenomenon or development of immune sensitization might be expected with the use of allogeneic cells. However, these reactions were not seen clinically with Gintuit. In the pivotal study (Protocol 95-DUS-001) that supported the approval of Apligraf for cutaneous wounds (chronic diabetic foot ulcer), in tests of subjects' sera, there were no

observations of antibody responses against bovine type I collagen, bovine serum protein or Class I HLA antigens on human dermal fibroblasts and human epidermal cells.T-cell-specific responses were not observed against bovine type I collagen, human fibroblasts, or human keratinocytes.

Reviewer Comment

1. *The lack of acute rejection at Gintuit-treated sites is may be due to the lack of Gintuit vascularization, presumably reducing immune cell migration from the host tissue to Apligraf and HLA antigen transport from Apligraf to the host tissue. These factors may contribute to the absence of immune reaction.*

Potential for Malignant Transformation

Laboratory:
There have been no documented histological reports of tumor formation at the site of Apligraf/Gintuit application.

Testing for the Potential for Malignant Transformation:
Information regarding the tumorigenic potential of Apligraf is provided by testing conducted on the keratinocyte and fibroblast cell banks used to manufacture Gintuit, according to the ICH and 1993 cell substrate guidelines. The testing includes:

- Donor screening and quantitative PCR testing for potential oncogenic viruses (e.g., human papilloma viruses, bovine polyoma virus)
- Senescence testing did not demonstrate neoplastic transformation of the cell lines.
- In vivo testing in nude mice injected with the cells which did not show a tumorigenic result at 3 months with any of the cell strains used to date.

Reviewer Comment

1. *There have been no malignancies attributed to Gintuit in any completed clinical trials or in the commercial use of Apligraf since its approval for the treatment of chronic cutaneous wounds. There have been no documented clinical or histological reports of tumor formation at the site of Gintuit application. The risk for malignancy is low, for use as indicated in the product labeling. However, tumorigenicity is a general concern for cellular therapies. In addition, karyotypic stability of the culture-expanded fibroblasts and keratinocytes was identified as a potential safety concern at the AC meeting (see CMC review for further details). To address this concern regarding malignancies, expedited reporting of malignancies identified occurring at either the graft site or remote locations is recommended through March 31, 2013, after product approval. Expedited reports are submitted within 15 days after learning of the event.*

7.4 Safety Summary and Conclusions

The safety data come from these Studies 05-PER-001 and 06-PER-002 and a third study that used a different application procedure (submerged under a flap). This BLA seeks approval of Gintuit for a non-submerged use; however, the submerged study provides additional safety information for Gintuit in the oral environment. Additionally, there is extensive safety information derived from post-market experience with Apligraf for chronic cutaneous wounds.

The integrated safety population consists of 136 trial subjects, all of whom received one application of Gintuit (25 from Study 05-PER-001, 96 from Study 06-PER-002, and 15 from Study 07-PER-003, an early-phase study that used a different application procedure (submerged under a flap), but provides additional safety information for Gintuit in the oral environment). Except for the three serious adverse events (SAEs) that were reported in 06-PER-002, the adverse events (AEs) that were reported were similar across the three studies. The most common adverse reactions observed in the clinical trials (≥1%) included sinusitis, nasopharyngitis, respiratory tract infections, aphthous stomatitis, and the local effects of oral surgery.

During Study 05-PER-001, 22 AEs were reported among 17 subjects. There were no deaths, serious adverse events, or subject drop-outs and the investigators did not consider any adverse events to be related to Gintuit treatment. An adjunct tissue biopsy study that was conducted along with Study One (n=2 subjects) showed no evidence of Gintuit DNA persistence at Gintuit-treated sites at six months. However, due to the small number of subjects and absence of a positive control, these results cannot be considered conclusive at this time.

During Study 06-PER-002, 25% of the subjects experienced an AE, with a total of 43 AEs reported; fifteen of the AEs were judged related. Three SAEs were reported: two (pneumonia and chest pain) were assessed not related by the investigator and the third (metastatic malignant fibrous histiocytoma, diagnosed at the site of a mass that was present prior to treatment with Gintuit) was assessed unlikely related. Gintuit was applied locally to oral mucosa, and review of adverse reactions that occurred at Gintuit-treated sites showed two "mild" adverse reactions related to treatment (gingival pain and gingival injury due to inadvertent failure to removing a polycarbonate membrane from the product before applying the product to the subject) and one report of "mild" ulceration unrelated to treatment. There were no deaths or subject dropouts during Study 06-PER-002.

No malignancies were reported during Study 05-PER-001. Two non-oral malignancies were reported during Study 06-PER-002: one subject, as noted above, had a pre-treatment mediastinal mass and was diagnosed at Study Day 154 with a metastatic malignant fibrous histiocytoma, judged unlikely related; and one subject with a previous history of hypothyroidism was diagnosed on Study Day 92 with a follicular thyroid tumor (Hurthle Cell), judged not related, in the clinical review of this BLA.

Study Three (planned n=26) was terminated after 15 subjects were treated, due to modifications to study procedures during the study, resulting in uninterpretable efficacy data. A total of 20 adverse reactions were reported for nine subjects in this study. All

adverse reactions were judged by the investigator to be mild in severity, except for a case of moderate esophagitis. There were no malignancies reported.

There were no reported serious immunologic adverse events that were attributed to Gintuit in any of these trials. The safety of Gintuit beyond six months has not been evaluated in these clinical studies.

Since Apligraf was approved (for cutaneous ulcers), 1998 through June 30, 2011, eleven medical device reports (MDRs) have been submitted to the FDA MAUDE database, within the categories of skin inflammation/blistering/erosion, wound infection/cellulitis, and allergic reaction. A case of malignancy (squamous cell carcinoma, from a preexisting lesion prior to Apligraf treatment) was assessed by the reporting physician as unlikely related. There have been no reports of clinical signs or symptoms of acute rejection or allergy that could definitely be attributed to Apligraf in the commercial use of the product. Because these reactions are reported voluntarily from a population of uncertain size (with no controls), it is not possible to determine their frequency or establish a causal relationship to Apligraf exposure with certainty. It is also uncertain whether information obtained from the post-marketing safety database for use of Apligraf in cutaneous wounds can be extrapolated to use in the oral environment. The safety profile of Gintuit is adequate for approval for the revised indication and for use as stated in the label.

Safety Review Issues

- Tumorigenicity is a general concern for cellular therapies. There have been no documented clinical or histological reports of tumor formation at the site of application.
- As discussed above, there have been no malignancies that have been attributed to Gintuit in any completed clinical trials or in the commercial use of Apligraf since its approval over 12 years ago for the treatment of chronic cutaneous wounds.
- However, regarding the stability of cell banks, karyotypic stability of the culture-expanded fibroblasts and keratinocytes was identified as a potential safety concern at the AC meeting.

8 LABELING

The proposed Prescribing Information (PI) has been reviewed and revised during the review of this BLA. The most significant changes made are summarized below.

- The Indication statement has been revised to “Gintuit is an allogeneic cellularized scaffold product indicated for topical (non-submerged) application to a surgically created vascular wound bed in the treatment of mucogingival conditions in adults. Gintuit is not intended to provide root coverage.”
- Sections on Contraindications, Warnings and Precautions, and Adverse Reactions were modified according to FDA labeling guidelines.
- The Clinical Trials section was revised to include efficacy results from Study 05-PER-001.
- Tables and graphs depicting results of post-hoc efficacy analyses were deleted.

- The Clinical Pharmacology section was revised to state that the mechanism of action by which Gintuit increases keratinized tissue at the treated site has not been identified.

The proposed label provides adequate directions for the safe and effective use of Gintuit in the indicated population.

9 CONCLUSIONS – OVERALL

The BLA included study reports from two clinical studies (Study 05-PER-001 and Study 06-PER-002) for topical (non-submerged) application of Gintuit, and from Study 07-PER-004 for the submerged (under a flap) application of Gintuit. These studies evaluated the efficacy and safety of Gintuit for the treatment of gingival recession-type defects associated with insufficient zones of keratinized tissue. The first oral indication, Study 05-PER-001, failed to demonstrate non-inferiority for attached gingiva (AG) compared to a free gingival graft (FGG) control.

The data supporting efficacy claims were derived from Study 06-PER-002 (n=85 for efficacy analysis). The study met its primary efficacy endpoint; 81/85 subjects (95.3%) met success criteria of ≥ 2mm KT at the Gintuit site in comparison to a pre-defined standard of 50% of subjects at six months. The mean KT width increase at the Gintuit site was 3.21 mm. Gintuit was superior to control in three secondary endpoints: color and texture matching, and patient preference. It was not superior to control for the last two secondary endpoints (surgical site sensitivity and absence of pain after three days).

There have been no significant safety issues that were attributed to Gintuit. In Studies 05-PER-001 and 06-PER-002, the most common adverse reactions observed in the clinical trials (≥1%) included sinusitis, nasopharyngitis, respiratory tract infection, aphthous stomatitis, and the local effects of oral surgery. Local adverse reactions (at the Gintuit site) included gingival pain, gingival injury (due to inadvertent failure to remove a polycarbonate base from Gintuit before application), and ulceration. Gintuit is expected to have a favorable risk-benefit profile when used as described in the label.

Efficacy Conclusion:
Based on the results of Studies 05-PER-001 and 06-PER-002, and considering the deliberations of the Advisory Committee, this BLA contains substantial evidence of the effectiveness of Gintuit for the proposed indication.

Reviewer Comments

1. *A 50% success rate seems low for the Study 06-PER-002 primary efficacy endpoint and it is unclear why it was chosen. However, efficacy results for 06-PER-002 showed that 95% of Gintuit-treated sites met the primary efficacy endpoint.*
2. *Although the product was deemed effective, based on the benchmark KT from the trial data, the precise wording for the indication (i.e., what the product was*

effective for) was discussed, but was not resolved at the November, 2011 AC meeting.

10 CLINICAL RECOMMENDATIONS AND RISK / BENEFIT ASSESSMENT

10.1 Recommendation for Approval or Non-Approval

I recommend approval of this BLA for the revised indication statement, "Gintuit is an allogeneic cellularized scaffold product indicated for topical (non-submerged) application to a surgically created vascular wound bed in the treatment of mucogingival conditions in adults. Gintuit is not intended to provide root coverage."

10.2 Risk/Benefit Assessment

The overall risk profile associated with Gintuit for topical application in the treatment of mucogingival conditions is acceptable in adults. The quality, efficacy, and safety of Gintuit have been reviewed and have been determined to be acceptable for the revised indication.

10.3 Recommendations for Postmarketing Risk Management Activities

There has been no safety issue identified that warrants a Risk Evaluation and Mitigation Strategy (REMS) in adults. Gintuit is expected to have a favorable risk-benefit ratio when used as described in the label.

10.4 Recommendation for Postmarketing Actions and Pediatric Waiver

Study Deferral and Pediatric Waiver

During the Advisory Committee (AC) meeting on November 17, 2011, some members of the AC were concerned that should Gintuit become approved, dentists would use it in children when there are no trial data to assess the safety and efficacy of Gintuit in the pediatric population. Some AC members stated that Gentuit would be used in adolescents for gingival conditions related to orthodontal therapy. However, AC members also stated that Gintuit would not be used in children prior to acquiring permanent teeth, i.e., children under the age of 12 years.

To address these concerns, a Postmarketing Requirement (PMR) is recommended under the Pediatric Research Equity Act (PREA) for the Applicant to conduct a postmarketing study to evaluate the safety and effectiveness of Gintuit for topical (non-submerged) application to a surgically created vascular wound bed in the treatment of mucogingival disorders in pediatric patients between 12 and 18 years of age. The applicant has agreed to conduct the study and has submitted a protocol synopsis for the Pediatric Clinical Study (PMR) study, as outlined below:

Study Design: A prospective, uncontrolled, multicenter trial, N=25

Protocol Title:	A Clinical Trial to Evaluate Gintuit to Enhance Soft Tissue Regeneration and Wound Healing in Adolescents.
Indication:	Insufficient zone (≤ 1 mm) of KT requiring soft tissue grafting around permanent teeth in adolescents
Objective:	To evaluate Gintuit as safe and effective for augmenting KT in adolescents with recession type defects around permanent teeth that have an insufficient zone of KT.
Treatment:	Treatment of recession defects around permanent teeth with Gintuit in adolescents

Criteria for Evaluation:

- Efficacy: The primary endpoint is the ability of Gintuit to achieve ≥ 2 mm KT at 6 months.
- Safety: Type, incidence, timing, severity and relationship to treatment-specific and systemic adverse events will be reported
- Study Duration: Following screening, subjects will receive Gintuit with final endpoint evaluations at Month 6.

Major Inclusion Criteria:

1. Subject is at least 12 years of age but no more than 18 years of age.
2. Subject has at least 1-3 fully erupted permanent teeth with an insufficient zone (≤ 1mm) of keratinized tissue that requires soft tissue grafting.
3. Females of childbearing potential must have a documented negative urine pregnancy test.
4. Subjects and/or their Legal Guardian must have read, understood and signed an institutional review board (IRB) approved Informed Consent Form. If applicable, subjects must be willing and able to provide assent on an IRB approved Research Subject Assent Form.
5. Subjects must be able and willing to follow study procedures and instructions.

The PMR deferral study and the partial pediatric waiver were recommended by the PeRC on February 22, 2012.

Based on internal review of the study protocol and in consultation with Dr. Mark Reynolds (SGE consultant; periodontist), the following protocol changes must be made to correct the deficiencies that were identified:

1. Change the primary endpoint from generation of ≥ 2 mm keratinized tissue to generation of ≥ 1 mm attached gingiva at Month 6.
2. Change the threshold for success from 50% to 65%; recalculate sample size accordingly.
3. Utilize either a 2-sided (0.05) or 1-sided (0.025) test
4. Submit the final protocol by December 31, 2012

The Applicant has agreed to make these revisions and has agreed to submit the final study protocol by December 31, 2012; to complete the study by September 30, 2016; and to submit the final study report by March 31, 2017.

Reviewer Comments

1. *Early in the review of this BLA, gingival recession-type surface defects were initially believed to exist primarily in adults. A full pediatric waiver for this BLA was requested and recommended by the PeRC on August 17, 2011. At the CTGT Advisory Committee (AC) meeting on November 17, 2011 for this BLA, the potential use of this product in the adolescent population in orthodontia-related conditions was identified. Consequently, I recommend a PMR to address this pediatric concern.*
2. *The study protocol for the deferred pediatric study in adolescents is in development. The preliminary protocol proposes final evaluations at six months for safety and efficacy. Discussions are ongoing regard how long safety and treatment effect should be followed for the adolescent population in this study. The final protocol will be submitted by December 31, 2012.*

10.5 Expedited Postmarketing Adverse Events Reporting

To address the safety concerns regarding malignancy, I recommend that the Applicant submit expedited reports of any events in the MedDRA System Organ Class *Neoplasms benign, malignant and unspecified (including cysts and polyps)*, occurring at either the graft site or remote locations, within 15 days after learning of the event, through March 31, 2013.

11 APPENDICES

11.1 Appendix A: Abbreviations

AC	Advisory Committee
AE	Adverse Event
ANG	Angiogenin
ANT	Angiostatin
BLA	Biologics License Application
BIMO	Bioresearch Monitoring
Bx	Biopsy
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
CMC	Chemistry, Manufacturing, and Controls
CMH	Cochran-Mantel-Haenszel
CRFs	Case Report Forms
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CTG	Connective Tissue Graft
CTGTAC	Cellular, Tissue, and Gene Therapies Advisory Committee
CWHS	Clinical Wound Healing Score

DAGID	Division of Anesthesiology, General Hospital, Infection Control, and Dental Devices
DCEPT	Division of Clinical Evaluation & Pharmacology/Toxicology (FDA)
DE	Dermal Equivalent
DEDB	Dental Devices Branch
DFU	Diabetic Foot Ulcers
EE	Efficacy Evaluable
EKG	Electrocardiogram
ER	Emergency Room
--b(4)--	----b(4)----------
--b(4)--	----b(4)----------
ELISA	Enzyme Linked Immunosorbent Assay
EPI	Epidermal Layer
FDA	Food and Drug Administration
FGF-2	Fibroblast Growth Factor-2
FGG	Free Gingival Graft
--b(4)--	---b(4)----------
GCF	Gingival Crevicular Fluid
GCP	Good Clinical Practice
GM-CSF	Granulocyte Macrophage Colony-Stimulating Factor
GMP	Good Manufacturing Practice
-b(4)-	----b(4)----------
H&E	Hematoxylin and Eosin
ICH	International Conference on Harmonisation
IHC	Immunohistochemistry
IDE	Investigational Device Exemption
IL-8	Interleukin-8
IND	Investigational New Drug Application
IP-10	Interferon-inducible protein-10
ITT	Intent-To-Treat
KT	Keratinized Tissue
MAUDE	Manufacturer And User Facility Device Experience database
MCB	Master Cell Bank
MDR	Medical Device Report
MedDRA	Medical Dictionary for Regulatory Activities
mm	Millimeter
mITT	Modified Intent-To-Treat
MO	Medical Officer
MTT	Mitochondrial Tetrazolium Test
OBE	Office of Biostatistics and Epidemiology
OCP	Office of Combination Products
OCTGT	Office of Cellular, Tissue and Gene Therapies
ODE	Office of Device Evaluation
PAL	Post Air-Lift
PDGF-BB	Platelet Derived Growth Factor-BB
PI	Patient Information (medication package insert)

PCR	Polymerase chain reaction
PeRC	Pediatric Review Committee
PMA	Premarket Approval Application
PMC	Post Marketing Commitment
PMR	Post Marketing Requirement
PVCO	Pharmacovigilance Contract Organization
PVP	Pharmacovigilance Planning
REMS	Risk Evaluation and Mitigation Strategy(ies)
RT-PCR	Reverse Transcription - Polymerase Chain Reaction
SAE	Serious Adverse Event
SCTG	Subepithelial Connective Tissue Graft(s)
SCC	Squamous Cell Carcinoma
SOC	System Organ Class(es)
TEAEs	Treatment-Emergent Adverse Events
TGF	Transforming Growth Factor
TIMP-1	Tissue Inhibitor of Metalloproteinases-1
TIMP-2	Tissue Inhibitor of Metalloproteinases-2
Tx	Treatment
UNC-15	University of North Carolina-15 periodontal probe
US	United States
VEGF	Vascular Endothelial Growth Factor
VLU	Venous Leg Ulcers
WCB	Working Cell Bank
WF	Wound Fluid

11.2 Appendix B: Documents Reviewed/Consultations

Organogenesis BLA 125400, original submission

CDRH PMA #**:** P090027

FDA/ CDRH/ DAGID Consultations:

- Robert Betz, D.D.S., CDRH/ DAGID, Clinical Review Memorandum 9/1/2011: Efficacy Review of BLA 125400
- Robert Betz, D.D.S., CDRH/ DAGID, Clinical Memorandum 11/30/2011
- Robert Betz, D.D.S., CDRH/ DAGID, AC Slide Presentation 11/17/2011: Overview of Dental Condition Studied

Final FDA/CBER Review Memorandums:

- Robert Betz, D.D.S., CDRH/ DAGID, Final Clinical Review 12/21/2011
- John Scott, Ph.D., OBE, Min-Cycle and Final Statistical Reviews
- Mark Lee, Ph.D., CBER/OCTGT, Mid-Cycle and Final CMC Reviews
- Patrick Au, Ph.D., CBER/OCTGT/DCEPT, Mid-Cycle and Final Pharmacology/Toxicology Reviews
- Faith Barash, M.D., OBE, Mid-Cycle and Final OBE Reviews
- Janet White, OCBQ, Final BIMO Review

SGE Periodontal Consultant:

- Mark Reynolds, D.D.S., University of Maryland Dental School

11.3 Advisory Committee Meeting

The Cellular, Tissue, and Gene Therapies Advisory Committee met in open session on November 17, 2011. Clinical topics covered at the AC meeting included clinical effectiveness and safety of Gintuit, statements describing the indication, and intended patient population.

Clinical topics covered at the AC meeting included clinical effectiveness, indication statement and the patient population, and the safety of Gintuit for the proposed oral indication.

There were two voting questions:

1. Effectiveness: Based on the data provided, is Gintuit effective for the treatment of surgically created gingival surface defects in adults?

Discussion:
Members of the Committee agreed that the product was effective, in that it met the primary outcome of increasing the zone of keratinized tissue, and met four of the secondary endpoints, including color matching, texture matching, patient preference, and keratinized tissue ≥ 1 mm.

Effectiveness voting: Yes: 15/15 voting members.

2. Safety: Do the data presented demonstrate the safety of Gintuit for the proposed indication?

Discussion:
Committee members did not raise any significant safety concerns based on the data. However, some members of the Committee thought that there could be safety issues related to possible inflammatory and immune responses, including the risk of tumorigenicity in at-risk populations, e.g., individuals at risk for oral cancer. Some members recommended safety follow-up of greater than 6 months to evaluate the risks of inflammation and tumorigenicity.

Safety voting: Yes: 14; No: 1

Additional clinical discussion included the following:

The proposed indication is for the "treatment of surgically created gingival and alveolar mucosal surface defects in adults." However, alveolar mucosal defects were not studied in the two trials.

There was no consensus regarding the precise patient population that would be appropriate for Gintuit. Members stated that the product could be indicated for aesthetic improvements in color and texture. Some members stated that the product, if licensed, would be used in children and suggested conducting clinical trials in children with safety follow-up of greater than 6-months.

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